

I N D E X

APPENDIX

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XII	TOXICOLOGICAL DATA
XIII	EXTRACTS FROM LITERATURE RELATING TO THE MANUFACTURE OF BPA

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Manufacture of Plastics, Volume 1
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Vinyl Chloride-Associated Disease

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Key words: *Acroosteolysis – Angiosarcoma of the Liver – Portal Fibrosis and Portal Hypertension – Pseudoscleroderma – Raynaud's Phenomenon – Vinyl Chloride*

1 Introduction

The history of vinyl chloride-associated disease, its recognition and prophylaxis is a classic example of shutting the stable door after the horse has bolted. It should help to emphasize the need to shift our attention to preventing exposure from occurring rather than to reparative measures. In view of the large number of new and potentially hazardous chemicals introduced each year into the workplace and the environment, this account should again alert us to the necessity of pretesting chemicals adequately for their potential health effects, even at the risk that technological progress will develop at a more modest rate.

Large-scale production of the synthetic resin polyvinyl chloride (PVC), a thermoplastic material suitable for the most widely diversified industrial use, was begun around 1930 in the United States and in Germany. The monomer, vinyl chloride (VCM), a rather simple aliphatic compound, was believed until the early 1960s to be

one of the least harmful later turned out, had an evaluation of acute effects to reveal its carcinogenicity might have continued in place, considering that vapour phase under an reactive double bond.

Today vinyl chloride formation and data on precisely a quarter of a century attributable to this new disease with the shocking discovery that the monomer compound did not alert the workers engaged in it, published in 1949 (Tribukait).

Ultimately, it was the occurred in workers exposed a causal relationship: (1) pseudoscleroderma; (2) liver. Particularly, the danger among a comparable alarming experience with a connection between the lungs or the gastrointestinal the prolonged latency of sarcoma of the liver, not these two fatal consequences the conclusion that VCM cancer meeting in Houston to VCM was a very serious.

It should be stressed, precise, an intermediate mainly in the mammalian merization products (PVC) cated from the polymer, they contain unreacted PVC (thermal decomposition toxicity of pyrolysis products mainly due to the release Abar 1969; Dyer and Ex and only very small or none (O'Mara et al. 1971 cite

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one of the least harmful chlorinated hydrocarbons. Early animal experiments, as it later turned out, had indeed been carried out with dosages sufficiently high for the evaluation of acute effects, but chronic exposure had not been of sufficient duration to reveal its carcinogenic properties. On purely theoretical grounds, however, one might have continued to feel uneasy with this compound as a pollutant of the workplace, considering that it is (1) a halogenated hydrocarbon which (2) exists in its vapour phase under ambient conditions (inhalative exposure) and (3) contains a highly reactive double-bond.

Today vinyl chloride-associated pathology is well documented. A large body of information and data on this topic has been accumulated, notably since 1974, but precisely a quarter of a century had to pass before the full range of symptomatology attributable to this new occupational health hazard became recognized in January 1974 with the shocking discovery that haemangiosarcoma of the liver occurred in production workers heavily exposed to PVC. Early and not easily accessible reports suggesting that the monomer might be an environmental risk for workers handling this compound did not alert the experts sufficiently. The earliest indication of adverse effects in workers engaged in the production and processing of PVC, a Russian study published in 1949 (Tribukh et al. 1949), received little attention.

Ultimately, it was the exceptional character of the three major lesions which occurred in workers exposed to VCM that contributed most to the final appreciation of a causal relationship: (1) the syndrome of acroosteolysis, Raynaud's phenomenon and pseudoscleroderma; (2) non-cirrhotic portal hypertension; and (3) angiosarcoma of the liver. Particularly, the discovery of a cluster of four cases of this extremely rare malignancy among a comparatively small group of workers (Creech et al. 1974a) was an alarming experience which called for immediate action. It can easily be imagined that a connection between VCM and the more common malignancies, such as cancer of the lungs or the gastrointestinal tract, might still have gone unnoticed. On the other hand, the prolonged latency periods of both non-cirrhotic portal hypertension and angiosarcoma of the liver, roughly 10 and 20 years respectively, delayed the recognition of these two fatal consequences of chronic exposure to VCM. But one can hardly escape the conclusion that Viola's discovery of cancer in experimental animals, presented at a cancer meeting in Houston in 1970, was sufficient evidence to indicate that exposure to VCM was a very serious occupational hazard (Peters 1976).

It should be stressed that the noxious agent is solely the monomer, or to be more precise, an intermediate of the monomer's metabolic bioactivation, which takes place mainly in the mammalian liver and yields certain highly reactive epoxides. The polymerization products (PVC), i.e., the solid plastic and the plastic consumer goods fabricated from the polymer, are chemically inert articles which carry no health risk unless they contain unreacted residual monomer. Even the combustion of articles made from PVC (thermal decomposition in fires) does not yield free vinyl chloride monomer; the toxicity of pyrolysis products of polyvinyl chloride polymers and formulations is mainly due to the release of hydrochloric acid and carbon monoxide (Cornish and Abar 1969; Dyer and Esch 1976; Sorenson 1976; Moser 1976; Colardyn et al. 1976) and only very small or no quantities of phosgene derived from residual monomer (O'Mara et al. 1971 cited by Colardyn et al. 1976).

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2 Technological Details

2.1 Vinyl Chloride Monomer (VCM)

At standard (ambient) conditions of temperature and pressure, vinyl chloride ($\text{CH}_2=\text{CHCl}$; chloroethylene, chloroethene) is a non-irritating, colourless gas with a faintly sweet odour, inflammable at concentrations above 3.8% by volume in air, which is only slightly soluble in water, soluble in ethyl alcohol and easily soluble in ether and carbon tetrachloride. VCM is mainly used as an intermediate in the manufacture of plastics, as a refrigerant and in organic synthesis. It was formerly also employed as a propellant for aerosols. It is easily liquefied under pressure and is usually handled and shipped as a liquid. Gaseous VCM condenses at -13.8°C and 760 Torr ($= 101.3 \text{ kPa}$) to a colourless liquid of low viscosity (Lefaux 1966). Its physical properties are listed in Table 1, the most important of which are its low boiling point, its high specific gravity (gaseous VCM is 2.15 times heavier than air), its low solubility in water and the half-life in air, ranging from 3 to 20 h.

Table 1. Physical properties of VCM

Mol. wt.:	62.503												
B. p.:	-13.8°C (-13.7 to -13.9)												
F. p.:	-153.7°C												
Flash point:	-78.5°C (Cleveland open cup)												
Limits of flammability:	3.8%-29.3% by volume in air above -78.5°C (= 38 000-293 000 ppm)												
Autoignition temperature:	472°C												
Vapour pressure:	<table><tr><td>mm Hg</td><td>10</td><td>100</td><td>692</td><td>2300</td><td>2660</td></tr><tr><td>°C</td><td>-87.5</td><td>-55.8</td><td>-15.8</td><td>+20</td><td>+25</td></tr></table>	mm Hg	10	100	692	2300	2660	°C	-87.5	-55.8	-15.8	+20	+25
mm Hg	10	100	692	2300	2660								
°C	-87.5	-55.8	-15.8	+20	+25								
Vapour density:	2.15 g/litre (calculated at 25°C and 760 mmHg (air = 1))												
Sp. gr. of liquid VCM:	0.9121 at -20°C/4°C 0.99 at -25°C/4°C												

Sources: Fairhall 1957; Irish 1963; Zapp 1964; Lefaux 1966; Ostermayer 1967; Roubal 1972.

2.1.1 History

The French chemist, *Regnault* (1835) was apparently the first to study systematically the synthesis and analysis of vinyl chloride. *Liebig*, who had done some earlier preliminary experiments, encouraged *Regnault* to investigate this compound when *Regnault* spent several months in *Liebig*'s laboratories. All compounds containing the vinyl group ($\text{CH}_2=\text{CH}-$) polymerize readily (Fairhall 1957). Spontaneous polymerization of vinyl chloride to a white opaque solid mass under the influence of sunlight was first described by *Baumann* in 1872; he also quotes a paper by *Savtser* and *Glinka* (who

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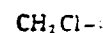
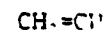
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2) Conversion



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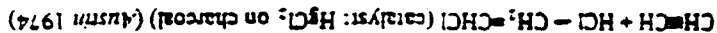
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succeeded in decomposing vinyl chloride to monochloroacetaldehyde with the aid of oxidizing substances such as hypochlorous acid.

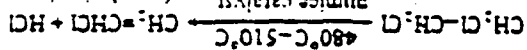
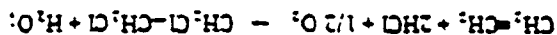
2.1.2 Production of VCM

Large-scale commercial synthesis of VCM with a high yield was made possible much later by employing two principle methods, the second having now largely replaced the first:

1) Conversion of acetylene to VCM by hydrochlorination:



2) Conversion of ethylene by vapour-phase or liquid-phase oxychlorination to 1,2-dichloroethane and subsequent pyrolysis (thermal cracking) to VCM (Albright 1967a):



(pyrolysis: thermal cracking, Austin 1974).

VCM was usually manufactured in closed systems and stored in outdoor facilities.

Thus, any leakage of the gas was readily diluted in the ambient air. VCM concentrations in the atmosphere at some distance from manufacturing plants were found to be in the range 1-2 ppm. In close proximity, the concentration ranged up to 50 ppm.

(IARC 1974). Spontaneous polymerization in light has also been repeatedly observed when VCM comes into contact with atmospheric air due to container leakage (Ostermayer 1967). A prerequisite for the polymerization process is a high degree of purity in commercially produced VCM. Impurities retard the polymerization process (Leclercq 1966; Ostermayer 1967).

In the early discussion about the cause of vinyl chloride-associated disease it was conjectured that other compounds or impurities contained in prepolymers or in retrieved VCM might have been the causative agent(s) (Thies and Vosen 1974). Analyses carried out by six West German manufacturers of PVC, however, showed that the sum of all impurities (such as saturated or unsaturated hydrocarbons and their halogenates) was 0.01% by volume for prepolymers and 0.1% for retrieved unsaturated monomer. Only methyl chloride was found in concentrations of 50-300 ppm in prepolymers and 100-500 ppm in retrieved VCM (in one instance only). But it should be kept in mind that even 1000 ppm methyl chloride in VCM would mean, at 500 ppm VCM in air, a methyl chloride concentration in air of only 0.5 ppm. All other impurities (propylene, isobutane, n-butane etc.) would then be in the ppb range. Besides, no significant difference in purity could be found between VCM from acetylene and from ethylene.

1 chloride ($\text{CH}_2=\text{CHCl}$) as with a fairly in air, which is soluble in ether and manufacture of usually handled and Fort (= 101.3 kPa) properties are listed as high specific grav- in water and the

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2.2 Production of Polyvinyl Chloride (PVC)

2.2.1 Technology of Polymerization

The following description is meant to serve merely as a rough sketch of the procedures and technological details involved in the production of polyvinyl chloride.

Vinyl chloride monomer is polymerized in large autoclaves (reactors) at temperatures between 40°C and 80°C and pressures of 6–16 (8–12) atmospheres. There are usually several reactors (up to 10–30) located in one building. The reactivity of the monomer is a function of its double-bond. The second functional site of the vinyl chloride molecule, the chlorine atom, does not react easily. The double-bond of VCM is not only the site from which the polymerization originates but is also the source of the toxicity and carcinogenicity of this compound when it is being metabolized in the body. The polymerization of VCM, which is a strongly exothermic reaction (Barnes 1976), is initiated with the aid of compounds soluble in VCM that form free radicals at relatively low temperatures. Initiators are such compounds as lauroyl peroxide, isopropyl percarbonate, azo-bis-isobutyronitrile, and others. The free radicals react with the double-bond of the monomer, transforming it in turn 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 which often involves a reaction between two growing chains (Malten and Zielhuis 1964; Lefaux 1966; Albright 1967; a-c-Dominghous 1972; Slater 1972). The random character of such termination steps accounts for the production of chains of different length and hence different degrees of polymerization, with molecular weights of the finished PVC being statistically distributed around a mean value.

Commercial PVC polymers have average molecular weights that vary from about 50 000 to 150 000 daltons (Albright 1967b). Degree and velocity of polymerization, which are influenced by temperature and the concentration of initiators, determine the specific type of PVC produced (Frey 1973). During polymerization considerable amounts of the monomer are at first dissolved in the polymer, but most of this is later also transformed to PVC as polymerization progresses. The polymer which is not soluble in the liquid monomer precipitates out. The process of polymerization slows down towards the end of the reaction. It is terminated, depending on the method used, when approximately 80%–90% of VCM is polymerized. The timing of this termination of the process is essential for the physical properties of the resins produced. The heat generated during the exothermic process of polymerization must be removed to keep the temperature of the reaction under control. Mechanical agitation aids in transferring the heat across the colloidal system to the cooling jacket of the reactor. During the process of polymerization certain quantities of the polymer adhere to the walls of the reactor and form a slowly thickening continuous film or crust. This polymer crust on the inner surface of the reactor vessel, which contains cavities filled with unreacted monomer, impedes the conductance of heat; it has, therefore, to be cleaned away after termination of the batch process (Barnes 1976).

After completion of the polymerization process, the slurry is released from the reactor into a dump tank. Residual unreacted vinyl chloride monomer is partly solvated in the polymer (about 10%); the remainder is dispersed in the water phase or is present

in the vapour phase. VC monomer is then purified by the finished polymer and must diffuse out of the raw PVC resin. (VKE 1975). Bar approximately 500

The slurry free large enough to be are then pumped wet polymer, a drying methods, merization, yielding fine solid particles drying temperature polymer. A cyclo The solid polymer storage bins or silo dried powder con

2.2.2 Methods of

Four different methods of PVC (Frey 1973)

Suspension Polymerization which monomer (such as polyvinyl) conjunction with this method which

Emulsion Polymerization was added in the except that large are added. Emulsifiers cannot

Bulk (Mass) Polymerization the addition of oil The first reactor second one is used solid state, to ensure reaches a level of characterized by good optical clarity

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in the vapour phase above the slurry. While a batch is in the dump tank, this unreacted VC monomer is retrieved by pumping it off into a VCM storage tank. Retrieved VCM is then purified by subsequent distillation for recycling purposes. Monomer solvated in the finished polymer cannot easily be extracted since it has a strong affinity for PVC and must diffuse through the particles; this diffusion depends on time and temperature. Raw PVC resin, therefore, still contains certain quantities of unreacted monomer (VKE 1975). Barnes (1976) reported that the polymer in the slurry still contains approximately 500 ppm of vinyl chloride.

The slurry from the dump tank is pumped into a storage tank (blend tank) which is large enough to hold several batches of the product. The contents of the blend tank are then pumped into a centrifuge which separates the wet solids from the water. The wet polymer, a granular mass, is dried either in rotating tubular dryers or by spray-drying methods, the latter being used mainly for products formed by emulsion polymerization, yielding a polymer which is similar to a very fine white flour. These very fine solid particles are fed directly into a spray-drying column without dewatering. The drying temperature should not exceed 60°C to prevent thermal decomposition of the polymer. A cyclon separator at the exit end of the dryers removes coarser particles. The solid polymer particles are then sized by multiple-layer screens, air-conveyed to storage bins or silos and finally packaged for shipment (Albright 1967d). The resultant dried powder contains about 50 ppm of monomer (Barnes 1976).

2.2.2 Methods of Polymerization

Four different methods of polymerization are used for the commercial production of PVC (Frey 1973), the first two now being the most widely used:

Suspension Polymerization. Polymerization is carried out in an aqueous system in which monomer droplets are maintained in suspension by means of protective colloids (such as polyvinyl alcohol, gelatin, substituted celluloses) under heat and pressure in conjunction with brisk agitation. Relatively large polymer particles can be obtained by this method which 'dry blend' well.

Emulsion Polymerization is the oldest technique, to which suspension polymerization was added in the 1950s. The process is similar to that in suspension polymerization, except that large amounts of emulsifying agents (such as soaps or other surfactants) are added. Emulsion polymerization yields resins of a very small particle size. The emulsifiers cannot be completely removed.

Bulk (Mass) Polymerization. In this process VCM is polymerized in two stages without the addition of other liquids. The two reactors are operated batch-wise and in series. The first reactor (a 'prepolymerizer') provides for the initial liquid phase, while the second one is used for agitating the slurry, which is transformed, through a sticky solid state, to essentially dry particles until the conversion from monomer to polymer reaches a level of about 75%–80%. The resins obtained by bulk polymerization are characterized by high purity and particle uniformity, resulting in an end-product of good optical clarity.

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Solution Polymerization. This type of precipitation polymerization is carried out in organic solvents such as *n*-butane or cyclohexane. It accounts for only a small percentage of the total amount of all PVC resins produced and it is used for the production of copolymers. Copolymers are mixtures of comonomers (such as vinyl acetate, vinylstearate, vinylidene chloride, propylene, acrylonitrile etc.) and vinyl chloride. The comonomers tend to improve flexibility and limited solubility of the product in solvents and exert an influence on the temperatures required for compounding.

2.2.3 Compounding

As a next step, depending on the end use, the dried polymer, a whitish powdery or granular product, is then compounded (or dry blended) under pressure at fusion temperature with the aid of plasticizers (mainly phthalate or other organic esters) and light and heat stabilizers (heavy metal salts, organotin compounds, and other stabilizers). Lubricants or dyes can be added. Plasticizers are added for the production of flexible PVC; rigid PVC contains little or no plasticizer. These additives can also be a source of toxicity. The plasticizers may slowly diffuse out of the final product depending on its compatibility. Lead-containing stabilizers may also pollute the working atmosphere (Smolčić 1966; Tola 1975). Compounding is carried out by hot mixing at fusion temperatures below or within the softening range (120°C–160°C). Diversified compounding and processing technologies were developed about 1950.

The compounded polymers are used for the production of diverse end-products. The final conversion of the thermoplastic PVC resins into consumer end-products is accomplished by such procedures as extruding, calendaring, injection or compression moulding, blow moulding, dipping (coating) and hot spraying. Temperatures used in these processes range from 100°C to 300°C. End-products include a vast number of articles used in almost every sphere of daily life. The temperatures during the fabrication operations (compounding and conversion of compound polymer into consumer articles) drive off part of the small concentrations of residual monomer still contained in the polymer. Barnes (1976) calculated that the final fabricated articles contained approximately 5 ppm VCM and those for foodstuff packaging (bottles, films, foils) even less.

2.2.4 Sources of Exposure to VCM in PVC Production

Both polymerization of VCM and subsequent processing (centrifuging, drying, screening, bagging) are usually carried out in closed buildings. Exceptions can be found in hot climates (Aryapur 1977). Polymerization is of necessity a batch process that requires a large number of single operations. Therefore, valves, gaskets, shaft-openings and control gear are subject to heavy wear and thus to leakage. Other sources of pollution of the working atmosphere are exchange of parts and repair jobs. The degree of pollution also depends to a large extent on the quality and effectivity of monitoring equipment and special exhaust systems. Opening of autoclave vats for cleaning and control purposes resulted in larger spill-over of the tank atmosphere into the work environment. Numerous reports of workers with prenarcoctic symptoms (dizziness etc.)

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permit the conclusion that episodes of acute overexposure to VCM were not rare events in the past.

There is no doubt, however, that those workers who manually cleaned the autoclave vats by scraping away or chipping off the 'polymer skin' formed on the reactor walls ('poly cleaners'), and who in the past had to spend several hours inside the reactors, had been exposed to the highest concentrations of VCM. Although the vats were degassed prior to entry, unreacted monomer remained trapped in the polymer skin, and larger amounts of VCM were released when cavities formed in the polymer crust were opened by chipping. The later introduction of automatic cleaning systems reduced the frequency of entry into the reactors, but some manual cleaning of shorter duration still had to be done after every 20th-30th run. It is, therefore, plausible that, primarily, the most severe adverse effects of exposure to VCM were fully recognized in those workers who had been employed in this job category. But the subsequent steps (centrifuging, drying, screening) also involve the release of some of the lesser quantities of unreacted residual monomer from the particles to pollute the environment if ventilation, notably of the drying facilities, is inadequate. Finished polymer, ready for shipment or subsequent compounding, still contains small quantities of unreacted monomer, which either slowly diffuse out and pollute the bagging areas during storage or are driven out by the high temperatures necessary for compounding.

Table 2. Conversion table for concentration of VCM in ambient air

$1 \text{ ppm} = \frac{\text{Mol. wt.}}{1\,000 \times 24.45} \text{ mg/litre}$	
$1 \text{ mg per litre} = \frac{24.45 \times 1\,000}{\text{Mol. wt.}} \text{ ppm}$	
(Patty 1958)	
1 mg/litre =	391 ppm
1 mg/m ³ =	0.391 ppm
1 ppm = 2.56 mg/m ³	= 0.00256 mg/litre
1% = 10 000 ppm	= 25.6 mg/litre

2.2.5 The Explosion Hazard

In the past only the explosion and fire hazard of VCM was thought to be the dominant monitoring problem in handling gaseous vinyl chloride (Irish 1963). This hazard covers a concentration range of 4%-22% by volume of air (40 000-220 000 ppm) (Lefaur 1966). It was observed that VCM, being 2.15 times heavier than air, may collect as a compact layer at the floor of a polymerization building after spill-over from opened tanks and may catch fire. At least two instances of disastrous VCM explosions became known: In 1964, a large plant for the polymerization of VCM in the United

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States was almost completely destroyed when VCM escaping from a leak detonated (Albright 1967a). Another explosion in one of the two Rumanian factories operating at that time was mentioned by Suciu et al. (1975). Monitoring of VCM concentrations polluting the work environment was then directed largely towards preventing VCM from reaching the flammability limit.

2.2.6 The Odour Threshold

Unfortunately, gaseous VCM has no irritating or unpleasant warning properties. Its mild odour is described as faintly pleasant, sweet or ethereal. Some of the PVC workers we interviewed reported that they had even enjoyed 'sniffing the gas', which soon resulted in a feeling of light-headedness. For the early days of PVC production, when appropriately sensitive monitoring equipment was not yet available, workers' reports about perception of the odour of VCM can be taken as circumstantial evidence for a rough estimate of the actual degree of exposure. It should be kept in mind, however, that in chemical production units the presence of other odoniferous chemicals and the possibility of olfactory fatigue, as well as different levels of individual sensitivity, may render it very difficult to determine the factual odour threshold of a certain gaseous substance unless it possesses irritating warning properties.

In 1929, Schmidt and Schaumann declared that the faintly sweet gas is practically odourless at concentrations of 5%–10% by volume. Veltman and Lange (1977a, b) assumed an odour threshold of 5 000–10 000 ppm. Volunteers exposed to VCM detected a slight odour at 4 100 ppm; a distinct odour was noted at 6 600 ppm for 30 min and this was accompanied by subjective symptoms of dizziness and sleepiness (Irish 1963). Gehring et al. (1979) recently mentioned a threshold of approximately 3500 ppm. Others have claimed that a concentration of 400–500 ppm is the lower limit for detection of VCM by its odour (Baretta et al. 1969; Cook et al. 1971; Markowitz et al. 1972; Lefèvre 1975, cited by Hublet 1975). Baretta et al. (1969) conducted experiments with concentrations of 50, 250 and 500 ppm in an exposure chamber, in which 13 volunteers participated. At 500 ppm only some of them claimed that they were able to detect the odour, but this was inconstant. Table 3 shows that differences between the various estimates are at least one order of magnitude. The close proximity between the perception of the odour of VCM and incipient CNS symptoms as reported by Irish (1963), however, makes it likely that the actual odour threshold can be assumed at or above 4000 ppm.

In contrast to VCM, the comonomer vinyl acetate, for instance, has distinct warning properties and can be detected by its odour at a level as low as 0.4 ppm; eye and throat irritation begin upward of 5 ppm and are noted by all test subjects at a concentration of 21.6 ppm (Deese and Joyner 1969).

2.2.7 VCM as an Anaesthetic Agent

VCM was once even considered for use as an anaesthetic agent. In 1929, Schmidt and Schaumann speculated about using VCM as a supplementary narcotic at concentrations of 3%–5% (v/v) (= 30 000–50 000 ppm) in combined nitrogen oxide oxygen

Table 3. Odour

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2.2.8 Effects

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Table 3. Odour threshold

Lower limit of detection	Author
5 000–10 000 ppm	Veltman and Lange 1977a, b
5 000 ppm	Viola 1974
4 100 ppm	Irish 1963
3 500 ppm	Gehring et al. 1979
500 ppm	Baretta et al. 1969
400–500 ppm	Lefèvre 1975 (cited by Hubier 1975)
400 ppm	Cook et al. 1971
400 ppm	Markowitz et al. 1972

anaesthesia because of its potent narcotic action and the wide margin between narcotic and lethal concentrations. In animals it produced anaesthesia at 7%–10% in air or oxygen; concentrations above 12% proved to be dangerous. The authors pointed out, however, that adverse late effects of this halogenated hydrocarbon could not be excluded. In toxicity studies with guinea pigs Parry et al. (1930) found concentrations of 10% VCM to be lethal within 30–60 min, 5% to cause marked narcosis, and 0.5% for several hours to be the maximum tolerable exposure without serious effects. They also commented upon the potential use of VCM for surgical anaesthesia but were undetermined about its practicability. In mice, the minimal anaesthetic range was found to be 3.5–5 mmol (85 000–122 000 ppm) for 10 min, the minimal lethal range 10–12 mmol (244 000–293 000 ppm) (Peoples and Leake 1933). It was not until 1947 that Orser et al., in contrast to Schaumann's earlier assumption (1934) of a relatively low cardiotoxicity, warned against the use of VCM as a potential general anaesthetic in man because of serious cardiac irregularities and ECG changes observed in dogs. VCM, like other halogenated hydrocarbons, sensitizes the heart to the effect of catecholamines (Irish 1963). We could not ascertain whether VCM has actually been used in the past for anaesthesia in man.

2.2.8 Effects of Acute Overexposure in Man

Some individual responses of volunteers to increasing concentrations of VCM are listed in Table 4. Lester et al. concluded in 1963 that the maximum concentration without acute effects in man lies between 8 000 and 12 000 ppm for 5 min, and that symptoms such as dizziness, light-headedness and disorientation should be taken as adequate warning signs for imminent acute danger. Two fatalities after occupational exposure to high concentrations of VCM are reported in the literature (Danziger 1960). A 21-year-old autoclave cleaner at a Canadian polymerization plant was found dead 10 min after entry at the bottom of a probably insufficiently ventilated reactor tank which had been declared safe solely after an explosiometer test. Heart failure cells and cardiac enlargement found at autopsy, however, implied that the cause of death might have been acute functional disturbance in pre-existing heart disease. In the second case which occurred at the same plant, however, circumstantial evidence apparently left no doubt that heavy VCM exposure was the cause of death in a 39-year-old worker. He was found dead within 20 min, lying in a pit near the opened valve of a recycling pipeline

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Table 4. Individual responses of volunteers to increasing concentrations of VCM

Concentration	Duration of exposure	Symptoms	Reference
500 ppm	7.5 h	(Inconstant odour detection) mild headache, dryness of eyes and throat in 2 of 7 subjects)	Buratta et al. (1969)
~4 000 ppm	-	Generally accepted odour threshold	Irish (1963)
6 600 ppm	30 min	(Distinct odour) dizziness, sleepiness	Irish (1963)
8 000 ppm 12 000 ppm	5 min ^a (twice on each of 3 successive days)	2 of 6 subjects 'slightly heady'	Lester et al. (1963)
		1 of 6 subjects had reeling, swimming head, 'just like getting gas'	
16 000 ppm		5 of 6 subjects, various degrees of intoxication	
20 000 ppm		All 6 subjects had more intense symptoms of acute intoxication than at 16 000 ppm	
25 000 ppm	3 min	2 experimenters: dizziness, disorientation, burning sensation in the soles of the feet	Patty et al. (1963)

^a Exposure to six different concentrations: 0 ppm; 4 000 ppm; 8 000 ppm; 12 000 ppm; 16 000 ppm; 20 000 ppm

through which non-polymerized residual VCM was pumped back into a reserve tank; another man coming to his rescue was himself overcome by the gas and only just escaped.

Two non-fatal cases of VCM gassing were reported in Great Britain in 1951 (Spiras et al. 1975). A maintenance worker experienced acute narcosis while repairing a VCM leak, and a worker cleaning a polymerization vat from outside with a water jet suddenly collapsed across the open manhole. Subsequently he complained about tightness of the chest, nausea, abdominal pain and headache. Occasional loss of consciousness was also reported by Lillis et al. (1975) in 14 of 354 workers at Niagara Falls and by Suciu et al. (1963) at a Rumanian plant. VCM-induced narcosis, at least on one occasion in the past, had occurred in 46 of 58 workers (79%) referred for medical surveillance from one British PVC-producing plant (Ward et al. 1976), with a 100% incidence of narcosis in 28 symptomatic workers (Raynaud's syndrome and/or acroosteolysis). Successful resuscitation after VCM-induced narcosis of several hours' duration without evidence of permanent damage was mentioned by Rery et al. (1974).

2.2.9 Monitoring

During the first data on VCM was directed an apparently 1954; Plesic Gronsberg to Russian poly: 0.05-0.08 mg/litre of concentration of Inspectorate or from the d mg/litre (= 1 mg/litre (= 3-

In the central air ranged from ppm, which ventilation. Titrations, some pursuit of improvement in the vic drying facilities concentrations of continued to be permitted concentrations.

In a plant, the range of 0.6 ppm (2.93 mg/l) indication apparatus remarkable that the liver, although past have problems.

Byrén et al. which occurred, indicated peak exposures between 1962. Rumanian PVC about 120 mg/l exposures to VCM 300 Rumanian Greek plant which resulted in high (Gitsios 1971). of the reactors up to 10 000 ppm.

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VCM

2.2.9 Monitoring VCM Concentrations in Working Areas

During the first two decades of PVC production (1950–1950) no publication contained data on VCM concentrations in the working environment. The main interest then was directed towards prevention of the explosion hazard. In 1957, the observation of an apparently toxic angioneurosis in Russian PVC production workers (*Smirnova* 1954; *Pleschchirser* et al., cited in *Filatova and Gronsberg* 1957) induced *Filatova* and *Gronsberg* to investigate environmental VCM concentrations in various parts of a Russian polymerization plant in Gor'kiy. Although most readings were in the range of 0.05–0.08 mg/litre (= 20–313 ppm), e.g. below the maximum permitted VCM concentration of 1 mg/litre (approximately 400 ppm) as specified by the State Sanitary Inspectorate at that time, escapes of VCM in the reactor areas from defective fittings or from the discharge of operating autoclaves resulted in excursions up to 29.5–41.4 mg/litre (= 11 500–16 200 ppm) for periods of 5–10 min. One peak reading of 87.3 mg/litre (= 34 000 ppm) was recorded.

In the centrifuging and drying area of this plant the VCM content of the ambient air ranged from 4 ppm to 3 100 ppm with most readings between 20 ppm and 195 ppm, which was attributed to release of residual VCM from wet PVC resin and poor ventilation. The screening and bagging area was characterized by high dust concentrations, sometimes exceeding the official upper limits set for non-toxic dusts. In the pursuit of improving industrial hygiene, the installation of modern ventilation equipment in the vicinity of the autoclaves, substitution of hand-operated by semi-automatic drying facilities, and avoidance of leakages succeeded in reducing the ambient concentrations of VCM to below 0.05 mg/litre (= 20 ppm), but toxic angioneurosis still continued to be diagnosed. This led the authors to recommend that the maximum permitted concentration of VCM should be reconsidered.

In a plant producing VCM, *Filatova* et al. (1958) found lower concentrations in the range of 0.04–1.1 mg/litre (16–430 ppm), with maximum values of about 1200 ppm (2.93 mg/litre), the latter having been observed in close proximity to the rectification apparatuses and having resulted from spillage during sample collection. It is remarkable that up to now the Soviet Union has reported no cases of angiosarcoma of the liver, although production of PVC resins started early and VCM exposures in the past have probably been in the same range as those observed in Western countries.

Byrén et al. (1976) pointed out that during the 1950s episodes of unconsciousness which occurred among workers of the one Swedish plant operating at that time indicated peak exposures of at least 10 000–15 000 ppm. *Suchi* et al. (1975) noted that between 1962 and 1972 a reduction of the average VCM concentration in the two Rumanian PVC plants had been achieved from 2298 mg/m³ (= 900 ppm) in 1962 to about 120 mg/m³ (= 50 ppm) in 1965–1972. In 1969, *Anghelescu* et al. mentioned exposures to VCM concentrations of 112–545 mg/m³ (44–213 ppm) for a group of 300 Rumanian workers, eight of whom (2.7%) had Raynaud's phenomenon. At a Greek plant which started operation in 1967, certain stages in the production process resulted in high concentrations of VCM in the work environment for brief periods (*Gitsios* 1971). In air displaced from reactors during addition of water and on opening of the reactors to obtain PVC samples at the end of a reaction cycle, concentrations of up to 10 000 ppm were found. In open waste-drums into which waste polymer scraped

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in 1970 in conformity with the proposal of *Torkelson et al.* (1961), which was based on the results of their animal experiments. In June 1974, when the carcinogenic properties of VCM had been well established, the MAK regulation for this chemical was repealed and instead a preliminary technical guideline (Technische Richtkonzentration) of 50 ppm was instituted (VKE 1975). The Chemical Industries' Liability Insurance Association (Berufsgenossenschaft der Chemischen Industrie) also issued instructions for the prevention of health hazards arising from handling of VCM in July 1974. As of July 1975, a technical guideline (TRK = Technische Richtkonzentration) of 5 ppm, defined as annual mean, for PVC-producing and -fabricating plants was instituted, permitting excursions up to 15 ppm during periods of not more than 1 h. In order to adapt operating plants, a provisional regulation was issued with reduction of the annual mean concentration to 20 ppm as of July 1975, and to 10 ppm as of July 1976 and peak concentrations over 1-h periods not exceeding 60 or 30 ppm, respectively (*Veltman and Lange* 1977a). The technical guideline (TRK value) was revised in 1977 (2 ppm annual mean/5 ppm per 1 h).

In the United States the threshold limit value for VCM was originally set at 500 ppm in 1947. It was reduced to 50 ppm in April 1974 as a temporary emergency standard and finally reduced to 1 ppm/8 h in 1976. *Haley* (1975) summarized the conflicting views on vinyl chloride regulations proposed by Government and industry in 1974. Table 6 shows threshold limit values in a number of PVC-producing countries.

2.2.12 Exposure to VCM Outside the Working Area

The Environmental Protection Agency estimated that PVC-producing plants in the United States discharged about 90 million kg VCM annually into the environment (4%–8% losses), most of it as air emissions and lesser quantities dissolved in water effluent streams and entrapped in sludge and solid wastes (*Schweitzer* 1975). In a pioneer study, concentrations of 1–2 ppm VCM were found in the ambient air near such a plant (IARC 1974), 2–3 ppm in the primary water effluent and 100–200 ppm in the sludge at the plant site, but sampling and analysis methods used were later found to have been inadequate so no conclusions were drawn from these figures since they could have been in error by as much as one order of magnitude (*Schweitzer* 1975). For people who live within 5 miles of monomer and polymer production facilities in the United States an average exposure of 17 ppb during the years of uncontrolled emissions was calculated (*Nicholson* 1977).

In the past VCM has been widely used as an aerosol propellant, either alone or mixed with fluorocarbons, hydrocarbons and inert organic gases, in household and cosmetic products (hair sprays, deodorants, pesticides, room disinfectants, paint sprays, furniture polish and window cleaners). In Germany, VCM was proposed as propellant for aerosols in 1958 (*Ostermayer* 1967), in Japan it has been used as a propellant since 1958, in the United States this use was probably introduced after 1962 (*Schweitzer* 1975). As an aerosol propellant, VCM has been a possible source of exposure for the public at large, particularly for women, the extent and the potential health implications of which are unknown. Use of aerosol products in confined spaces has been reported to result in air concentrations of VCM of up to 400 ppm in closed rooms, even after only short bursts (30 s) (*Gay et al.* 1975), which could persist for several

Table 6. 1

Country

Belgium
Canada
Finland
France
German Democratic Republic
Iran
Italy
Japan
Netherlands
Romania
Sweden
Switzerland
United Kingdom
USA
USSR
Federal Republic of Germany

Sources: IARC 1973; IARC 1977; *Schweitzer*

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which was based on carcinogenic properties. The official was recommended concentration) stability insurance issued instructions in July 1974. As concentration) of 5 ppm. was instituted, per- 1 h. In order to reduction of the an- m as of July 1976 ppm, respectively was revised in 1977

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ing plants in the the environment involved in water (Hoyer 1975). In a the ambient air near 100-200 ppm. were later in these figures since (Schweitzer mer production facili- the years of uncontrol-

me, either alone or mix- household and cosmet- its, paint sprays, posed as propellant and as a propellant since 1962 (Schweitzer of exposure for the atial health implica- al spaces has been re- in closed rooms. id persist for several

Table 6. Threshold limit values (TLV) in various countries

Country	Year	TLV (ppm)	Comment
Belgium	1975	25/50	TWA (8 h/15 min)
Canada	1975	10/25	TWA (8 h/15 min)
Finland	1975	5/10	TWA (8 h/15 min)
France	1975	25	TWA (8 h)
German Democratic Republic (DDR)	— 1976	200 ± 12	MAC (Schottek 1969) (Könetsche et al. 1978)
Iran	1976	25/50	TWA (8 h/1 h)
Italy	1975 (future)	50 (25/50)	TWA (8 h) (TWA 8 h/15 min)
Japan	1970 1974 1975	500 200 ± 10	MAC MAC (25 mg/m ³)
Netherlands	1975	10	TWA (8 h)
Rumania	—	100 mg/m ³ (40 ppm)	MAC (Prodan et al. 1975)
Sweden	1975 1976	5/20 1/5	TWA (8 h/15 min) TWA (8 h/15 min)
Switzerland	1975 (future)	100 10	MAC TWA (8 h)
United Kingdom	1975 October 1975	25/50 10/30	TWA (8 h/15 min) TWA (personal/ceiling)
USA	1947 April 1974 October 1974 1976	500 50 25 1/5	MAC (Amer. Conf. Governm. Industr. Hygienists) TWA (8 h), temporary emergen- cy standard (OSHA) TWA (8 h), temporarily permit- ted exposure TWA (8 h/15 min)
USSR	— —	1 mg/litre (391 ppm) 30 mg/m ³ (± 12 ppm)	MAC, provisional ceiling concen- tration: State Sanitary Inspec- torate, 1957 (Filatova and Gronsberg 1957) MAC (Schottek 1969; Kettner 1975) (Sanitarnye normy)
Federal Republic of Germany	1966 1970 June 1974 1975 1977	500 100 50 5/15 2/5	MAK MAK TRK (preliminary technical guideline), Amendment of MAK regulation. TRK (annual mean/1 h) TRK (annual mean/1 h)

Sources: Smyth 1956; Filatova and Gronsberg 1957; Schottek 1969; Henschler 1972/73; IARC Report 1974; Haley 1975; Sakabe 1975; Prodan et al. 1975; Aryanpur 1977; Schütz and Wolf 1977; MAK-Werte-Liste 1977; Kettner 1975

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hours after repeated spraying in smaller-sized rooms (IARC 1974). Haley (1975) presented a list of pesticide products containing VCM as a propellant and registered for indoor use, which were banned in 1974 by the Food and Drug Administration. In Japan, the monomer was also banned as a propellant in 1974 (JAMA 1974, 229:855). There is a case on record of a worker who died from noncirrhotic portal hypertension and angiosarcoma of the liver after 14 years' employment at a chemical plant in southern Germany where he had been engaged in loading such pesticide cans (Reint and Weber 1974). The report of a female office worker suffering from typical Raynaud's phenomenon, pseudoscleroderma, acroosteolysis and mandibular osteolysis who never had occupational contact with VCM (Meyerson and Meier 1972) is apt to make one wonder what influence the frequent indoor use of VCM-propelled spray cans (Bridford et al. 1975) may have had in this unique case. Sputum samples collected from frequent users of pressurized spray cans who had no respiratory symptoms were found to contain a significant excess of moderate and marked atypical metaplastic bronchial cells compared with two groups of controls (Good et al. 1975).

PVC bottles, films and foils have been used for many years for packaging food and beverages (cooking oil, margarine, meat, mineral water, fruit squashes and other soft drinks, hard liquor etc.). The content of residual VCM in PVC bottles was found to have ranged formerly between 5 and 400 ppm (w/w), and in PVC foils up to 800 ppm (van Esch and van Logten 1975). The problem of migration of unreacted VCM from the PVC containers into the foodstuffs became recognized in 1973. Reports of unpleasant tastes in American brands of vodka and whisky which had been stored in PVC bottles led to the discovery that VCM had leaked into the liquors; in some samples levels up to 10–20 ppm (w/w) were found (van Esch and van Logten 1975; Davies and Perry 1975). Data available in 1974 to a group of WHO experts revealed that samples of gin and whisky had contained 0.57 and 0.62 ppm (w/w) of VCM respectively, after storage in miniature PVC bottles for periods up to 3 years; VCM concentrations in orange squash and cooking oil were found to be in the range of 0.01–0.08 ppm and 0.01–0.04 ppm, respectively (IARC 1974). Levels of 0–0.4 ppm found in British PVC-bottled liquids were mentioned by Davies and Perry (1975); in their own analyses of samples of PVC-bottled spirits supplied by British Airways they found concentrations of 0–0.25 ppm (w/w). Methods were developed for the detection of VCM in liquids with a maximum sensitivity down to the 1 ppb level (van Lierop and Siek 1976; Dressman and McFarren 1977). It was tentatively estimated that even during the years when PVC-packaged food and beverages had not been heeded as a potential source of contamination, the likely average daily human intake of VCM from this source could have been in the order of 0.1 mg/person (IARC 1974). Schlatter (1976) calculated that today it would be less than 0.01 mg/person (equalling 250 mg during a whole life time); in comparison, he calculated that the inhalational intake of VCM in diseased workers who had been exposed to concentrations of 500–1000 ppm during a period of 10–20 years would have amounted to at least 25 kg. The Association of the German Plastics Industry expects that the use of technology available at present for the production of PVC food-packaging materials decreases the VCM content of foodstuffs to below 50 µg/kg (50 ppb) even after prolonged storage (VKE 1975). Results of carcinogenicity assays in experimental animals after oral administration of VCM are discussed in Sect. 3.3.

3 Toxicology of

3.1 Acute Toxicity

During the first three the assessment of the concentrations varying and Lake 1933; Schimatteo et al. 1960; L anaesthesia, deep narc this range of exposure tive and haemorrhagic hepatocellular injury inducing substances (s

3.2 Chronic Toxicity

Torkelson et al. (1961) exposure to concentrat 4.5–6 months. All spec however, caused an incr histological changes in r pigs and dogs. An incre in rats exposed to 20 00 (1963); no histological Gor'kij Institute were m exposure of experiment mias, bradycardia, chan 0.05 mg/litre) for 5 mon creased secretion of cate posterior hypothalamus 3500–4000 ppm (9–10 of the cortex and the an comutant changes in circ posure of rats and rabbit resorptive bone changes nervous system dysfun available evidence for VC VCM should be suspected statutory maximal allowa cratic Republic) should b Of particular importat Violu et al. 1971) with ex full year. It was only after

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aging food and... and other soft... as found to... up to 800 ppm... d VCM from... parts of un... stored in PVC... one samples... 1975. Davies and... that samples... tively, after... tations in... 18 ppm and... in British... own analyses... concentra... VCM in... and Stark 1976... ring the years... tial source of... source could... calculated... a whole... CM in diseased... ring a period... of the... present for... tent of food-... 1975). Results... n of VCM

3 Toxicology of VCM

3.1 Acute Toxicity

During the first three decades of PVC production, animal experiments were limited to the assessment of the acute inhalational toxicity of VCM in short-term exposures to concentrations varying between 50 000 and 400 000 ppm (Patty et al. 1950; Peoples and Leuke 1933; Schaumann 1934, 1938; Oster et al. 1947; Carr et al. 1949; Mastromarino et al. 1960; Lester et al. 1963). In mice, rats, guinea-pigs, rabbits and dogs anaesthesia, deep narcosis, cardiac arrhythmias and lethal effects were observed within this range of exposure but no relevant organ pathology was noted except for congestive and haemorrhagic changes in lungs, liver and kidneys on fatal outcome. Acute hepatocellular injury was later found only in animals pretreated with potent enzyme-inducing substances (see Sect. 3.4.2.2).

3.2 Chronic Toxicity

Torkeison et al. (1961) were the first to describe results of experiments with prolonged exposure to concentrations ranging from 50 to 500 ppm, 7 h/day, 5 days/week, for 4.5–6 months. All species tolerated exposure to 50 ppm for 6 months; 100 ppm, however, caused an increase in liver weight and 200–500 ppm caused, in addition, histological changes in the liver and kidneys of rats and rabbits, but not in guinea-pigs and dogs. An increase in liver weight and decrease in spleen weight was also seen in rats exposed to 20 000 ppm, 8 h/day, 5 days/week, for 3 months by Lester et al. (1963); no histological lesions were found after 3 months. Soviet investigators at the Gorkij Institute were mainly interested in neuroendocrine changes after prolonged exposure of experimental animals to various concentrations of VCM. Cardiac arrhythmias, bradycardia, changes in phonocardiogram in rats exposed to 12–20 ppm (0.03–0.05 mg/litre) for 5 months were reported (Vazin and Plokhova 1969b) as well as increased secretion of catecholamines in rabbits and changes in the biopotential of the posterior hypothalamus (Vazin and Plokhova 1969a). After a 5.5-month exposure to 3500–4000 ppm (9–10 mg/litre) changes in the bioelectric activity (EEG recordings) of the cortex and the anterior and posterior hypothalamic nuclei in rabbits with concomitant changes in circulatory functions were seen (Vazin and Plokhova 1968). Exposure of rats and rabbits to 0.03–0.04 mg/litre (12–16 ppm) for 6 months produced resorptive bone changes and osteoporosis in addition to cardiovascular and central nervous system dysfunction (Basalov et al. 1972). In 1969 Schorrek summarized available evidence for VCM toxicity and warned urgently that chronic exposure to VCM should be suspected of causing toxic liver damage. He moved that the currently statutory maximal allowable concentration of 200 ppm (MAC value, German Democratic Republic) should be lowered.

Of particular importance as pioneer work were Viola's experiments (1970a, b; Viola et al. 1971) with exposure of rats to 30 000 ppm, 4 h/day, 5 days/week, for a full year. It was only after this length of exposure that histopathological examination

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tential carcinogenicity was studied in rats administered 0, 10, 50, or 100 ppm in the diet for 6 days/week for 2 years. A tumor ratio only at the 100 ppm dose was not considered to be statistically significant. The tumor placed the chemical in the category of the no-toxicological concern. In Sprague-Dawley rats, the chemical proved to be noncarcinogenic in a 2-year study. In the dose-related study, the exposure level was 100 ppm in the diet. The histological changes in the liver and the induction of hyperplasia in the endothelial cells of the liver sinusoids were observed in the rats exposed to 100 ppm in the diet (Al. 1974b; LA. 1974b; LA. 1974c). The hyperplasia and even in the endothelial cells was scanty at lower doses. In the 100 ppm dose, the fibrosis was not observed. The effect of ossifying hyperplasia was suggested by the offspring of the rats exposed to VC (Al. 1975). The rats exposed to VC in the diet were found to be matured from 100 to 2000 ppm in the diet. It was seen that the maturity of the rats was reached by 2000 ppm in the diet. The foci of hepatocellular carcinoma were observed in the rats exposed to VC in the diet.

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rental carcinogen may significantly vary the type of neoplastic response. In a subacute study of oral VCM toxicity, lasting only 13 weeks in which rats were given VCM dissolved in soya bean oil by gavage in daily doses of 30, 100 and 300 mg/kg body wt., 6 days/week, *Feron et al.* (1975) found a significant increase in liver-to-body weight ratio only at the highest dose level. This was interpreted as a merely nonspecific reaction not necessarily indicative of a toxic response. Based on these results, *Feron et al.* placed the oral no-toxic-effect level at 30 mg VCM/kg body wt./day and suggested that the no-toxic-effect level may actually be even higher. Zymbal gland carcinoma, hepatic angiosarcomas and nephroblastomas had never occurred spontaneously in the breed of Sprague-Dawley rats used at the Bologna Institute. The neoplastic response to VCM proved to have a direct dose-time relationship. Even levels of 50 ppm were carcinogenic in rats and mice. Later *Maltoni* (1977) found exposure to 25 ppm VCM also to be carcinogenic in rats, whereas no carcinogenic effect was observed at lower levels of 10, 5 and 1 ppm in a study which, however, is still incomplete (quoted from *Griciute* 1979). Another American study designed to complement *Maltoni's* results confirmed the dose-related induction of liver angiosarcoma and mammary carcinoma in mice at exposure levels of 2500, 200 and 50 ppm (*Kieplinger et al.* 1975). On reexamining histological slides of his past experiments, *Viola* later also detected angiosarcomas of the liver and other malignancies of skin, lung and intestine in his rats; he also reported the induction of skin acanthomas and pulmonary adenocarcinomas in rabbits after exposure to 10 000 ppm VCM, 4 h/day, 5 days/week, for at least 15 months (*Maltoni et al.* 1974b; IARC 1974). *Maltoni* and *Lefemine* (1975) considered the effect of VCM on endothelial tissue to be a systemic one since they found dilatation of blood spaces, hyperplasia and atypia of endothelial cells also in organs and tissues other than the liver, even in the absence of angiosarcomas or benign angiomas. Evidence of hepatic fibrosis was scanty and inconsistent in their animals and was more likely to occur at the lower doses. In the spleen of treated rats and mice fibroangioblastic proliferation undergoing fibrosis was frequently observed. No acroosteolytic lesions were found, but a few cases of ossifying angiosarcoma were observed. A potential transplacental carcinogenic effect was suggested in 1975 by the development of subcutaneous angiosarcomas in the offspring of breeding animals exposed for 7 days during pregnancy (*Maltoni and Lefemine* 1975). Later, *Maltoni* (1976) detected angiosarcoma in the offspring of rats exposed to VCM during the period between the 12th and 18th day of pregnancy (quoted from *Griciute* 1979). Hepatocellular carcinoma was not found in adult animals but it was seen to develop readily in newborn animals, possibly in connection with the immaturity of their bioactivation pathways (*Maltoni* 1977). Exposure of newborn rats to 2000 ppm VCM, 8 h/day, 5 days/week, for at least 4 weeks elicited preneoplastic foci of hepatocellular ATPase deficiency, notably in female animals (*Laib et al.* 1979). *Hobnberg et al.* (1976) exposed mice to 50 and 500 ppm VCM, 5 h/day, 5 days/week, for 52 and 26 weeks respectively. They did not observe hepatic fibrosis or spleen changes, but multiple benign alveologenic adenomas developed in 13 of 24 animals exposed to 50 ppm and in all 24 animals exposed to 500 ppm¹. In addition, subcutaneous and/or subperitoneal haemangiosarcoma developed in 14 animals of the 50-ppm group and in 8 of the 500-ppm group. Only one haemangiosarcoma of the liver

1 See also *Winell et al.* (1976)

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was found in an animal exposed to 500 ppm. A few mammary adenocarcinomas, one rhabdomyosarcoma and one renal haemangiosarcoma were also seen. From their experiments *Holmberg et al.* concluded that a lower exposure over a longer period may intensify the cancerogenic response and that an inverted relationship between dose level and latency time seems to exist in the case of VCM, as had already been observed with other carcinogens. Recently the results of still another animal experiment with exposure of Wistar rats to 5000 ppm, 7 h/day, 5 days/week, for 52 months was published by *Feron et al.* (1979a, b; *Feron and Kroes* 1979) in an eventually fruitless attempt to elaborate suitable parameters for early detection of VCM-disease in man. Early effects were a shortening of blood clotting time and the occurrence of swollen and malformed hepatocytic mitochondria. At a later stage progressive tubulonephrotic changes in the kidneys, foci of cellular alterations in the liver with reduced glucose-6-phosphatase activity in hepatocytes, strong sinusoidal activity of alkaline phosphatase and increase of smooth endoplasmic reticulum in parenchymal liver cells were observed. In the final stage areas of necrosis in the liver parenchyma, focal dilatation of sinusoids and proliferation of normal and atypical sinusoidal cells, multicentric hepatic angiosarcoma and Zymbal gland carcinoma occurred. *Feron et al.* (1979b) also observed hepatocellular carcinoma in three animals. Surprisingly, the induction of very malignant metastasizing carcinomas of the nasal cavity originating from the olfactory epithelium and Bowman's gland was noted, which had not been reported before in connection with VCM. Marked hepatic fibrosis was only seen within fully developed angiosarcoma or as a reaction to extensive necrosis of the hepatic parenchyma. The in-

lived but highly mutagenic and creatable product (1975). The relative velocities of its reaction of VC so that above following a concordance with

3.4.1 Uptake

Pulmonary uptake in the animal with the pool shown by *com Bolt et al.* (1975) as albumin, and compound goes into. After oral ingestion has to be considered



exclude the possibility of other, more subtle interactions which may impair the control of cellular replication. Alkylation of nucleic acids, however, cannot at present be excluded as the mechanism for VCM-induced carcinogenesis after repeated exposure and above all, in the target cells rather than the hepatocytes.

This aspect carries on to an unresolved problem on which future experimental work will have to focus. Although the site of formation of the active metabolite is the endoplasmic reticulum of the hepatocyte, the liver cell itself is not particularly susceptible to VCM-induced toxicity. Acute hepatocellular injury has not been observed morphologically after exposure to VCM unless pretreatment with potent inducers of the mixed function oxidase system had preceded the exposure; in pretreated rats centrilobular, midzonal and periportal hepatocellular vacuolization and even necrosis was found (Jaeger et al. 1974, 1975, 1977; Reynolds et al. 1975a, 1976; Connolly et al. 1978). Secondly, the site of carcinogenicity in the liver is not the hepatocyte but the

endothelial cell of the hepatic sinus.

At present it can only be speculated which of the following four most likely processes are effective, either singly or in conjunction: (1) The active metabolite leaves the hepatocyte and is conveyed to the endothelial cell. (2) The endothelium itself has some metabolic capacity (Bolt 1978), as may tissues of organs other than the liver.

(3) Mechanisms for the detoxification of the active metabolites are insufficient in tissues other than the hepatocytes. (4) Repair mechanisms for the correction of aberrant cell replication are less effective than they are in the hepatocyte (Watanabe et al. 1978b).

An equally puzzling problem is the role of VCM in the pathogenesis of the distal

nonneoplastic vascular lesions which are responsible for the development of the syndrome was the earliest indication of adverse effects of chronic exposure to VCM in Raynaud's phenomenon, scleroderma-like skin indurations and acroosteolysis. This syndrome was the earliest indication of adverse effects of chronic exposure to VCM in

man. Besides, its latency period was considerably shorter than either the nonmalignant liver lesions or angiosarcomas of the liver. Whereas it is now established that hepatic bioactivation of VCM plays the central part in the pathogenesis of both nonneoplastic

portal fibrosis and angiosarcomas of the liver, it is not at all clear whether the development of the acral lesions is due to VCM itself or to active metabolites which may exert a direct or indirect toxic action on (a) medullary vasomotor centres, (b) the sympathetic nervous system, (c) smooth muscle cells of the media of arteries, (d) endothelial lining cells of small arteries (with fibroblast transformation and endothelial proliferation) or whether (e) the action is mediated by the formation of immune complexes.

4 Clinical Spectrum

During the mid-1950s it began to emerge that chronic occupational exposure to VCM might prove to be not quite as harmless as had been claimed. The historical synopsis presented in Table 7 summarizes those clinical studies from the world literature that marked the gradual recognition of the full spectrum of damage due to this new occupational hazard.

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Table 7. Gradual emergence of evidence for VCM-associated pathology.

Year	Reference	Findings
1949	Tribuh et al.	Hepatomegaly, more or less marked "anicteric hepatitis", chronic gastritis, hypotension, anaemia, skin lesions
1954	Smirnova	Toxic angioneurosis
1957	Filatova and Gronsberg	Toxic angioneurosis
1960	Danziger	Symptoms similar to Raynaud's phenomenon
1961	Smirnova	Two cases of accidental fatal poisoning by VCM, 1 nonfatal acute overexposure
1963	Suciu et al.	Reversible axillary lesions of distal phalanges, pseudoclubbing, thickening of skin on volar side of forearms, slight haemolysis and reticulocytosis
1966	Cordier et al.	CNS: prenarctic symptoms (dizziness, euphoria, somnolence), nervousness, insomnia, blurring of memory, general asthenia, headache
1967	Harris and Adams	Dermatol.: pruritus, reversible scleroderma-like changes, Raynaud's syndrome
1967	Benoit	Occupational acroosteolysis with Raynaud's symptoms, scleroderma-like skin changes, pseudoclubbing
1968	Anionvuchenko	Mentions thrombocytopenia
1971	Dinman et al.	Prevalence of acroosteolysis and Raynaud's phenomenon
1971	Dodson et al.	Vascular lesions preceding the bone lesions
1972	Kramer and Mutschler	Increased BSP retention and raised icterus index related to degree of exposure

A first indication of plant production non ("toxic and in detail in her personnel with hourly sampling, drome was also (Kubota 1957) and CNS symptoms (1954) also mentioned on durations of there was evidence of red cells, evidence of dermal acroosteolysis (operators) and pseudoclubbing was found in lesions to be reversible changes vibration trauma the full range of occupational and In 1963 Smith analysis of the

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Table 7 (continued)

Year	Reference	Findings
1972	Markowitz et al.	Progressive thickening of hands and forearms, arthralgia. Blanching upon exposure to cold with cyanosis of hands accompanied by severe pain. Skin biopsy
1972	Jühe and Lange	1st German report of 7 workers with scleroderma-like skin lesions, Raynaud's syndrome, and acroosteolysis. Tests showed abnormal liver in 2, occlusion of digital arteries in 1 worker
1973	Marsteller et al.	Noncirrhotic portal fibrosis with portal hypertension and splenomegaly
1974a)	Creech et al.	4 cases of angiosarcoma of the liver

4.1 The Triad: Raynaud's Phenomenon, Pseudoscleroderma and Acroosteolysis

A first indication of adverse effects due to chronic VCM exposure arose in workers at a plant producing VCM who presented with symptoms similar to Raynaud's phenomenon ('toxic angioneurosis'). This was reported by *Smirnova* in 1954 and later described in detail in her thesis (1959). The syndrome was found predominantly in laboratory personnel who had intermittently been exposed to high concentrations of VCM during hourly sampling for chemical analysis (purity of the product). In 1954 Raynaud's syndrome was also observed among several workers at a Japanese PVC producing plant (*Kubota* 1957). Apart from a painful vasospastic disorder of the hands, impaired thermoregulation, acrocyanosis, positive cold test, capillaroscopic alterations, paraesthesias, and CNS symptoms such as headache, blunting of memory and sleep reversal, *Smirnova* (1954) also mentioned swelling of fingers and development of circumscribed skin indurations on the volar side of the forearms in those most severely affected. In addition, there was evidence of mild haemolysis (borderline anaemia, decreased osmotic fragility of red cells, urobilinuria, and reticulocytosis). In 1961 *Smirnova* described radiographic evidence of destructive bone lesions of terminal phalanges in the hands identical with acroosteolysis in three workers at a PVC-producing plant (one fitter, two centrifuge operators) after exposure for 3-9 years. Since these bone lesions developed in conjunction with 'toxic angioneurosis' and since complete recalcification of the defects was found in two workers 3 years after removal from exposure, *Smirnova* believed the lesions to be characteristic of chronic VCM intoxication. She pointed out that their reversible character might serve to distinguish the lesions from similar defects seen in vibration trauma. In retrospect, *Smirnova's* observations are the earliest descriptions of the full range of symptoms which much later became known as 'the syndrome of occupational acroosteolysis'.

In 1963 *Sucht* et al. (see also 1967 and 1975) published the first comprehensive analysis of their observation of a multiform symptomatology in subacute and chronic

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VCM intoxication. During a 4-year period, they examined 168 mostly young workers from two Rumanian PVC-producing plants who had not previously been employed in other industries. In their classic paper, the authors described in detail the various central nervous, digestive, angioneurotic and cutaneous symptoms (listed here in their order of manifestation). Acroosteolysis, however, was not mentioned. Episodes of acute overexposure (usually occurring at the end of a batch run, during retrieval of unreacted monomer, or at repair jobs) rapidly resulted in a state of light-headedness and transient euphoria similar to a mild degree of inebriety and were accompanied by a feeling of heaviness in the legs and disturbed locomotor coordination. Several workers claimed to have been able to identify escaping monomer by its faint but agreeable odour. Apparently during periods of particularly high ambient concentrations, workers repeatedly noticed formication in the lower limbs and a general feeling of bodily warmth. Six subjects had experienced loss of consciousness when repairing leakages, but recovered rapidly after being carried out into the open air. After a few months of work, unusual fatigue and sleepiness set in, there were complaints about persistent somnolence, even outside the work premises, and a tendency to fall asleep at the work place, particularly during night-shifts. In addition, headache, dizziness, irritability, blunting of memory, paraesthesias, and general weakness were reported: some workers noticed insomnia or sleep reversal.

A reappraisal of these nonspecific complaints (see also Vale et al. 1976) 6 years later, after improvement in industrial hygiene, revealed that the frequency of their occurrence had considerably decreased (Suciu et al. 1975). Following a prolonged period of repeated overexposure, vague nonspecific digestive symptoms also developed, such as anorexia with ensuing weight loss, nausea, fullness, upper abdominal discomfort, bloating and epigastric pains. Enlargement of the liver was found in 51 workers (30%); in 6% there was also splenomegaly. Classic Raynaud's phenomenon was found in 6%, but a tenfold higher percentage of the total work force showed evidence of vasospastic alterations on plethysmography (Raucher et al., cited by Suciu et al. 1975). Pruritus of the hands, forearms and face was an early complaint followed later by what was thought to be (allergic?) 'contact dermatitis': finally, nodular and scleroderma- or scleroedema-like cutaneous lesions developed in some workers, involving the dorsal surface of the hands, the volar side of wrists and forearms and the face, with firm thickening of subcutaneous tissue or formation of whitish papular or slightly elevated plaquelike indurations. The cutaneous manifestations largely disappeared after removal from the work place. In addition, mention was made of features of hypothyroidism in a few workers. Also, transient loss of libido in 24% was recorded, with return to normal after a break from work or during holidays.

With the exception of acroosteolysis and the two most alarming late sequelae — noncirrhotic portal hypertension and hepatic angiosarcoma — Suciu's early documentation of the prevalence of disease in PVC production workers encompassed a comparatively complete description of the various aspects of chronic VCM intoxication. Later publications supplemented the spectrum of knowledge mainly by providing additional information on epidemiological, roentgenological, thermographic, angiographic, and histomorphological aspects of the lesions encountered in subjects chronically exposed to VCM.

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Table 8. Publications

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4.1.1 Familial and Idiopathic Acroosteolysis

Acroosteolysis is a very rare disease. The aetiology and pathogenesis of this condition is still obscure. Osteolytic bone changes in late stages of so-called Raynaud's disease (accompanied by necrosis and gangrene), characteristically presenting as loss of part or of an entire distal phalanx of one or more fingers and also of toes, have been mentioned in the literature since 1921 (*Assmann 1921; Monahan 1926; Borak 1927; Kornblum 1929*). Kornblum attributed the lytic bone defects to vascular abnormalities and noted that he had found identical lesions in early stages of scleroderma and in leprosy. The term acroosteolysis was first introduced by *Laroche and Hochfeld (1948)*, who held a neuroendocrine syndrome responsible for the lesions. Independently *Harnasch (1949)* reported another case of symmetrical idiopathic acroosteolysis, particularly involving the terminal phalanges of the fingers with preservation of tufts, progressive clubbing and shortening, and ill-defined symptoms of disturbed peripheral circulation. By 1952 *Giacci* mentioned that 68 cases of the familial type of acroosteolysis and 33 cases of the nonfamilial, idiopathic form had been reported in the medical literature. He added another five cases, but his case reports pertain almost exclusively to mutilating processes involving only the feet, with recurrent ulceration and discharge of bone fragments (see also *Harms 1954*). In 1957 *Lièvre and Gama* listed 16 observations of idiopathic acroosteolysis and commented extensively upon these lesions: the whole range of differential diagnosis (various congenital, neurogenic and endocrine osteolytic diseases, leprosy, arthritis mutilans, progressive systemic sclerosis, ainhum etc.) was considered in their study and could be rejected with reasonable certainty. In a later review, *Cheney (1965)*, who added another four cases of the familial type, stated that this variety and the nonfamilial idiopathic type may actually belong to the same disease entity and may be part of a degenerative bone process more generalized than the term implies. It was the puzzling character and the rarity of this peculiar bone lesion that captured the attention of site medical personnel and industrial hygienists when in November 1963 the condition was detected in two Belgian autoclave cleaners (*Lejèvre 1972*).

4.1.2 Epidemiology of Occupational Acroosteolysis

Attempts at assessing the prevalence of OAOL among personnel involved in VCM manufacture and polymerization revealed that in general this occupational type of osteolytic bone lesion was found in only 1%–3% of the work population at risk. *Hubler et al. (1977)* considered the fact that only 3% of all workers who had been engaged in manual cleaning of autoclaves at a Belgian plant suffered from OAOL and Raynaud's phenomenon to be indicative of the importance of individual factors. *Wilson et al. (1967)* observed 31 cases among 3000 employees of one large company. In 1971 *Dinman et al.* conducted a survey in 32 plants belonging to 19 corporations throughout the United States and Canada. The details of this elaborate epidemiological study, comprising a total of 5011 employees, illustrates the difficulties and limitations encountered in a retrospective study of this dimension. All of these 5011 workers had been engaged in various stages of VCM and PVC manufacturing, but 1257 of them were workers who only handled finished PVC polymer. Five of the 32 plants worked

exclusively with only 25 clearly defined as chronic: 18 of which with experience were jobs, both re (1 case per 7 appeared not was detected use for reactivity into the

Table 9. Prevalence

Country	Number of cases
France	5
USA	3
United Kingdom	1
Fed. Rep. Germany	1
United Kingdom	1
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More correlated symptoms: Lange and V. ological check pathological: were affected cold, 15 work morbidity was found classic numbness and 8.7% and inv Allen test indicated people with pseudoclubbing finding that the duration of p.

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exclusively with the finished PVC-derived consumer products. *Dimman et al.* found only 25 clear-cut cases of OAOL among the 5011 employees (mean age: 35.8 years), defined as characteristic X-ray film abnormalities combined with Raynaud's phenomenon; 18 of them had been reactor cleaners at some time; another 16 individuals (10 with experience in reactor cleaning) with early stages or minimal degrees of the syndrome were suspected of suffering from OAOL. It emerged that the two lowest-paid jobs, both reactor cleaning and bagging/packing, had a strong association with OAOL (1 case per 72, or 86 workers at risk, respectively). Manipulation of the finished polymer appeared not to be associated with a risk of contracting OAOL. Only 1 case of OAOL was detected in those plants where high-pressure water lances or solvents had been in use for reactor cleaning. Furthermore, it seemed that the extent of degassing prior to entry into the autoclaves correlated with the manifestation of the disease.

Table 9. Prevalence of acral disease in VCM-exposed populations

Country	Size of group at risk	Number of cases				References
		OAOL	Classical Raynaud's phenomenon	Severe sensitivity to cold	Sclero-dermoid skin lesions	
France	130	5	12	15	5	<i>Benoit 1967</i>
USA	354	4	20	63	23	<i>Lillis et al. 1975</i>
United Kingdom	37	1	5	8	4	<i>Walker 1976</i>
Fed. Rep. Germany	100	9	9	33	10	<i>Lange and Veltman 1977</i>
United Kingdom	104	1	25	—	1	<i>Maricq et al. 1978</i>
Total	725	20 (~3%)	71 (~10%)	119 (~16%)	43 (~6%)	

More commonly seen than OAOL were Raynaud's phenomenon (see Table 9) and related symptoms of abnormal peripheral circulation (*Benoit 1967; Lillis et al. 1975; Lange and Veltman 1977*). *Benoit* pointed out that a complete medical and roentgenological check-up of all 528 employees at a French PVC-producing plant revealed pathological manifestations only among the group of 130 reactor cleaners of whom 32 were affected (OAOL, 5; Raynaud's phenomenon without OAOL, 12; sensitivity to cold, 15 workers). He stressed the fact that in this group of workers at risk the overall morbidity was almost 25%. Similar results were obtained by *Lillis et al. (1975)*, who found classic Raynaud's phenomenon in 5.6% of 354 heavily exposed PVC workers, numbness and tingling in 24%, excessive sensitivity to cold in 18%, pseudoclubbing in 8.7% and involvement of the toes in 7%. Besides, in 26.6% of the total an abnormal Allen test indicated impaired peripheral arterial circulation. It was noted that in some people with past exposure Raynaud's phenomenon had gradually faded, whereas pseudoclubbing persisted or even progressed. Most important, however, was *Lillis'* finding that the prevalence of all these abnormalities increased significantly with the duration of past exposure to VCM.

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Occupational acroosteolysis is a condition predominantly observed in younger workers. The age range was 20–45 years and half of all cases reported fell in the 30–39 years age-group. Duration of VCM exposure prior to onset of Raynaud's phenomenon ranged from 1 to 23 months (Dodson et al. 1971). For OAOL the latency period was at least 12 months (Wilson et al. 1967); in most cases, OAOL developed insidiously within 2 to 4–6 years. There is at least one patient on record in whom OAOL was first discovered two years after termination of exposure (Benoit 1967). Longitudinal studies of the bone lesions demonstrated partial or complete but mostly defective restitution, resulting in shortened and deformed distal phalanges, within 2–3 years after removal from VCM exposure, but Raynaud's phenomenon and cutaneous lesions may persist (Williams and McLachlan 1976). Stein et al. (1973a, b) reported partial healing with restitution of tufts but progressive lysis of the proximal portion of terminal phalanges 3 years after termination of exposure.

Although OAOL developed predominantly in PVC production workers who had at least for some time been engaged in reactor cleaning, the syndrome has also been observed in association with other job assignments which were believed to carry a substantially lower risk of exposure. Trapp et al. (1974) reported a 31-year-old white male suffering from Raynaud's phenomenon, clubbing of the fingers and typical bilateral acroosteolysis, in whom specific inquiry revealed that his employment by an industrial chemical company had included daily handling of small concentrations of vinyl chloride (no details given). Typical OAOL was also observed in a worker after 6 years' employment as spray dryer/bagger, pre-mix operator, recovery and charging operator who had never cleaned autoclave vats (Stewart et al. 1975). According to routine plant monitoring of VCM levels in the past and as measured in 1973 by gas chromatography of grab samples, his average exposure had been within the threshold limit values of the day (200 ppm). Radiographs taken in 1966 at the end of his first year during an earlier survey of OAOL were normal; in 1972 he presented with Raynaud's phenomenon, pseudoclubbing, typical OAOL and dermal thickening of hands and wrists. Arteriography demonstrated narrowing of most digital arteries, even in fingers without bone defects, and abnormal collections of small vessels in the pulps of deformed finger tips, but no vascular occlusion.

Apart from the chemical insult by inhalational (rather than transdermal – Dinman et al. 1971; Stewart et al. 1975) exposure to VCM, individual susceptibility or idiosyncrasy appears to have played some (undefined) role in the development of the syndrome. It does not seem likely, however, that repeated physical microtrauma during cleaning operations (removal of polymer crusts by hand scraping or chiselling) was a decisive factor in the pathogenesis of the condition as had been speculated by Wilson et al. (1967).

4.1.3 Clinical and Roentgenological Features

4.1.3.1 Occupational Acroosteolysis

In the majority of cases osteolytic lesions are confined to the hands. Involvement of the feet was observed only rarely in OAOL. Wilson et al. (1967) believe that OAOL differs from familial or idiopathic acroosteolysis in several respects. Although the bone

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defects in the distal phalanges are similar in both conditions, other features, such as osteoporotic compression fractures of the spine, basilar impression fracture of the skull, destruction of mid-phalanges or osteosclerotic changes of wrists and hand bones, shortening of metacarpals and cortical thickening of the shafts of long bones seen in the nonoccupational type have never been found in OAOL. *Wilson et al.* worked out roentgenological criteria for the diagnosis of OAOL:

1) The earliest changes in OAOL are marginal defects and loss of cortex in tufts of one or more of the terminal phalanges of the hands.

2) In the next stage this is followed by small 'half-moon' cuts in the cortex of the tufts, or a so-called slice-effect along one or more tufts.

3) The advanced stage of destruction is characterized by either a complete loss of tufts together with a portion of the shaft or there may be transverse or oblique bone defects (see Fig. 2) cutting off the shafts from the remaining distal rim of the tufts ('bandlike acroosteolysis').

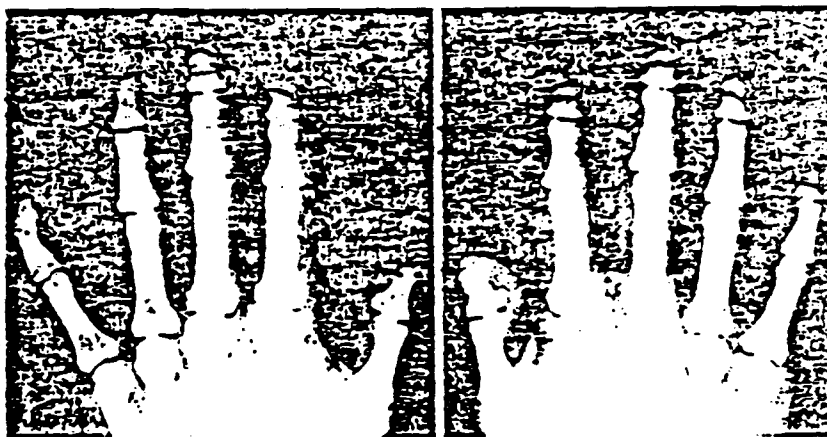


Fig. 2. Occupational acroosteolysis. Transverse or oblique bone defects ('bandlike acroosteolysis') or partial loss of terminal phalanges in all fingers of both hands. (33-year-old autoclave cleaner; duration of exposure 3 1/2 years)

4) In the healing stage there may be either complete bony union with shortening and broadening of the residual parts of the end phalanx or a fibrous union of bone fragments. Fingertips remain short and plump with persistent clubbing of soft tissues and increased lateral and longitudinal curvature of fingertips.

Sodium fluoride ^{18}F scintiscan data of affected bones suggested that active demineralization (resorptive) and remineralization (reparative) processes may occur simultaneously even in the same hand (*Dodson et al. 1971*). In some cases, bones of

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other body regions were also involved. Erosive and sclerotic changes in the sacro-iliac joints and circumscribed resorptive defects (cortical erosions) in patella, clavicle, mandible, humerus, styloid process of ulna, femoral condyles, os calcis, cuneiform and metatarsal bones have repeatedly been observed (Cordier et al. 1966; Harris and Adams 1967; Dodson et al. 1971; Jühe et al. 1974; Lange et al. 1974a; Preston et al. 1976; Jayson et al. 1976a; Lange and Veltman 1977).

4.1.3.2 Pseudoscleroderma

Concomitant with the manifestation of paraesthesias, pain, tenderness of the fingers and Raynaud's phenomenon, cutaneous lesions similar to stigmata seen in progressive scleroderma develop with thickening of the skin of fingers, hands and forearms, sometimes accompanied by swelling or puffiness and coarsening of the skin of the face (mostly on the forehead and cheeks). Raised, ivory-coloured, firm nodules or elevated, sharply delineated plaquelike skin indurations are seen on the dorsal surface of fingers and hands and on the volar side of the wrists and lower forearms. It was this combination of Raynaud's phenomenon and cutaneous lesions which first prompted a search for other symptoms of progressive systemic sclerosis in affected workers. The syndrome of OAOL, however, can be clearly distinguished (Table 10). Notably, the diffuse immobil-

Table 10. Differential diagnosis: syndrome of occupational acroosteolysis (Raynaud's phenomenon, sclerodermoid skin changes, AOL), progressive scleroderma with (rare) osteolytic lesions

	Occupational AOL	Progressive scleroderma
Sex ratio	Exclusively σ	$\sigma/\eta = 1:2$
Hands	Clubbing and shortening of finger tips; hyperhidrosis; no ulceration	Atrophy and tapering off of fingertips; anhydrosis; ulcerative lesions
Perioral puckering of skin	Not observed	Common
Skin appendages	Preserved	Loss of skin appendages
Telangiectases	Not observed	Common
Shortening of frenulum	Not observed	Early symptom
Subcutaneous deposits of calcium salts	Not observed	Common
Dysphagia (oesophageal involvement)	Not observed	Common
Renal, cardiac and intestinal involvement	Not observed	(Common)
Occupational history	Obligatory	—
Prognosis	Favourable (skin and bone lesions tend to heal after removal from exposure)	Usually spontaneous progression

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izing sclerosis of occupational syndrome readily than the

4.1.4 Histology

4.1.4.1 Cutaneous

Several investigations of disease (Cordier et al. 1972; Lange et al. 1972; we found only (1967; Marin et al. 1967) neural changes who suffered from

Dermal changes with disorganized broad interlacing faintly stained in Schiff (PAS). An histiocytes was present. The most notable of elastic fibres, full thickness of tissue. Skin appendages (Walker (1976) found not exceeding some fibrous tissue.

Vascular lesions capillaries were dilated and pericapillary thickening of lumina. Myocytes, was due to narrowing of Degenerative (Benoit 1967; M) hyalinosis of the Meissner, Pacini

4.1.4.2 Bone lesions

The most striking worker with OAOL, thinning and hyalinization of the most layer. Supra-

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izing sclerosis of the skin with tapering off of fingertips was never seen in the occupa-
tional syndrome. After cessation of exposure the skin lesions seem to regress more
readily than the osteolytic changes.

4.1.4 Histology

4.1.4.1 Cutaneous Lesions

Several investigators described the histomorphology of skin lesions in vinyl chloride
disease (Cordier et al. 1966; Harris and Adams 1967; Marin et al. 1967; Markowitz et
al. 1972; Lange et al. 1974a; Veltman et al. 1975; Walker 1976; Hahn et al. 1979), but
we found only one description of bone histology in OAOL in the literature (Benoit
1967; Marin et al. 1967). Skin biopsies showed various degrees of dermal, vascular and
neural changes which were essentially identical in patients showing OAOL and in those
who suffered 'merely' from Raynaud's phenomenon.

Dermal changes consisted of hyperkeratosis and pronounced thickening of the der-
mis with disorientation, swelling and nonfibrillary eosinophilic homogenization of
broad interlacing collagen bundles. There was some degree of interstitial oedema which
faintly stained metachromatically with toluidine blue, alcian blue and periodic acid-
Schiff (PAS). An inflammatory reaction with infiltration of lymphocytes and a few
histiocytes was scanty and, if present at all, of predominantly perivascular distribution.
The most notable feature was marked disorganization, fragmentation and rarefaction
of elastic fibres. In areas corresponding to nodular or plaque-like skin indurations, the
full thickness of the dermis consisted of an acellular, partly hyalinized collagenous tis-
sue. Skin appendages were preserved. In 15 apparently less severely affected workers,
Walker (1976) found only some destruction of elastic tissue of the dermis, probably
not exceeding normal age changes; in one worker with severe Raynaud's phenomenon
some fibrous thickening of the media of dermal arterial was seen.

Vascular lesions affected capillaries and small dermal arteries. Numerous dilated
capillaries were seen in the subepidermal papillae with swelling of endothelial cells
and pericapillary oedema. Capillaries of the cutis showed cufflike hyperplasia of per-
ithelial cells with fibroblast transformation, hyalinosis of vessel walls and final oblitera-
tion of lumina. Marked medial thickening of dermal arterioles, due to hypertrophy of
myocytes, was accompanied by parietal fibrosis and hyalinosis, which ultimately led
to narrowing or even complete occlusion of the lumen.

Degenerative lesions of small *dermal nerves* were mentioned by French investigators
(Benoit 1967; Marin et al. 1967; Chatelain and Motillon 1967). They found sclerosing
hyalinosis of the perineurium with atrophy of neurofibrils. Tactile corpuscles (Wagner-
Meissner, Pacini) were unaffected.

4.1.4.2 Bone Lesions

The most striking feature in a biopsy specimen of the bone, obtained from a French
worker with OAOL (case 4 of both Benoit 1967; Marin et al. 1967) was marked thick-
ening and hyalinization of the periosteum with chondroid metaplasia of the inner-
most layer. Supplying capillaries and arterioles showed occlusive changes identical with

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those observed in the dermis. The bone matrix per se was barely affected. There was minimal thinning of cortex, normal spongy bone and only mild fibrosis of the bone marrow.

Experience with histomorphology of bone lesions in the familial and idiopathic type of acroosteolysis is limited. In the few cases where biopsy material could be obtained, there was replacement of bone by nonspecific fibrous tissue, but inflammatory and degenerative changes or osteoid formation were not found (*Dipas et al. 1936; Elson and Burnstein 1954; Greenberg and Street 1957; Schwarzweiller 1957*).

In this context, it should be kept in mind that *Viola* succeeded in reproducing dermal, vascular, neural and skeletal lesions in the skin of the paws and in small metatarsal bones of experimental animals which were very similar to those observed in man. *Viola* exposed rats to 30 000 ppm VCM, 4 h/day, 5 days/week, for 12 months and described the histology of these lesions in detail (1970b).

4.1.5 Arteriography, Capillaroscopy, Infrared Thermography

Arteriographic evaluation of the vascular tree of the hands revealed patency of the large arteries in all cases examined. The vascular lesions were almost invariably confined to the small digital arteries, although the superficial and deep palmar arterial arch may occasionally show some narrowing and a paucity of side-branches (*Lange et al. 1974a; Moulin et al. 1974*). The most prominent arteriographic features were irregularities and segmental stenosis of digital arteries, ranging from localized or diffuse narrowing to subtotal or even total occlusion with development of collateral vessels. Besides, a conspicuous retardation of flow of contrast medium was noted, and peculiar tortuosities of patent digital arteries were found. Circumscribed hypervascularity of the terminal tufts and in the region of the wrists was noted in some cases (*Benoit 1967; Lange et al. 1974a; Veltman et al. 1975; Preston et al. 1976; Stewart et al. 1975; Gama and Meira 1978*). Angiographic findings in a larger group of 19 symptomatic PVC workers with either Raynaud's phenomenon and/or acroosteolysis (5/19) were recently described in detail by *Koischwitz et al. (1980)*. Raynaud's phenomenon had been observed to persist in these patients for prolonged periods after termination of exposure and even after roentgenological evidence of healing of resorptive bone defects in those who had formerly suffered from acroosteolysis. In addition to varying degrees of stenosis or occlusion of digital arteries with reopening of small collateral vessels, acral hypervascularity and considerable retardation of perfusion in spite of premedication with tolazoline (Priscoline, United States), the most conspicuous features observed in the majority of these patients (14/19) were circumscribed elongations and tortuosities of digital arteries resembling cirroid aneurysms. An example is shown in Fig. 3 of generalized tortuosity and elongation of digital arteries in a 54-year-old patient who started to complain of severe sensitivity to cold 3 years after cessation of VCM exposure (about 1 year prior to death from both angiosarcoma of the liver and hepatocellular carcinoma). The pathogenesis of these peculiar vascular alterations is not clear, but the possibility presents itself that they may be due to destruction of elastic fibres in the vessel walls in analogy to similar alterations of digital arteries seen in rheumatoid arthritis (*Laws et al. 1963, 1967*).

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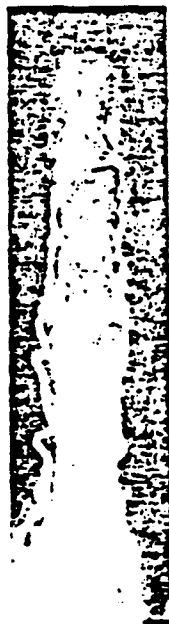


Fig. 3. Conspicuous tortuosities and elongation of digital arteries

Studies of microvascular changes by wide-field *capillary microscopy* (direct observations complemented by photography) of selected skin sites – such as nail folds, fingerpads, dorsum of phalanges and of proximal interphalangeal joints – demonstrated a variety of capillary abnormalities, i.e. dilated or giant capillary loops, pale avascular areas, capillary and subungual haemorrhages. The abnormalities were similar to those seen in scleroderma but were usually less conspicuous, less numerous and of different distribution. In a survey of a group of 152 American PVC workers, these capillaroscopic findings proved to be significantly more prevalent than in 50 nonexposed control subjects (Maricq et al. 1976). There was also a statistically significant difference in the prevalence of these abnormalities between symptomatic and asymptomatic PVC workers. The alterations were not only found in workers with clinical symptoms of disturbed acral circulation but also in 6 nonsymptomatic males with either VCM-induced angiosarcoma of the liver (2) or splenomegalic portal hepatic fibrosis (4).

A similar survey was later undertaken in an unselected sample of 129 employees of a PVC-producing chemical plant in England with 26 employees of a non-PVC-producing chemical plant serving as controls (Maricq et al. 1978). The prevalence of capillary abnormalities found in these British workers, which were of the same type and degree, was comparable to that in the American sample, although the latter included a larger number of more severely affected symptomatic patients with greater mean length of employment (15 years vs 3.5 years). In the authors' opinion, this suggested that VCM-related disease may develop independently of differences in manufacturing procedures. It also suggested that this easily detectable type of microvascular lesion may precede more serious VCM-induced disorders. In a small subgroup of 15 clinically affected

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British workers who were examined 6–24 months after leaving the plant (termination of exposure), the prevalence of capillary abnormalities was not less than that among those who continued work. For an evaluation of the reversibility of this condition, however, the group was considered to be too small. The same type of capillaroscopic changes was also observed in three of 4 Polish workers (2 reactor cleaners, 2 fitters) who were found to suffer from Raynaud's phenomenon after exposure for 2–5 years (Byczkowska and Langauer-Leiwowicka 1974).

Infrared thermography, another non-invasive method, used by Reid et al. (1974) for the study of acral circulation, revealed abnormalities of surface temperature ranging from marked hypothermia of terminal phalanges (which are normally warmer than the rest of the fingers) to "complete terminal amputation" in four PVC workers suffering from OAOL. In one of them vascular disturbances as evidenced by infrared thermography persisted in spite of complete healing of OAOL. Stewart et al. (1975) demonstrated uneven blood flow in the fingers and patchy hyperthermia in the distal part of the OAOL-affected left index and middle finger of their atypical case. Localized acral hyperthermia seen on IR thermography corresponded to the angiographic finding of circumscribed abnormal collections of small vessels (compensatory collaterals?) in the pulps of the affected fingers. Using IR thermography in a survey involving 143 PVC production workers and 56 controls, Williams et al. (1977) assessed the time needed for heat return after immersion of one hand for 10 s in a water bath kept at 19°C; however, no difference between VCM-exposed subjects and controls and between groups within the exposed population was noted.

4.1.6 Immunological Studies

Early experience with the syndrome of occupational acroosteolysis suggested certain similarities between this disorder and corresponding lesions seen in progressive systemic sclerosis (diffuse scleroderma). Differential diagnosis of these two unrelated conditions is now well established (Table 10). Such similarities stimulated the search for other manifestations of a systemic collagen disease, notably immunological features, as proposed by Marin et al. in 1967. Ward et al. (1976a, b) carried out immunological studies in 58 workers from a British polymerization plant who were referred to them out of a total past and present work force of 320. Mean duration of exposure to VCM was 39 months (6–75 months). Of these 58 workers, 28 were symptomatic (Raynaud's phenomenon, 9; scleroderma of hands or feet, 6; OAOL, 2; sensitivity to cold, excessive fatigue, limb pain, paraesthesias). Slight hyperimmunoglobulinaemia, usually IgG, the presence of mixed cryoglobulins, and in vivo conversion of both C₃ and C₄ were found in 19 patients in the symptomatic group, with additional evidence of reduced T-cell population and increased B-cell proliferation. Mixed cryoglobulins, in vivo conversion of complement and depressed values for C₃ or C₄ were taken as evidence for the presence of circulating immune complexes. Autoantibody screening demonstrated low-titre antinuclear antibodies (IgG 1/20–1/50) in eight of the nine patients with Raynaud's phenomenon. Aggregates of IgG, C₄, C₃, and fibrinogen/fibrin were revealed by direct immunofluorescence in the lumen of vessels, adherent to vascular endothelium. Aggregates were similarly seen in the media and subintimal regions of small

and medium-sized arteries and veins of lung (1 case).

The autoimmune nature of the disease was suggested by the fact that the anti-endothelial and bone marrow plasma cells showed evidence of clonal expansion, which stimulated the immune response to further disease. In an earlier study, Jayson et al. (1974) found that patients suffering from OAOL had a higher incidence of autoimmune disease than in normal controls.

In an earlier study, in four Polish workers, there was a decrease in the incidence of autoimmune disease. However, Langauer-Leiwowicka (1974a) assessed the time needed for heat return after immersion of one hand for 10 s in a water bath kept at 19°C; however, no difference between VCM-exposed subjects and controls and between groups within the exposed population was noted. In an earlier study, in four Polish workers, there was a decrease in the incidence of autoimmune disease. However, Langauer-Leiwowicka (1974a) assessed the time needed for heat return after immersion of one hand for 10 s in a water bath kept at 19°C; however, no difference between VCM-exposed subjects and controls and between groups within the exposed population was noted. In an earlier study, in four Polish workers, there was a decrease in the incidence of autoimmune disease. However, Langauer-Leiwowicka (1974a) assessed the time needed for heat return after immersion of one hand for 10 s in a water bath kept at 19°C; however, no difference between VCM-exposed subjects and controls and between groups within the exposed population was noted. In an earlier study, in four Polish workers, there was a decrease in the incidence of autoimmune disease. However, Langauer-Leiwowicka (1974a) assessed the time needed for heat return after immersion of one hand for 10 s in a water bath kept at 19°C; however, no difference between VCM-exposed subjects and controls and between groups within the exposed population was noted.

In summary, the autoimmune nature of the disease was suggested by the fact that the anti-endothelial and bone marrow plasma cells showed evidence of clonal expansion, which stimulated the immune response to further disease. In an earlier study, Jayson et al. (1974) found that patients suffering from OAOL had a higher incidence of autoimmune disease than in normal controls.

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Table 11. 17 PVC workers with advanced portal hypertension (marked oesophageal varices, episodes of upper GI bleeding, splenomegaly)

No.	Age at diagnosis (years)	Duration of exposure (years months)	Pentonescopic and histological diagnosis
1	30	5	Noncirrhotic fibrosis
2	31	5/9	Noncirrhotic fibrosis
3	32	3/6	Noncirrhotic fibrosis
4	35	4	Noncirrhotic fibrosis
5 ^a	35	9	Noncirrhotic fibrosis
6	39	10/6	Noncirrhotic fibrosis
7	39	13/6	Noncirrhotic fibrosis
8	41	7	Noncirrhotic fibrosis
9 ^a	41	18	Postnecrotic cirrhosis
10 ^a	47	18	Noncirrhotic fibrosis
11	50	6/6	Noncirrhotic fibrosis
12	51	17	Noncirrhotic fibrosis
13	52	15/3	Noncirrhotic fibrosis
14	52	11	Noncirrhotic fibrosis
15	54	6/6	Noncirrhotic fibrosis
16 ^a	58	21	Postnecrotic cirrhosis
17 ^a	61	13	Noncirrhotic fibrosis

³ On follow-up patients 5, 9, 10, 16 and 17 subsequently developed angiosarcoma of the liver and died 3-6 years after diagnosis of portal hypertension. Patients 6 and 14 are at present (1981) under observation for suspected development of angiosarcoma of the liver, 6 and 11 years after peritoneoscopic diagnosis of portal fibrosis.

associated portal hypertension, Smith et al. (1976a) observed later development of angiosarcoma in one of them. If a rough estimate based on these two small series were acceptable, it would appear that approximately one of five to seven individuals suffering from advanced VCM-induced portal hypertension might be expected to develop angiosarcoma later, although PVC-induced hepatic fibrosis per se is probably not a premalignant lesion.

4.2.1 Clinical Manifestations of Non-malignant Liver Disease

Physical examination is usually disappointing. In the more advanced stages of VCM-induced nonmalignant liver disease, palpable splenomegaly and a slightly to moderately enlarged liver may be the only physical signs. On palpation, we found hepatomegaly in 31 and splenomegaly in 16 of 50 selected PVC production workers who had been heavily exposed in the past (Marsteller et al. 1975a). Lillis et al. (1975) reported hepatomegaly in 15% and splenomegaly in 3.4% of 354 consecutively examined employees (267 currently employed, 87 former workers) of one PVC polymerization plant in New York State, USA, a number which included virtually the entire current production work force. A significantly higher prevalence of hepatomegaly was found in those

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Assessment of urinary excretion of porphyrins and porphyrin precursors in symptomatic workers who had been engaged in the production of PVC (n = 23) or the manufacture of PVC articles (n = 17) revealed varying but mostly mild degrees of secondary coproporphyrinuria in the majority of them (Lange et al. 1976b). The significance of

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these findings as an indication of toxic liver damage is not clear and the relation to previous exposure to VCM remains to be determined.

4.2.3 Gross Inspection of the Liver and Spleen

The gross appearance of the liver, as assessed by peritoneoscopy (Marsteller et al. 1975a, b; Marsteller and Leibach 1977; Leibach and Marsteller 1977) or at exploratory laparotomy, is that of a normal-sized or slightly to moderately enlarged organ with often blunted and irregular anterior edge. Inspection of the liver at peritoneoscopy also permits exclusion of partial nodular transformation as described by Sherlock et al. (1966). In most cases, the surface of the liver is smooth or slightly uneven with shallow indentations, but it may be finely granular, trabeculated or have a peau d'orange-like appearance. At most, there are micronodular changes but the diffuse coarse nodularity of cirrhosis is only rarely seen. Progression to frank cirrhosis with severe derangement of hepatic lobular architecture was observed by Smith and Williams (1974), and also in two of our recent cases in combination with development of angiosarcoma.

On palpation (direct or by peritoneoscopic probe), the texture of the liver is normal or only slightly firmer than usual. Indirect peritoneoscopic evidence of portal hypertension is presented by increased vascularity of the falciform ligament and the intestinal serosa or numerous dilated tortuous vessels in adhesions draining to the abdominal wall. Even in advanced stages, symptoms of pronounced portal hypertension often



Fig. 4. Peritoneoscopic view of left hepatic lobe in noncirrhotic portal hypertension (January 1979). Blunted anterior edge, smooth to finely granular surface, conspicuous patchy capsular fibrosis. (42-year-old autoclave cleaner. VCM exposure 1963-74, 1973 thrombocytopenia as first sign. From 1974 to 1979, marked progression of portal hypertension with splenomegaly and one episode of bleeding from oesophageal varices.) See also Fig. 5 (patient 6 in Table 11)

Vinyl Chloride

contrast studies. The lesion is a focal, well-circumscribed, stellate scar. The surrounding tissue is normal. The lesion is seen in the right lobe of the liver.

4.2.4 Histology

Histological examination of the liver is generally normal. There is no evidence of fibrosis or other pathological changes. The liver is normal in size and shape. The histological examination is normal.

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4.2.4.1 Histology

In its fully developed stage, the liver is normal. The liver is normal in size and shape. The histological examination is normal.

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contrast sharply not only with minimal alterations of the surface but also with unexpectedly scanty histological evidence of hepatic fibrosis. The most conspicuous feature is a focal or diffuse capsular fibrosis of varying pattern (Fig. 4), presenting as whitish opacities. The degree of capsular involvement ranges from diffuse tiny commalike or stellate scars to coarsely reticular and irregularly patchy milk-white capsular thickening (Marsteller et al. 1975a). Histology showed that this focal increase of connective tissue in Glisson's capsule may extend into the parenchyma and connect with septa extending from enlarging fibrosed portal tracts (Popper and Thomas 1975). The connective tissue capsule of the enlarged spleen also seems to be sensitive to VCM-induced processes that have taken place in the underlying tissue so that focal white thickening or more diffuse opacities together with circumscribed subcapsular haemorrhagic cysts are seen in cases with marked splenomegaly.

4.2.4 Histology

Histological examination of biopsy specimens shows that normal lobular architecture is generally maintained, but varying patterns of portal and, in some cases, septal fibrosis, striking intralobular perisinusoidal fibrosis, and focal capsular and subcapsular fibrosis are found in combination with peculiar alterations of sinusoidal lining cells (Fig. 5a-d). Hepatocellular changes usually play a negligible role and inflammatory reactions, if present at all, are insignificant. The lesions are distributed quite irregularly throughout the liver and may vary from minor inconspicuous degrees to quite striking fibrosis. Surgical wedge biopsy of sufficient depth appears to be more suitable for histological evaluation than needle biopsy specimens (Smith et al. 1976a; Blendis et al. 1978).

Depending on length and degree of exposure, interval between last exposure and date of biopsy, as well as individual factors, histopathology of VCM-induced nonmalignant liver disease is represented by the following features whose manifestation is subject to marked interindividual and topical variation: the same variability of tissue alterations is seen in the nontumorous areas of the liver in angiosarcoma (Popper and Thomas 1975; Thomas et al. 1975; Berk et al. 1976; Gedigk et al. 1975; Weinbren 1976), but in these cases the nontumorous lesions may be even more conspicuous (Popper et al. 1978).

4.2.4.1 Hepatic Fibrosis

In its fully developed form, minimal to marked enlargement of portal tracts by excess of dense, paucicellular connective tissue, which in advanced cases contains proliferated bile ducts and some periductular inflammation, may in rare instances be combined with formation of periportal septa linking portal tracts or, even more rarely, connect central and portal canals. Other portal areas appear almost normal. Focal accumulation of connective tissue in the thickened Glisson's capsule may be connected by septa with enlarged infracapsular portal tracts. A more striking feature is an intralobular perisinusoidal 'netlike' fibrosis with more or less prominent collagenization of sinusoidal walls, in some areas even progressing to frank capillarization (Gedigk et al. 1975; Müller et al. 1975). The focal intrasinusoidal fibrosis may be subtle and in some cases

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Fig. 5a. Needle biopsy specimen of the liver shown in Fig. 4. Enlargement and fibrosis of portal tracts. Moderately large droplet steatosis. Focal dilatation of sinusoids. H & E, $\times 80$. b Close-up of Fig. 5a. Indistinct border of enlarged and fibrosed portal tract towards parenchyma (*left*). Proliferation of capillaries ($> <$) with polymorphism and hyperchromasia of endothelial cells. PAS, $\times 400$

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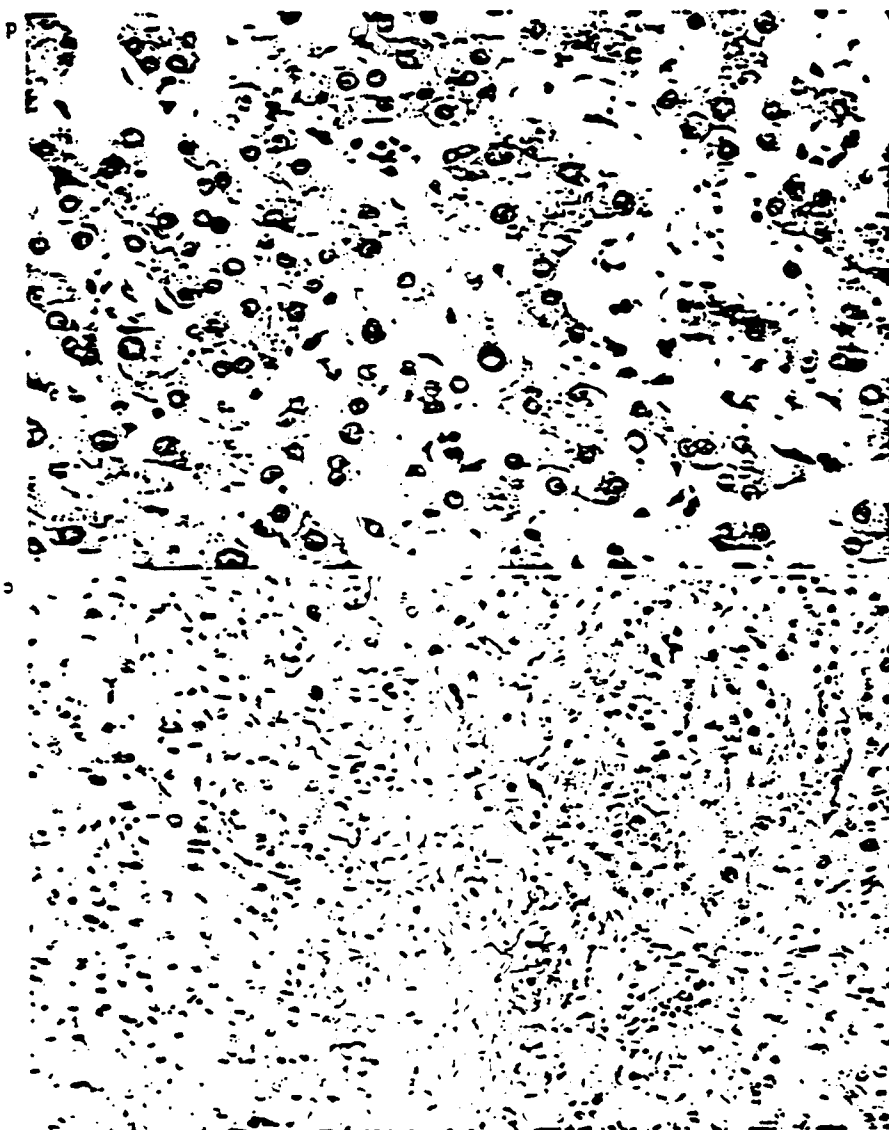


Fig. 5c. Focal portal fibrosis (left upper corner) and activated proliferating and pleomorphic sinusoidal lining cells with activated proliferating and pleomorphic sinusoidal lining cells. Trichrome (Gold-ner) stain, blue filter, x 250. d. Conspicuous focal dilatation of sinusoids. Activation and moderate polymorphism of proliferated hyperplastic sinusoidal lining cells. Enlarged hepatocytes with hyperchromatic nuclei, some of them binuclear. Potential precursor stage of angiosarcoma? Courtesy of Professor Müller-Wallat, Institute of Pathology, Årberg, H. & E. x 400

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may be recognized only in connective tissue stains. *Triche* et al. (1975) pointed out that in one worker with severe acroosteolysis but normal hepatic function and essentially normal liver histology on light microscopy (except for a minimal and easily overlooked increase of perisinusoidal collagen in occasional lobules), electron microscopy revealed a striking centrilobular increase in collagen between hepatocytes and in Disse's spaces together with proliferation and hyperplasia of sinusoidal lining cells (see also *Kurokawa* et al. 1977). The same ultrastructural deposition of perisinusoidal collagen was observed by *Schattenberg* et al. (1977) in 15 PVC workers in whom we could obtain liver tissue for electron microscopy at peritoneoscopy. Similar changes (enlargement of Kupffer cells, abundant deposits of collagen in the Disse's space and resulting reduction of sinusoidal diameter suggesting a possible factor in the pathophysiology of 'sinusoidal' portal hypertension) were seen on electron microscopy in a number of cases of idiopathic portal hypertension of unknown aetiology (occupational histories not mentioned) (*Sommerschild* and *Kluge* 1971; *Kluge* et al. 1970; *Tandon* et al. 1970).

4.2.4.2 Sinusoidal Lining Cells

Marked focal proliferation and hyperplasia of sinusoidal lining cells with nuclear polymorphism and hyperchromasia are the most impressive features of the mesenchymal lesion. The hyperchromatic nuclei of these cells may show a bizarre shape or resemble short pegs, and are often arranged in a chainlike fashion (*Gedigk* et al. 1975). These perisinusoidal and sinusoidal cells include three types: (1) normal endothelial cells, (2) lipocytes (Ito cells), considered to be precursors of fibroblasts and (3) plump cells with spindle-shaped nuclei and PAS-positive cytoplasm. Formation of excess reticulin suggests fibroblastic activity of some of these cells. Focal dilatation of sinusoids, not explained by passive congestion, is another peculiar feature usually associated with particularly pronounced alterations of these mesenchymal cells. There is reason to believe that this combination of changes may represent a premalignant stage.

4.2.4.3 Hepatocytes

Unimpressive, nonspecific, degenerative and adaptive lesions (such as minor degrees of fatty degeneration, cloudy swelling, ballooning or vacuolar degeneration, increase of lipofuscin pigment and proliferation of smooth endoplasmatic reticulum of hepatocytes in focal areas without inflammatory reactions), can be seen to disappear gradually with increasing intervals between the last exposure and the date of biopsy, in contrast to the apparently irreversible damage to mesenchymal structures (*Gedigk* et al. 1975, 1977; *Müller* et al. 1975). In poorly demarcated areas there is hyperplasia and hypertrophy of hepatocytes with polyploidy and increased number of binucleated cells. Two types of focal hepatocytic proliferation associated with varying degrees of sinusoidal cell alterations were recently described and are thought to play some as yet undefined role in the precursor stage of angiosarcoma (*Popper* et al. 1978).

4.2.4.4 Histology of the Spleen

Unless splenectomy is carried out in vinyl chloride disease, tissue specimens of the spleen are less easily obtainable than liver biopsy material. *Popper* and *Thomas* (1975)

and *Thomas* et al. to be characteristic: congested red pulp follicles with macrophages and endothelial cells, occasional fresh spicuous fibrosis.

In ten cases with splenectomy, *Heusermann* and *Thomas*, together with *Thomas*, reported the process. Excess connective tissue, notably white pulp, was found. There was scarring, meshwork and reduction of diameter of the pulp cords, formation of bizarre collagen fibrils. Notably, the reticular connective tissue volume with para-arterial formation of capillaries found within the thrombocytes by enhanced pooling of blood. This helps to explain the stages of vinyl chloride disease and *Heusermann* and *Thomas* VCM-induced splenomegaly of the liver or extrahepatic in the spleen in vinyl chloride disease. To indicate a primary portal hypertension, reports correlating changes in the spleen in non-alcoholic liver disease are available for comparison.

4.2.5 Pathophysiology

The pathophysiology of vinyl chloride disease is an unresolved problem. To splenoportography of intrahepatic venous radicles (*Bjork* and *Thomas*, 1975) and a normal, or or

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and Thomas et al. (1975) found the cut surface of surgically removed enlarged spleens to be characterized by conspicuously hyperplastic Malpighian follicles in a beefy homogeneous red pulp. Histologically, they noted large germinal centres of the Malpighian follicles with merging of perfollicular zones, dilatation of red pulp sinuses lined by endothelial cells of variable, often cuboidal shape, thickening of the pulp cords with occasional fresh haemorrhages, and in one case Gandy-Gamna bodies, but only inconspicuous fibrosis of the red pulp.

In ten cases we obtained needle biopsy specimens of spleen tissue at pentoneoscopy. Heusermann and Stutte (1977b) and Stutte and Heusermann (1978) studied this material, together with spleen tissue specimens available from three spleens obtained at splenectomy. They found evidence for an involvement of the spleen in the fibrosis process. Excess amounts of newly formed extracellular elements of reticular connective tissue, notably collagen, produced by stimulation of fibroblastic cells of the red and white pulp, particularly in perfollicular and subcapsular areas, were observed. There was scarring of periarterial lymphatic sheaths, obliteration of the pulp cord meshwork and reduction of pulp cord volume, in addition to an increase in number and diameter of sinuses. The reticular connective tissue of the walls of the sinuses and of the pulp cords showed marked alterations with thickening of reticular fibres and formation of bizarre platelike amorphous structures containing irregularly distributed collagen fibrils. Narrowing of the labyrinthine cordal tissue with marked increase of the reticular connective tissue caused a reduction of microcirculatory sequestration volume with parallel decrease of the number of pulp cord macrophages and approximation of capillaries and sinuses. Frequently, focal accumulation of platelets was found within the narrowed pulp cordbed in addition to increased phagocytosis of thrombocytes by residual macrophages. This lends support to the hypothesis of enhanced pooling of platelets in the spleen (Heusermann and Stutte 1977a), and may help to explain the pathogenesis of thrombocytopenia often seen even in the early stages of vinyl chloride disease. By structural analysis of histometrical results, Stutte and Heusermann (1978) outlined certain diagnostic criteria for the differentiation of VCM-induced splenic alterations from those seen in portal hypertension due to cirrhosis of the liver or extrahepatic portal vein occlusion. They concluded that fibrotic changes in the spleen in vinyl chloride disease are not the result of portal hypertension but indicate a primary action of VCM or its metabolites on the spleen. A comprehensive report correlating clinical and morphological data gathered from this group of 13 patients is being prepared for publication at present. Results of histometrical studies of the spleen in noncirrhotic portal hypertension of unknown aetiology are now available for comparison (Seki 1965; Yamamoto 1978, 1979).

4.2.5 Pathophysiology of Portal Hypertension

The pathophysiology of portal hypertension in VCM-induced liver disease is as yet an unresolved problem. Patency of the portal vein was demonstrated in all cases subjected to splenoportography. Portography usually showed no or only minimal derangement of intrahepatic vascular pattern such as tapering or 'cut-off' of small peripheral portal venous radicles (Blendis et al. 1978; Villeneuve et al. 1976). High intrasplenic pressure and a normal, or only slightly raised, wedged hepatic vein pressure indicate that the

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portal flow is obstructed at the sinusoidal or presinusoidal level. In a group of five PVC workers selected for haemodynamic studies, *Blendis et al.* (1978) could not demonstrate a direct relationship between the degree of hepatic fibrosis in needle biopsy specimens and portal hypertension. But it should be kept in mind that the distribution of fibrosis in these workers is quite irregular. It has also been suggested by *Popper and Thomas* (1975) and *Thomas et al.* (1975) that the increased splenic and hepatic blood flow as a result of decreased splenic resistance in splenomegaly cannot properly be accommodated in the hepatic portal vein bed owing to impairment of adaptive distension of portal veins and sinusoids by the subcapsular, portal and perisinusoidal fibrosis. *Blendis et al.* (1978) found no correlation between spleen or estimated liver blood



Fig. 6a, b. Progression of noncirrhotic portal hypertension despite termination of exposure. Oesophageal varices. (Autoclave cleaner, age at diagnosis: 35 years. VCM-exposure, 1962–1972. 1972 Raynaud's phenomenon, sklerodermoid skin indurations, thrombocytopenia, splenomegaly, and grade I oesophageal varices. Gradual progression of portal hypertension. Sudden death from ruptured anaplastic angiosarcoma of the liver in June 1978. Histologically only mild perisinusoidal fibrosis in nontumorous areas)

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flow and the portal pressure. However, they point out that this relationship may be veiled by the amount of blood bypassing the liver via a collateral circulation.

4.2.6 Follow-up of Non-malignant VCM-induced Liver Disease

In 1974 Martin et al. (see also Berk et al. 1975) pointed out that VCM-associated hepatic fibrosis, once established, may progress even after cessation of exposure. They could demonstrate this progression despite normalization of all routine liver function tests in a 27-year-old worker on a follow-up examination including peritoneoscopy and biopsy 2 1/2 years after cessation of exposure. Progression of fibrosis and appearance of bridging between portal and central veins were indicative of persisting activity of the fibroblastic process, whereas the previously observed activation of both hepatocytes (marked variation of cell size and numerous binucleated cells) and sinusoidal lining cells had disappeared. Since 1973 we have observed a number of workers who on follow-up showed evidence of progressing portal hypertension with development of massive oesophageal varices and subsequent bleeding episodes despite removal from exposure (Fig. 6). In five (??) of these patients with progressing portal hypertension angiosarcoma of the liver finally developed. In this context, it is of interest to note that more or less conspicuous hepatic fibrosis (or rare progression to cirrhosis) was the parental terrain in which the majority of cases of VCM-induced angiosarcoma of the liver developed (see Tables 13-18).

Liver and spleen scans with 99m technetium-labelled sulphur colloid, quantitated determination of spleen size with the aid of ^{197}Hg -bromomercure-hydroxypropane (BMHP) labelled artificially damaged red cells, and sequential perfusion scintigrams after bolus injection of ^{99m}Tc -pertechnetate have been found useful in the diagnosis and follow-up of nonmalignant liver disease in PVC-polymerization workers. With the aid of these noninvasive methods, inhomogeneous uptake of labelled sulphur colloid in the reticuloendothelial system of the liver and enhanced uptake in the spleen, gradual increase in spleen size and reduction of portal venous perfusion have been observed in PVC polymerization workers developing portal fibrosis and portal hypertension (Bierack et al. 1975a, b, 1977a, b).

4.3 Angiosarcoma of the Liver

4.3.1 Epidemiology

Primary angiosarcoma of the liver (ASL) is described under a variety of synonyms (angioblastic sarcoma, angioblastic reticulosarcoma, endothelioma, endothelioblastoma, haemangioblastoma, haemangioendothelioma, haemangioendothelial sarcoma, Kupffer cell sarcoma, malignant haemangioma, metastasizing haemangioma, reticuloendothelial sarcoma, primary sarcoma of the liver). It is an exceedingly rare malignancy, arising from vascular lining cells. It occurs spontaneously with two peaks in the age distribution: one at early infancy (infantile haemangioendothelioma) and the other in late adulthood (fourth to sixth decade). The numerous synonyms render it difficult to estimate the number of reported cases and to determine its true incidence. In a recent review

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of the literature. *Alrenga* (1975) listed 165 published cases of primary angiosarcoma of the liver in adults. In the six autopsy series collected by *Alrenga*, ASL constituted only 1.8% (0.9%–2.7%) of all primary malignant tumours of the liver, which of themselves are rare findings in the Western World. Autopsy statistics show that the incidence of ASL ranged from 2 to 20/100 000 autopsies during different periods with a mean incidence of 12/100 000 autopsies (Table 12). According to *Heath* et al. (1975) it was estimated that in the United States the expected annual incidence of ASL is 0.014 in 100 000 inhabitants or 25–30 cases per year for the entire United States.

Table 12. Incidence of angiosarcoma of the liver (ASL) in autopsy series

Authors	Year	Observation period	No. of autopsies	No. of cases of ASL	Region
<i>Simpson et al.</i>	1955	1914–1953	24 196	1	Mayo Clinic, Rochester, Minn., USA
<i>Edmondson</i>	1958	1918–1954	52 000	1	Los Angeles, County Hosp., USA
<i>MacSween et al.</i>	1973	1900–1969	— ^a	3	Western Infirmary Glasgow, U.K.
<i>Alrenga</i>	1975	1951–1973	39 700	6	Cook County Hosp. Chicago, USA
<i>Rein and Huth</i>	1975	1954–1974	30 079	4 (6) ^c	Düsseldorf, Fed. Rep. Germany
<i>Byrén and Holmberg</i>	1975	1958–1969	— ^b	12 (adult cases)	Sweden
<i>Dalderup et al.</i>	1976	1960–1975	At least 40 000	8	Netherlands (population: 10–14 million)

^a Among 120 cases of primary malignant liver tumours studied post mortem during this 70-year period.

^b Among 8 million inhabitants.

^c 4 Angiosarcomas, 1 haemangioendothelioma, 1 malignant haemangiopericytoma

Accordingly, the identification of 4 cases of ASL among approximately 270 employees of the vinyl chloride polymerization section at a B.F. Goodrich plant near Louisville, Kentucky, between September 1967 and December 1973 was duly recognized as an alarming situation indicative of a serious new occupational hazard (*Creech et al. 1974a; Creech and Johnson 1974*).

Until 1974, only two carcinogenic agents were known to be associated with the development of ASL in man, i.e. the administration of a radioactive colloidal prepara-

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In retrospect, it was discovered that the first case of VCM-induced ASL had already occurred in 1955 in a Canadian polymerization worker. For the 67 VCM polymerization workers for whom details were available, total years of exposure ranged from 4 to 31 years (mean and median 18 and 19 years, respectively). In comparison, mean duration of exposure in our group of 17 individuals with advanced nonmalignant liver disease (see Table 11) was 10 3/4 years (range: 3 1/2–21 years). The latency period (years from first exposure to diagnosis of ASL) ranged from 9 to 38 years (mean and median: 21 years). The average age at diagnosis of ASL was 50 years (range: 37–71 years).

Table 14. Clinical and morphological data on 68 polyvinyl chloride (PVC) production workers with angiosarcoma of the liver reported to NIOSH by August 1978

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Table 14. Clinical and morphological data on 68 polyvinyl chloride (PVC) production workers with angiosarcoma of the liver reported to NIOSH by August 1978

No.	Hepato- megaly	Spleen	Oesophageal varices	Hepatic fibrosis	Thrombo- cytopenia	Acro- osteolysis	Raynaud's phenomenon	Metastases
1	+	Atrophic, slightly indurated	(+)	Noncirrhotic, perisinusoidal & capsular	?	0	β	β
2				Capsular				
3				Capsular, portal, perisinusoidal				
4				Sclerosis of wall of portal vein				
5				Capsular, portal, perisinusoidal				
6				?				
7	7 cases: (+) - + (1860 - 5200 g)	No details available		Capsular, portal, perisinusoidal		No details available		1 case: multiple metastases (lung, pleura, pericardium, ileum, colon, kidneys, left adrenal)
8				Capsular, portal, perisinusoidal				1 case: mediastinal lymph node
9				Portal, perisinusoidal				1 case: peritoneal spread
10				Capsular, portal, perisinusoidal				1 case: local spread
11				Capsular, portal, perisinusoidal				

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Table 14 (continued)

No.	Hepato- megaly	Spleen	Oesophageal varices	Hepatic fibrosis	Thrombo- cytopenia	Acro- ostolysis	Raynaud's phenomenon	Metastases
12	+	Moderately enlarged (7300 g)	(+)	(Cirrhosis), fibrosis	?	β	+	β
13	+	(2750 g) ?	+	(Cirrhosis)	?	β	β	Left lung
14	+	Spleno- megaly	?	?	?	β	β	4th left rib
15	+	Slightly enlarged	?	?	?	β	β	β
16	+	Spleno- megaly (830 g)	+	Capsular, portal, septal	+	β	β	1st thoracic vertebra
17	+	Spleno- megaly	+	+	?	β	β	Brain
18	?	Perisplenitis	?	?	+	β	+	3rd lumbar vertebra
19	(+)	Spleno- megaly (1450 g)	(+)	Progressive perisinusoidal, (80 000, portal and 47 000, septal cirrhosis 30 000)	+	β	β	β
20	?	?	?	?	?	?	?	?
21	+	Spleno- megaly (1900 g)	+	+	?	β	β	β
22	+	Spleno- megaly	?	Capsular, portal, perisinusoidal	+	β	β	β
23	+	Spleno- megaly (455 g)	β	Focal peri- sinusoidal	?	β	β	β
24	+	?	?	?	?	β	?	?

CONTINUATION

20	+	+	?	?	?	?	?
21	+	Spleno- megaly (1900 g)	+	?	?	?	?
22	+	Spleno- megaly	?	?	?	?	?
23	+	Spleno- megaly (2700 g)	?	?	?	?	?
24	+	?	?	?	?	?	?
25	+	Spleno- megaly (1610 g)	+	?	?	?	?
26	+	?	?	?	?	?	?
27	+	Spleno- megaly (2230 g)	?	?	?	?	?
28	+	Spleno- megaly (650 g)	+	?	?	?	?
29	+	'Modifications fibro- congestive' (1750 g)	?	?	?	?	?
30	+	?	?	?	?	?	?
31	+	Spleno- megaly (3000 g)	?	?	?	?	?
32	+	?	?	?	?	?	?
33	+	?	?	?	?	?	?

portal fibrosis

Table 14 (continued)

No.	Hepato- megaly	Spleen	Oesophageal varices	Hepatic fibrosis	Thrombo- cytopenia	Acro- osteolysis	Raynaud's phenomenon	Metastases
34	+	Slight (2625 g)	β	β	+	β	β	β
		splenomegaly			(80 000)			
35	+	Congested, (3240 g)	+	Noncirrhotic fibrosis	?	β	β	β
		firm (200 g)						
36	+	?	+	?	?	β	β	Local spread to abdominal wall and colon; lymph nodes
37								
38								
39								
40								
41	+	Splenomegaly	?	?	?	?	?	?
42	?	?	?	?	?	?	?	?
43								
44	+	Splenomegaly	+	Subcapsular and portal fibrosis	+	β	β	β
45	+	Spleno- megaly	+	Markedly thickened capsule; marked fibrosis	+	β	β	β
46	+	Spleno- megaly	?	Portal fibrosis	?	β	β	Spread to duodenum
		(1860 g)						
47	+	Spleno- megaly	?	Portal fibrosis	+	β	β	Spread to diaphragm and abdominal wall
					(35 000)			
48	+	?	?	Slight focal	?	β	β	Times three and small

45	+	Splenomegaly	+	thickly thickened capsule; marked fibrosis	♂	♂	♂
46	+	Splenomegaly (1860 g)	?	Portal fibrosis	♂	♂	Spread to duodenum
47	+	Splenomegaly	?	Portal fibrosis (35 000)	♂	♂	Spread to diaphragm and abdominal wall
48	+	? (5200 g)	?	Slight focal hepatitis ('minimal hepatitis')	♂	♂	Lungs, large and small bowel, pleura, pericardium myocardiolum, kidneys, left adrenal
49	?	Normal	?	Capsular and portal fibrosis	♂	♂	Diaphragm, regional, retroperitoneal and mediastinal lymph nodes, lungs, adrenal glands, cerebellum
50 } 51 }	Details not published						
52	+	? (2810 g)	?	Peculiar - portal fibrosis, moderate cirrhosis	♂	♂	Diaphragm, gallbladder, regional lymph nodes, lungs, scalp, skull
53 54 55 56 57 58 59 60 61 62 63 64 65 66 67	{ Details not published						
68	+	?	+	?	♂	♂	♂

Table 15. Publications on the 68 cases of angiosarcoma of the liver listed in Tables 13 and 14

No.	References	Additional relevant information
1	Hublet et al. (1977)	Hypertrophic, hyperchromatic and atypical endothelial cells in the <i>glomeruli</i> ; foci of haematopoietic cells in liver and spleen
2	Delorme and Makk (1975) Makk et al. (1976) Delorme (1978a, b) Delorme and Thériault (1978)	Case no. 7: ASL associated with hepatocellular carcinoma (Delorme 1978b) (All cases from one plant in Shawinigan, district Trois Rivières, Quebec)
3		
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12	Schmidt and Bátor (1976)	At the same plant: 4 cases of VCM-induced cirrhosis of the liver plus 1 case of cirrhosis and generalized reticulosarcoma and 4 cases of carcinoma of the GI tract or lungs
13		
14	Lange et al. (1974b)	See also Reinl and Weber (1974)
15	Gedigk et al. (1975)	See also Reinl and Weber (1974)
16	Gokel et al. (1976)	Foci of haematopoiesis within the tumour areas
17	Amann (1975) Rübsamen (1976)	1974 portocaval anastomosis; cholecystectomy; Hypertrophic, hyperchromatic and markedly atypical endothelial cells in the <i>glomeruli</i> and in the capillaries of the lungs
18	Reinl et al. (1976)	
19	(Observed in Bonn)	Moderate hepatic siderosis; chronic fibrosing <i>pancreatitis</i> ; tubular and interstitial fibrosis of the <i>testes</i>
20	Reinl et al. (1976)	
21	Reinl et al. (1977)	
22	Reinl et al. (1977)	
23	(Observed in Bonn)	Focal interstitial fibrosis of the <i>pancreas</i>
24	Ravier et al. (1975)	See also Berrod et al. (1978)
25	Roche et al. (1978)	1942 gastrectomy, 1974 splenectomy, right hepatic lobectomy (640 g). See also Roche (1977); Puech et al. (1977); Bonneton et al. (1975, 1977); Berrod et al. (1978)
26	Rety et al. (1976)	No autopsy (see also Berrod et al. 1978)

Table 15 (continued)

No.	Ref.
27	Reinl
28	Reinl
29	Reinl
30	Berrod
31	
32	
33	
34	Lein
35	Sm.
36	Mc.
37	-
38	-
39	-
40	-
41	Byr.
42	Byr.
43	-
44	Bl.
	(ca.)
45	Bl.
	(ca.)
46	Bl.
	(ca.)

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Table 15 (continued)

No.	References	Additional relevant information
27	Roche et al. (1978)	Chronic alcoholic. See also Roche (1977); Puech et al. (1977); Berrod et al. (1978)
28	Roche et al. (1978)	First symptoms: vertebral and costal metastases. Right hepatic lobectomy. See also Roche (1977); Puech et al. (1977); Pillichowski et al. (1979); Couderc et al. (1976); Berrod et al. (1978)
29	Roche et al. (1978)	1960 scleroderma-like skin induration (hands), swelling of face, upper extremities and feet. 1971 bilateral acroosteolysis. Tumour penetration of the abdominal wall (fistula). Severe interstitial fibrosis of testes: fibrosis of interstitial wall; slight mesangial fibrosis of glomeruli. Variable but generally slight fibrohyalinosis of arterial and venous vessel walls (skin, heart, lungs, intestine, testes)
30	Berrod et al. (1978)	
31		
32		
33		
34	Lee and Harry (1974)	
35	Smith et al. (1976b)	Latency period (1st exposure - death) only 8 years (see also Fox and Collier 1977)
36	Maltoni (1974)	
37	-	
38	-	
39	-	
40	-	
41	Byrén and Holmberg (1975)	
42	Byrén et al. (1976)	
43	-	
44	Block (1974) (case 3)	1965 portocaval shunt. 1970 cholecystectomy. See also Falk et al. (1974a) (case 4); Whelan et al. (1976) (case 1)
45	Block (1974) (case 2)	No autopsy. See also Creech and Johnson (1974); Falk et al. (1974a) (case 3); Whelan et al. (1976) (case 2); Makk et al. (1976) (case 6)
46	Block (1974) (case 4)	See also Falk et al. (1974a) (case 5); Makk et al. (1976) (case 10)

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Table 15 (continued)

No.	References	Additional relevant information
47	<i>Block</i> (1974) (case 1)	See also <i>Falk et al.</i> (1974a) (case 2); <i>Makk et al.</i> (1976) (case 4)
48	<i>Block</i> (1974) (case 5)	See also <i>Falk et al.</i> (1974a) (case 1); <i>Makk et al.</i> (1976) (case 2)
49	<i>Block</i> (1974) (case 6)	See also <i>Falk et al.</i> (1974a) (case 6); <i>Whelan et al.</i> (1976) (case 4); <i>Makk et al.</i> (1976) (case 14)
50	—	
51	—	
52	<i>Whelan et al.</i> (1976) (case 3)	Chronic alcoholic. See also <i>Makk et al.</i> (1976) (case 13); <i>Berk et al.</i> (1976) (case 2)
53-67	—	
68	<i>Zonica et al.</i> (1975)	Among a work force of 180-120, PVC polymerization; 60, production of VCM) employed at this plant, 15 died of malignant disease (2 ASL, 5 bronchogenic carcinomas, 1 case each of carcinoma of the larynx, rib, mamma, spermatic cord; glioma, melanoma, leukaemia, Hodgkin's disease)

First exposure to VCM for these 67 cases of ASL dated back to the period 1939-1966 (median: 1951). Twenty-one years later, i.e. from 1972 onwards, a gradual increase in the number of new cases diagnosed and reported to NIOSH can be observed (Fig. 7). The onset of this gradual increase coincides with the calculated mean latency period of 21 years (*Spiras and Kaminski* 1977). *Spiras and Kaminski* also suggested that in future cases the age at diagnosis and the length of the latency period may increase as a result of the later reduction in levels of exposure.

From the synopsis in Table 13-18 it can be seen that in about two-thirds of the cases of ASL for which morphological details are available varying degrees of associated hepatic fibrosis in nontumorous areas of the liver were mentioned. Less often, evidence of portal hypertension and splenomegaly were noted. Metastasis of angiosarcoma to distant sites was observed in approximately half the published cases. It is of note that acroosteolysis and cutaneous stigmata of scleroderma have been observed in only 1 of these 76 patients, a French PVC worker who had apparently not been engaged in reactor cleaning (case 29; *Roche et al.* 1978). Another noteworthy piece of information is that strikingly atypical endothelial cells with hypertrophic and hyperchromatic nuclei have also been found in organs other than the liver (kidneys, lungs) in autopsy material from two patients (cases 1 and 17, *Hublet et al.* 1977; *Rübsamen* 1976). *Hublet et al.* (1977) also found such cells in the myocardium and in the adipose tissue enveloping the adrenals. All this may lend support to the idea that the effect of VCM metabolites is not restricted to the vascular endothelium of the liver and spleen. Angio-

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Table 16. Personal data on eight cases of angiosarcoma of the liver among VCM-exposed personnel not employed in PVC production (as reported to NIOSH by August 1978)^a

No.	Country	Birth date (m/d/y) ^b	Date of death (m/d/y)	Age at death	Total years exp.	Job classification
A	D (3)	07.16.30	10.10.73	43	14	Loading pesticide cans with VCM propellant
B	D (6)	05.09.36	12.16.74	38	3.5	Assistant factory chemist
C	GB (2)	09.08.14	12.00.70	55	11	Pouring PVC oil mix- ture onto fabric bases
D	I (1)	06.15.34	04.16.71	36	3	Fabrication of PVC sacks and wrappings (extrusion at tempera- tures of 120° C)
E	S (2)	11.27.11	08.16.71	61	23	Assistant factory chem- ist (production of VCM)
F	USA (15)	00.00.25	02.15.73	47	?	Accountant at plant producing PVC fabric
G	YU (2)	11.15.31	07.12.73	42	18	Production of VCM
H	YU (3)	12.21.31	01.11.76	45	22	Production of VCM

^a Update of NIOSH register, August 1978, prepared by Kaminski as in Table 13.

^b 00, data not available

sarcoma arising from the kidneys or other types of malignant renal neoplasms, however, have not been described in VCM-exposed individuals, although malignant nephroblastoma has been induced in experimental animals.

The extremely rare coincidence of angiosarcoma and hepatocellular carcinoma was found in three instances (case 7, *Delorme* 1978b; case E, *Byrén* and *Holmberg* 1975, and a case not included in the 1978 NIOSH update *Tamburro et al.* 1978a). In the case reported by *Tamburro et al.* chronic alcoholism may have played a cofactor role in the development of liver cancer. We can now add a fourth case observed in 1978 at the Department of Medicine in Bonn (see Sect. 4.1.5 and Fig. 3). This patient (patient 9 in Table 11), a PVC-polymerization worker (total period of exposure: 18 years) was first admitted to our department in February 1975 and was found to suffer from atypical cirrhosis of the liver with portal hypertension, splenomegaly and Raynaud's phenomenon. During follow-up ASL was clinically suspected but could not be confirmed during life, despite exploratory laparotomy and generous surgical biopsies. The patient

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Table 17. Clinical and morphological data on eight cases of angiosarcoma of the liver among VCM-exposed persons not employed in PVC polymerization

No.	Hepato- megaly	Spleen	Oesophageal varices	Hepatic fibrosis	Thrombo- cytopenia	Acro- osteolysis	Raynaud's phenomenon	Metastases
A	+	Splenomegaly (6000 g)	+	Portal fibrosis	+	β	β	Diaphragm, gastric mucosa, abdominal lymph nodes
B	+	Splenomegaly (3650 g)	+	Focal capsular fibrosis, portal and centrilobular fibrosis	β	β	β	Diaphragm, pleura, abdominal lymph nodes
C								
D	(+)	Not enlarged	β	?	?	β	β	Lungs, pericardium
E	+	?	?	?	+	β	β	?
					(104 000)			
F								
G	+	Splenomegaly	?	?	?	β	β	Dura, cranium
H								

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Table 18. Publications on the eight cases of angiosarcoma of the liver listed in Tables 16 and 17.

No	References	Additional relevant information
A	<i>Reini and Weber</i> (1974)	1967 idiopathic portal hypertension; portocaval shunt
B	<i>Zimmermann and Eck</i> (1975) <i>Reini</i> (1975)	1973 right heminephrectomy for unilateral hydronephrosis associated with bilateral double kidney. Foci of haematopoietic cells in spleen and kidney. Fibrosis of the pancreas. Slight fibrosis of testes and of the small intestinal serosa
C		
D	<i>Maltoni</i> (1974)	Autopsy: angiomatous epulis. Angiosarcoma involving liver, lungs and pericardium. The pericardium might have been the primary site!
E	<i>Byrén and Holmberg</i> (1975)	Probable coexistence of a hepatocellular cancer of both low and high grade differentiation
F		
G	<i>Zorica et al.</i> (1975)	
H		

died on 7 August 1978, after a massive haemorrhage from oesophageal varices. Autopsy revealed both multicentric metastasizing angiosarcoma and hepatocellular carcinoma of the liver as well as slight fibrosis of the pancreas (to be published in detail).

It is still unexplained why hepatocytes are generally exempted from the carcinogenic effect of VCM metabolites but, as predicted by *Popper* in 1975, three anecdotal cases of hepatocellular carcinoma, one German (*Gokel et al.* 1976) and two British PVC workers (*Fox and Collier* 1977), have now also been observed after exposure to VCM. It may be mentioned that a review of the distribution of primary liver cancer in the Province of Quebec covering the period 1969–1972 showed a preponderance of adult male cases in urban areas clustered in the district of Trois-Rivières in congruence with the distribution of the plastics industry, a coincidence which calls for further investigation of a possible exposure to industrial carcinogens (*Jacob and Thériault* 1975).

Not included in the NIOSH register are several anecdotal cases of ASL, capillary and cavernous angiosarcoma of the liver and haemangiosarcomatosis of sites other than the liver, for which a relation to occupational or even possibly residential exposure to VCM has been discussed (*Noria et al.* 1977; *Brady et al.* 1977; *Dor et al.* 1975; *Wallnöfer and Zinnagl* 1977).

Although of undetermined relevance, it should finally be mentioned that, in addition to hepatic fibrosis, varying degrees of interstitial fibrosis of the pancreas were noted at autopsy in four German workers (cases 19, 23, B and the above-mentioned

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patient with both angiosarcoma and hepatocellular carcinoma). Fibrosis of the testes was observed in three cases (19, 29, B), and Roche et al. (1978) also reported fibrosis, hyalinosis in vessels of skin, heart, lungs and intestinal wall.

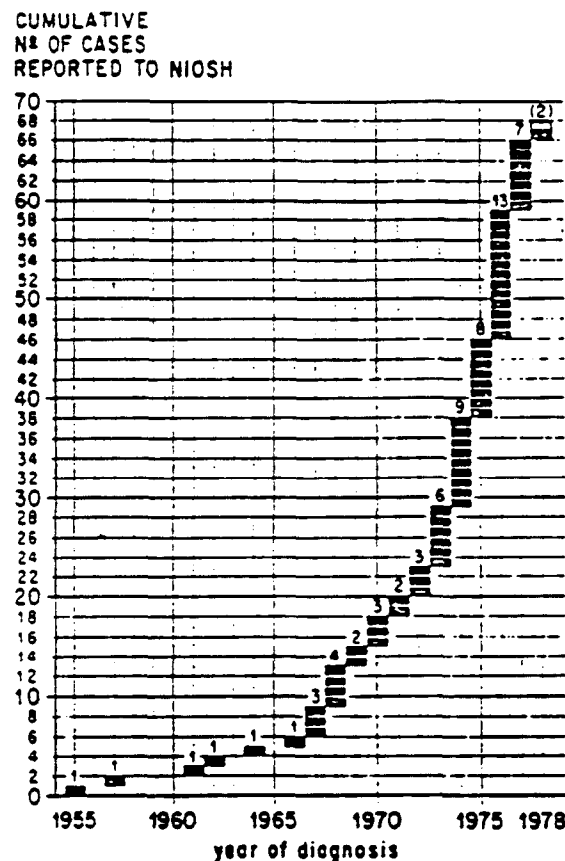


Fig. 7. Cumulative number of cases of ASL among PVC production workers reported to NIOSH up to August 1978, arranged according to year of diagnosis (data from Spiras and Kaminski 1977, 1978)

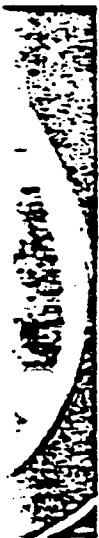
4.3.2 Clinical Manifestations

The clinical symptomatology of usually multicentric ASL is unspecific. Gradually declining general health and loss of weight combined with ill-defined upper abdominal discomfort and slight epigastric or right upper quadrant pain are usually the first symptoms. Recurrent bleedings from oesophageal varices may have been antecedent events in patients with portal hypertension who otherwise felt fairly well. In a number

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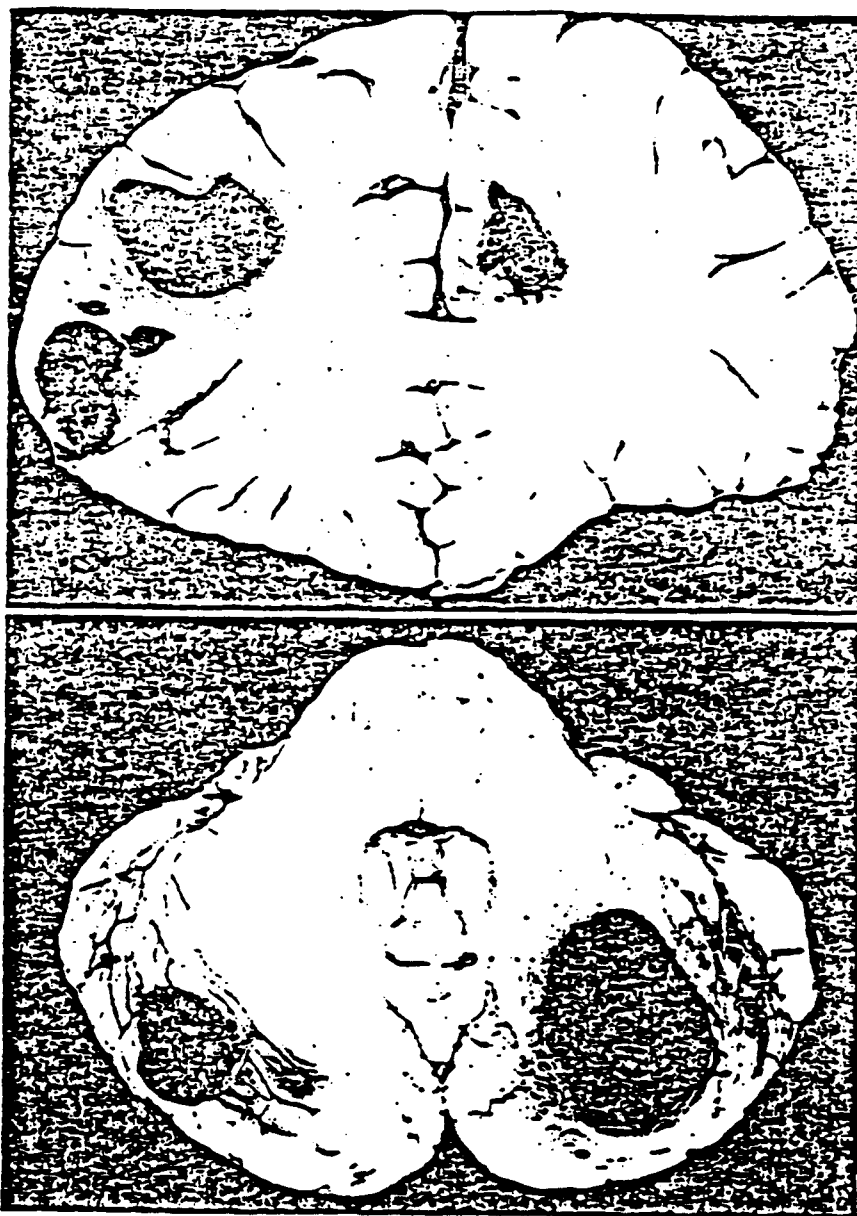


Fig. 10. Multiple brain metastases of angiosarcoma of the liver. Courtesy of Professor Gullotta, Institute of Neuropathology, University of Bonn

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11 months after peritoneoscopic diagnosis of severe hepatic fibrosis (case 19; see also Leibach and Marsteller 1977). In addition to the findings described in connection with hepatic fibrosis, there may be hypervascularized or cystic tumour formation visible on the surface of a nodular, quasi-cirrhotic liver, or a gross aspect resembling hepatic metastases if the vascular malignancy involves the superficial regions of the liver. It should be stressed here that needle biopsy is absolutely contraindicated if there is any suspicion of ASL.

4.3.4 Gross and Histological Morphology

The liver is usually markedly enlarged. Liver weight in cases of ASL ranged from 1600 to 7300 g (Thomas and Popper 1975; Roche et al. 1978). The gross appearance of angiosarcoma of the liver is mostly that of large bulky, irregularly shaped cystic tumour masses; a multinodular form with numerous, sometimes umbilicated nodules, is less often encountered. Extensive haemorrhagic and necrotic areas or solid and spongy portions of tumour tissue replace much of the liver parenchyma. Rupture of large cavernous cysts may cause fatal intraperitoneal haemorrhage.

Thomas et al. (1975) and Thomas and Popper (1975) distinguished four basic developmental patterns of histomorphology of ASL, which can be found in different portions even of the same tumour and appear to represent stages of progressive evolution: sinusoidal, papillary, cavernous and anaplastic patterns. Indistinct areas of transition and merging of patterns can be observed.

Dilated sinusoidal spaces lined by hypertrophic and hyperplastic sarcoma cells with pleomorphic, elongated, hyperchromatic and often bizarre nuclei characterize the sinusoidal pattern, which is the most frequent type. Tumour cells of varying differentiation envelop liver cell plates and may invade enlarged and fibrosed portal tracts, accompanied by proliferation of bile ductules (Fig. 11). In papillary angiosarcoma atrophy of liver cells results in larger and more irregular blood-filled vascular spaces, into which loose papillary strands of surviving hepatic cords on an axis of connective tissue project, lined by sarcomatous cells (Weinbren 1976). Even larger blood-filled spaces are seen in the cavernous type, where they may be surrounded by thick fibrotic walls. In a smaller percentage of cases, solid areas or nodules of anaplastic sarcoma are found, resembling solid spindle-cell sarcoma, or even suggesting an epithelial type of tumour. Gedigk et al. (1975) also observed a reticulosarcomalike pattern. The differentiation of the tumour cells varies widely: it ranges from the inconspicuous endothelial lining cell type to irregularly shaped, grossly distorted giant-cell forms. Morphologically, vinyl chloride-related ASL cannot be distinguished from ASL associated with other aetiological factors or from the cryptogenic type (Popper et al. 1978).

In tumour-free portions of livers with angiosarcoma widely varying degrees of excess formation of fibrous connective tissue are usually observed, analogous to that seen in nontumorous livers of heavily exposed persons. Fibrosis of enlarged portal tracts with modest proliferation of bile ductules, mostly only scanty infiltration of lymphocytes and occasional formation of perlobular septa or thin connective-tissue septa extending into the lobular parenchyma can be found. A more or less conspicuous intra-lobular, perisinusoidal fibrosis is often detected only by special staining methods for collagen or reticulin fibres. As a rule, irregular focal or nodular fibrotic thickening of

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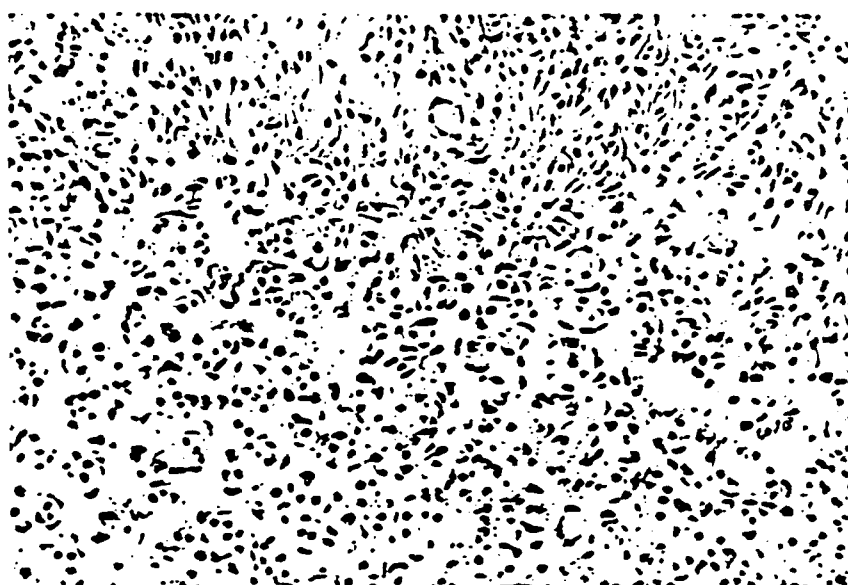


Fig. 11. Angiosarcoma of the liver (upper part of photomicrograph) invading adjacent liver parenchyma (case 14 = D1; see Table 13). Note hyperplastic and hyperchromatic nuclei of proliferating neoplastic lining cells enveloping hepatic cords. Reproduced by permission, Ann NY Acad Sci 246:278-285 (1975). Courtesy of Professor Gedigk, Institute of Pathology, University of Bonn. H & E, $\times 250$

of Glisson's capsule is present; these fibrotic capsular areas may extend into the underlying parenchyma and may connect with adjacent enlarged subcapsular portal tracts. The cellular and nuclear size of hepatocytes may vary widely; groups of binucleated or even multinuclear parenchymal cells with abundant cytoplasm are seen. Focal proliferation of sinusoidal lining cells may be encountered, especially within foci of sinusoidal dilatation.

In connection with conspicuous sinusoidal dilatation, two types of focal hyperplastic precursor lesions were described by Popper et al. (1978):

- 1) Poorly circumscribed foci of hyperplastic, often binucleated hepatocytes with increased number of various sinusoidal lining cells and only insignificant increase of reticulum framework.
- 2) Almost nodular areas of conspicuously hyperplastic and hypertrophic hepatocytes with more pronounced variation of markedly increased sinusoidal cells without degeneration or necrosis of liver parenchyma, but accompanied by excess formation of reticulum framework and compression of surrounding parenchyma.

The transition of sinusoidal lining cells to angiosarcoma cells is characterized by increasing atypia and anaplasia of these proliferating endothelial cells accompanied either

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by formation of excess connective tissue or by accentuation of sinusoidal dilatation leading to primary peliosis. Involvement of portal areas in the evolution of angiosarcoma results in considerable fibroplasia and formation of hyalinized collagen together with proliferation of bile ductules. In occasional cases connective tissue bridging between portal tracts or between portal tracts and central veins with subdivision of lobules followed by rearrangement of hepatocytic plates may lead to a cirrhotic picture.

4.3.5 Therapy

The multicentric development of ASL (Thomas and Popper 1975) as well as the diffuse spread of the tumour usually encountered by the time of diagnosis precludes effective surgical or radiation therapy in the majority of cases. A survival period of two years after surgery (Berrod et al. 1978) or chemotherapy (Dannalier et al. 1979) is a rare exception. Results of systemic chemotherapy studied in a small group of five patients showed that, at best, quality and duration of survival may improve to a very limited extent (Dannalier et al. 1979). At present, no generally accepted guidelines for chemotherapy are available.

4.3.6 Risk Assessment

When in the United States 13 white male cases of ASL had been detected from 1961 to May 1974, among an estimated total population of VCM polymerization workers of roughly 20 000, a risk ratio (ratio of observed to expected cases) for this population of at least 400:1 was calculated (Heath et al. 1975). This calculation was based on data from the National Cancer Institute's Third National Cancer Survey (1969-1971), which expected for the total United States population an annual incidence of this tumour in the order of 0.014/100 000. This would have meant only about 0.03 cases per 20 000 polymerization workers within a 10-year period. Dose-response and attendant biotransformation data on experimental animals have since been used to elaborate several different models of extrapolation to man. These were calculated with reference to relative body surface areas, for estimating the risk of ASL in human populations exposed to VCM and for establishing guidelines to assist the research for 'realistic safe doses' that do not affect the average lifespan of a person exposed (Schneiderman et al. 1975; Gehring et al. 1979, 1978; Woods 1979). Gehring et al. (1979) consider a probit percent model to be a reliable tool for risk prediction, which works without the assumption of a threshold. They predicted a cancer risk of 1.5 cases of ASL in 100 000 000 workers on exposure to the current National Standard in the United States of 1 ppm VCM 8 h/day, 5 days/week, for a 35-year working life, an incidence which does not significantly deviate from the spontaneous incidence rate. A linear model modified by adjustments for differences in the rate of inhalation, distribution, metabolism, cell proliferation and tumour latency times between rats and humans was described by Woods (1979). This model arrives at an incidence of 3.9 cases per 100 000 000 workers after a lifetime exposure to 1 ppm. Much controversy, however, about the validity of risk extrapolation from animal experiments to man and from high- to low-level exposure and the problem of threshold doses has been voiced (Maugh 1978; Hooper et al. 1979; Schneiderman 1979; Weigert 1979; Reitz et al. 1979).

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Results of a recent survey by *Brady et al.* (1977) indicated that for New York State (excluding New York City), a highly industrialized area, the annual incidence rate of ASL during the 6-year period from 1970 through 1975 was 0.25 per million residents. This considerably exceeded the national average rate of 0.14 per million per year in the United States. In a concomitant case-control study, 26 patients with histologically confirmed ASL were found in the study area from 1955 to 1975, and 7 of these had had documented long-term exposure to either As, TiO_2 or VCM. Five (all female) of the remaining 19 patients lived at a distance of 500—500 feet from VC fabrication or polymerization facilities for long periods. No pertinent exposure or residential history was obtained from the other 14 patients. Discharge of unreacted monomer into the environment as result of losses in the PVC production process was estimated to have exceeded 200 million pounds annually, most of which escaped into the atmosphere with lesser amounts dissolved in water effluent (*Schweitzer* 1975). Concerning the order of magnitude of ambient exposure beyond the work place, i.e. outside the industrial setting, an average annual exposure concentration of 17 ppb was estimated for the 4.6 million persons throughout the United States who resided within a 5-mile radius of vinyl chloride emission sources (*Kutzmack and McGaughy* 1975). If the risk assessment model elaborated by *Woods* (1979) is applied to this population of 4.6 million people, the estimated incidence of angiosarcoma per year would not be above expected background levels.

4.3.7 Mortality and Cancer Morbidity Studies

For a tumour disease as rare as angiosarcoma of the liver even quite small increases in hazard over background levels should be detectable (*Doll* 1975). The situation with the common types of cancer is far more difficult. Since 1974 a number of mortality studies of VCM-exposed populations have suggested that in humans long-term exposure to VCM may also be associated with cancer of sites other than the liver, notably the lungs, and the lymphatic and central nervous system (*Monson et al.* 1974; *Ott et al.* 1975; *Tabershaw and Gaffey* 1974; *Nicholson et al.* 1975; *Wagoner et al.* 1976; *Warweiler et al.* 1976; *Nicholson* 1977; *Buffler et al.* 1979). Epidemiological studies of British workers failed to confirm this suggestion (*Duck et al.* 1975; *Duck and Carter* 1976; *Fox and Collier* 1976, 1977), as did a prospective study of a VCM/PVC-exposed cohort of 1618 employees of a West German chemical plant (*Frentzel-Beyme et al.* 1978). Criticism of design and interpretation of some of the studies has been voiced (*Falk et al.* 1974b; *Purchase and Williamson* 1974; *Rieger* 1977; *Daklenup* 1975; *Berry and Rossiter* 1976). A follow-up of all VCM-exposed persons (750 traced) ever employed at the one Swedish factory, which started operation in 1945, for mortality and cancer morbidity patterns revealed a fourfold excess of pancreas/liver tumours but no deviation in the number of brain tumours from the expected level (*Björn et al.* 1976).

In addition to the three extensive mortality studies of *Tabershaw and Gaffey* (1974), *Warweiler et al.* (1976), and *Fox and Collier* (1977), a fourth comprehensive epidemiological study (*Reinl and Weber* 1976) was completed in 1977 by *Reinl et al.* (1978), which included three study populations from 11 VCM- and PVC-producing factories in the Federal Republic of Germany, covering the period from before 1959

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through 1974: (a) 7021 workers engaged in the production of VCM and PVC; (b) 4910 chemical workers from the same plants not exposed to VCM; and (c) 4007 workers engaged in PVC manufacture. Not included were non-German workers of Mediterranean origin. This German study permits comparison not only with the mortality ratio of the total male population but also with a comparable occupational group exposed to VCM. With regard to the 'healthy worker effect' (McMichael et al. 1975), overall mortality was elevated for the VCM-exposed population (group a), but not for the other chemical workers (group b). Apart from the markedly elevated standardized mortality ratio (SMR) for malignant liver tumours (1.523), which proved to have been closely related to the duration of exposure, a significantly elevated SMR was found for tumours of the lymphatic and haematopoietic system (2.14). The group of chemical workers not exposed to VCM (b) also showed a significant elevation of the

bone lesions presented with mild to marked thrombocytopenia ($30-119 \times 10^9$ /litre). Bone marrow aspirates in 6 patients permitted exclusion of disturbed platelet formation or osteomyelofibrosis/sclerosis, but in 12 of them splenomegaly was found. Except for slight reticulocytosis in 8 and leucopenia in 5 of the workers, other haematological tests were negative. The reduction of the number of leucocytes and platelets as well as reticulocytosis appeared to be attributable to splenomegaly, but further studies on the nature of thrombocytopenia were thought necessary, and it was suggested by the authors that a decrease in the number of platelets might serve as an early and easily detectable symptom. The high prevalence of thrombocytopenia (as determined by phase-contrast microscopy) found later on detailed analysis of platelet function and other parameters of blood coagulation in the total cohort of PVC production (and also fabrication) workers from this plant strengthened this suggestion (Bachner et al. 1974a, b, 1975a, b, 1976; Sehart-Bachner and Etzel 1977). Wegman (1975) also commented upon abnormal platelet counts in 13 of 37 PVC fabricating workers who had only handled PVC powder which, however, might have contained substantial amounts of residual monomer. In contrast, Lillis et al. (1975) detected thrombocytopenia in only 1 of 354 polymerization workers, but an electronic cell counter was used for platelet counts (personal communication).

According to Sehart-Bachner and Etzel (1977), the mean platelet count in a cohort of 132 PVC polymerization (and processing) workers was significantly lower than that in a nonexposed control group of 150 healthy men. As could be expected, Bachner et al. (1975b) also demonstrated a positive correlation between the degree of thrombocytopenia and the prevalence of an enlargement of the spleen (palpable splenomegaly or spleen size determined by selective scintigraphy with ^{199}Hg -bromo-mercury-hydroxypropane-labelled red cells) in 70 PVC polymerization workers (see Table 19). It ap-

Table 19. Prevalence of enlargement of the spleen^a among 70 PVC-polymerization workers in relation to increasing degrees of thrombocytopenia (Bachner et al. 1975a)

Group	No. of workers examined	Platelets ($\times 10^9$ /litre)		Enlargement of the spleen
		Range	Mean	
A	14	> 130	168	3 (21%)
B	24	100-130	117	11 (46%)
C	25	70-99	87	19 (76%)
D	7	< 70	44	6 (86%)

^a As determined by palpation or by selective spleen scintigraphy.

pears, however, that the development of thrombocytopenia is not dependent on the presence of splenomegaly since we observed mild thrombocytopenia ($100-120 \times 10^9$ /litre) in a small number of workers in whom spleen size was definitely within normal limits on selective spleen scintigraphy (Milzflächenindex $< 4.5 \times 10^{-3}$ according to Fischer and Wolf 1963).

Thrombocytopenia was accompanied by abnormalities in platelet function tests. There was an increase in the number of large ($> 10 \mu\text{m}$) 'juvenile' platelets (increased

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