VINYL-CHLORIDE-INDUCED LIVER DISEASE

From Idiopathic Portal Hypertension (Banti's Syndrome) to Angiosarcomas

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Abstract Histologic examination of liver tissue (eight autopsy and 18 biopsy specimens) and five spleens from 20 workers with vinyl chloride polymerization showed hepatic angiosarcomas in 15. In addition, a peculiar pattern of progressive portal-tract, inconspicuous intralobular and conspicuous capsular fibrosis was observed in the five workers without angiosarcoma, in all the seven patients with angiosarcoma from whom tumor-free portions of the liver were available, and in two tumor-free biopsies from patients subsequently found to have angiosarcoma. The fibrosis was accompanied by splenomegaly. Hypertrophy and hyperplasia of both hepatocytes and hepatic and splenic mesenchymal cells were also seen. The histologic similarity to chronic inorganic arsenical poisoning, in which angiosarcomas also occur, and to idiopathic portal hypertension (Banti's syndrome) suggests that the latter syndrome at times results from unknown toxic, possibly environmental, chemicals. (N Engl J Med 292:17-22, 1975)

THE development of hepatic angiosarcomas in workers exposed to vinyl chloride gas in the manufacture of polyvinyl chloride has been well documented.[1-3] Histologic study of hepatic and splenic specimens taken from such workers suggests to us, moreover, that other diseases that have not in the past been related to industrial exposure may be involved. Specifically, a case will be made for the concept that splenomegaly with portal hypertension associated with slight hepatic fibrosis, previously designated as Banti's syndrome,[4] may be the result of exposure to known or unknown chemical agents.

HISTORY OF THE VINYL CHLORIDE LIVER INJURY

Polyvinyl chloride, one of the most widely used synthetic plastics, has been manufactured for more than 40 years by polymerization of gaseous vinyl chloride in the United States and in many other countries. Concern about untoward side effects in workers had centered primarily on a disease, acro-osteolysis,[5] which is characterized by Raynaud's syndrome, dermal induration and bone lesions. Two reports[6,7] also dealt with nonspecific alterations of hepatic structure and function, and a lesion designated "chronic epithelial hepatitis" was found in about 25 per cent of the examined workers in Russia.[6] Hepatic abnormalities, which did not attract major attention, became far more important because of the discovery of three cases of angiosarcomas of the liver, an otherwise very rare tumor, in workers in a polyvinyl chloride production plant in this country.[1] The introduction of a surveillance system in this plant detected a total of seven cases of hepatic angiosarcoma.[2,8] Animal experiments confirm the relation between hepatic angiosarcoma and exposure to gaseous vinyl chloride. In 1971, Italian investigators reported that prolonged inhalation of vinyl chloride produced carcinomas of the zymbal gland in rats,[9] and Maltoni[10] subsequently described angiosarcomas of the liver and other organs as well as nephroblastomas in rats exposed to vinyl chloride gas. Recently, angiosarcomas of the liver have been seen in mice after exposure to as little as 50 ppm of vinyl chloride.[11]

When specimens of human angiosarcoma from vinyl chloride polymerization workers were reviewed in the Laboratory of Pathology of the National Cancer Institute, the lesions in areas of the liver not involved by angiosarcoma appeared similar to alterations recently reported in vinyl chloride workers in Germany.[12] In these patients inconspicuous portal and perisinusoidal fibrosis was associated with impressive hepatic capsular fibrosis as seen by peritoneoscopy. Hepatic-function tests revealed variable abnormalities. Clinical manifestations included portal hypertension with splenomegaly, thrombocytopenia and bleeding esophageal varices. This German report focused our interest on the appearance of the liver not only in patients with hepatic angiosarcomas but also in other workers with hepatic fibrosis exposed to vinyl chloride who had been diagnosed as having cirrhosis because of portal hypertension, variceal hemorrhage and splenomegaly.

By coincidence, there have been several recent reports of portal hypertension without obvious cause in patients with psoriasis who had received an inorganic arsenic preparation, Fowler's solution, for prolonged periods.[13-15] These observations were interesting in view of earlier reports from Germany and France of hepatic angiosarcomas developing in vintners exposed to insecticides containing inorganic arsenic.[16] Roth's report included 47 workers with chronic arsenic intoxication. Of these, four had hepatic carcinomas, five had sarcomas (angiosarcomas), and 13 of 27 autopsied by him had unusual types of cirrhosis.[16]

MATERIAL STUDIED

The observations recorded here are based on the study of hepatic tissues obtained from 20 workers who had industrial exposure to vinyl chloride for prolonged periods, usually exceeding two years and extending up to 18 years. The tissues were derived from 15 patients with angiosarcoma and five with hepatic fibrosis but without angiosarcoma. The majority of these specimens were initially obtained, studied, and in some cases reported by others,[1-3] but all were submitted to the Laboratory of Pathology, Na-

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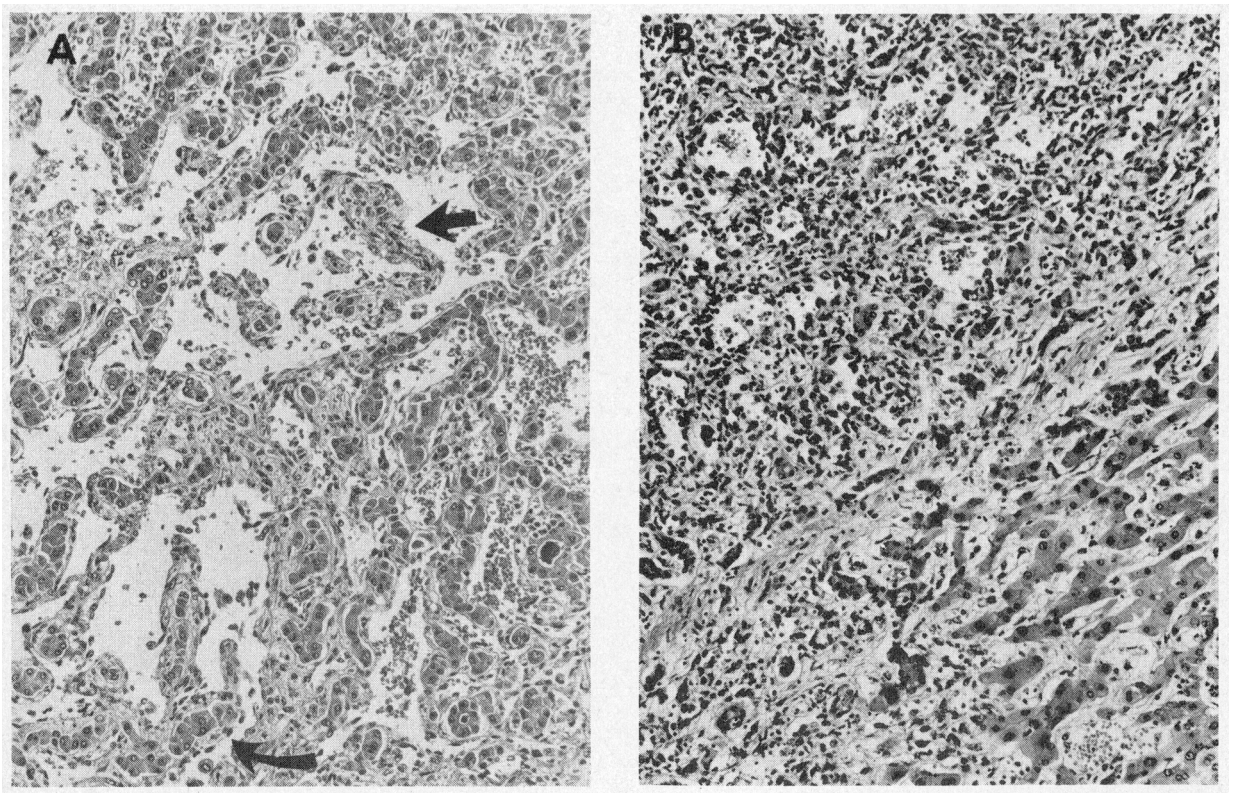

Figure 1. Hepatic Angiosarcoma in a Worker Engaged in Polymerization of Vinyl Chloride.
A shows sinusoidal pattern progressing to a papillary pattern (straight arrow) (hematoxylin and eosin stain × 100). Note enveloping tumor cells separated by widened tissue space of Disse (curved arrow).
B shows small cavernous spaces with transition to anaplastic growth in angiosarcoma in the upper part of the photomicrograph and liver-cell plates enveloped by sarcoma cells in the right lower corner (hematoxylin and eosin stain × 100).

tional Cancer Institute, for review. Because of the nature of our access to the material, these specimens do not represent a consecutive series and cannot be considered to indicate the relative frequency of these vinyl-chloride-associated hepatic lesions.

Twenty specimens from the 15 patients with angiosarcoma were reviewed, and 18 of these (eight autopsy and 10 biopsy), showed angiosarcoma. In addition, two of these patients had previous liver biopsies that had been obtained six and three months before the diagnosis of hepatic angiosarcoma was made. In seven of the patients (four autopsy and five biopsy specimens) sufficient liver tissue was present outside the angiosarcoma and free of pressure effects to permit an evaluation of the morphology of the tumor-free portions of the liver.

Liver tissue was obtained by biopsy (five surgical and one needle-biopsy specimens) in the five patients with hepatic fibrosis without known angiosarcoma. In one patient in whom hepatic fibrosis had been observed in an initial surgical biopsy specimen, a follow-up needle biopsy was obtained during peritoneoscopy after an interval of two years, the patient having had no further exposure to vinyl chloride.

Observations of the splenic changes were made on three surgical and two autopsy specimens. All specimens were fixed in formalin and studied by conventional microscopical technics.

Observations

Angiosarcoma

Although the presence of angiosarcomas in vinyl chloride workers has previously been reported, the histologic characteristics of the tumors are briefly described in an attempt to distinguish them from hepatic angiosarcomas apparently not induced by chemicals and to trace their possible relation to the fibrotic lesions. Three basic patterns, listed here in order of frequency, were seen in different parts of the angiosarcomas.

The first, the *sinusoidal* pattern, was characterized by focal, often multicentric, dilatation of sinusoids, with hypertrophic and hyperplastic sarcoma cells forming a lining for the dilated sinusoids. The sarcoma cells enveloped liver-cell plates and bile ductules and infiltrated fibrotic portal tracts (Fig. *1A*). The enveloped hepatocytes were usually hypertrophic and hyperplastic and thus appeared as cords around dilated bile canaliculi, which often contained bile plugs. Loosely arranged reticulin and collagen fibers were present in the widened tissue space of Disse together with increased numbers of non-neoplastic-appearing fibroblasts and macrophages.

The second, the *papillary* pattern, had larger and more irregular vascular spaces. Loose strands of hepatic cords enveloped by sarcomatous cells projected into these spaces. Atrophy and disappearance of hepatic cord cells developed, with increased fibrosis of the widened space of Disse.

The third, the *cavernous* pattern, was characterized by even larger, blood-filled spaces surrounded by thick, fibrotic walls lined by sarcomatous cells (Fig. *1B*).

In addition, one fourth of the angiosarcomas had more solid nodules of anaplastic sarcoma. These nodules com-

pressed the surrounding parenchyma, and in one tumor, anaplastic sarcoma cells invaded portal-vein branches.

Focal dilatation of sinusoids with proliferation and enlargement of the sinusoidal cells associated with perisinusoidal fibrosis may represent an early stage in the evolution of angiosarcoma. This lesion was noted in six of the seven available tumor-free liver specimens from patients with angiosarcoma, and in the two biopsies taken before angiosarcoma was detected. It was also observed in two patients in whom angiosarcoma has not developed, and in whom, accordingly, careful follow-up observation is indicated. In the patients with angiosarcoma, some of the sinusoidal lining cells had enlarged, atypical nuclei and bulky cytoplasm that was PAS negative in contrast to many of the lining cells in the uninvolved parenchyma (Fig. 2). There were gradual transitions between the areas of focal dilatation of sinusoids to multiple, microscopic-sized angiosarcomas with a sinusoidal pattern.

In three patients other organs besides the liver were involved by angiosarcoma: the duodenum in one, the lung in a second, and the lung, heart, kidney and lymph nodes in a third patient.

Hepatic fibrosis

All the livers without angiosarcomas and the uninvolved portions of the livers with angiosarcomas showed the same basic changes, the extent of which varied widely within each specimen. Excess fibrous connective tissue caused variable enlargement of most portal tracts (Fig. *3A*). A distinctive feature was the tendency for single hepatocytes and groups of hepatocytes at the margins of the portal tracts to be separated from adjacent hepatic cord cells and surrounded by this progressive fibrosis. Proliferation of bile ducts was noted in these fibrotic portal tracts together with a variable infiltration of lymphocytes. Occasionally, the walls of portal-vein branches showed focal fibrosis. Adjacent portal tracts were often connected by connective-tissue septa in the sense of a perilobular fibrosis and some thin septa traversed the parenchyma and extended irregularly toward central veins. In two cases, both with angiosarcomas elsewhere in the liver, these septa separated parts of the parenchyma to produce nodules. The hepatic capsule showed focal thickening and nodular fibrotic areas that often extended into subcapsular hepatic tissue to connect with adjacent portal tracts. The sinusoidal lining cells were focally increased in number, especially in areas where sinusoids were dilated. Intralobular, perisinusoidal fibrosis, though inconspicuous in hematoxylin-eosin-stained sections, could be demonstrated in these areas by special stains for reticulin and collagen fibers. In other areas, groups of hepatocytes, with no particular intralobular localization, varied conspicuously in cellular and nuclear size, many of them being distinctly enlarged (Fig. *3B*). Binuclear and multinucleate hepatocytes, some with much cytoplasm, were intermixed with a few hepatocytes that were smaller than normal. Degeneration and necrosis of hepatocytes, although present, were not more conspicuous than in any routine surgical specimen. In the second biopsy specimen, obtained in one patient two years after cessation of exposure to vinyl chloride, these abnormal changes in both hepatocytes and sinusoidal lining cells had disappeared, but the capsular, portal-tract and intralobular fibrosis persisted.

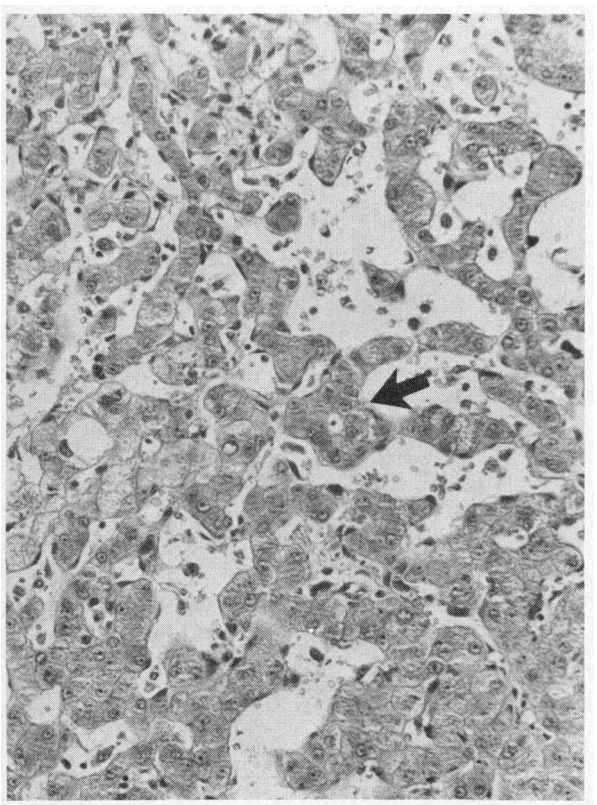

Figure 2. Focal Dilatation of Sinusoids, with Hyperplastic Hepatocytes (Arrow) and Excess Sinusoidal Lining Cells, Some with Hyperchromatic Nuclei (This Appearance Contrasts with That of Normal Sinusoids in the Right Lower Corner) (Hematoxylin and Eosin Stain × 160).

Splenic Changes

The available spleens were large, weighing 560 to 1050 g, and showed on cut section enlarged Malpighian follicles and a firm, beefy red pulp. Microscopically, the follicles were hyperplastic and had large germinal centers and wide perifollicular zones (Fig. 4). Occasionally, fresh hemorrhage was found around penicillary arteries and follicles. The red-pulp sinuses were widened and often lined by a continuous layer of cuboidal reticuloendothelial cells. The slightly thickened pulp cords contained many lymphoid and histiocytic cells as well as erythrocytes. Fibrosis of the red pulp was absent or inconspicuous, and hemosiderinophages were only occasionally seen.

Discussion

The relatively frequent development of hepatic angiosarcomas in workers engaged in the polymerization of vinyl chloride has now been established. In this report the emphasis is on a peculiar hepatic fibrosis in such workers and its relation to the angiosarcomas. This fibrosis, which appears to represent a second hepatic lesion attributable to vinyl chloride exposure, was found in the tumor-free

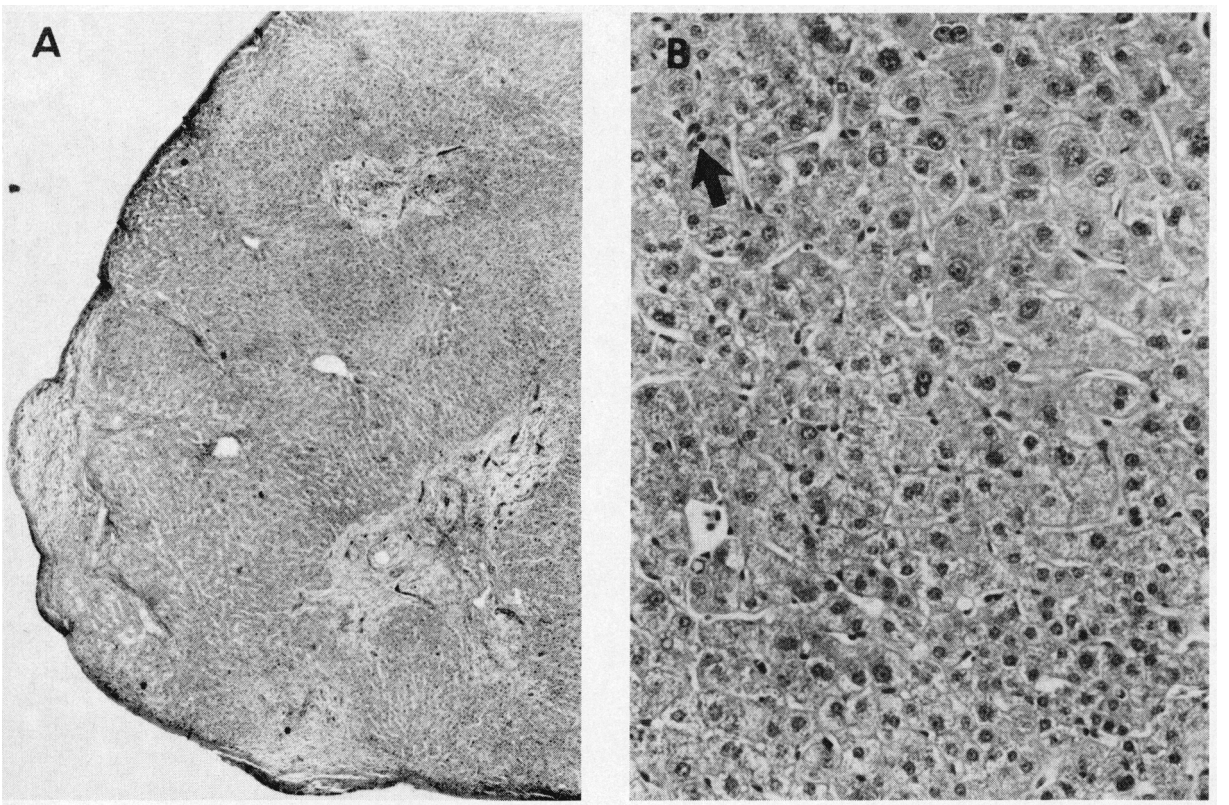

Figure 3. Subcapsular Portion of a Surgical Specimen of the Liver of a Worker with Portal Hypertension.
Note A the focal fibrotic thickening of the capsule and variable fibrotic enlargement of the portal tracts with fibrous connective tissue extending between periportal liver-cell plates. The lobular architecture is intact (hematoxylin and eosin stain × 25). B shows indistinct groups of hepatocytes with enlarged cytoplasm and nuclei, sometimes binucleate, particularly in the upper part of the photomicrograph in contrast to small hepatocytes. In places the sinusoidal lining cells are somewhat enlarged (arrow) (hematoxylin and eosin stain × 160).

portions of the liver of patients who had or were subsequently shown to have angiosarcomas, and also in patients without angiosarcoma who came to attention because of splenomegaly and manifestations of portal hypertension. The fibrosis is characterized by a conspicuous, focal capsular fibrosis, which is most impressive on gross inspection and was demonstrated in German workers by peritoneoscopy,[12] by a variable and irregular fibrosis of portal tracts, and by inconspicuous areas of intralobular, perisinusoidal fibrosis. This fibrosis is topographically related to proliferation and activation of sinusoidal lining cells and cells in the tissue space of Disse. These changes are associated with focal hypertrophy and hyperplasia of hepatocytes. The hepatocytes are not severely injured, nor is reactive intralobular inflammation seen. The apparent integrity of the hepatocytes explains why hepatic tests that indicate hepatocellular alterations yield erratic or even normal results in this stage.[7,8,12] These tests, therefore, cannot be depended upon to detect the hepatic fibrosis. In the spleen proliferation of lymphoid and reticuloendothelial cells is observed, but fibrosis is not seen.

Although the characteristic hepatic fibrosis was present in all cases of angiosarcoma in which adequate hepatic tissue was available, there is no evidence that all cases of hepatic fibrosis proceed to angiosarcomas. In the workers engaged in the polymerization of vinyl chloride who were studied by us, the combination of hepatic angiosarcomas and fibrosis was more common than the fibrotic lesions alone. In other studies of workers exposed to vinyl chloride in Germany,[12] Romania,[7] and Russia[6] the fibrotic lesions without angiosarcomas have been more frequent, and a survey in this country revealed an increased incidence of splenomegaly in such workers, depending on the duration of their exposure.[17]

The relation of the fibrotic lesions to the development of angiosarcomas requires further study. However, a transition from the fibrotic stage to angiosarcoma is suggested by the focal proliferation both of the sinusoidal lining cells and of the hepatocytes that is seen in the fibrotic stage but becomes even more pronounced in the initial stages of angiosarcoma development. Further progression is indicated by proliferation and piling up of atypical, sarcomatous-appearing sinusoidal and perisinusoidal cells that envelop proliferated hepatocytes in the areas of sinusoidal dilatation. These features, which characterize the multicentric angiosarcomas with a sinusoidal pattern, can be traced further to the angiosarcomas with papillary and cavernous growth patterns. In only a few cases, nodules composed of anaplastic sarcoma cells are observed. Thus, the evolution of the hepatic lesions and the enlargement

of the spleen suggests a stimulating effect by vinyl chloride or its metabolites on several types of hepatic and splenic cells.

The prominence of the enveloping growth pattern of the tumor cells, rather than a nodular growth pattern, is characteristic of hepatic angiosarcomas that develop after vinyl chloride exposure. Many cases of hepatic angiosarcoma of unknown cause fail to show this prominence.[18,19] On the basis of experience to date absence of this prominence in a given case militates against vinyl chloride as the origin. These observations may be of assistance in epidemiologic surveys. Enveloping features are prominent in angiosarcomas induced by thorium dioxide suspension (Thorotrast) in which large and irregular areas of fibrosis are observed.[20,21] Similar features are emphasized in angiosarcomas induced by inorganic arsenicals,[16,22] which, like vinyl chloride, may also produce inconspicuous hepatic fibrosis. Through the courtesy of Drs. P. J. Scheuer and M. Schmid, we were able to study histologically three cases of mild hepatic fibrosis with portal hypertension after long-term treatment of psoriasis with Fowler's solution, two of them reported.[14] We observed hepatic changes similar to those in the patients exposed to vinyl chloride — namely progressive portal fibrosis, mild intralobular fibrosis and focal hypertrophy and hyperplasia of hepatocytes.

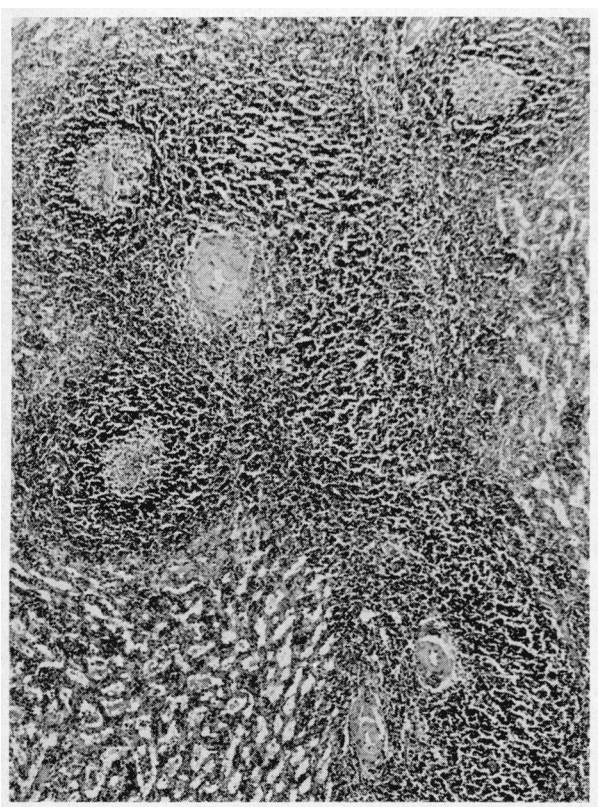

Figure 4. Surgically Removed Spleen of a Worker with Moderate Hepatic Fibrosis.

Note hyperplastic Malpighian follicles, which merge and exhibit large germinal centers. Sinuses are widened, and red-pulp cords are slightly thickened (hematoxylin and eosin stain × 40).

Inconspicuous hepatic fibrosis accompanied by splenomegaly and portal hypertension is the syndrome described by Banti.[4] An identical clinical picture is observed in some workers exposed to vinyl chloride. In contrast to splenomegalic cirrhosis, in which the splenic enlargement is caused by the hemodynamic alterations in the cirrhotic liver, in Banti's syndrome the splenomegaly precedes the hepatic fibrosis or is associated with inconspicuous fibrosis. It may, however, be followed by cirrhosis eventually.[23] Most cases of Banti's syndrome are associated with portal hypertension and are now usually designated as idiopathic portal hypertension.[24] Some authors associate the portal hypertension with a primary[25] or secondary[26] alteration of the wall of the portal vein or its branches (hepatoportal sclerosis), but this lesion was not conspicuous in our cases. Conditions resembling Banti's syndrome have been produced in animal experiments by stimulation of splenic lymphoid and reticuloendothelial cells.[27] It is possible, therefore, that one of the results of prolonged exposure to vinyl chloride may be splenomegaly due to stimulation of splenic cells, with a consequent increase in splenic and hepatic blood flow. Portal hypertension might be the result of an inability to accommodate this increased hepatic blood flow because distention of portal-vein branches is prevented by the portal fibrosis, and that of the sinusoids by the capsular and subcapsular fibrosis.

Whatever the origin of the idiopathic portal hypertension or Banti's syndrome, its apparent induction by prolonged exposure to vinyl chloride or inorganic arsenicals suggests that unidentified chemicals may cause other similar conditions in which the cause is unknown. Such cases are observed sporadically in the Western world[26,28] but are rather frequent in India,[25,29] Uganda,[30] North Africa[31] and Japan, where they are studied extensively.[32] This geographic distribution is an additional reason for suspecting environmental factors. In Banti's syndrome of unknown origin development of angiosarcoma has not been reported, but this fact does not negate the possibility that chronic exposure to vinyl chloride or inorganic arsenicals will produce either Banti's syndrome or hepatic angiosarcoma or both.

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HODGKIN'S DISEASE, TONSILLECTOMY AND FAMILY SIZE

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Abstract The association of tonsillectomy and Hodgkin's disease was investigated by comparison of 136 young adult patients with their 315 siblings and 78 spouses. On the basis of a case-spouse comparison, the risk ratio of Hodgkin's disease among tonsillectomized persons was 3.1 (1.5 to 7.7, 95 per cent confidence limits); on the basis of a case-sibling comparison it was 1.4 (0.8-2.6). The case-sibling analysis was repeated according to sibship size, and increased risk of disease was associated with tonsillectomy only within the 37 sibships of size two. A similar variation of risk ratio with sibship size was found in data from a prior study. The range of the association implies that the relation between tonsillectomy and Hodgkin's disease either is noncausal or is complex and modified by family size. Risk of Hodgkin's disease was found to increase as sibship size decreased, suggesting that a cause of Hodgkin's disease is correlated with childhood social class. (N Engl J Med 292:22-25, 1975)

IT was reported that young adults with a history of tonsillectomy have about three times the risk of development of Hodgkin's disease as non-tonsillectomized persons.[1] This observation is consistent with an infectious agent as suggested by epidemiologic, histologic and clinical features of the disease in this age group.[2] However, subsequent studies,[3-8] though conflicting, generally have not supported this finding. Tonsillectomy rates are directly correlated with socioeconomic status,[9,10] and Hodgkin's disease may also be.[11,12] Thus, the reported association, even if real, may be noncausal and cannot be assessed adequately unless socioeconomic status is closely controlled. This study of Hodgkin's disease uses two comparison groups, siblings and spouses, to control socioeconomic status in childhood and adulthood, respectively.

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METHODS

In December, 1972, all living white persons diagnosed by biopsy between the ages of 15 and 44 as having Hodgkin's disease, and being followed at that time, were identified from the records of the Joint Center for Radiation Therapy, Harvard Medical School. The Center treats patients at six hospitals in Greater Boston. Eighty-one per cent of the cases were diagnosed in 1968 or later. All 137 patients were sent a questionnaire regarding their own, their spouse's and their siblings' histories of tonsillectomy and appendectomy. All but 19 responded after two mailings. Each subject was then telephoned to verify the information or to obtain information from non-respondents. This procedure resulted in 100 per cent response. When a patient was uncertain about information concerning a sibling or spouse, that person or another relative was questioned. One patient gave unreliable information and was excluded.

Two control groups were assembled. One consisted of all 315 living siblings of the patients. The other consisted of the 46 wives and 32 husbands of the 78 married patients. Since controls were matched to cases for factors that might correlate with tonsillectomy, matched analyses were used in all comparisons. For case-spouse matched pairs, the tonsillectomy history of each patient was compared with that of the spouse. For case-sibling matched sets, each patient was compared with all living siblings. The method of Miettinen[13] and its extension for a varying control to case ratio[14] were used to obtain the maximum-likelihood estimate of the risk ratio. The risk ratio expresses the risk of Hodgkin's dis-