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The Hepatic Role in Carcinogenesis and Its Early Detection—The Vinyl Chloride Model[1,2]

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The liver's role in vinyl chloride toxicity and carcinogenicity is providing a better understanding of the chemical carcinogenesis mechanism. A variety of both malignant and benign hepatic tumors has been demonstrated with prolonged exposure to vinyl chloride. The multi-system involvment of this carcinogen and toxin has provided a model for the study of chemical carcinogenesis common to both man and animal. Clinical studies have shown the usefulness of biochemical, radioisotopic, and radiological studies in the detection of toxic and carcinogenic lesions. Animal studies have demonstrated the biochemical metabolism by the liver of vinyl chloride-produced intermediates which are mutagenic in bacterial systems and may be the ultimate carcinogens. Hepatic subcellular enzyme studies prove preliminary evidence of cellular adaptation and increased detoxification. Disruption of this oxidization and detoxification balance may be the key to the malignant transformation of cells. A working hypothesis is presented which may explain the metabolism of vinyl chloride into mutagenic intermediates by the liver cell and the development of malignant transformation by extra hepatic sinusoidal lining cells, lung cells, and brain tissue.

INTRODUCTION

Currently there is a growing concern that chemical compounds may be responsible for most human cancer through environmental contact. Although 100,000 to 200,000 new chemicals are introduced into industry each year, little is known about their effects. These compounds are primarily synthetics and thus not natural to the environment. The view that industrial chemicals may be latent carcinogenic hazards has again been brought into sharp focus by the discovery of vinyl chloride-induced angiosarcoma. Vinyl chloride ($CH_2 = CH-Cl$ monochloroethyene, a gas) is the basic molecule or monomer of polyvinyl chloride and its co-polymers and one of the most important organic intermediates in the plastics industry. The resulting plastic resin, polyvinyl chloride, is used in innumerable consumer and industrial products, such as containers, wrapping film, electrical insulation, pipelines, credit cards, etc. Until recently (early 1970's) vinyl chloride was regarded as being relatively non-toxic [1,2]. Initially this opinion seemed to be supported by the facts that it was used transiently as an anaesthetic and had been used commercially in industry for many years [3].

The direct information on the toxicity of vinyl chloride to man was obtained from experiments by research workers on themselves, from the evaluation of its suit-

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[2]This article is the thirteenth in a series entitled, "Seminars on Liver Disease," that have been presented as part of the Training Program in Liver Disease at the Veterans Administration Hospital, West Haven, Connecticut. Dr Harold O. Conn, Professor of Medicine, Yale University School of Medicine, and Director of the Training Program in Liver Disease, is guest editor.

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ility as an anaesthetic [4, 5], and from study of the cases of vinyl chloride poisoning contracted during industrial use [6, 7, 8, 9].

Sporadic studies with vinyl chloride polymerization workers demonstrated varying degrees of hepatic biochemical derangements, hematological abnormalities, and skin changes [9]. Acute short term exposures led to disturbances of the central nervous system, cardiac arrythmias, severe irritation of the mucosal membrane of the eyes and the respiratory tract, and in some cases—severe pulmonary edema with obstruction of the liver and kidneys. Chronic inhalation trials in animals clearly showed that vinyl chloride was toxic to the liver and kidneys as well as irritating to the mucosal membranes and the lungs. Microscopic examination of liver sections showed degeneration of the central lobules while the damage to the kidneys chiefly involved the tubule and the interstitial lining somewhat like that of carbon tetrachloride damage [10, 11, 12].

BACKGROUND

The literature, however, contained virtually no information on damage to man after chronic exposure until Filatova et al. reported disturbances of the blood vessels and nerves in individuals exposed with 20–300 ppm of vinyl chloride on a continuous basis [13]. Cordier et al. [14] and Wilson et al. [15] were the first to report the hitherto unrecognized disorder termed occupational acroosteolysis (AOL) which included the symptoms of tenderness of the fingertips, gradual destruction of bony integrity of the fingers and a Raynaud's-like phenomena.

Studies were initiated in animals to reproduce the acroosteolysis. In 1971, Viola et al. [16] while exposing animals to 30,000 ppm to induce acroosteolysis, accidentally discovered cancer. Maltoni et al. [17] while studying various levels of exposure demonstrated that angiosarcoma occured at 250 ppm; the Manufacturing Chemists Association's studies [18] demonstrated these liver cancers even at 50 ppm. At the same time, Dr. John Creech, at the B.F. Goodrich Chemical Company Plant in Louisville, Kentucky, discovered an hepatic angiosarcoma in one employee. Creech, recalling an earlier hepatic angiosarcoma at the plant, reviewed the medical histories of previous employees. Four additional angiosarcomas were found, further supporting the connection between vinyl chloride exposure and tumor development. Measures to control the levels of vinyl chloride exposure were then instituted following federal regulation.

THE CHEMICAL

Vinyl chloride's chemical structure is a double-bonded, 2-carbon halogenated hydrocarbon which has structural similarities to tri-chloroethylene, an inhalation anaesthetic. As previously noted, vinyl chloride was once considered as an anaesthetic but was discarded because it caused myocardial irritability. Some of its important physical properties include a low boiling point, a high specific gravity, a low solubility in water, and a half-life in air which ranges from 3–20 hours. Knowledge of these physical properties may be important in determining how this agent produces a cumulative effect in the environment which ultimately leads to cancer formation.

Vinyl chloride is both toxic and carcinogenic, as recognized by the wide variety of associated disorders which have been found among vinyl chloride polymerization workers and vinyl chloride-exposed animals. A yet incomplete list of these