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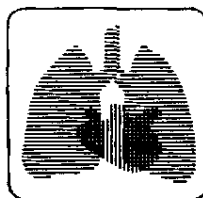
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Pulmonary Manifestations of Vinyl and Polyvinyl Chloride (Interstitial Lung Disease)*

Newer Aspects

*E. M. Cordasco, M.D., F.C.C.P.; S. L. Demeter, M.D.; J. Kerkay, Ph.D.;
H. S. Van Ordstrand, M.D., F.C.C.P.; E. V. Lucas, M.D.; T. Chen, Ph.D.;
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Newer varieties of occupational lung diseases primarily due to the vast increase in industrial technology have been reported recently. Preeminent among such newer agents are vinyl chloride (VC) and polyvinyl chloride. Very few cases have been reported, in Europe only, with descriptive histopathologic changes. To our knowledge, no pathologic studies of VC exposure have been described in the American literature. The biopsy abnormalities in our patients disclosed desquamation of alveolar macrophages into the alveolar lumina and minor interstitial and alveolar inflammatory changes. Pulmonary function abnormalities included restrictive insufficiency. Preventive therapy consists of the avoidance of further exposures, frequent industrial hygiene monitoring, and total avoidance of tobacco smoke, as well as associated atmospheric pollutants. Thus far, none of these patients has exhibited evidence of pulmonary neoplasm. All three patients survived their occupational injuries, and two are still disabled to varying degrees. Urine and blood levels of phthalic acid derivatives were elevated in two patients, the exact significance of which is not fully known. It probably represents a toxicologic response, but must be further pursued before conclusions can be reached.

Newer varieties of occupational lung diseases have been reported recently, primarily due to profound advances in industrial technology. Preeminent among such newer agents are vinyl chloride (VC)

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and polyvinyl chloride (PVC), substances used extensively in the plastics industry. More than 18 billion lbs were produced in 1972, with approximately 25 percent produced in the United States. Between 36,000 and 50,000 workers were exposed at that time to VC or PVC fumes, either during the polymerization process or during the processing of finished products.¹ The number of people exposed, owing either to alteration of the finished product or de-

struction of these products, or simply to living near a plant where any of these diverse processes may take place, is unknown. However, evidence has been presented that such exposures may be harmful. According to a recent Environmental Protection Agency report, approximately 90 million kg of PVC are discharged annually into the atmosphere.²

The emergence in 1974 of VC as a new occupational carcinogen, producing angiosarcoma of the liver, focused attention on other toxicologic manifestations of this group of chlorinated hydrocarbons. Pulmonary effects were first described in 1970, but few cases have been reported characterizing the histopathologic changes of the human respiratory tract, all published from abroad.

Three patients with extensive exposure to the fumes of either VC monomer or PVC are herein reported. Lung biopsy results and the implications of their exposures are discussed. In addition, ultra-microscopic findings are included, and new biochemical analyses are reported in two patients. A summary on this subject of PVC-induced disease was presented by the authors at a symposium in the Soviet Union in October, 1978.³

MATERIALS AND METHODS

Our experience involves the diagnosis and management of three patients with a pathologic diagnosis of interstitial fibrosis and work-related exposure to either VC or PVC gas or solids. All three patients had a lung biopsy, one transbronchial, and one by open method.

Pulmonary function studies were done by the Systems Research Laboratory method and included total vital capacity, timed vital capacity, flow rate, and diffusion capacity with carbon monoxide. Arterial blood gas determinations were performed by the Instrumentation Laboratory method, and distribution studies were measured with the nitrogen washout method.

Routine screening tests included complete blood counts (CBC), urinalysis, serology, SMA-12 chemistry profile, ECGs, and sputum studies for routine bacteriology. Smears and cultures of sputum for fungi and Mycobacterium were also performed. Each patient also had a sputum cytologic examination. Immunologic testing was performed on each patient and is detailed under the case discussion.

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CASE 1

A 55-year-old woman had an 18-month history of cough and fatigue and a six-month history of progressive dyspnea and digital cyanosis. At the present time the cough is dry, occurring in paroxysms; it may be initiated by breathing deeply or changing positions.

Medical history, family history, travel history, and review of systems were noncontributory. She had never smoked or had any pulmonary symptoms until the onset of her present illness.

For the last 20 years the patient has been employed as a

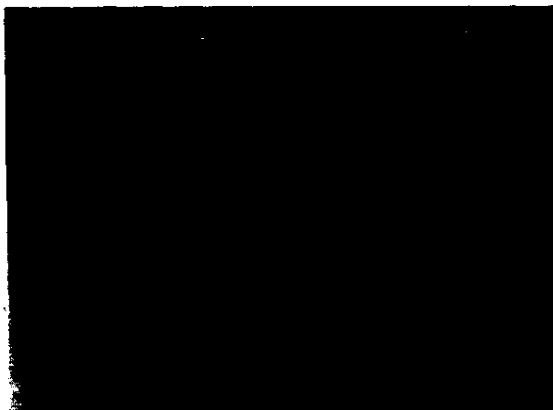


FIGURE 1A. X-ray of chest. Diffuse nodular pneumonitis.

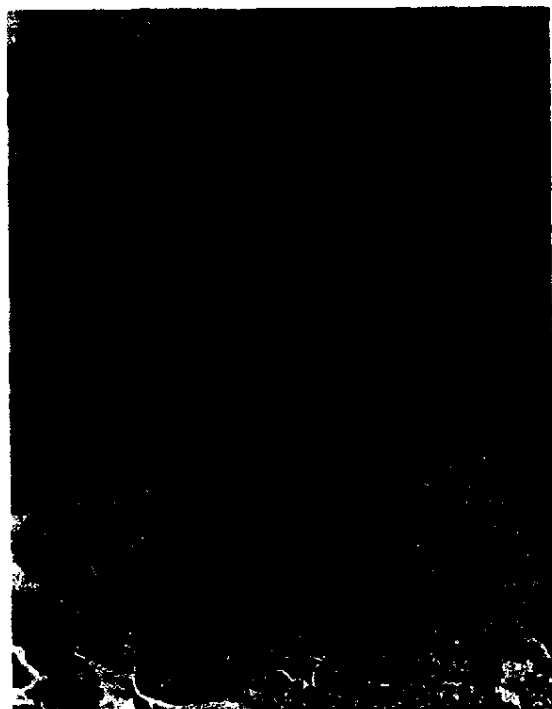


FIGURE 1B and 1C. Diffuse fibrosing pneumonitis with interstitial thickening and desquamation of cells into alveolar lumen.

meat wrapper. The process involves cutting and sealing the plastic wrap by melting it on a hot wire or hot plate. She also worked with adhesive label stamping during the past year. She has never experienced cough or shortness of breath in relation to her work exposure. However, she does state that her fatigue is more profound as the week goes on and that each Sunday night is her best time. The fatigue has lessened now that she limits her work to two-day periods. Physical examination results were normal except for the lungs and hands. There were fine inspiratory crackles heard diffusely over the lung fields, but more prominently at the bases. There were no wheezes. All fingers showed clubbing; this apparently had occurred over the last six months. Her toes were normal.

Laboratory values, which were normal, included CBC, liver and renal function tests, urinalysis, and ECG. A hypersensitivity screen for various fungi was negative. The sedimentation rate, latex fixation, rapid plasma reagin (RPR), antinuclear antibody (ANA), and Clq were all normal. Circulating immune complexes by Clq-binding assay were negative. The lymphocyte transformation test against PVC was also negative. The chest x-ray film revealed diffuse reticulonodular changes. Doppler ultrasound examination of the fingers demonstrated decreased blood flow, more pronounced after cold exposure. Pulmonary function study disclosed a restrictive abnormality (the vital capacity was 61 percent of predicted normal), with a diffusing capacity (DLco) of 11.2. Other new tests included a blood level for the measurement of phthalic acid derivatives, namely phthalic anhydride, a decomposition product of PVC, which measured 82.8 ng/ml, which is considerably elevated. The urine test for thermoplastic products revealed a remarkable elevation of two components—the phthalic anhydride derivative diethylhexyl phthalate known as DEHP, and another component that has been unidentified to date and is probably a fatty acid ester. These tests were performed at the Cleveland State University Biochemical Laboratories. It is the opinion of the biochemists that these levels are significant and have been demonstrated in animal studies using PVC tubing when the E factors are at a range associated with the release of thermoplastic resins and derivatives. This aspect of the study is still being assessed, and a future report is planned for publication.

It was thought that interstitial fibrosis accounted for the patient's signs, symptoms, and laboratory abnormalities. It was further thought that she also showed signs of PVC exposure toxicity with digital angitis. We postulated that the interstitial fibrosis may have been induced by her PVC exposure. Accordingly, she underwent an open lung biopsy of the right lower lobe for pathologic confirmation. An x-ray film of the chest disclosed a diffuse nodular pneumonitis without localized disease (Fig 1A). There were no pleural or hilar abnormalities. Light microscopy (Fig 1B and 1C) demonstrated diffuse fibrosing pneumonitis with prominent terminal bronchiolar cell hyperplasia of the alveolar lining or desquamation. Immunofluorescence was negative for complement and immunoglobulins. Large numbers of alveolar macrophages containing phagocytized material of undetermined composition was seen on electron microscopy (Fig 2). All cultures of lung tissue were negative.

The special blood and urine studies for thermoplastic resins were positive and will be further pursued.

The patient was discharged receiving 40 mg of prednisone per day.

Comment: This patient showed nonspecific signs and symptoms of fibrosing interstitial pneumonitis, which was



FIGURE 2. Alveolar macrophages with phagocytized material (electron micrograph).

confirmed by biopsy specimen. There was apparently no evidence of a hypersensitivity reaction either by history (type II), laboratory (type IV), or immunopathology (types II or III), according to the criteria proposed by McComb⁴ as a modification of the Cell and Coombs classification. Digital angitis, as demonstrated here, can be a manifestation of PVC toxicity.

CASE 2

A 41-year-old man complained of "not feeling well." For the past 3½ years he had experienced vague feelings of not being in good health, with weakness, fatigue, diffuse arthralgias, and myalgias. In the last eight months he had noticed an accentuation of his symptoms as well as dyspnea on exertion, wheezing, and a productive morning cough. A diagnosis of asthmatic bronchitis was made at that time, and he was given multiple drugs without improvement. Three months before referral, he was hospitalized at another institution for further evaluation. A bronchoscopy was negative, and transbronchial lung biopsy of the right lower lobe was reported to show pigmented macrophages in the air spaces. The chest x-ray film showed increased interstitial markings. Sputum examination showed moderate WBCs and alveolar macrophages. Laboratory test results, which were normal, included latex fixation, ANA, VDRL, ECG, and sputum cytology. Serum immunoelectrophoresis revealed decreased IgM, slightly decreased IgA, and normal IgG. Pulmonary function studies showed a decreased PaO_2 with small airway disease. An exercise tolerance test was performed and indicated that the patient was capable of moderate exercise. He was given bronchodilators and antibiotics, with no re-

sponse, and later, corticosteroids (for suspected connective tissue disease) with a favorable response.

He returned to work after two weeks and again noticed myalgias and arthralgias, easy fatigability, exhaustion toward the end of the day, and stiffness in his joints. He was referred to this institution for further evaluation.

For the past 14 years he had been employed in the dental mold industry and had extensive daily use of VC spray paint. Review of systems, family history, medical history, and exposure history were otherwise negative. He had smoked one half pack of cigarettes per day for the last five years. The initial physical examination results were normal. The lungs were clear. A rheumatology consultation revealed no evidence of connective tissue disease. Laboratory and roentgenographic examinations were positive for osteoarthritis. Normal or negative laboratory tests included an ECG, serum T_3 , T_4 , anti-thyroid binding globulin, VDRL, sedimentation rate, latex fixation, LE cell prep, ANA, urinalysis, CBC, SMA-18, and serum protein electrophoresis. The chest x-ray film showed diffuse, small, interstitial, and nodular densities scattered throughout both lungs.

The patient returned to work. His symptoms were stable over the next two months; however, two days before his admission, he complained of a "flu-like" syndrome, with an increase in his generalized aching, a slight, dry cough, an increase in shortness of breath, and chest tightness. On examination he was afebrile, with few bibasilar crepitant rales and a palpable lymph node in the right supraclavicular fossa. An immunoglobulin electrophoresis now showed increased IgA (330; normal, 156 ± 92), low normal IgM (51; normal, 145 ± 105), and decreased IgG (950, normal, $1,380 \pm 255$). The remainder of laboratory and physical examina-



FIGURE 3. Thickened alveolar septum with accumulation of mononuclear cells, alveolar macrophages anthracotic pigment.

tion results were unchanged. The chest x-ray film was unchanged and was interpreted by the ILO/UC classification as being 1/1. On biopsy, the lymph node showed histiocytosis consistent with chronic inflammation. He underwent a trephine lung biopsy, which was reported to show large numbers of alveolar macrophages in the alveolar air spaces, thickening of the peribronchiolar connective tissue, and alveolar septa with accumulation of mononuclear cells and anthracotic pigmentation, hypertrophic bronchiolar epithelium, and macrophages containing large amounts of hemosiderin and a few anthracotic pigments (Fig 3).

The patient was discharged receiving corticosteroids, with gradual clearing of his symptoms over the next 2½ years. Follow-up laboratory examination results have remained unchanged. The chest x-ray film has remained abnormal.

Comment: The biopsy specimen showed changes consistent with interstitial fibrosis; no immunologic testing was performed on the tissue. This patient differs from patient 1 in that his exposure was to the VC monomer as opposed to PVC fumes.

CASE 3

This 55-year-old man was exposed to PVC dust during a



FIGURE 4A. Chest x-ray film abnormality; interstitial infiltrates.



FIGURE 4B. Desquamation of cells into alveolar lumen.

reactor cleaning operation. He was a nonsmoker. His initial exposure occurred over a five- to six-week period, resulting in the development of continuous and progressive dyspnea of approximately ten days' duration. He had severe dyspnea in the 24-hour period before admission.

Air samples of PVC in the immediate operational area varied between 200 and 315 parts per million. Examination of the chest showed bibasilar coarse, inspiratory, crepitant rales. Because he initially failed to respond to oral aminophylline therapy prescribed by his local physician, steroids and high-flow oxygen with a Venturi-type mask were added, with considerable subsequent improvement over the next 48 to 72 hours. There was a gradual reduction of the steroid dose over the next two-week period as the patient showed progressive improvement. Concomitantly, there was complete resolution of the roentgenographic lesions. The pulmonary function tests in this person disclosed a moderate reduction of vital capacity and in the mid-expiratory flow rates and moderate impairment of diffusion capacity to 12.8. The arterial PaO_2 measured 80 mm Hg at room air. The remainder of the routine laboratory studies, which included an SMA-12 chemistry profile, urinalysis, serology, and CBC, were normal, except for minimal leukocytosis of 12,200 cells. Figure 4b shows his chest x-ray film at the time of the six-week exposure. The histopathologic changes were compatible with a desquamative interstitial pneumonitis. The section of his lung biopsy disclosing these findings is shown in Figure 4a.

DISCUSSION

Vinyl chloride ($\text{CH}_2 = \text{CHCl}$) is a monomer used as a chemical intermediate in the polymerization of PVC resin in the production of copolymers such as Saran, and as a solvent.⁵ VC monomer under normal temperature and pressure is a gas (BP 13.5 °C). It readily polymerizes under pressure at a temperature of 40 to 70° C to form PVC, a white, solid material. Although the polymerization process was discovered in the 1800s, PVC production did not begin in the United States until 1928.⁶ The list of materials made from PVC is extensive and includes foils, films, tapes, tubing, fiber, cables, artificial leather, foam rubber, paint, varnish, toys, and automobile upholstery coverings.

The acute, toxic effects of VC gas (anesthesia and narcotic-effect) were quickly discovered and were thought to represent the only toxic effect of exposure until 1949, when Tribukh et al⁶ in Russia reported a hepatitis-like effect following long-term exposure. Other toxic manifestations were reported during the 1960s (Table 1), and in 1974, the association between VC exposure and angiosarcoma of the liver was made. Further toxic manifestations were discovered during epidemiologic studies that were performed both on production workers and on populations living near the plants. The clinical spectrum of PVC-induced toxic organ damage is broad (Table 1). The most widely reported manifestation is a scleroderma-like syndrome, and the most widely discussed is the angiosarcoma of the liver. Table 2 lists

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Table 1—Toxic Effects of VC and PVC Exposure by Organ System

Organ	Toxic Effect(s)	Reference(s)
Liver	Hepatitis (elevated enzymes)	30,31
	Hepatomegaly or abnormal liver scan	31,32
	Hepatic fibrosis	30
	Angiosarcoma	30,31
Skin	Dermatitis (resembles scleroderma)	2,29
Vascular	Digital angitis (resembles Raynaud's)	3,29,30
Hematologic	Thrombocytopenia	24,29
Skeletal	Acroosteolysis	3,29
Pulmonary	Acute airflow obstruction	4,22
	Chronic airflow obstruction	6,7
	Interstitial fibrosis	21,22,32

other manifestations of PVC toxicity. Other than the acute narcosis, the diseases on this list were discovered by epidemiologic studies and were thought to represent statistically significant association. The teratogenic effect applies to communities surrounding PVC production plants.

The effects of VC and PVC exposure on the pulmonary system include both acute and chronic airflow obstruction. "Meat wrapper's asthma" is a syndrome of acute bronchospasm due to the inhalation of PVC fumes from melted plastic wrap. It closely resembles an acute hypersensitivity response that can be seen with other industrial exposures, but no documented immunologic complexes have been reported to date,⁷ with one exception: a report from abroad.⁸ Decreased flow rates are also seen with chronic exposure. One study found a decreased FEV₁/FVC ratio in 30 percent and 50 percent of nonsmokers with one to 20 years and more than 20 years of exposure, respectively.⁹ Another study found decreased flow rates in 50 percent of PVC production workers who were older than 30 years.¹⁰ Others have disputed such claims.¹¹ We have recently encountered three patients with PVC-induced asthma. This is the subject of a separate report.¹²

Table 2—Nonorgan System Toxic Manifestations of VC and PVC Exposure

Effect	Reference(s)
Acute narcosis	33
Increased mortality	16,34
Increased cancer rates	10,13,15,16,35
Chromosomal abnormalities	5,36,38,39
Increased teratogenicity and fetal mortality	35,37,40

The risk of pulmonary neoplasms may also be higher in VC and PVC production workers. Animal data are highly suggestive,¹³⁻¹⁵ but the standardized mortality ratios (SMRs) vary from 112,¹⁶ 156,¹⁷ 160,¹⁸ to 168,¹⁹ and other studies could find no increase in the expected amount of cancer.²⁰⁻²² Another study supports a carcinogenic effect because of differences in expected cell types (with no increase in the total number of lung cancers).²³ In addition, the effect of concomitant cigarette smoking is unknown but probably additive. Other industrial exposures (*eg*, asbestos, chromium, and chloromethyl ether) indicate a probable synergism in carcinogenic effects. The cell types of lung neoplasms reported by Waxweiler are shown in Table 3.

Interstitial fibrosing pneumonitis due to PVC or VC exposure has been reported only rarely,²³⁻²⁵ primarily from the foreign literature, although nodular infiltrates on chest x-ray film have been described in 3/37 workers in one report.²⁷ Of 985 workers in another study, 13.3 percent showed a similar abnormality (1/0 or 1/1, ILO/UC classification).¹⁰ Interstitial changes have also been delineated in experimental animals.²⁸

We report three further cases of histologically proved interstitial fibrosing pneumonitis in patients exposed to either VC or PVC fumes. Signs, symptoms, and laboratory abnormalities do not differ significantly in patients with interstitial disease associated with VC or PVC exposure from those with idiopathic interstitial fibrosis. Usual symptoms include the insidious onset of dyspnea, exertional weakness, and dry cough. Physical examination reveals fine bibasilar inspiratory crackles. Other signs of PVC toxicity may be seen as well. The chest x-ray

Table 3—Lung Cancer Cases Histologically Confirmed Among Cohort Workers Exposed to Vinyl Chloride/Polyvinyl Chloride¹⁰

Case No.	Histologic Diagnosis	Age at Death, Exposure, Latency, yr		
		yr	yr	yr
1	Large cell undifferentiated	39	14	15
2	Large cell undifferentiated	40	13	18
3	Large cell undifferentiated	52	22	22
4	Large cell undifferentiated	61	16	17
5	Large cell undifferentiated	61	8	17
6	Adenocarcinoma	45	19	19
7	Adenocarcinoma	57	12	12
8	Adenocarcinoma	72	15	22
9	Mesothelioma (?; possible, our patient)	...	12	28

film shows diffuse reticulonodular infiltrates; pulmonary function testing demonstrates a restrictive pattern and depression in the DLCO with variable levels of PaO₂. Lung biopsy specimen discloses interstitial infiltration with mononuclear cells, fibrosis, alveolar hyperplasia, and desquamation into the alveolar lumina. Diagnosis is best confirmed by lung biopsy.

At present it is highly presumptive, but strongly indicated, that there is an association between the exposures and the development of interstitial fibrosing pneumonitis. No cause-effect relationship can categorically be proved with certainty in such a small series. However, the patient with a history of exposure in the polymerization process coupled with the clinical studies of other authors (Lilis, Meloni, and Szende) almost certainly substantiates the diagnosis, at least in the one patient.

The mechanism of the response remains speculative, although a dysfunction in the immune system is probably implicated. Of 320 workers in a VC polymerization plant, 28 were found to have Raynaud's phenomenon, and 19 of the 28 were found to have circulating immune complexes.⁸ Circulating cryoimmunoglobulins are found in 41 percent of patients with usual interstitial fibrosis and play an etiologic role.²⁹ In addition, markers of abnormalities of the immune system (ANA, latex fixation, sedimentation rate) are found in approximately 25 to 30 percent of patients with fibrosing alveolitis.³⁰ It is tempting but purely hypothetical to speculate on an immunologic basis for this response, despite the total absence of these markers in our patients. The other mechanism is toxicologic, namely, dose-effect relationship to exposure.

In his review of idiopathic pulmonary fibrosis, Crystal³¹ points to several "clues" in attempting to answer the question "What triggers the disease?" Some "triggers" (or etiologic factors) found in patients with interstitial fibrosis may include: (1) infection (25 to 40 percent of patients antedate their illness to a viral chest syndrome); (2) hereditary factors (familial clusterings and relative increase in HLA-12 and HLA-29); and (3) cell-mediated immune reactions (directed against lung collagen). Perhaps toxic exposures eventually will find their place in this list as more associations of the type we have just presented are brought to light.

The identification of diethylhexyl phthalate (DEHP) in the serum and urine of excessive amount (190 times that of the control) in one patient is interesting and presumably significant. Recently, similar elevations of the substance in both serum and urine were identified in the second patient. The substance is a decomposition product of PVC chemically similar to dicyclohexyl adipate. It

accompanies dicyclohexyl adipate, a major emission during hot-wire cutting of meat wrap plastic, as another plasticizer present in PVC. It may also occur as a decomposition product during the adhesive stamp-labeling process. The major ingredient of the latter process is dicyclohexyl phthalate.

Four major thermal decomposition products of dicyclohexyl phthalate are cyclohexanol, dicyclohexyl ether, phthalic anhydride, and cyclohexyl benzoate. The presence of these compounds, along with DEHP, was readily demonstrated in the serum and urine of two patients. In addition, urine samples also contained significant amounts of MEHP (monoethylhexyl phthalate), phthalic acid, benzoic acid, and O and P-hydroxy benzoic acid. These urine components are probably metabolites of DEHP and other plasticizers present in PVC. Complete evaluation of the metabolism of decomposition products of PVC in man is presently being pursued at Cleveland State University.

Treatment is primarily prophylactic, with immediate removal of the affected patients from the offending fumes being of paramount importance. Corticosteroids may be helpful in the treatment of the early stages of this disease. Other immunosuppressive agents have not been used, to our knowledge. The efficacy of steroids was verified in one of our patients and is highly probable in our second patient who had long-term exposure to PVC fumes. The use of other immunosuppressive agents has not been reported to our knowledge. Prophylactically, frequent industrial hygiene monitoring is of utmost importance for the early detection of abnormal atmospheric levels in the occupational environment. Close medical surveillance of such persons exposed may prevent the occurrence of severe adverse health effects.

CONCLUSIONS

The awareness of newer hazards of chemical substances increasingly present in our environment is of paramount importance to every employee, as well as to the entire community, because of the obvious occupational and public health implications. Examples of such newer agents have been reported. Newer biochemical studies of both the serum and urine, notably decomposition products of thermoplastic resins of the phthalic acid group, were abnormal in two patients. The total clinical significance of these factors is yet unknown and will be further pursued.

This is one of the first reports in this country to delineate the histopathologic changes of the respiratory tract that constitute such excessive exposures of the VC/PVC group. Therapeutic implications include the necessity of earlier medical surveillance as

well as the institution of diagnostic and prophylactic industrial hygiene procedures on a more frequent basis. This is of paramount importance, since VC and PVC are toxic agents. Therefore, it is of utmost significance to institute such close medical surveillance to prevent serious adverse health effects.

REFERENCES

- 1 Berk PD (mod). Vinyl chloride-associated liver disease. *Ann Intern Med* 1976; 84:717-31
- 2 Zenz C. Occupational medicine principles and practices application. Chicago: Year Book Medical Publishers; 1975:789
- 3 Cordasco EM, Demeter S. Pulmonic manifestations of polyvinyl chloride exposures. Presented at Symposium, Republic Hospital, Dushanbe, Tajikistan, USSR, October 1978
- 4 McCoombs RP. Disease due to immunologic reactions in the lungs. *N Engl J Med* 1972; 286:1186-94; 1245-52
- 5 Heath C, Falk H, Creech J. Characteristics of cases of angiosarcoma of the liver among vinyl chloride workers in the United States. *Ann NY Acad Sci* 1975; 246:231-38
- 6 Kramer CG, Mutchler JE. The correlation of clinical and environmental measurements for workers exposed to vinyl chloride. *Am Ind Hyg Assoc J* 1972; 33:19-30
- 7 Sokol WN, Aelony Y, Beall GN. Meat-wrapper's asthma: a new syndrome? *JAMA* 1974; 222:639-41
- 8 Ward AM, Udnoon S, Watkins J, Walker AE, Darke CS. Immunological mechanisms in the pathogenesis of vinyl chloride disease. *Br Med J* 1976; 1:938-38
- 9 Miller A, Teirstein A, Chuang M, Selikoff S, Warshaw R. Changes in pulmonary function in workers exposed to vinyl chloride and polyvinyl chloride. *Ann NY Acad Sci* 1975; 246:42-52
- 10 Selikoff S, discussant in Barnes AW. Vinyl chloride and the production of PVC. *Proc R Soc Med* 1976; 69:277-81
- 11 Gamble J, Liu S, McMichael AJ, Waxweiler RJ. Effect of occupational and nonoccupational factors on the respiratory system of vinyl chloride and other workers. *J Occup Med* 1976; 18:659-70
- 12 Cordasco EM, Demeter S, Lira R, Wagner W. Occupational asthma updated. *J Occup Health Safety* 1980; 49:42-45
- 13 Lee CC, Bhandari JC, Winston JM, et al. Carcinogenicity of vinyl chloride and vinylidene chloride. *J Toxicol Environ Health* 1978; 4:15-30
- 14 Viola PL, Bigotti A, Caputo A. Oncogenic response of rat skin, lungs, and bones to vinyl chloride. *Cancer Res* 1971; 31:516-22
- 15 Maltoni C, Lefemine G. Carcinogenicity bioassays of vinyl chloride: current results. *Ann NY Acad Sci* 1975; 246:195-218
- 16 Tabershaw JR, Gaffey WR. Mortality studies of workers in the manufacture of vinyl chloride and its polymers. *J Occup Med* 1974; 16:509-18
- 17 Waxweiler RJ, Stringer W, Wagoner JK, et al. Neoplastic risk among workers exposed to vinyl chloride. *Ann NY Acad Sci* 1976; 271:40-48
- 18 Monson RR, Peters JM, Johnson MN. Proportional mortality among vinyl chloride workers. *Lancet* 1974; 2:397-98
- 19 Byren D, Engholm G, Enghund A, Westerholm P. Mortality and cancer morbidity in a group of Swedish VCM and PCV production workers. *Environ Health Perspect* 1976; 17:167-70
- 20 Duck DW, Carter JT, Coombes EJ. Mortality study of workers in a polyvinyl chloride production plant. *Lancet* 1975; 2:1197-99
- 21 Falk H, Waxweiler R. Epidemiological studies of vinyl chloride health effects in the United States. *Proc R Soc Med* 1976; 69:303-06
- 22 Saric M, Kulcar Z, Zorica M, Celic I. Malignant tumors of the liver and lungs in an area with a PVC industry. *Environ Health Perspect* 1976; 17:189-92
- 23 Mason TJ. Cancer mortality in U.S. counties with plastics and related industries. *Environ Health Perspect* 1975; 11:79-84
- 24 Arnaud A, Pommier D-S, Garbe L, Payan H, Charpin J. Polyvinyl chloride pneumoconiosis. *Thorax* 1978; 33:19-25
- 25 Darke CS (discussant) in Barnes AW. Vinyl chloride and the production of PVC. *Proc R Soc Med* 1976; 69:277-281
- 26 Szende B, Lapis K, Nemes A, Pinter A. Pneumoconiosis caused by the inhalation of polyvinyl chloride dust. *Med Lav* 1970; 61:433-36
- 27 Lange CE, Juhe S, Stein G, Veltman G. Further results in polyvinyl chloride production workers. *Ann NY Acad Sci* 1975; 246:18-21
- 28 Prodan L, Suciu J, Pislariu V, Ilea E, Pascu L. Experimental chronic poisoning with vinyl chloride (monochlorethene). *Ann NY Acad Sci* 1975; 246:159-63
- 29 Fulmer JD. Clinical aspects of idiopathic pulmonary fibrosis, in Crystal RG (moderator). Idiopathic pulmonary fibrosis. *Ann Intern Med* 1976; 85:770-73
- 30 Turner-Warwick M, Hoslam P. Antibodies in some chronic fibrosing lung disease: I. Non-organ-specific antibodies. *Clin Allergy* 1971; 1:83-85
- 31 Crystal RG. Biochemical concepts and overall perspective of idiopathic pulmonary fibrosis, in Crystal RG. Idiopathic pulmonary fibrosis. *Ann Intern Med* 1970; 85:783-85
- 32 Veltman G, Lange C-E, Juhe S, Stein G, Bachner V. Clinical manifestations and course of vinyl chloride disease. *Ann NY Acad Sci* 1975; 246:6-17
- 33 Lillis R, Anderson H, Nicholson WJ, et al. Prevalence of disease among vinyl chloride and polyvinyl chloride workers. *Ann NY Acad Sci* 1975; 246:22-41
- 34 Creech JN. Industrial screening, in Berk PD (moderator). Vinyl chloride-associated liver disease. *Ann Intern Med* 1976; 84:720-22
- 35 Marsteller HJ, Leibach WK, Mueller, R, Gedigk P. Unusual splenomegaly liver disease as evidenced by peritonoscopy and guided liver biopsy among polyvinyl chloride production workers. *Ann NY Acad Sci* 1975; 246:95-134
- 36 Wagoner JK, Infante PF, Saracci R. Vinyl chloride and mortality? *Lancet* 1976; 1:194-95
- 37 Infante PF, Wagoner J, Waxweiler R. Carcinogenic, mutagenic and teratogenic risks associated with vinyl chloride. *Mutat Res* 1976; 41:131-42
- 38 Purchase IFH, Richardson CR, Anderson D. Chromosomal and dominant lethal effects of vinyl chloride. *Lancet* 1975; 2:410-11
- 39 Funes-Cravioto F, Lambert B, Lindsten J, et al. Chromosome aberrations in workers exposed to vinyl chloride. *Lancet* 1975; 1:459
- 40 Infante PF, Wagoner JK, McMichael AJ, Waxweiler RJ, Falk H. Genetic risks of vinyl chloride. *Lancet* 1976; 1:734-35