Acro-osteolysis Occurring in Men Engaged in the Polymerization of Vinyl Chloride

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[WITH SPECIAL PLATE BETWEEN PAGES 708 AND 709]

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The polymerization of vinyl chloride has been undertaken in this and other countries for over 20 years without apparent harm to the workers, apart from some accidental exposure to the vapour of vinyl chloride, the anaesthetic effects of which have been well known for years. The process consists, briefly, in submitting a mixture of liquid vinyl chloride and water in the presence of a catalyst to the effects of heat in large pressure vessels known as autoclaves. This produces polyvinyl chloride in slurry or latex form which is discharged from the vessel and conveyed elsewhere to be dried into a powder. When the autoclave is emptied at this final stage a deposit of white polymer is found on its inner wall. Air is then blown through the open vessel for at least a quarter of an hour, after which an atmosphere test for vinyl chloride is done inside it. If the autoclave is found to be clear of vinyl chloride vapour the cleaner enters it to scrape the wall with a small hand pallet.

An unusual condition affecting two men employed as autoclave cleaners in this process was first reported by Cordier *et al.* (1966). After doing this work for several months they developed symptoms resembling those of Raynaud's phenomenon and later a skin eruption of the hands, and in one case of the forearms, together with general asthenia and drowsiness. The most striking sign, however, was the radiological evidence of lysis of some terminal phalanges of the hands, and in one case of the feet. Most of these abnormalities disappeared and the bones showed signs of healing a year or two after the men had stopped work.

In view of that article, the hands of 588 men engaged in the manufacture of polyvinyl chloride were radiographed

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April 1966, 150 of them were autoclave cleaners Two cases with *x*-ray changes in the fingers similar to those described by Cordier *et al* (1966) were found.

Case 1

A 44-year-old man who had worked on the autoclave section of the plant since 1950 had an interesting history in that he was diagnosed as a case of scleroderma by a consultant physician and dermatologist in 1957 The diagnosis was made on clinical grounds because of Raynaud's phenomenon, accompanied by puffiness of the face and thickening of the skin of the hands, fingers, and left forearm. The symptoms cannot have been very troublesome, because he had made no complaint, and the condition was noticed by his doctor only when he went to collect a prescription for his wife

On being questioned about his condition during the present investigation he still made no complaints, and it was only with reticence that he admitted that his hands often felt unduly cold

Examination revealed no evidence of the skin condition that had existed in 1957, and the only abnormalities were (*a*) pseudo-clubbing of all the fingers of both hands, this is not true clubbing, since the angle between the base of the nail and the adjacent skin was not obliterated, and (*b*) the liver was palpable on inspiration

Radiological Reports—"*Hands*: Periarticular erosions are present in the proximal interphalangeal joints The proximal interphalangeal joint of the left little finger is disorganized There are erosions of the terminal phalanges of index and middle fingers of both hands (Special Plate, Fig 1) *Feet* The fifth proximal phalanges of both feet show erosions on both their distal ends The fifth proximal interphalangeal joint is disorganized on the left (Special Plate, Fig 2) *Pelvis* There is a widening of the joint space of the sacroiliac joint with cystic marginal sclerosis *Chest* Normal *Skull* Normal *Cervical spine* Normal *Teeth* Normal *E C G* Normal"

Laboratory tests were carried out, and the only abnormality found was a persistently raised serum bilirubin

Case 2

A 30-year-old man who had been an autoclave cleaner since 1960, having been self-employed as a window-cleaner before that date, recalled no previous serious illness, but had consulted his doctor in 1964 because of shortening of his finger-nails, which he thought to be due to biting them and "lack of calcium"

In April 1966 he had no symptoms, but radiologically he showed evidence of acro-osteolysis Pseudoclubbing of the fingers was found to be present (Fig 1) Raised nodules in the skin, described as "xanthomatous-like" patches, were noted round his wrists

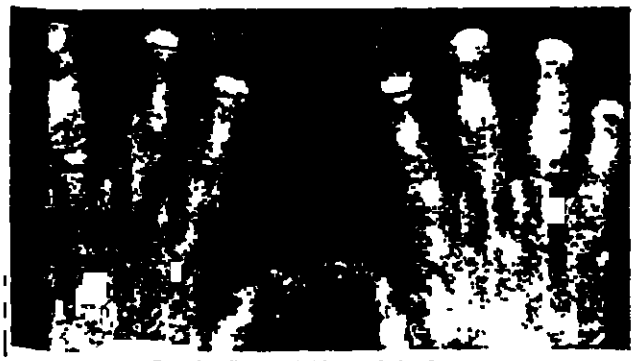

FIG 1—Pseudoclubbing of the fingers.

Radiological Reports—"*Hands*: Osteolysis is present in the shafts of all the terminal phalanges of the fingers and thumb, with the exception of the left ring finger" (Special Plate, Fig 3) (Incidentally it is of interest to note that in most of the *x*-ray films of these cases seen by us here and in America the ring finger is unaffected.) "*Sacrum* Widening of the joint spaces of the sacro-iliac joint with cystic marginal sclerosis (Special Plate, Fig 5) *Chest* Normal"

The most notable feature was the comparative absence of abnormal findings, apart from those shown on the *x*-ray films Laboratory tests showed nothing abnormal

In July, however, he came to see one of us (W G F A) complaining of fairly persistent pain and frequent attacks of coldness in the fingers, accompanied by pallor On examination at this time there was some tenderness of the finger-tips, more skin nodules were seen to be developing on the dorsum of his fingers, and some thickening and coarsening of the skin of the face was noted

In the course of the next week or two the pains in the fingers and metacarpophalangeal joints increased, and Raynaud's phenomenon was troublesome even in warm weather He was therefore admitted to hospital in August for further investigation

The same tests as on the previous occasion were repeated, and once again the results were within normal limits, except in the case of the serum proteins In this test the serum $\alpha 2$-globulin was 1 mg/100 ml (normal 0·4–0·8 mg) Hyland screening tests for rheumatoid arthritis and lupus erythematosus were normal Serum transaminase was within normal limits The E S R had fallen to 4 mm in one hour (Westergren) Blood pressure was 140/80

Skin biopsy was performed on one of the nodules on the wrist, the histological report being as follows "The full thickness of the dermis is incorporated in an interlacing acellular collagenous nodule, oedematous and partly hyalinized, enclosing normal sweat glands and covered by normal epidermis (Fig II) The oedematous interstices contain a fine granular and filamentous material, metachromatic with toluidine blue, and staining faintly with alcian blue and periodic-acid Schiff, probably breaking up elastic (Fig III) Two small dermal arteries are extremely thick-walled as a result of marked medial hypertrophy and intimal fibrous

FIG II—Case 2. General appearance of thickened dermal collagen—also showing lymphocytic cuffing of small dermal blood vessel. (H and E ×55)

FIG III—Case 2 High-power view of fragmented elastic in upper dermis (Verhoeff ×270)

thickening (Fig. IV). The appearances are similar to those described by Cordier *et al.* (1966)."

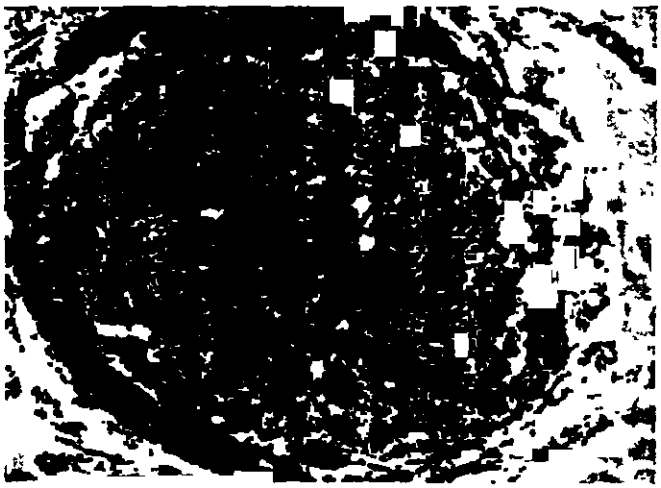

FIG IV.—Case 2. High-power view of artery situated deeply within the zone of thickened dermal collagen. (H. and E. ×180)

For a few months after his discharge from hospital he improved, and by the end of 1966 the Raynaud's phenomenon was less marked and the skin nodules were disappearing. About this time, however, he began to develop pain in the left knee and toes. *X*-ray examination of the left knee showed a cortical erosion on the posterior surface of the patella (Special Plate, Fig. 4). By June 1967 he felt reasonably well, though he still complained of pain in the left knee and stiffness of the hands, particularly at the metacarpophalangeal joints. The skin of the hands and face was practically normal.

Comment

No treatment was required in Case 1, and the treatment in Case 2 was directed towards relieving the symptoms, since no specific remedy is known for the condition.

Both men were removed from the job of autoclave cleaning as soon as the diagnosis was made, but it is not yet certain how this measure will affect the course of the illness. It would appear that Case 1 went through the acute stage while still doing his normal job, and the condition has become quiescent in spite of this.

Two more possible cases were found in our most recent survey. One of these is a 30-year-old autoclave cleaner who has had Raynaud's phenomenon for three years, but in whom no bony changes have been found. The other man is an ex-autoclave-cleaner in whom a suspicious appearance has been noted radiologically in the right thumb, which had, however, been recently subjected to injury.

Discussion

In view of the similarity of the findings in these men to the cases described in the paper of Cordier *et al.* (1966), it was thought that this condition was almost certainly linked with the men's occupation. Inquiries subsequently made in America and Europe revealed that similar cases had occurred there. In all cases the features appearing most consistently were Raynaud's phenomenon accompanied by osteolysis of the terminal phalanges of the fingers, occurring mainly in autoclave cleaners and not in those engaged in handling the finished product.

Many raw materials may be used in small quantities in manufacturing the polymer, but the only substance common to all cases is probably vinyl chloride. Though every autoclave is washed with water and has air blown through it at the end of each reaction, small quantities of vinyl chloride may remain and escape when the vessel lid is opened. It is also possible that very small pockets of gas may be trapped beneath the polymer adhering to the inner wall, and these can be liberated during the subsequent cleaning process. Vinyl chloride, however, has been manufactured and handled in this country for over 20 years without apparent harm apart from accidental exposure to its well-known anaesthetic action.

A point of general interest is the possible relationship of this condition to the collagen diseases. One patient (Case 1) had, in fact, been diagnosed as a case of scleroderma on clinical grounds 10 years previously. The histologist remarked on the superficial similarity of the biopsy taken in Case 2 to scleroderma, but a number of pathologists consider the appearance of the section to be unique. Cordier *et al.* (1966) mention an unusual skin condition seen in their cases. Suciu *et al.* (1963), in a paper describing conditions produced by vinyl chloride, referred to a skin lesion resembling scleroderma, but acro-osteolysis was not mentioned.

Finally, at a clinicopathological conference at the Royal Postgraduate Medical School (*B.M.J.*, 1966) it was stated that bony changes were commonly found in the terminal phalanges in scleroderma. It should be made quite clear, however, that the many radiologists who have looked at the films of our cases stated that they had not previously seen this particular lesion.

It would appear from our own and other cases that this condition is probably a self-limiting disease, which in spite of bone destruction leaves the patient with little disability. In *x*-ray films taken a year after the original diagnosis no further bony changes were noted in Case 1. In Case 2, however, there was evidence of partial ossification of the osteolytic bands in the terminal phalanges of both hands.

It is our intention to continue annual radiological examination of the hands of all men engaged on this work. Mechanical methods of cleaning new autoclaves have been introduced, and it is hoped in due course to extend this method to older vessels and thus eliminate the human factor.

Summary

Two cases of acro-osteolysis occurring in men engaged in the polymerization of vinyl chloride are described. The bones affected were the terminal phalanges of the fingers and the sacroiliac joints, but in one case the patella and in the other the phalanges of the feet were involved. The condition was accompanied by Raynaud's phenomenon and skin lesions.

It would seem that this condition is probably a self-limiting disease.

We acknowledge with gratitude the help given throughout this investigation by Dr Thelwall Jones and other members of the medical staff of the David Lewis Northern Hospital, Liverpool, and by Dr K. A. Rowley and his colleagues at Blackpool Victoria Hospital.

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[Acro-osteolysis (acro-osteopathia ulcero-mutilans) in a worker exposed to vapours of synthetics (author's transl)].

[Article in German]

Kind R, Hornstein OP.

The neuro-cutaneo-osseous syndrome of "sporadic" acrosteolysis (of Bureau-Barriere), localized to the ends of the feet, has occasionally been seen in workers engaged in the polymerization of vinyl chloride, A case of the disease is described in a 42-year-old worker exposed to different vapours during the manufacture of plastic products, but he had never worked with vinyl chloride Outstanding signs were dysproteinaemia, moderate thrombocytopenia, while symptoms of Raynaud's disease as well as scleroderma-like changes in hands and feet (typical of vinyl chloride disease) were absent The onset of the osteolytic and ulcerative process corresponded to prolonged exposure to cold on the job It is, therefore, assumed that there was concealed chronic intoxication with synthetic vapours which, in connection with cold exposure and other individual factors, may have aided in the manifestation of the disease It is possible that under certain conditions synthetics other than vinyl chloride may contribute to the occurrence of sporadic cases of acro-osteolysis

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VINYL CHLORIDE AND POLYVINYL CHLORIDE

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Polyvinyl chloride (PVC) is one of the most widely used plastic materials, second in production only to polyethylene. The physical properties of PVC can be readily modified through the addition of plasticizers and other additives, leading to diverse applications in construction, tubing, coatings, and packaging. The PVC industry has maintained a position of prominence and steady growth for over 50 years—an impressive feat considering that in the mid-1970s the industry was the center of a major occupational health crisis. Today, nearly 25 years after the recognition of the unusual occurrence of hepatic angiosarcoma in three workers at a Louisville PVC production plant, vinyl chloride health research continues to provide insights into the causes and mechanisms of occupational cancer.

Industrial processes and exposures have changed dramatically in this industry. After originating during the 1940s in the United States and Europe, PVC production expanded to other parts of the world. Exposures have varied based on production methods, product composition, emission control, and governmental regulations. Like the plastics industry in general, the PVC industry is divided into segments, each characterized by relatively distinct exposures to hazards. Appreciation of these distinctions, along with the changes in industrial processes and controls over time, is critical to the assessment of the health risks for current and past industry workers.

THE POLYVINYL CHLORIDE PRODUCTION PROCESS

PVC is produced through the polymerization of vinyl chloride monomer (VCM).[4,62,63,91]

VCM production results in limited exposures because the toxicity and volatility of the compounds involved generally has required the use of enclosed systems PVC resin production is the industry segment with the highest potential exposures, particularly in the early years when polymerization reactions were incomplete and left significant amounts of monomer unreacted Manual cleaning of reactor vessels was also a characteristic of this segment of the industry PVC compounding involves the addition of plasticizers and other additives to the polymerized resin to alter its physical properties. Finally, PVC fabrication involves the production of finished goods through molding and extrusion.

While each of these segments is a distinct business, companies often have performed multiple activities at the same plant site. Monomer and resin operations typically were combined, particularly in the early years of the industry, resulting in a direct flow of monomer to the resin operation. Resin producers also may perform compounding, adding certain components to the PVC prior to shipping to fabricators. Finally, fabricators may perform their own compounding operations to produce materials with the unique properties necessary for their finished products.

Vinyl Chloride Monomer Production

Vinyl chloride is a colorless gas with a faintly sweet odor and low acute toxicity (Table 1). It was first synthesized in 1835 through the reaction of acetylene and hydrogen chloride.[63] This process, involving the use of a mercury catalyst, was the primary method of production when vinyl chloride manufacturing for industrial purposes began in the 1930s in Germany and the U.S. Production in Japan started in 1946. Since 1960, the primary methods of production have been either direct or oxychlorination of ethylene In these processes, ethylene dichloride is formed followed by cracking to produce vinyl chloride and hydrogen chloride. The finished product is transported as a liquid in pressurized tank cars.

By 1976 there were 14 VCM production facilities in the U.S. with an annual production of over 3 billion Kilograms (kg).[63,91] At the same time, production in Western Europe and Japan was 3.9 and 1.3 billion kg, respectively. Vinyl chloride

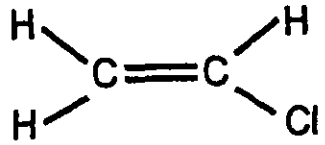

TABLE 1. Characteristics of Vinyl Chloride Monomer

CAS Number	75-01-4
Synonyms	Chloroethylene, chloroethene, ethylene monochloride
Description	Colorless gas with sweet, mild odor
Odor threshold	Approx. 3000 ppm
Molecular weight	62.50
Boiling point	-13 9° C (7° F)
Specific gravity	2.15
Vapor pressure (20° C)	2530 mm
Explosive limits	4–20% by volume
Conversion	1 ppm equals 2 6 mg/m^3

CAS = Chemical abstract service, ppm = parts per million

currently is used almost exclusively in the production of PVC resins. Prior to 1974, VCM saw limited use as a anesthetic, refrigerant, aerosol propellant, and intermediate in sulfonamide production.[24 63 98]

Exposure control in vinyl chloride monomer plants always has been critical Chlorine and hydrochloric acid are potent respiratory irritants requiring strict material containment procedures. Ethylene dichloride is also highly toxic. The finished product is highly flammable and is transferred directly from storage vessels to pressurized railcars Thus, the toxicity of intermediates, volatility of the product, and bulk handling and transfer methods all served to limit worker exposure in monomer production. In addition to low levels of exposure to fugitive emissions, VCM production workers may be exposed to low concentrations of VCM when connecting and disconnecting hoses, obtaining samples, or conducting quality control analyses. While exposures are better controlled in this segment of the industry today, exposures likely were quite limited historically, as well.

Polyvinyl Chloride Resin Production

Commercial synthesis of PVC resins began in 1933. Production was accelerated in the U.S., Japan, and Germany during World War II.[91] The primary method of production is **suspension polymerization.** Production occurs in large, stainless steel reactor vessels (termed "polys"). Using a batch process, vinyl chloride is mixed with water, a suspending agent (polyvinyl alcohol or cellulosics), and a surfactant. With addition of a catalyst (usually organic peroxide) and heat, an additional polymerization reaction is initiated, after which the reaction becomes exothermic. Through cooling and agitation, PVC particles of varying sizes are suspended in the colloid as the reaction proceeds. After the reaction is completed, the unreacted VCM is removed and recovered. The PVC slurry is centrifuged, dried, and screened, forming a powdered resin. This material may be bagged and shipped or further processed.

Emulsion polymerization is similar; however, an additional emulsifying agent in which the polymer is soluble is used, resulting in a smaller particle size. Dispersion resins formed in this manner may have particle sizes ranging from 0.1 to 1 micron. Two additional methods include **bulk polymerization** (which does not use other liquids) and **solution polymerization** (using an organic solvent).

By the mid-1970s there were 38 PVC production facilities in the U.S. operated by 21 companies.[63] Annual U.S. capacity was approximately 2 billion kg in 1976, accounting for one-third of the world production. Western Europe production in 1976 was approximately 3.7 billion kg, with another 1 billion kg produced in Japan.[91] There was substantial growth in production between 1950 and 1970, averaging over 10% per year. After slowing in the 1970s and early 1980s, annual production worldwide has continued to increase by 5–6% per year (Fig. 1).

Historically, PVC production operations have resulted in the highest levels of worker exposure. In the 1940s and 1950s, VCM was considered to be relatively nontoxic.[25 62 100] The inherent challenges of handling large volumes of a volatile gas in large-scale production were evidenced in the early years by plant explosions caused by spontaneous combustion of VCM (when concentrations exceeded 20,000–40,000 parts per million [ppm]).

VCM's volatility, high odor threshold, and minimal irritant effects all likely contributed to high levels of exposure. Sources of emissions included leakage during transport or storage, charging of reactor vessels, and sampling. In addition, the polymerized PVC absorbed VCM, and the reaction slowed considerably when the conversion approached 95%. Thus, the PVC resin contained significant amounts of

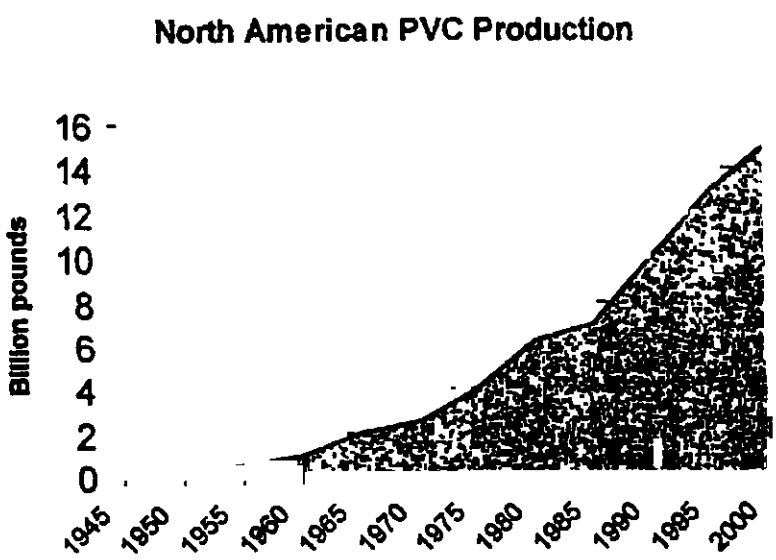

FIGURE 1. North American polyvinyl chloride production, 1940–1998.

residual VCM. The trapped VCM was released primarily during the drying process, with lower amounts emitted during compounding and processing.

One problem in the early years of PVC production was the accumulation of residual material on the inside of large reactor vessels (autoclaves or "polys"). Operators or helpers would enter these reactors to manually clean them. If the reactor had not been properly exhausted, anesthetic levels of VCM could be present, causing inebriation or unconsciousness. Pockets of VCM gas also were encountered during the manual scraping of resins from reactor walls.[24] Peak exposures during reactor cleaning may have routinely exceeded several thousand ppm.[4,62,95] In addition, reactor cleaners may have been exposed to residual catalysts, solvents, or comonomers (e.g., vinylidiene chloride, vinyl acetate).[19] Today, exposures during reactor cleaning have been eliminated by exhaust venting with VCM recapture, air testing prior to vessel entry, and the use of respiratory protection.

Estimates of historical exposures suggest that VCM concentrations in PVC production operations may have ranged from 500 to over 1000 ppm prior to 1960.[4,19,62,63,95,120] Peak exposures may have been much higher. In 1961 the American Conference of Governmental Industrial Hygienists (ACGIH) recommended a threshold limit value of 500 ppm based primarily on prevention of neurologic and anesthetic effects. Levels continued to drop to 100–300 ppm by the early 1970s. In 1974, after the recognition of an association between exposure and hepatic angiosarcoma, the Occupational Safety and Health Administration (OSHA) set the permissible exposure limit for vinyl chloride at 1 ppm as a time-weighted average. Similar standards limiting both short-term and peak exposures to VCM were adopted in the mid-1970s around the world. Modern production processes maintain strict exposure control, often using continuous monitoring systems.

Polyvinyl Chloride Compounding and Fabrication

PVC resin may be shipped as pellets, powders, or liquid latex. All PVC undergoes some form of compounding to modify its properties prior to being formed into a final product. Rigid PVC is comprised of 85–90% resin, while flexible PVC contains 40–60% resin. The compounding of the resin consists of the addition of plasticizers,

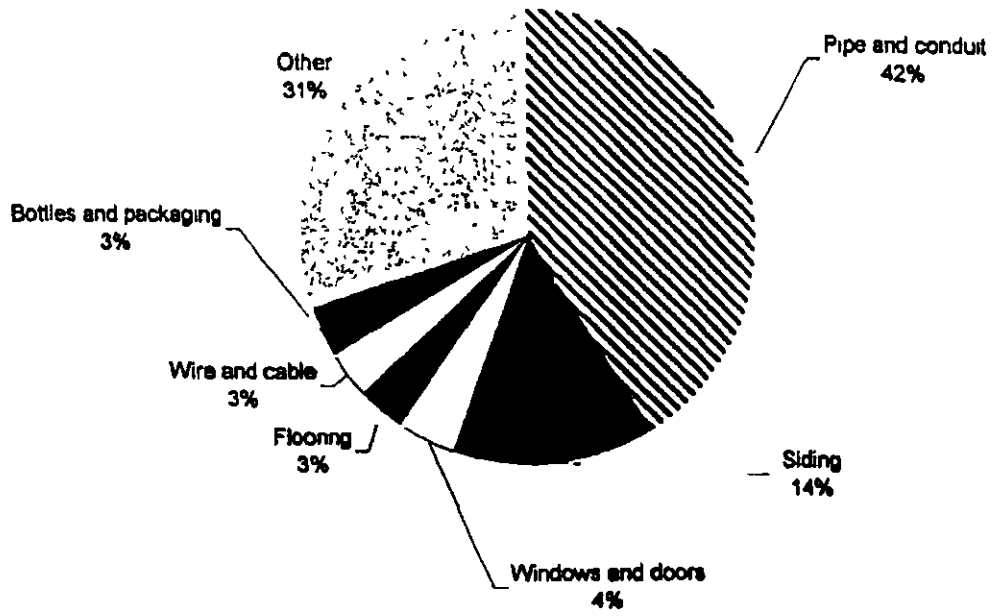

FIGURE 2. End uses of polyvinyl chloride resin.

impact modifiers, stabilizers, fillers, colorants, flame retardants, and biocides. Compounding may be performed by the resin manufacturer, the fabrication plant, or by specialty compounding companies.

The compounding process consists of reheating and melting the resin, then adding additional materials during mixing. The compounded PVC resin may be sent directly to the molding process or be cooled and reformed into a secondary resin for later processing. The majority of PVC is processed using **extrusion**, **calendering**, or **injection molding** (see Lewis' chapter "Health Issues in Plastics Production and Processing").

PVC is one of the most versatile plastic materials due to its blending capability with a wide range of additives (Fig. 2). The majority of PVC is used in construction primarily as pipe and conduit and as siding. These are formed by extrusion. Calendering and coating processes are used for flooring and textiles. Injection molding is used to produce bottles, containers, and fittings.

Worker exposure to VCM always has been limited in compounding and fabrication. A survey by the National Institute of Occupational Safety and Health (NIOSH) in 1975 reported levels of 0.85 ppm for calender personnel, 0.16 ppm for compounding, and 0.1 ppm for extrusion.[69] Other hazards of fabrication include potential exposure to asbestos, used as a filler in floor tiles and other materials in past years (generally pre-1970). Lead stabilizers also have been used in PVC production, although the elevated exposure levels of lead toxicity are rare in the industry. Molding processes involving the heating of plastic and occasional overheating of PVC materials may generate hydrochloric acid and other respiratory irritants. Apart from the chemical hazards of PVC fabrication, trimming of parts can result in both lacerations and upper extremity problems, particularly with rigid, durable formulations.

RECOGNITION OF INDUSTRY HAZARDS

Acro-osteolysis

The first reports of an unusual occupational condition affecting PVC production workers came out of France, England, Japan, and the U.S. in the early 1960s.[8,87,109,139,149]

This condition was characterized by pain and clubbing of the fingers and Raynaud's phenomenon Termed acro-osteolysis, it was observed exclusively in workers who entered reactors for cleaning and used hand scrapers. Diagnostic criteria varied in clinical case reports, but generally was based on a combination of symptoms of pain or numbness of the fingers and x-ray evidence of erosion of the distal tufts of the phalanges. The condition was self-limited and usually resolved after removal from work. Clinical evaluation of the majority of these individuals failed to reveal evidence of systemic poisoning or hepatotoxicity.[30,106,149] Alteration in manual cleaning methods eliminated the condition.[19,109]

While often listed as an effect of VCM exposure, acro-osteolysis is more appropriately ascribed to PVC production. Several aspects of this condition were unusual. While PVC production began in the early 1940s, acro-osteolysis was not seen until 20 years later. The cases occurred in persons working for as little as 1 month in reactor cleaning. While it is possible that the condition could have been missed in earlier years, a more likely explanation is that it was related to some combination of vinyl chloride and other exposures. PVC production methods varied, and many facilities produced copolymers of VCM with vinyl acetate, vinylidiene chloride, and other materials.[19] The attack rate was low, reported at 10–15 cases per thousand workers.[29,109,149] In a survey of U.S. operations only 7 of 32 plants reported any cases (defined as Raynaud's phenomenon and x-ray findings).[29]

The ultimate cause and significance of acro-osteolysis likely will remain uncertain. There have been no new outbreaks reported since the early 1970s. Early reports of abnormalities in collagen metabolism and immune complex formation remain intriguing, but have not been further evaluated.[65,140] What is more notable is that the identification of a new occupational disease focused research on this industry, but failed to identify the ultimate risk: the development of a rare occupational cancer.

Hepatic Angiosarcoma

The recognition of the association between hepatic angiosarcoma and work in PVC production is one of the classic **sentinel health events** in occupational medicine history. Hepatic angiosarcoma is exceedingly rare, with an estimated annual incidence of approximately one case per 100 million population.[6,47,82] In 1971 a patient of Dr. John Creech, a Louisville surgeon, died of this condition. Creech, who also served as the facility physician at the B.F. Goodrich PVC production plant in Louisville, became aware of a second case in a plant worker in 1973. Knowing the rarity of the condition, Creech and Dr. Maurice Johnson (medical director for B.F. Goodrich) reviewed facility medical records and identified two other cases of hepatic angiosarcoma in plant workers. Noting that all four workers had been involved in PVC production for 14–27 years, the angiosarcoma cluster was reported in both medical literature and lay press.[11,22] This report was immediately followed by reports of additional cases around the world.[87]

Based on the angiosarcoma experience, OSHA implemented an emergency temporary standard, lowering occupational VCM exposure to 50 ppm. This standard was followed by a final rule in 1975, which established a permissible exposure limit of 1 ppm and a short-term exposure limit (15 minutes) of 5 ppm. The OSHA Vinyl Chloride Regulation (29 CFR 1910.1017) also required annual medical examinations and biochemical testing of liver function, with semiannual examinations for persons who had worked for over 10 years in the PVC industry (see Medical Surveillance, page 734).

TABLE 2. Distribution of Vinyl Chloride–Exposed Workers Who Developed Hepatic Angiosarcoma, by Year of Hire*

Year of Hire	No of VC-Exposed Workers With HA	% of VC-Exposed Workers	North America	Western Europe	Other
Prior to 1945	22	13%	15	7	0
1945–49	25	15%	16	9	0
1950–54	35	20%	9	21	5
1955–59	42	24%	10	29	3
1960–64	31	18%	5	26	0
1965–69	16	9%	1	13	2
1970 and later	1	1%	0	1	0
TOTALS	172	100%	56	106	9

* Cases reported through 1993
VC = vinyl chloride, HA = hepatic angiosarcoma

Shortly after the discovery of the association between VCM exposure and hepatic angiosarcoma, several case registries were established.[45,116] **The Worldwide Register of Cases of Angiosarcoma of the Liver** (ASL Register) established in Europe in 1975 is still maintained today by physicians affiliated with the Association of Plastic Manufacturers of Europe. By 1993, the ASL Register had recorded 173 cases from 14 countries.[32] The majority of the cases have come from North America and Western Europe.

The majority of persons who developed hepatic angiosarcoma were hired in the early years of the industry, with nearly half hired prior to 1955 (Table 2). The North American cases appear to have been hired earlier than those reported from Western Europe. As of 1993, there was only one case reported with a year of hire after 1970. This case is also unusual in that it represents the rare occurrence of angiosarcoma in a fabrication worker involved in bag extrusion, *not PVC production.*

To date there have been 21 cases of hepatic angiosarcoma in workers from the original Louisville plant (Fig 3), more than any other manufacturing facility. What is most striking is the continuing occurrence in the retiree population. Rather than indicating a risk to workers entering the industry in later years, however, the Louisville experience demonstrates that persons who entered the industry in the pre-1960 years remain at risk for the rest of their lives. While the latency period for patients diagnosed prior to 1975 is 12–28 years, those diagnosed subsequently have shown a latency of 27–47 years. This suggests that exposures in the early years of the industry resulted in some form of damage that is a permanent precursor to malignant degeneration.[18,46,68,129]

Another notable aspect of this disease is that the risk of developing hepatic angiosarcoma was not evenly distributed among PVC production operations.[32,41] Of the 33 VC/PVC plants that were in operation in the U.S. prior to 1965, only 14 (42%) have reported cases (Table 3). There appears to be a strong clustering of cases, with a few facilities accounting for the majority. In North America, four plants (including the original Louisville plant) account for over 80% of the reported cases. A similar, although less pronounced, clustering is seen in Europe. At present, the basis of this finding is unknown. It may be related to absolute VCM exposure levels, but it also could be due to combined exposures for cofactors. PVC production may have involved addition of various catalysts and modifiers. In addition, facilities may have produced PVC copolymers with vinylidiene chloride, vinyl acetate, or other materials.[19,36,63] One observation at Louisville was the possible association of

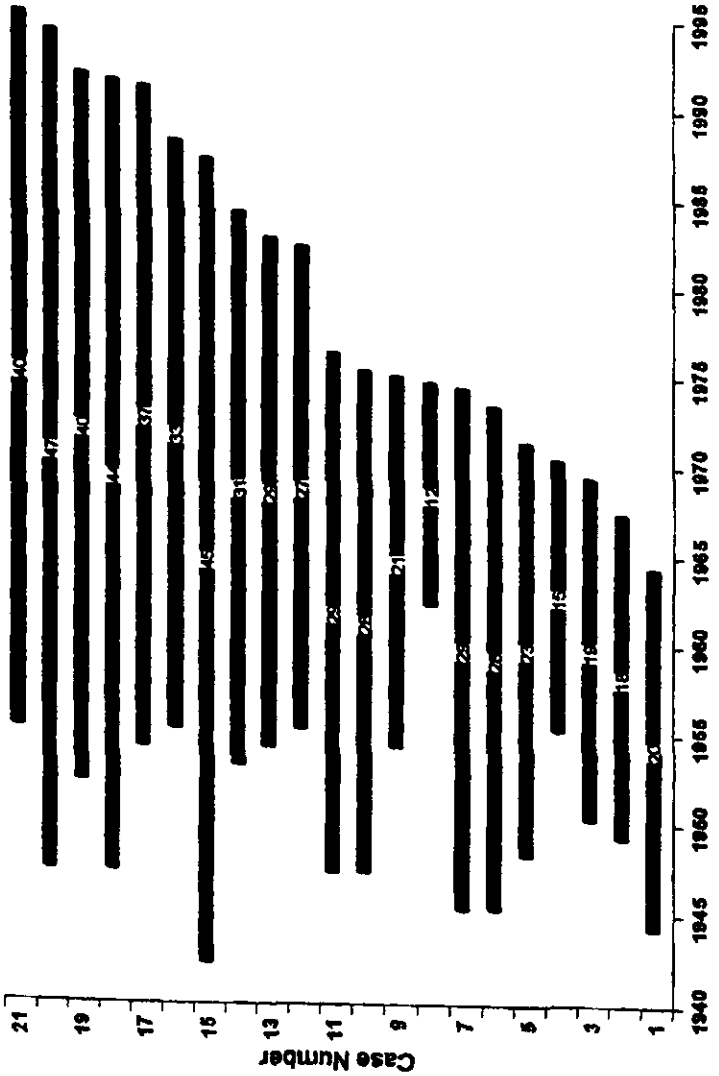

FIGURE 3. Years of hire and diagnosis, showing latency, for 21 cases of hepatic angiosarcoma from a single PVC production plant

TABLE 3. Clustering of Angiosarcoma Cases

	North America		Western Europe	
VC/PVC Plants Operating Pre-1970	48		44	
Plants Reporting Angiosarcoma Cases	14 (29%)		23 (52%)	
	No of Plants	*No of Cases*	*No of Plants*	*No. of Cases*
Plants Reporting > 10 Cases	3	40 (70%)	4	57 (54%)
Plants Reporting 3–10 Cases	1	6 (11%)	7	32 (30%)
Plants Reporting 1–2 Cases	10	11 (19%)	12	17 (16%)
Total Angiosarcoma Cases		57 (100%)		106 (100%)

angiosarcoma with diethyl maleate, a chemical that depletes hepatic glutathione.[18,56] The clustering phenomenon and risk based on year of hire both suggest that factors in addition to VCM exposure intensity may be important in the pathophysiology of this condition.

CLINICAL ASPECTS OF HEPATIC ANGIOSARCOMA

The clinical presentation of hepatic angiosarcoma has been variable and nonspecific.[9,27,36,44,59,73,75,84] Right upper quadrant pain is common, and cases may be diagnosed during a workup for gall bladder disease. Fatigue, nausea, and weight loss are reported frequently, as might be expected with a rapidly progressive hepatic malignancy. This disease should be suspected in persons who have worked in PVC production prior to 1970, particularly those who performed reactor cleaning. In addition to VCM exposure, other risk factors for the development of hepatic angiosarcoma include exposure to Thorotrast (thorium dioxide, a radiocontrast agent used in the 1930s and 1940s),[40,65] arsenic (both Fowler's solution and arsenical pesticides),[38] anabolic steroids,[39] and dioxin.[90]

Clinical signs include hepatosplenomegaly and right upper quadrant tenderness. Jaundice and ascites may be present in advanced cases. Laboratory evaluation usually reveals minimal elevations of GGPT, alkaline phosphatase, bilirubin, and transaminases in relation to the extent of disease.[21,36,59,60,73,87,126,127] Many of the initial cases diagnosed in the 1970s presented with more significant evidence of liver disease, including portal hypertension and esophageal varices.[10,84,87,105] These have been uncommon in the cases diagnosed in later years and may reflect differences in exposure intensity and underlying histopathology. More recently there have been reports of a marked increase in von Willebrand factor in persons with hepatic angiosarcoma, a significant observation based on the endothelial origin of the tumor.[48]

Filling defects may be evident on liver spleen scans and blood-filled cystic lesions on ultrasound or by arteriography.[130,145,147] CT scans and nuclear magnetic resonance imaging are useful in establishing a diagnosis.[45,73,146] Imaging studies should be pursued prior to needle biopsy due to the risk of hemorrhage with this multifocal lesion. Open biopsy often is necessary to establish the histologic diagnosis.

Hepatic angiosarcoma is a tumor arising in the endothelial cells of liver sinusoids.[35,46,53,84,103,104,128,134,144] The histologic diagnosis of hepatic angiosarcoma may be difficult. The tumor is usually multicentric at the time of presentation, with numerous areas of normal liver tissue replaced by hemorrhage and necrosis. There is envelopment of hepatic cords by neoplastic sinusoidal lining cells with irregular nuclei and elongated cytoplasm (Fig. 4). The sinusoidal spaces are dilated, and in early lesions

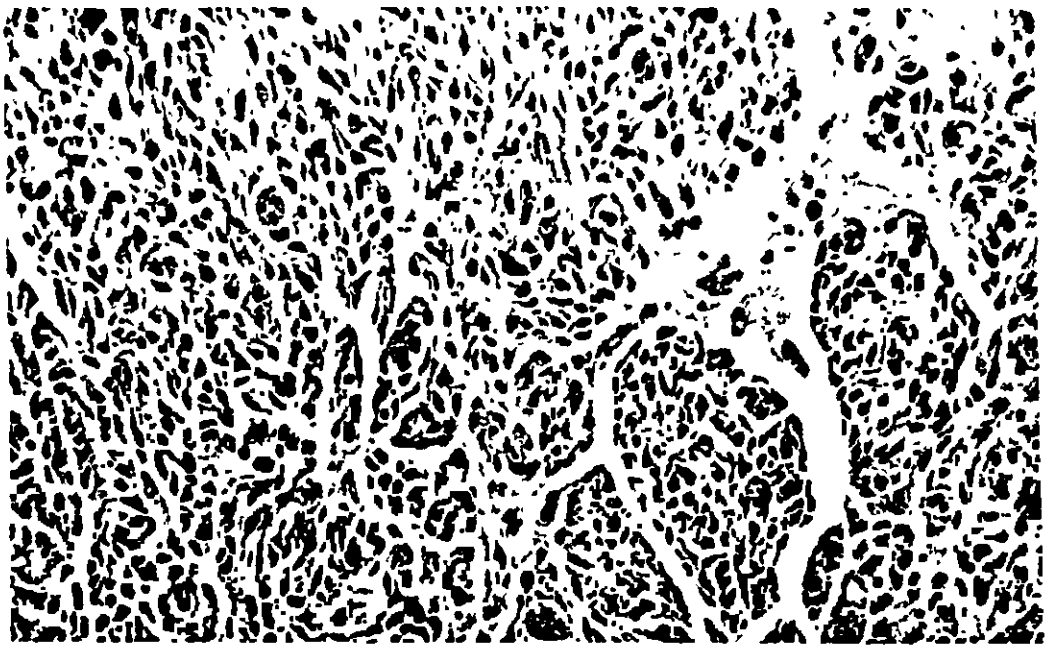

FIGURE 4. Hepatic angiosarcoma (courtesy of C. Tamburro, M.D.).

there is reactive fibrosis. Hepatocytes are initially spared, but later show reactive hypertrophy. Ultimately, large regions of the liver are replaced by cystic hemorrhagic spaces. The tumor cells stain positively for factor VIII–related antigen on immunofluorescence[103]—further support for the endothelial origin of the malignancy.[46]

The early cases also were characterized by subcapsular fibrosis, with rice-like lesions apparent on gross examination.[84,87,134] Microscopically, there was proliferation of atypical sinusoidal lining cells and periportal fibrosis (Fig. 5). These

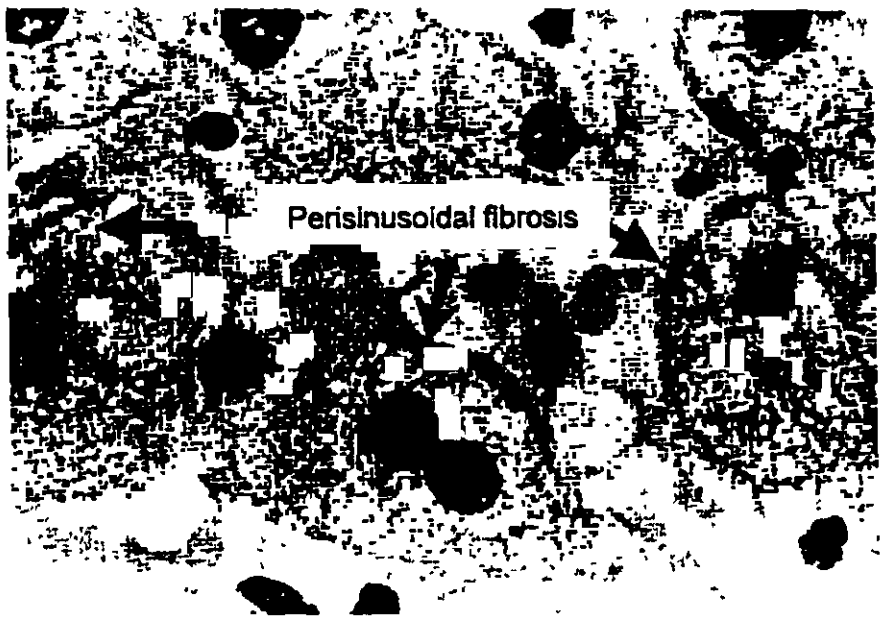

FIGURE 5. Perisinusoidal fibrosis in areas of liver not infiltrated by hepatic angiosarcoma (courtesy of C. Tamburro, M D.).

lesions also have been observed in persons without angiosarcoma.[128] Whether these represent precursor lesions or are a necessary factor in malignant degeneration is unknown

The localization of the liver injury to the sinusoidal region accounts for many of the clinical characteristics of this disease. The diffuse fibrosis involving the sinusoidal spaces causes liver enlargement, blockage of flow through the portal vein, and portal hypertension. Within the liver parenchyma, however, there is only limited damage to the hepatocytes. Thus, cases present primarily with gastrointestinal bleeding or liver and spleen enlargement, not signs of liver failure. The lack of direct involvement of the liver cells explains why routine liver enzyme testing has not been useful in detecting either fibrosis or angiosarcoma until the condition is far advanced. While the malignancy may metastasize, local spread, hemorrhage, and hepatic compromise are the primary causes of death.[73,84]

Prognosis has been poor. Most patients die less than a year after diagnosis, many within weeks to months of presentation. One patient from the Louisville plant was apparently cured after wedge resection. A second patient survived for 6 years after receiving several cycles of chemotherapy (doxorubicin and cyclophosphamide).[23] Recurrence after resection and liver transplantation also has been reported.[54] At present, resection of an early lesion confined to a single lobe of the liver appears to be the only treatment with a reasonable chance of extended survival or cure. Because of the rarity of the condition and sporadic nature of occurrence, clinical treatment protocols have not been adequately developed or studied.

MOLECULAR MECHANISMS OF CARCINOGENICITY

The basis for the development of hepatic angiosarcoma in PVC production workers is unclear. One possibility is that when VCM exposures are very high, metabolic pathways of detoxification in hepatocytes are overwhelmed, resulting in presentation of reactive metabolites to adjacent sinusoidal cells.[129] At lower levels of exposure, vinyl chloride is metabolized by alcohol dehydrogenase to monochloroacetic acid, which is then excreted in the urine.[129] At higher exposure levels, vinyl chloride is metabolized by the cytochrome P450 system to the electrophilic metabolites chloroethylene oxide (CEO) and chloroacetaldehyde (CAA).[125,129] These reactive compounds are detoxified through interaction with glutathione to form thiodoglycolic acid (Fig. 6). Impaired detoxification due to excessive exposure or depletion of glutathione results in the reactive metabolites covalently binding to macromolecules, including bases on nucleic acids. At the molecular level, a combination of high peak exposures or exposures to other substances (such as to vinyl acetate, vinylidiene chloride, or diethyl maleate) may explain the clustering phenomenon described previously.

Studies of workers with current and past exposure to vinyl chloride have identified increased rates of nonspecific genetic alterations, including chromosomal aberrations, micronuclei, and sister chromatid exchange frequencies.[50,51,55] The reactive vinyl chloride metabolites CEO and CAA have been shown to form DNA adducts in both animal studies and in vitro systems.[42,55,123] The etheno adducts are persistent and may result in point mutations in cellular oncogenenes and tumor suppressor genes. Workers with hepatic angiosarcoma have been shown to have A:T to T.A missense mutations of the p53 tumor suppressor gene that can be detected through measurement of antibodies in serum.[61,112,136] Exposed workers also have been shown to have point mutations of the c-Ki-*ras* oncogene, detected through measurement of an abnormal p21 protein.[13,28,49,83] This is caused by a GC:AT transition

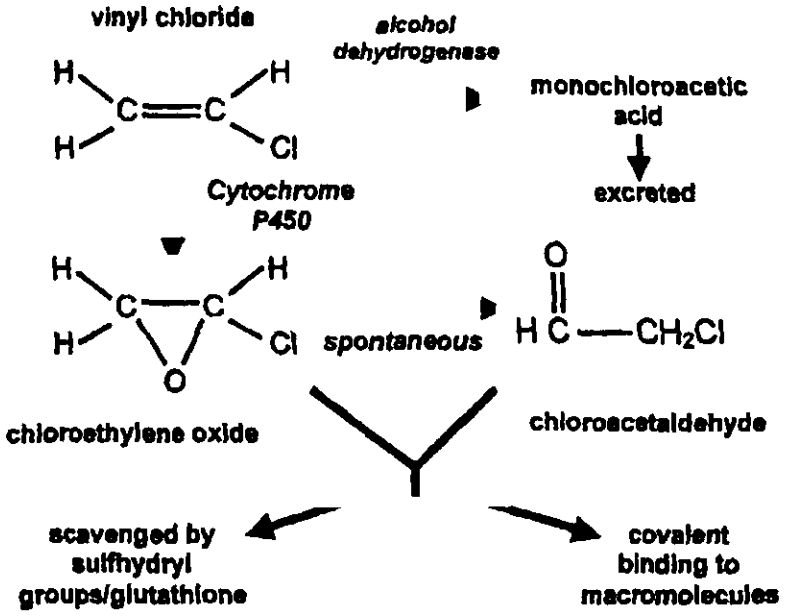

FIGURE 6. Metabolism of vinyl chloride.

in the second nucleotide of codon 13 (Fig. 7). While these findings hold promise in understanding the underlying cellular pathophysiology of this chemically-induced malignancy, it is still uncertain whether these are markers of exposure, susceptibility, or disease.

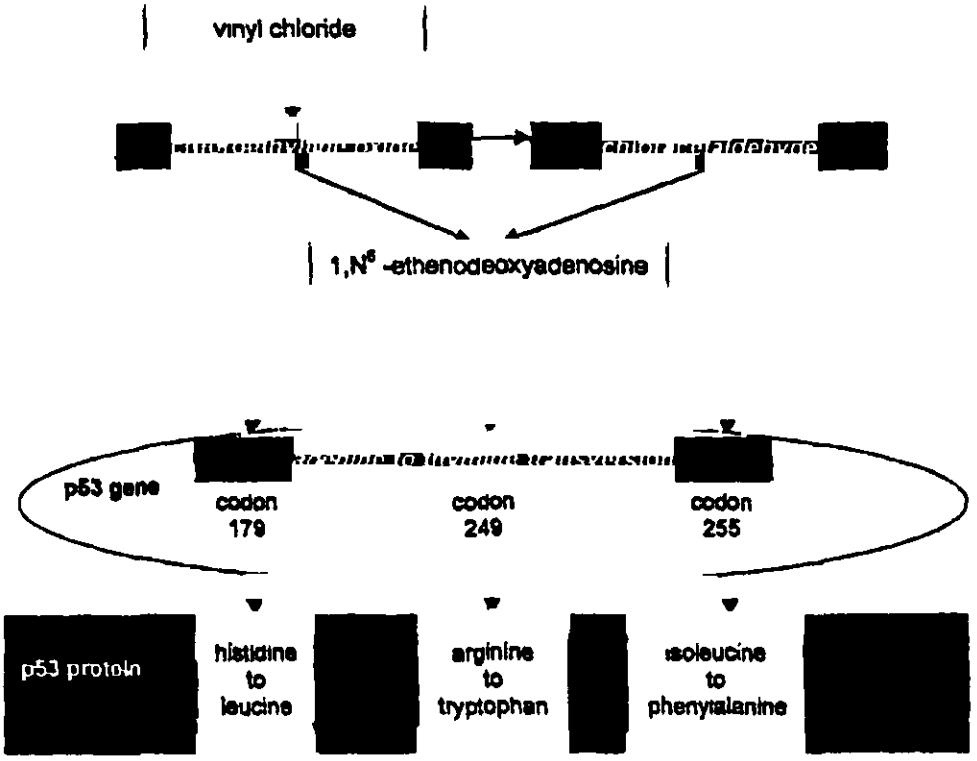

FIGURE 7. Proposed mechanism of vinyl chloride–induced p53 mutation resulting in abnormal p53 protein.

Respiratory Disease

Several investigations have suggested that exposure to PVC dust may cause a decrease in lung capacity, airway obstruction, and chest x-ray changes, and cross-shift drops in lung volumes.[34,74,78,81,92,94,115] PVC dust exposure may occur in drying, mixing, and bagging operations. Particle size varies depending on the polymerization method and form of the final product. Dispersion resin particles are very fine and fall into the respiratory (< 1 micron) range. Suspension polymerization produces resin particles that are slightly larger, but this process still may result in exposure to respirable dust. In addition to exposure to PVC, compounding operations can involve exposure to plasticizers and other additives. In pre-1975 production operations, workers also may have experienced relatively high levels of exposure to VCM. Finally, PVC operations may result in over-heating of the resin, releasing hydrochloric acid or other respiratory irritants.

Initial animal studies had considered PVC dust to be inert. Subsequent studies of relatively high exposure levels have demonstrated some evidence of a mild fibrotic process with granuloma formation.[1] There are several case reports describing evidence of pulmonary fibrosis in persons who have been exposed to PVC. Pneumoconiosis was described in a 53-year-old man with 23 years of exposure to PVC dust.[3] Biopsy revealed diffuse areas of fibrosis with small focal lesions. Lung function was only mildly reduced, and there was no evidence of impairment in gas-exchange.

Several epidemiologic studies have been conducted on workers exposed to PVC dust. The findings in the positive studies in many respects parallel the case report described above. When detected, chest x-ray evidence of pulmonary fibrosis has been subtle.[88,94,115] While the incidence is low, the abnormalities seem to occur in persons with longer exposure histories. Changes in lung function have been slight and generally not associated with respiratory impairment. Several cross-sectional studies have failed to find any evidence of respiratory disease in workers exposed to VCM or PVC dust.[17,52,96,97] Overall, the risk of respiratory disease in workers exposed to PVC dust appears to be low, particularly in current compounding operations. Interpretation of historical reports requires consideration of exposures to additives or thermal degradation products, in addition to PVC dust.

Other Health Effects Reported in PVC Production

There are several other historical reports of findings in PVC production workers. In 1949, a Russian study reported evidence of hepatitis, anemia, and gastritis in PVC compounders exposed to chlorinated naphthalenes used as plasticizers.[87] Since the chlorinated naphthalenes are potent hepatotoxins, the relationship of this early study to the general VCM/PVC experience is uncertain.

Several early reports from Germany and Eastern Europe described a condition termed "vinyl chloride disease."[120,137] This was characterized by hepatosplenomegaly, thrombocytopenia, musculoskeletal symptoms, and a variety of other findings. The exact cause of this syndrome is also uncertain. In some of these studies, exposure levels were such that narcosis from over-exposure to vinyl chloride was common. In addition, potential exposure to other materials, such as ethylene dichloride, vinylidiene chloride, and other chlorinated solvents, may have contributed to the findings.

Several anecdotal reports have associated vinyl chloride exposure with scleroderma and other connective tissue diseases.[99,119] Central and peripheral nervous system effects were reported in workers with high levels of exposure.[71,97,101]

Angiosarcomas of other tissues, including the finger and mandible, have been reported.[26,148] Vinyl chloride is an animal teratogen.[67] Early reports of possible birth defects in communities surrounding PVC plants were not substantiated in later studies.[107,137]

EXPERIMENTAL STUDIES

Animal studies conducted in the 1930s identified that exposures at 200,000–400,000 ppm were lethal.[100] Hyperemia of lungs, liver, and kidneys were seen on necropsy. Followup studies in 1961 on multiple species with exposures at 50–500 ppm daily for several months revealed only subtle findings of increased liver weight and granular degeneration.[76,89] Based on these studies, the recommended exposure level of 500 ppm for vinyl chloride was based primarily on prevention of central nervous system narcosis.[107]

Experiments on the toxicity of vinyl chloride were renewed in the late 1960s following the identification of acro-osteolysis in workers, an unusual degeneration of bones in the hands. In a 1971 study,[138] rats were exposed to 30,000 ppm for 4 hours per day for 12 months in an attempt to reproduce acro-osteolysis. In addition to demonstrating alterations in hepatocytes and centrilobular necrosis, tumors were identified in lung and bone tissue. Subsequent investigations have demonstrated dose-related excesses of hepatic angiosarcoma in rats at 30,000–50,000 ppm.[85,86] The experiments also showed an excess of zymbal gland tumors, along with excesses of neuroblastomas and nephroblastomas.

EPIDEMIOLOGIC INVESTIGATIONS OF THE POLYVINYL CHLORIDE INDUSTRY

Immediately after the recognition of the association between vinyl chloride exposure and hepatic angiosarcoma, several epidemiologic investigations were undertaken. A large cohort of over 10,000 workers from 17 U.S. facilities were assembled in 1974, and mortality has been evaluated in four sequential studies.[3,20,124,150] Several other large cohort mortality studies have been reported from Europe and around the world (Table 4).[15,47,70,72,111,113,133,143]

The most consistent finding has been the excess of digestive system cancers, due to marked increase in mortality from hepatic angiosarcoma. While the exact rates for hepatic angiosarcoma are not available, the magnitude of the excess is staggering when compared with other occupational cancers. From the plant population in Louisville (2500 workers) there have been 23 cases of hepatic angiosarcoma over the past 35 years. The expected rate is 1 per 100 million per year. Thus, the estimated standard mortality rate for this population exceeds 25,000![6,37]

Because of the rarity of hepatic angiosarcoma, many mortality studies have used "best evidence" to distinguish cases from those of primary liver cancer. In the most recent update of the U.S. cohort, 17 of 47 deaths (36%) classified as liver cancer on the death certificate were found to actually be cases of hepatic angiosarcoma.[2] In the European study, 16 of 17 cases in which tissue was available were found to be angiosarcomas based on histologic review.[111] This diagnostic uncertainty has confounded efforts to determine whether vinyl chloride exposure also presents a risk of primary liver cancer.[12,31] After removal of the hepatic angiosarcoma cases, slight excesses of liver cancer remain in some of the cohort studies. Several case reports have identified primary liver cancer in conjunction with histologic evidence of vinyl chloride–induced fibrosis in heavily exposed workers.[35,110] Morbidity from liver disease also may be increased, although confounding by hepatitis B and alcohol

TABLE 4 *Epidemiologic Studies of Vinyl Chloride–Exposed Workers Showing Brain Cancer Mortality and Cases of Hepatic Angiosarcoma*

Study	Cohort Number—End Year	Hepatic Angiosarcomas	Digestive Cancers Observed/Expected	Respiratory Cancers Observed/Expected	Brain Cancers Observed/Expected
United States	*Exposed 1 year*				
Tabershaw & Gaffey, 1973	8384—1973	6 cases	19/21.7 (SMR 94)	25/23 9 (SMR 112)	7 cases*
Cooper, 1980	10,173—1978	8 cases	29/40 8 (SMR 75)	45/44.3 (SMR 112)	12/5 09 (SMR 203)
Wong, et al , 1989	10,173—1983	15 cases	99/89.2 (SMR 111)	115/112.3 (SMR 94)	23/12 76 (SMR 180)
Applied Epidemiology, 1999	10,109—1995	51 cases	253/215.8 (SMR 117)	315/330 5 (SMR 95)	36/26 17 (SMR 138)
Sweden	*Ever exposed*				
Byren, et al , 1976	750—1974	3 cases	—	3/1.78 (SMR 168)	2/0 33** (SMR 606)
Great Britain	**Exposed**		Primary liver	Lung	
Fox and Collier, 1977	7409—1974	2 cases	1/0.71 (SMR 148)	46/51.3 (SMR 89.8)	2/3 66 (SMR 54 6)
Jones, 1988	5498—1984	7 cases	4/1.9 (SMR 212)	81/92.1 (SMR 88)	4/6.13 (SMR 65)
Canada	Employed 5 yrs				
Theriault and Allard, 1981	1455—1977	7 cases	14/5 4 (SMR 259)	2/5 8 (SMR 35)	0 in exposed
Europe	Employed 1 yr		Liver (excluding angio)	Trachea/lung	
Simonato, et al., 1991	12,706—1988	17 cases	7/8.4 (SMR 84)	144/148 3 (SMR 97)	14/13.1 (SMR 107)
Russia	*VC exposed for 1 mo*				
Smulevich, et al , 1988	3232—1977	0 cases	25/29.8 (SMR 84)	18/13.4 (SMR 134)	4/2.6 (SMR 153 8)

* Brain cancers included in other and unspecified cancers
** One patient developed brain cancer less than 1 year after hire
VC = vinyl chloride, SMR = standard mortality rate

may be important.[33,129] At present, however, it appears that if vinyl chloride does cause primary liver cancer, the attributable risk is small.

A possible brain cancer excess in vinyl chloride–exposed workers has been reported in several studies, and this association often is listed in reviews of the subject. A recent investigation has revealed that the brain cancer excesses reported in U.S. vinyl chloride studies have been related to a cluster at a single facility.[77,93,141,142,151] Detailed exposure evaluation at that facility by multiple investigators, however, has failed to reveal any relationship between the brain cancers and vinyl chloride exposure. In two other studies reporting an increase in brain cancer, one featured only two cases and inadequate latency (1 year),[15,31] and the other had no cases of hepatic angiosarcoma.[113]

Vinyl chloride exposure and PVC production do not appear to place workers at risk for other cancers.[7,31] The large cohort studies have consistently failed to demonstrate any risk of lung cancer. One study found an excess of suggested that this was associated with PVC dust exposure, but a second study using different methods found no relationship.[141,151] One Italian study of PVC fabricators reported an excess mortality from lung cancer.[116] A Swedish study also reported excess lung cancer morbidity in PVC fabricators, although the population also was exposed to asbestos (used as a filler in floor tile).[57]

There are reports of possible relationships between vinyl chloride exposure and other cancers, including lymphosarcoma[2,131] and malignant melanoma.[117] Given the large number of studies conducted and the number of cancers evaluated, these isolated reports of associations should be interpreted cautiously.

MEDICAL SURVEILLANCE

In the U.S., OSHA requires annual medical surveillance for all workers exposed to vinyl chloride monomer in excess of 0.5 ppm as a time-weighted average (without regard to use of respiratory protection). This is required semi-annually for all persons employed in vinyl chloride or polyvinyl chloride manufacturing for over 10 years (Table 5).

The medical surveillance experience at the Louisville facility is typical of what has been seen in the industry in general. After the recognition of the angiosarcoma case, a medical screening program was initiated at the Louisville plant that included biochemical testing, ultrasonography, arteriography, and liver biopsies.[21] Evaluation of over 1000 workers led to approximately 100 liver biopsies and resulted in the identification of two additional cases of hepatic angiosarcoma (Fig. 8).

TABLE 5. Required Medical Surveillance Under the OSHA Vinyl Chloride Standard*

Type of Exposure	Frequency	Examination Content
VCM exposure 8 hr TWA in excess of 0.5 ppm	Annual	Medical history pertaining to liver disease (alcohol, blood transfusions, hepatitis, medications)
Employed in VCM or PVC production for over 10 years	Semi-annual	Physical examination of lungs, liver, kidneys, and skin Blood tests: bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase Optional: Lung function, chest x-ray, urinalysis, additional blood work, liver scans

* 29 CFR 1910.1017
TWA = time-weighted average

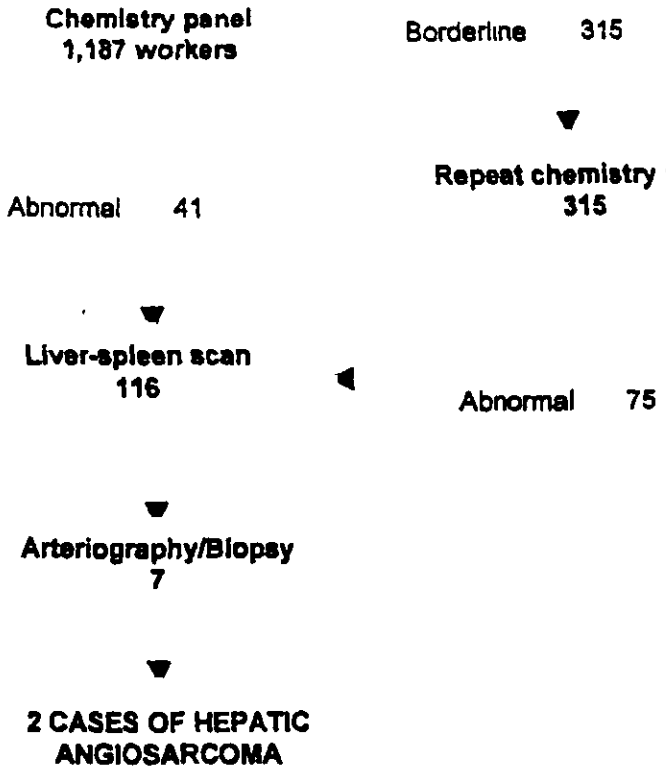

FIGURE 8. Results of mass screening of PVC production workers in 1975 after the initial discovery of hepatic angiosarcoma. (From Creech J, Makk L: Liver disease among vinyl chloride production workers. Ann NY Acad Sci 246:88–94, 1975; with permission.)

After two years, the program was altered to be in compliance with the OSHA testing requirements. However, the program has failed to detect any of the subsequent cases of hepatic angiosarcoma. This is related in part to the lack of sensitivity and specificity of liver enzyme testing.[126,127] Persons with significant tumor burdens may only have minimal enzyme elevations. At the same time, borderline elevations are common in persons due to alcohol use, medications, and other, nonspecific factors. Another problem has been the occurrence of disease in retirees who no longer participate in the program. For the most part, cases present as described previously, with abdominal pain, weight loss, and fatigue.

Other methods may be more valuable in detecting disease and/or risk. Both bile acids and clearance studies have been associated with evidence of chemically-induced liver toxicity.[80,118] These findings correspond to the periportal fibrosis seen on biopsies. What is uncertain is whether fibrosis represents a precursor lesion for tumor development and whether it is persistent or reversible. Other investigators have reported elevation of von Willebrand factor (factor VIII) in persons with hepatic angiosarcoma.[49] The levels correlated with tumor progression and may be valuable in both early diagnosis and tracking tumor progression. In general, workers with low levels of exposure to vinyl chloride show no abnormalities on diagnostic testing.[121]

SUMMARY

Polyvinyl chloride remains an important plastic resin. Exposures to vinyl chloride monomer, and possibly other materials, during the early years of production led

to the development of hepatic angiosarcoma in workers at facilities throughout the world. Several other syndromes, including acro-osteolysis, were associated with PVC production, but less clearly with vinyl chloride. Continuing research on the cellular mechanisms of this well-established occupational carcinogen may provide valuable insight into the pathogenesis of this disease in general. Continuing study of PVC production workers also may help to establish a threshold for the development of this rare malignancy.

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