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Classical Syndromes in Occupational Medicine

Pathological Lessons From Vinyl Chloride Angiosarcoma

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Hyperplastic or neoplastic nodules with potential transition to frank hepatic carcinoma may be produced in experimental animals particularly rodents [Newberne and Butler, 1978], by an abundance of industrial and other chemicals. On the other hand, firm epidemiologic evidence of causation of tumors in the human liver by the vast majority of the industrial agents is not available today [Popper and Selikoff, 1981a]. Hepatic tumors, however, in experimental animals are conventionally considered as proof of carcinogenic potential, possibly expressing itself in other organ sites in man, rather than evidence for likely hepatic carcinogenicity per se. Thus, they are viewed in this way by regulatory agencies [Nicholson, 1981]. The important exception to this uncomfortable uncertainty in regulatory action is the experience with vinyl chloride, where the relation between experimental production of hepatic lesions and the recognition of a specific tumor in man deserves recounting as an interesting example of a reliable application of observations in experimental animals to man.

Viola et al [1971] in 1970 described tumors of lung, bones, and particularly in the zymbal glands near the ear in rats which had been exposed to inhalation of gaseous vinyl chloride. In 1974 Maltoni of Bologna [Maltoni and Lefamine, 1974a] recorded in an

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Italian journal, not widely read in the United States, angiosarcomas in the liver and other sites in rats as the result of inhalation studies. Significant numbers of hepatic angiosarcomas developed under doses of from 30,000 to 250 ppm, given five times a week for 135 weeks. This observation had not been widely appreciated when Creech and Johnson [1974], also in 1974, described angiosarcomas of the liver in four workers in Louisville who had been engaged in the polymerization of vinyl chloride monomer to the plastic polyvinylchloride. Since this is a rare tumor in man, its observation in a relatively small work force raised the suspicion of a causal relation to vinyl chloride exposure. This called attention to Maltoni's observations. Nonspecific lesions in the liver had been previously reported, particularly in the Eastern European literature, and it also had been known that vinyl chloride workers frequently suffered from a characteristic scleroderma-like skin and bone abnormality, acroosteolysis [Jühe and Lange, 1972]. In Germany, therefore, workers in vinyl chloride plants were screened by dermatologists, who detected enlargement of the spleen. That led to thorough investigation of such workers by internists, who recognized by combined clinical, laparoscopic, and histologic investigations a peculiar hepatic fibrosis which produced in some of these workers the picture of idiopathic portal hypertension, which sometimes led to bleeding of esophageal varices [Marsteller et al, 1973]. Peculiarly enough, angiosarcoma was not found in this group at the time, although it was subsequently also noted [Lange et al, 1974].

Stimulated by the coincidence of these observations, a conference on the toxicity of vinyl chloride/polyvinylchloride was speedily convened by Doctors I. J. Selikoff and E. C. Hammond at the New York Academy of Sciences in May, 1974 [Selikoff and Hammond, 1975]. It surveyed older studies as well as recent investigations dealing with epidemiology, metabolism of the agent, clinical changes, and morphologic findings in animals and man. Ever since, a larger number of studies have been carried out all over the world. Moreover, Maltoni provided additional evidence about the lowest vinyl chloride levels which induce angiosarcoma in rodents [Maltoni and Lefamine, 1974b]. Evaluation of these data resulted in the reduction of the maximum permissible concentration in the ambient air in U.S. factories to 1 ppm with excursions not exceeding 5 ppm for short intervals. Similar reductions were legislated in other countries [Lelbach and Marsteller, 1981].

Here, the similarity in the evolution of the various stages of vinyl chloride-induced hepatic lesions in man and experimental animals [Popper et al, 1978; Popper et al, 1981b] will be detailed to provide lessons for environmental pathology. The initial lesion in both man and rodents (Figs. 1, 2) is focal proliferation of hepatocytes which show variations in size and appearance of nuclei, subsequently associated with an increase of sinusoidal cells of various types (Fig. 3). This in turn is accompanied by an increase of perisinusoidal collagen fibrils, recognized by electron microscopy, which also reveals an increase of fat-storing interstitial, or Ito, cells, which have been considered precursors of fibroblasts [Kent et al, 1976]. Silver impregnation visualizes the increase of reticulin fibers in circumscribed zones. These histologic features have served in coded routine microscopic examination of liver biopsy specimens to identify workers who have been exposed to vinyl chloride and other chemical agents. They were absent in controls [Tamburro et al, 1979]. They thus may represent a morphologic diagnostic criterion, since biochemical hepatic tests have been less useful in the identification of injury in such workers. However, the precursor lesion in the biopsy specimens does not exclude the simultaneous presence of fully developed angiosarcoma in other parts of the liver. It is therefore an indication for diagnostic follow-up by radionuclide scanning and angiography and subsequent confirmation by open liver biopsy [Dannaher et al, 1981a].

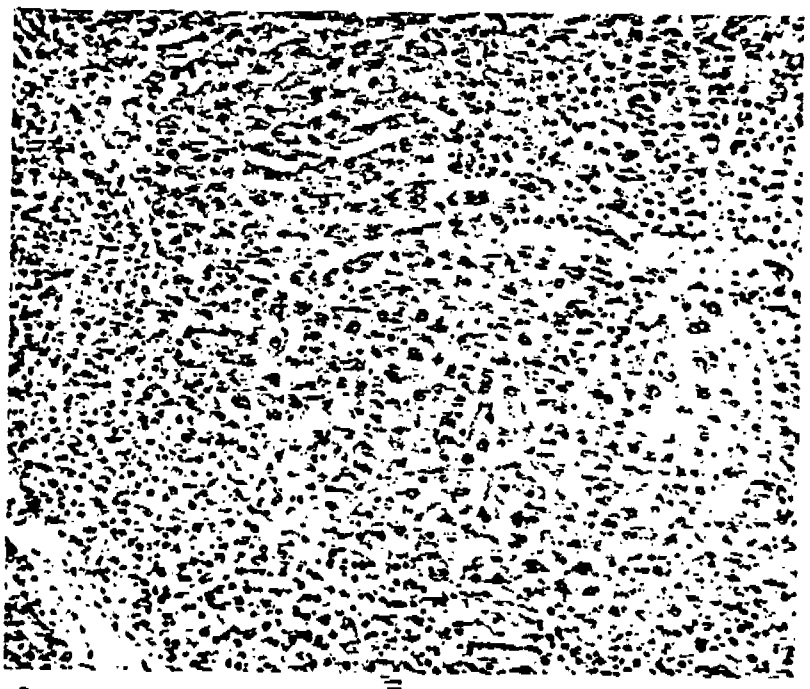

Fig. 1. Rat exposed to 500/ppm vinyl chloride by inhalation for 126 weeks (material of Dr. C. Maltoni, Bologna). In center note sharply defined area in which hepatocytes are markedly enlarged and sinusoidal cells somewhat increased (H&E, × 100).

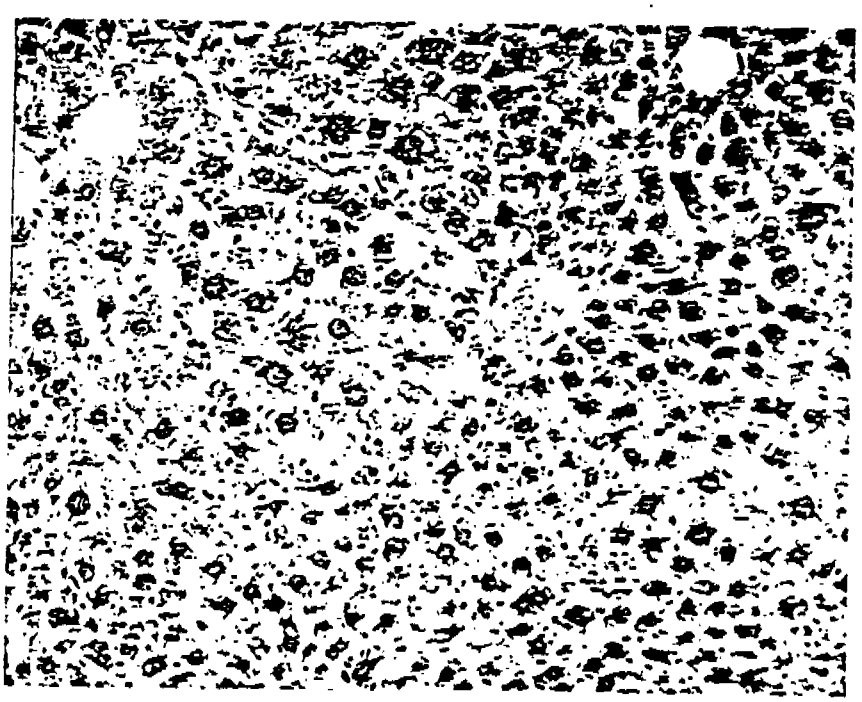

Fig. 2. Mouse exposed to 2500/ppm vinyl chloride by inhalation for 6 months. Note irregularly limited area in center where hepatocytes are markedly enlarged and sinusoidal cells are proliferated. (H&E, × 200).

Fig. 3. Biopsy specimen of vinyl chloride worker. Scattered hepatocytes are enlarged and sinusoidal cells of different type are conspicuously increased (H&E, × 240).

In both man and animals the proliferation of sinusoidal cells that is described above may become more conspicuous, and cells with hyperchromatic spindle-shaped nuclei gradually exceed the other sinusoidal cells in number (Fig. 4). Eventually the features of intralobular angiosarcoma develop which, in rodents, is always multicentric. Obstruction of the sinusoidal lumen by multiple layers of these cells leads to enlarging areas of necrosis.

While exposure of adult rodents to vinyl chloride results in angiosarcoma, similar exposure of newborn rats has produced mainly hepatocellular carcinoma [Maltoni and Lefemine, 1974b] (Fig. 5), which might be explained by altered hepatocellular biotransformation in the newborn state. Another frequent feature of the precursor stage is dilatation of the sinusoids with an increased number of lining cells. This dilatation is not predominant around the tributaries of the hepatic veins and therefore can not be explained by passive congestion. Rather it is a specific effect of the agents on the sinusoidal wall. Alterations of the lining cells have been seen here by electron microscopy, which also reveals accumulation of platelets [Popper et al, 1977]. The progressive sinusoidal dilatation leads to the more frequent form of angiosarcoma, the trabecular angiosarcoma (Fig. 6), which is characterized by large bloody cysts traversed by cords consisting either of initially hyperplastic hepatocytes or of portal and central canals. All these structures are lined by increased connective tissue and angiosarcoma cells which invade the cords (Fig. 7). Advancing fibrosis and neoplasia lead, as a rule, to atrophy and disappearance of the hepatocytes (Fig. 8), although in some instances they appear, even in later stages, rather hyperplastic and resemble hepatocellular carcinoma. Moreover, solid nodules of angiosarcomas often form. They might consist of spindle shaped cells, but also of large polyhedral tumor cells with abundant eosinophilic cytoplasm (Fig. 9). These have also been called

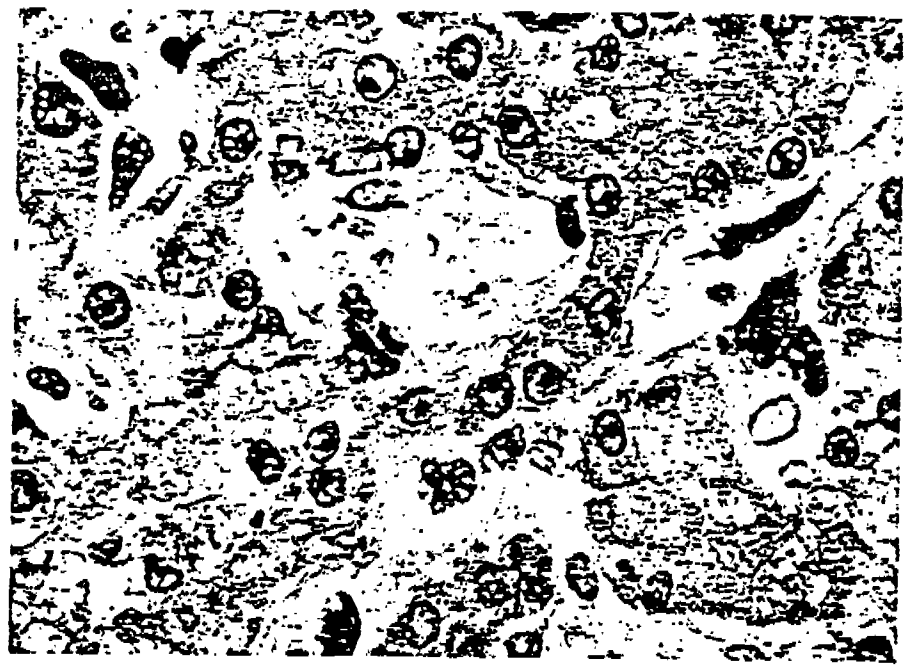

Fig. 4. Autopsy specimen of vinyl chloride worker. The sinusoidal cells, of different type, are enlarged, sometimes in layers, their nuclei are frequently hyperchromatic or multiple. Some sinusoids are widened (H&E, × 250).

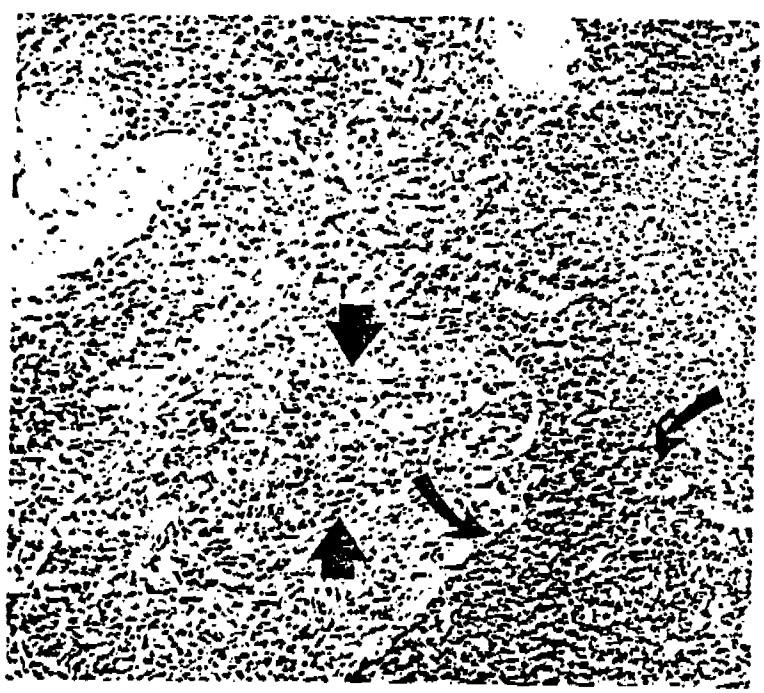

Fig. 5. Very young rat exposed to 500/ppm vinyl chloride by inhalation five times a week for 76 weeks (material of Dr. C. Maltoni, Bologna). Note neoplastic nodules (between curved arrows) and hepatocellular carcinoma (between straight arrows) with dilated vascular spaces (H&E, × 100).

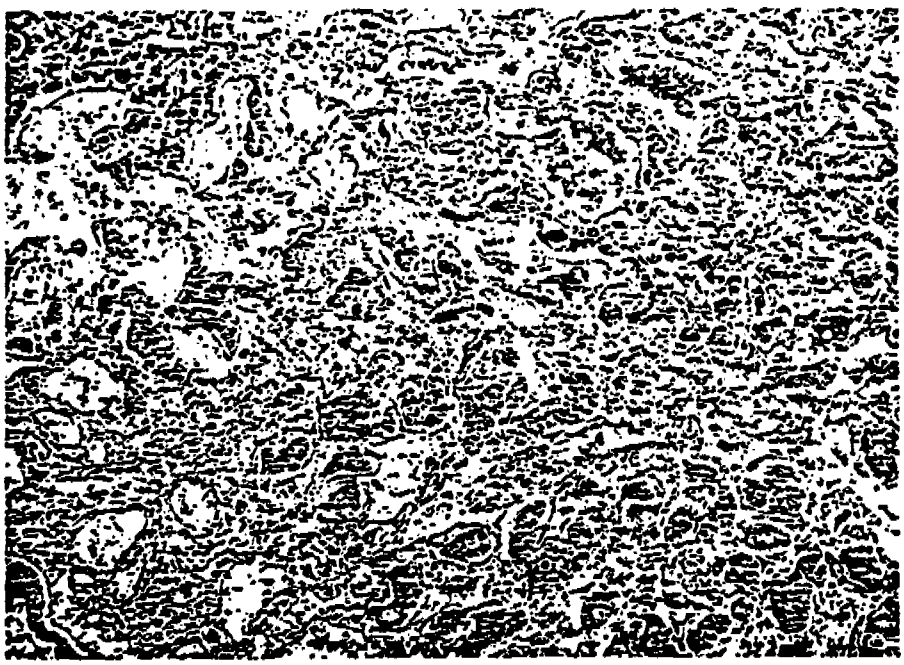

Fig. 6. Autopsy specimen of vinyl chloride worker. Trabecular angiosarcoma. The hepatocytes, arranged in cords, are hyperplastic (right lower aspect). The dilated spaces are lined by angiosarcoma cells (H&E, × 40).

Fig. 7. Mouse exposed at 2500/ppm vinyl chloride five times a week for 6 months by inhalation. Polyhedral angiosarcoma cells line dilated blood space which is traversed by hepatocytic cords (straight arrows) and remnants of portal tract (curved arrow). Both are surrounded by angiosarcoma cells (H&E, × 150).

Fig. 8. Autopsy specimen of vinyl chloride worker showing trabecular angiosarcoma. The hepatocytes are hyperplastic (in upper aspect) and squeezed by fibrosis becoming atrophic (curved arrow) in lower aspect. The perisinusoidal tissue spaces are sometimes expanded and contain angiosarcoma cells (straight arrow) (H&E, × 100).

Fig. 9. Autopsy specimen of vinyl chloride worker. Clusters and cords consisting of solid angiosarcoma (arrows) in blood spaces (H&E, × 100).

histiocytoid [Rosai et al, 1979]. The derivation of the tumor cells is not fully established, even on fine-structured analysis. However, demonstration of factor VIII in the tumor cells strongly supports an endothelial cell origin [Fortwengler et al, 1981] and speaks against a Kupffer cell tumor. Still, at this time, the noncommittal term 'angiosarcoma' is preferred. Usually the picture of trabecular angiosarcoma is so characteristic that it is readily diagnosed in biopsy specimens. At human autopsies, however, all forms of angiosarcoma are almost always multicentric. This observation discourages surgical intervention even in early stages. Chemotherapy offers limited promise [Dannaher et al, 1981b].

Thus vinyl chloride produces a well defined histologic sequence virtually identical in animals and man. Moreover, there is evidence on the basis of limited human material that prolonged exposure to inorganic arsenicals, for instance Fowler's solution in the treatment of asthma or psoriasis, has led to the same sequence. This however, has not been reproduced in experimental animals [see Popper et al, 1978]. Several decades ago the use of inorganic arsenical pesticides in vineyards, now prohibited, was associated with angiosarcoma, cirrhosis, and hepatocellular carcinoma [Roth, 1957]. In India, increased arsenic in drinking water has been associated with idiopathic portal hypertension [Datta, 1976], supporting the assumption that this rare disorder in the Western world may be explained by either arsenic or possibly other agents, so far unidentified. Study of more extensive material or oriental idiopathic portal hypertension suggests, however, a different pathogenesis, namely, a disorder of intrahepatic portal vessels [Futugawa et al, 1980]. Thorotrast, used years ago in radiologic visualization, mainly of cerebral vessels, has been followed by both angiosarcomas and carcinomas of either hepatocellular or cholangiocellular type; in a few specimens the precursor lesion has been identified, and animal experimental reproduction has also been reported [see Popper et al, 1978].

A survey of hepatic angiosarcomas observed during a ten-year period in the United States [Popper et al, 1978; Falk et al, 1981] has regularly shown the presence of the same precursor lesion in almost all instances. This suggests that at this time in idiopathic cases there are some so far unidentified environmental factors. Arsenic is a candidate. Moreover, this survey has discovered patients with angiosarcoma in whom a history of intake of large doses of androgenic/anabolic steroids was recorded [Falk et al, 1979]. This suggests that these steroids may join vinyl chloride, thorotrast, and arsenic as etiologic factors in angiosarcoma. Recently such tumors have also been observed following ingestion of oral contraceptives [Monroe et al, 1981] or long-term estrogen therapy for carcinoma of the prostate [Ham et al, 1980]. Since all these steroids produce, besides cholestasis, sinusoidal dilatation and adenomas, it appears now that there may be a group of agents responsible for a previously unrecognized sequence that is associated neither with cirrhosis nor with elevated serum alpha-fetoprotein. It starts with an identical precursor stage, namely, mixed sinusoidal and hepatocellular hyperplasia, not necessarily recognized by common hepatic tests. The sequence may terminate in idiopathic portal hypertension or hepatic tumors like adenoma, carcinoma, or angiosarcoma. Thus, a group of environmentally induced hepatic lesions is now being recognized which may possibly also be induced by other agents, so far not appreciated. Substances related to vinyl chloride, such as vinyl bromide [Bolt et al, 1979] or vinylidine chloride [Reitz et al, 1980] have produced a similar sequence in experimental animals. This calls for increased vigilance in the use of chemically related substances produced in industry. In contrast it should be stressed that for the hepatocellular nodules without significant participation of sinusoidal cells, produced in rodents by many industrial and other environmental agents, a human counterpart has so far not been convincingly demonstrated, with the exception of the

mycotoxin aflatoxin. Even for the latter, the human evidence is so far still circumstantial [Popper 1979]. This lack of proven examples of human hepatocellular carcinoma caused by industrial agents which produce lesions in experimental animals including, in the case of nitrosamines, primates, does not exclude their carcinogenic potential in man. Almost all are metabolized in the human liver and a promoting effect cannot be excluded. In recent years, the promoting action in hepatocarcinogenesis has been given greater importance over the initial effect of DNA alteration, recognized by mutagenesis. Moreover, since most human hepatocellular carcinomas are associated with two principal factors, namely alcoholism and hepatitis B infection [Popper, 1979] the causal relation may be more readily overlooked than in the case of agents producing the more unusual angiosarcoma. Delineation of the promoting effect of the other industrial agents, perhaps by alteration of microsomal biotransformation or by stimulation of proliferation of hepatocytes, is a task of the future.

So far the number of recorded human hepatic angiosarcomas defined as associated with vinyl chloride exposure seems not to exceed 95 worldwide [Falk et al, 1981; Baxter et al, 1980; Pialat et al, 1980; Wagoner et al, 1980], although listings are incomplete. Most recent cases have been reported in Germany and France but no new cases of angiosarcoma were detected in the last seven years from those plants in the U.S. where they were originally described [Dannaher et al, 1981a]. Hepatocellular carcinoma has been very rare [Koischwitz et al, 1981]. Other manifestations of "vinyl chloride disease" [Lelbach et al, 1981; Veltman, 1980] are also not common.

Recognition of the sequences induced by vinyl chloride and the other agents mentioned and their reproduction in experimental animals are an important lesson in environmental medicine. It has not only facilitated clinical recognition but, even more important, has led to control of exposure and avoidance of additional disease. Too, it has spurred the search for similar sequences resulting from chemically related agents. Finally, human pathology has been enriched by description of entities produced by exposure to environmental, including industrial, agents.

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