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Source (Journal, Vol., Number, Pages, Date)

1 2	61 62
	31
	32

Brief Summary

1 2 10	61 62
SUMMARY:	61
	62
	63
	64

COMMENTARY *This commentary provides editorial perspectives on the report which follows*

Vinyl Chloride and Polyvinyl Chloride Exposure and Occupational Lung Disease

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Several recent reports,[1,2] and one in this issue (see page 828), have contributed new observations on pulmonary disease in vinyl chloride (VC)-and polyvinyl chloride (PVC)-exposed patients.

Earlier reports, a few even preceding the identification in 1974 of vinyl chloride as a human carcinogen (with hemangiosarcoma of the liver the marker tumor, but most probably not the only tumor), had centered on the rather unexpected occurrence of roentgenographic abnormalities[3-6] or pulmonary function impairment,[3,7-10] or had indicated dyspnea as a prominent symptom[9,11] in VC- and/or PVC-exposed workers.

The roentgenographic pattern described was essentially that of reticular-linear and/or nodular (small rounded) opacities, involving both lungs, predominantly in the lower zones. Pulmonary function abnormalities, both restrictive and obstructive dysfunction, have been observed, with diffusion defects and arterial desaturation in some cases.

Two recent reports, one a case report,[1] the other an epidemiologic survey,[2] seem to identify *PVC dust as the etiologic agent in a peculiar type of pulmonary fibrosis associated with a granulomatous reaction.* Electron microscopic examination showed the giant multinucleated cells to contain a nonhomogenous material in their cytoplasm, which was identified to be PVC. A similar pattern was reproduced by incubation of human macrophages obtained by bronchial lavage, with PVC powder: absorption of PVC particles in the cytoplasm was rapid, with thinly granular lysosomal material deposited against the PVC particles.

Similar histologic lesions had been previously described in a human case[3] and in an experimental study in guinea pigs and rats.[12]

Exertional dyspnea, diffuse micronodular chest roentgenographic abnormalities, and restrictive pulmonary dysfunction were the main characteristics in the case of PVC pulmonary fibrosis associated with granulomatous lesions.[1] Experimental intratracheal administration of PVC dust in rats[13] has been shown to result in an increase in the activity of lysosomal enzymes, interstitial fibrosis, and granulomatous lesions surrounded by fibroblasts, reticulin, and collagen fibers.

An epidemiologic study of a large group of PVC- and VC-exposed workers[2] detected 20 cases of "typical pneumoconiosis," *ie*, chest roentgenogram changes consisting of irregular opacities or micronodular shadows of at least class 1 profusion, according to the ILO U/C classification. All these cases were found among PVC-exposed employees. The pattern of roentgenographic abnormalities described is very similar to that reported in the case in which the lung biopsy specimen revealed fibrosis and granulomatous reaction, with inclusion of PVC particles.

The same study reported the presence of less marked roentgenographic abnormalities, of the linear-reticular type, in a much larger proportion (32 percent) of the population examined; these changes were present in VC monomer-exposed and in PVC-exposed employees. While the prevalence was higher in smokers than nonsmokers, 65 of the 388 abnormal x-ray films were found in individuals who had never smoked. This observation is relevant since the pulmonary effects of vinyl chloride monomer *per se* are of great interest.

In the context of the multiorgan effects of vinyl chloride, including the peculiar syndrome of acro-osteolysis, scleroderma-like skin changes, vascular changes affecting the arteries, arterioles, and capillaries of hands and fingers, liver and spleen capsular fibrosis, liver fibrosis, abnormalities of the sinusoidal vessels in the liver, and portal hypertension, Ward et al[14] investigated the immunologic status of 58 workers from a VC polymerization plant. The findings included hyperimmunoglobulinemia, cryoglubulinemia, cryofibrinogenemia, *in vivo* complement activation via the classic pathway, with C_4 and C_3 conversion and an increase in the B cell lymphocyte population. Immunofluorescent examination of skin, muscle, and lung biopsy specimens revealed the presence of circulating immune complexes, with deposition on vascular endothelium and occlusion of small vessels. In areas with subintimal proliferation

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nd luminal occlusion, there was immunoglobulin, complement, and fibrinogen deposition in the subintimal regions of the vessel wall. The presumed sequence of changes was thought to be structural alteration of protein molecules, as a direct effect of a highly reactive metabolite of vinyl chloride, eliciting an immune response, with activation of B cells and hyperimmunoglobulinemia. Cryoprecipitable immune complexes (antigenic altered protein plus immunoglobulin) activate complement, with consequent vascular occlusion, through fibrinogen/fibrin conversion and polymerization. Collagen synthesis is stimulated in these ischemic areas.

Similar abnormalities of the immunologic status were found in another study of 22 workers exposed to vinyl chloride, with Raynaud's syndrome, and in some cases, acroosteolysis. Latent cryoglobulinemia was detected in 18 cases, with increases of immunoglobulins, IgA and IgG.

Circulating cryoimmunoglobulins are a prominent feature of idiopathic pulmonary fibrosis[15] and increased IgG levels have been shown to be characteristic for bronchoalveolar lavage fluid of such patients.

Interstitial pulmonary fibrosis is a possible effect of vinyl chloride exposure; the occurrence of more dramatic and specific abnormalities in other organ systems—liver, spleen, and peripheral circulation—has probably prevented more focused attention on pulmonary effects of vinyl chloride in the past.

Long-term effects of vinyl chloride include well-documented carcinogenicity. Lung cancer has been found to occur with an increased incidence in several mortality studies.[16-18] In experiments on mice, Suzuki[19] has described hyperplastic changes of the alveolar lining cells and pulmonary tumors in the majority of exposed animals. The ultrastructure was thought to indicate that the tumors originated in type 2 alveolar cells. Alveologenic tumors were also described in several other experimental studies.[20-22] Interestingly, other known carcinogens, such as polycyclic aromatic hydrocarbons, nitrogen mustard, and chromates produce pulmonary tumors in experimental animals similarly, originating in the type 2 alveolar cell.

The effects of vinyl chloride-polyvinyl chloride exposure on the respiratory system of exposed workers seem to indicate *two patterns of nonmalignant effects: a granulomatous reaction* to PVC dust, with inclusion of PVC particles in macrophages and histiocytes, and associated interstitial fibrosis, and *an interstitial pulmonary fibrosis* due to vinyl chloride monomer effect on protein molecules and the immunologic mechanisms triggered by the altered protein.

The long-term *carcinogenic effect*, with a significant increase in the incidence of lung cancer also is of concern, although the magnitude of this effect has not yet been completely evaluated.

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