



THE DOW CHEMICAL COMPANY

BENNETT BUILDING
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September 22, 1978

Joseph T. Seawell
MCA
1825 Connecticut Avenue, NW
Washington, D. C.

cc: MCA Vinyl Chloride Research
Coordinators

Dear Mr. Seawell:

This is to call to your attention a paper by Hans Popper et al. It is a long article with 6 pages of photographs.

Note that in the discussion section, the authors state they can not tell a vinyl chloride angiosarcoma from any other.

Sincerely,

T. R. Torkelson, Chairman
MCA Technical Panel on
Vinyl Chloride Research

Enclosure

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SEP 25 1978

Environmental Affairs

SL 095932

Development of Hepatic Angiosarcoma in Man Induced by Vinyl Chloride, Thorotrast, and Arsenic

Comparison With Cases of Unknown Etiology

Hans Popper, MD, PhD, Louis B. Thomas, MD, Norman C. Telles, MD,
Henry Falk, MD, and Irving J. Selikoff, MD

Examples of human angiosarcoma following exposure to vinyl chloride, Thorotrast, or arsenic (medicinal and industrial) and cases, including children, of unknown etiology were studied to establish diagnostic criteria and to study their evolution. The uniform evolution suggests an environmental factor also in the cases of unknown etiology, which may be established by epidemiologic studies. A precursor stage is characterized by areas of combined hyperplasia of hepatocytes and a variety of sinusoidal and perisinusoidal cells associated with excess of reticulin and with sinusoidal dilatation. The diagnostically useful picture in silver impregnations indicates reticulum formation by the perisinusoidal cells, presumably the lipocytes. The hepatocytic proliferation suggests a hepatocarcinogenic but usually not fully expressed potential. The mixed hyperplasia of the various sinusoidal cells proceeds to an overgrowth of angiosarcoma cells, presumably derived from endothelial cells. In early stages they are usually in contact with hepatocytes (intralobular growth). A trabecular arrangement results from loosening of the lobular plate arrangement by dilatation of sinusoids, leading to primary peliosis. With disappearance of the hepatocytes, various growth patterns develop, terminating in nodular, solid angiosarcoma composed of either spindle-shaped or polyhedral cells which undergo necrosis or hemorrhage (secondary peliosis). The interaction between hepatocytes and sinusoidal cells requires elucidation. (*Am J Pathol* 92:349-376, 1978)

THE RECOGNITION of the association between exposure to gaseous vinyl chloride during its polymerization to the common plastic polyvinyl chloride and the appearance of hepatic angiosarcoma¹ has increased the interest in this tumor. This concern was accentuated by its production in rodents exposed experimentally to vinyl chloride before the human lesion was recognized.² Until then, hepatic angiosarcoma had been considered rare in man, although it has been known that exposure to thorium dioxide (Thorotrast)³ and inorganic arsenicals⁴ may be followed by de-

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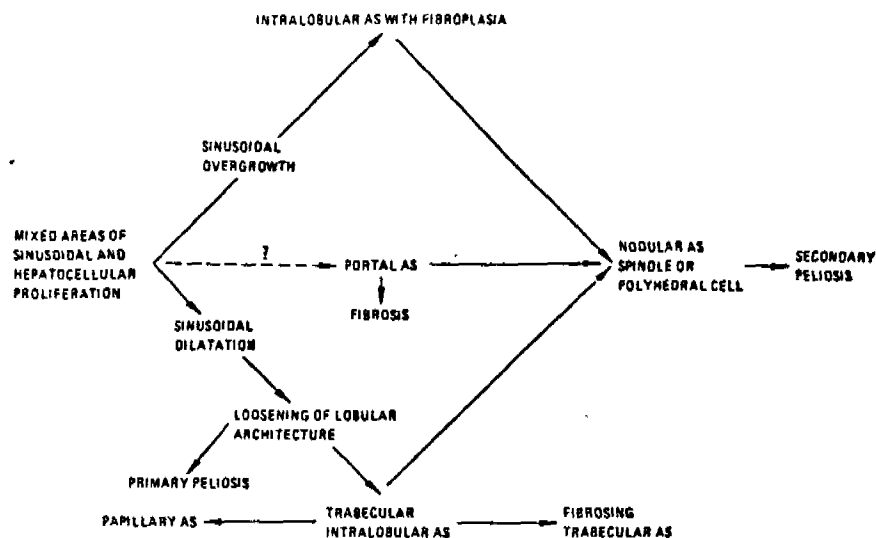
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Address reprint requests to Louis B. Thomas, MD, Chief, Laboratory of Pathology, National Cancer Institute, NIH, Building 10, Room 2A27, Bethesda, MD 20014.

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TEXT-FIGURE 1—Proposed schema of evolution of hepatic angiosarcoma (AS).

giopericytoma, mixed mesenchymoma, hemorrhagic hepatocellular carcinoma, or various types of metastatic tumor were diagnosed as angiosarcoma.

The mixed hyperplastic areas are not readily diagnosed in needle biopsy specimens. Silver stains are then most helpful.

Discussion

Morphologic study of a large number of cases of angiosarcoma and their developmental stages revealed few, if any, differences between the cases induced by agents such as vinyl chloride, arsenic, Thorotrast and those in which no etiologic agent has been established. Intensive study of a far larger number of cases did not confirm our early impression that vinyl-chloride-related angiosarcoma differs morphologically from cryptogenic cases.⁶ This suggests that in cryptogenic cases, environmental factors are responsible, the nature of which is being sought by intensive epidemiologic studies.⁷⁵ The available surveys^{19,20} indicate a recognized environmental etiology in only a small percentage of cases of hepatic angiosarcoma.

The observations provided information of potential assistance in the diagnosis of the lesion, including the precursor stage. This information should be helpful in the diagnosis of industrial hazards. The enforcement of strict hygienic regulations has reduced the levels of vinyl chloride in the polymerization plants or other places where polyvinyl chloride is proc-