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49. Vinyl Chloride and Polyvinyl Chloride

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The notification made by the B. F. Goodrich Company in early 1974 of the occurrence of several cases of hepatic angiosarcoma among its polyvinyl chloride (PVC) polymerization workers set off a rapid chain of events that had a dramatic impact on the field of occupational health. First, vinyl chloride monomer (VCM), the starting material in the production of PVC resins, to which tens of thousands of workers had been exposed in recent decades, was transferred from a relatively innocuous industrial substance to a carcinogen producing a fatal malignancy. Second, human epidemiologic data and animal experimental evidence for the carcinogenicity of VCM appeared almost simultaneously, providing definitive results that quickly brought about sharply lower occupational standards and changed industrial and environmental practices in many countries. Third, because of the many consumer uses of VCM and vinyl plastics, concern spread beyond the traditional confines of occupational health to the general public.

Several excellent review articles and conference proceedings discuss the multiple facets of disease induced by vinyl chloride [5, 26, 48, 57, 67, 74]. This chapter focuses primarily on the medical and epidemiologic findings.

PVC POLYMERIZATION

About 2.5 billion kg/yr of VCM ($H_2C=CHCl$) is produced in the United States, most of it for production of PVC resins. PVC is used primarily in building and construction (particularly PVC pipe, electrical wire and cable, and flooring), home furnishings, recreational products (e.g., records and toys), packaging (e.g., film, sheet, and bottles), apparel, and transportation materials (e.g., automobile tops, upholstery, and mats), besides a variety of other products, including medical tubing [48].

The PVC industry, begun in the United States in the early 1940s, consists of three separate processes. The first step is vinyl chloride monomer production, usually by direct chlorination or oxychlorination of ethylene. This is done in a closed system, although leaks or breaks in the process may lead to transiently high exposure levels. In the United States, ten companies (15 plants) were engaged in this process in 1976; several thousand

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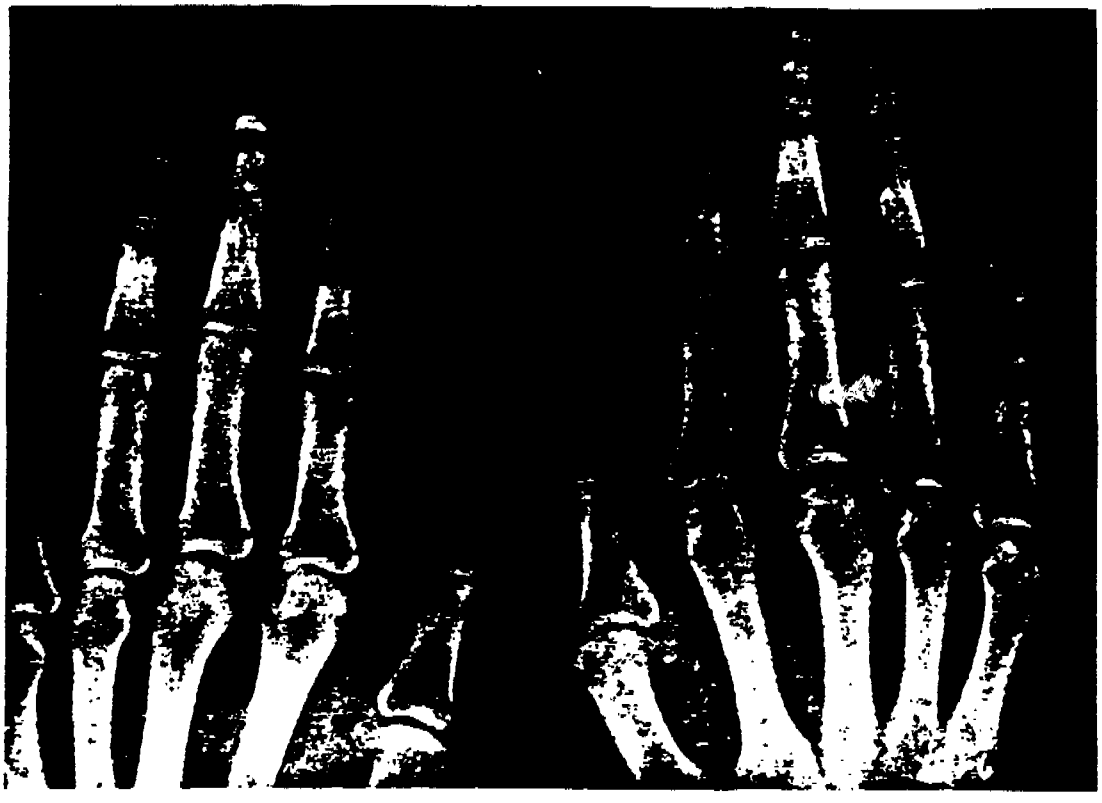

FIGURE 49-1. Hand x-ray of long-term polyvinyl chloride polymerization worker with marked acro-osteolysis, November 1964. (Courtesy of Dr. John Creech, B. F. Goodrich Company, Louisville, Kentucky.)

Ward et al. identified a number of abnormalities, including evidence of circulating immune complexes and their deposition in vessels [70]. The hypothesis that these immunologic changes may be related to the pathogenesis of AOL and to other aspects of VCM-induced disease needs further study.

A puzzling aspect is that AOL was not described in detail until the 1960s. Unlike HAS, which has a prolonged latency period of approximately 20 years, AOL can have a very short latency period of 1 to 2 years and thus should have occurred in the 1940s and 1950s. Either the disease was missed during those years or it did not occur because of unidentified factors that are yet to be explained. (One author suggested that AOL first occurred after the introduction of vinyl chloride–vinyl acetate copolymers [48]. Unfortunately, such exposure information is lacking in virtually all published reports of AOL).

Liver Disease. In studies carried out during the 1960s in Rumania, Suciu et al. described hepatomegaly in vinyl chloride workers (reversible in some after cessation of VCM exposure), which was often associated with abnormalities of liver function tests [60]. The spectrum of VCM-induced liver disease began to emerge from studies of PVC polymerization workers in Germany, starting in 1972. Lange et al. described workers with hepatic fibrosis, splenomegaly, and thrombocytopenia—all suggestive of portal hypertension—in the absence of significant hepatic parenchymal damage [38]. In a subsequent report, 81 percent of 70 workers studied were noted to have thrombocytopenia, 67 percent had increased Bromsulphalein (BSP) retention, and 57 percent had splenomegaly; 14 percent had increased serum enzyme levels, indicating hepatic damage [66]. Pathology studies demonstrated activation of hepatic sinusoidal cells and hepatic (particularly perisinusoidal) fibrosis, with lesser changes in hepatocytes

FIGURE 49-3. Circumscribed nodule, showing hyperplasia and hypertrophy of hepatocytes and sinusoidal cells, in a vinyl chloride worker. Hematoxylin eosin, 100×. (Courtesy of Dr. Hans Popper, Mount Sinai School of Medicine of the City University of New York.)

FIGURE 49-4. Trabecular angiosarcoma in a vinyl chloride worker. Note cords of hyperplastic hepatocytes, sometimes surrounding bile plugs. These cords are surrounded by layers of angiosarcoma cells. The sinusoidal spaces are dilated. Hematoxylin eosin, 60×. (Courtesy of Dr. Hans Popper, Mount Sinai School of Medicine of the City University of New York.)

have not detected increased abnormalities [72, 79]. Nevertheless, when incorporated into ongoing medical surveillance, standard liver function tests have been valuable in identifying VCM-induced hepatic disease, particularly when multiple abnormalities or prolonged abnormalities on repeated examination have been observed [42]. As a result, periodic screening with standard liver function tests has been included in NIOSH recommendations and U.S. regulations [65].

There is a generally perceived need for the development of reliable screening tests for the early stages of VCM-induced hepatic disease. Tamburro et al. utilized hepatic clearance of indocyanine green as a sensitive indicator of liver function and noted the value of radioisotopic liver scans in detecting early anatomic lesions [62, 76]. Other tests under evaluation include gray-scale ultrasonography and *in vivo* capillary microscopy [44, 77]. The degree of reversibility of the hepatic fibrotic precursor lesion has not been determined [4], but withdrawal from exposure is prudent, in the hope of preventing progression. Survival after HAS is diagnosed has been estimated to average only several months. Dannaher et al. recently reported on the use of chemotherapy in cases of VCM-associated HAS to improve the duration and quality of survival [15].

Pulmonary Effects. Lilis et al, reported a chronic decrease in pulmonary function in PVC polymerization workers exposed to VCM and PVC dust [39]. Gamble et al. found no evidence of a chronic decrease, but they did demonstrate acute loss of pulmonary function during the course of a single workshift [25]. A recent report from England de-

exposed at these lower levels, additional epidemiologic studies are needed to evaluate these associations. In a study of Thorotrast-induced HAS, the initially reported cases had high-dose exposures and relatively short latency periods, while a larger number of cases that appeared later had exposures associated with lower doses but prolonged latency periods [22]. Thus it is important to follow trends of VCM-related cases of HAS in the future for any shifts in epidemiologic patterns.

In nationwide reviews of HAS in the United States (1964–1974) and the United Kingdom (1963–1977), from 6 to 7 percent of pathologically confirmed cases occurred among PVC polymerization workers (12 of 168 in the United States; 2 of 35 in the United Kingdom) [3, 21].

OCCUPATIONAL MORTALITY STUDIES

Studies on animals have identified a multiplicity of tumors, in addition to HAS, following exposure to VCM (see below). As a result, a series of cohort mortality studies, primarily of PVC polymerization workers, have evaluated the risk for all malignant neoplasms in these groups [10, 12, 24, 49, 50, 61, 63, 75]. Some of the primary difficulties in conducting and interpreting these studies included the relative youth of the PVC industry (so that most of the workers in the various cohort studies have not passed through the age of peak cancer occurrence), the relatively small numbers of deaths among workers with prolonged exposure and latency in some of the studies, and the difficulty in precisely quantifying past exposure to VCM, PVC, and other chemicals used in the polymerization processes, such as other monomers used in the production of copolymers.

An increased risk of HAS was seen in the majority of studies [12, 24, 49, 61, 63, 75]. Waxweiler et al. noted an increased risk of respiratory cancer [74]. Detailed follow-up investigation demonstrated that the excess lung cancer risk was primarily in the large-cell undifferentiated histologic subtype (not previously related to either smoking or chemical exposure) and was related most closely to PVC dust exposure rather than to VCM exposure [74]. An increased risk of respiratory cancer was seen also by Buffler et al. at a VCM production plant, where exposure would have been to VCM rather than to PVC resin [10]. Increases in brain cancer and lymphatic tumors have been noted [75]. Therefore, it is imperative to continue follow-up of the already identified and studied cohorts and to distinguish between exposures to VCM and PVC in the analyses, to discover whether the trends of excess cancer risk noted above continue and are confirmed.

EXPERIMENTAL STUDIES

In 1971 Viola et al. first demonstrated the carcinogenicity of VCM in rats exposed to 30,000 ppm for 12 months [69]. Hepatocarcinogenicity, particularly HAS, was reported later in a series of experiments by Maltoni [43] and reproduced in other laboratories [67]. VCM has been reported to produce HAS at doses as low as 25 ppm in rats, and a variety of tumors, including Zymbal gland carcinomas, nephroblastomas, nonhepatic angiosarcomas, and skin, brain, lung, and mammary tumors, have been produced in multiple species (including rats, mice, and hamsters) [43]. Hepatocellular carcinomas also have been observed after exposure of newborns to VCM. Maltoni's data suggest an increase in mammary tumors at doses as low as one ppm [43].

It appears that a metabolite of vinyl chloride, rather than VCM itself, is the ultimate carcinogenic substance. In bacterial and other test systems, the mutagenicity of VCM is greatly increased by the addition of a metabolizing system (e.g., rat liver microsomes), and an evaluation of animal carcinogenicity data suggested a closer link of HAS formation with amount of VCM metabolized than with VCM exposure concentration [7, 28]. Although a number of mutagenic metabolites are formed, the reactive epoxide (chloroethylene oxide) formed during the oxidative metabolism of the VCM double bond appears of greatest concern. The short-lived active metabolites are formed in the hepatocytes but are carcinogenic in the adjacent sinusoidal cells, which, unlike the hepatocytes, appear to have limited ability for detoxification [51, 56]. The reactive metabolite(s) are thought to initiate the carcinogenic process by covalent bonding to hepatic macromolecules, including DNA [71].

The evidence for the carcinogenicity of vinyl chloride has raised considerable concern about the safety of a number of structurally related halogenated hydrocarbons [11]. Studies on animals indicate the probable hepatocarcinogenicity of vinylidene chloride [68] and vinyl bromide [8], and epidemiologic studies on humans (although of questionable quality) have raised concern about the carcinogenicity of chloroprene [36]. Reviewing

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