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

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Comparison With Cases of Unknown Etiology

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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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Supported in part by National Institute of Occupational Safety and Health (NIOSH) Contract 210-75-0044.

Accepted for publication March 30, 1978.

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0002-9440/78/0810-0349\$01.00

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velopment of the same tumor. By contrast, in domestic and experimental animals hepatic angiosarcoma is more common. In humans exposed to vinyl chloride,^{6,8} arsenicals,⁷ and Thorotrast,⁹ a peculiar hepatic fibrosis often associated with portal hypertension has been observed; transition of this antecedent lesion to angiosarcoma has been postulated. It therefore appeared important to study available cases of angiosarcoma associated with exposure to vinyl chloride, Thorotrast, or inorganic arsenicals and cases without known etiologic factors in an attempt to a) ascertain differences in pattern and evolution associated with various etiologic factors; b) describe a focal hyperplastic precursor lesion; c) trace the evolution of the precursor lesion and of the angiosarcoma; d) stress the connection of sinusoidal cell hyperplasia with the proliferation of the hepatocytes, since hepatocellular carcinoma has also been documented to result from exposure to Thorotrast⁹ and inorganic arsenicals⁴ and has been found in rodents exposed to vinyl chloride¹⁰ while in humans this association with vinyl chloride exposure is only suggested by anecdotal observations;¹¹ e) study the relation of a mixed mesenchymal cell reaction to intralobular fibrosis; and f) provide diagnostic criteria for both the precursor stage and angiosarcoma useful in epidemiologic surveys.

There were relatively few reports of hepatic angiosarcoma of unknown etiology¹²⁻¹⁶ before the vinyl chloride experience raised interest in the tumor. They are now supplemented by several others,¹⁶⁻¹⁸ but even large-scale surveys^{19,20} emphasized the rarity of the hepatic tumor. This tumor has been reported in all age groups, including children, and has no established sex predilection. These lesions have to be differentiated from benign but actively proliferating vascular tumors such as capillary hemangioendothelioma,²¹ particularly its infantile variety,²² as well as from malignant mesenchymal tumors with conspicuous participation of capillaries such as malignant mesenchymoma,²³ hemangiopericytoma,²³ and Kaposi's sarcoma, all of which have been found occasionally in the liver. Highly vascularized hepatocellular carcinomas sometimes also present diagnostic problems.

The proper designation of the tumor under discussion has been argued in cases of unknown etiology and in those associated with arsenic and Thorotrast exposure; terms such as "hemangioendothelial sarcoma,"²² "Kupffer cell sarcoma,"²⁴ "malignant hemangioendothelioma," and "hemangiosarcoma" have been used. In recent years, however, it has become the custom to use "angiosarcoma" as the most descriptive term although the recent nomenclature proposal for hepatic lesions²⁵ lists most of these terms with equal emphasis. For simplicity, the term "angiosarcoma" is used here.

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Review of Available Data

The first association of hepatic angiosarcoma with vinyl chloride was reported in the work force of one of the oldest polymerization plants in the United States¹ and additional cases have subsequently been reported and well-described histologically.²⁸⁻³⁸ Since then more instances have been reported in the United States⁶ as well as in Canada,³⁹ England,^{40,41} Germany,^{11,32-38} and France.³⁶⁻³⁸ The fibrotic antecedent lesion, initially recognized in Bonn, Germany,⁸ was well documented by laparoscopic and scintigraphic observations^{35,39-41} and subsequently reported in this country⁶ and in England⁴² in workers exposed to gaseous vinyl chloride. The German investigators were stimulated by the recognition of splenomegaly in workers with acro-osteolysis following exposure to high concentrations of vinyl chloride.⁴³⁻⁴⁴ Characteristic changes in the spleen associated with the antecedent fibrotic lesion were described as resembling the changes initially associated with the Banti syndrome.⁶ These observations confirmed previous reports of nonspecific hepatic lesions in vinyl chloride workers.^{45,46} Rare instances of cirrhosis were also reported.⁴⁷ Idiopathic portal hypertension following the long-term exposure to inorganic arsenicals in Fowler's solution used in the treatment of psoriasis has been reported,^{7,48-50} a treatment which also has been rarely followed by hepatic angiosarcoma.^{51,52} The largest series of angiosarcomas following exposure to arsenicals in pesticides, which also cause hepatocellular carcinoma and cirrhosis, although less frequently, comes from vineyard workers in the Rhineland.^{42,53-54} Hepatic angiosarcomas and carcinomas and, apparently, the fibrotic antecedent lesion following Thorotrast exposure have been well-described in Portugal.^{55,56} The number of angiosarcomas following Thorotrast exposure has increased in recent years,⁵⁷⁻⁶¹ and the lesion has been produced experimentally in rabbits.⁶² Finally, inorganic copper has also been incriminated.⁶³

The initial recognition that vinyl chloride has a carcinogenic potential in rodents⁶⁴ stimulated the extensive investigations of Maltoni,² and changes in the livers of workers exposed to vinyl chloride have been compared with those in rodents.⁶⁵ Angiosarcoma is more frequent in animals, both domestic and experimental, than in humans. It occurs spontaneously in dogs⁶⁶ and in some strains of inbred mice,⁶⁷ and it has been observed in rodents and primates exposed to carcinogens, particularly those which also produce hepatocellular carcinoma⁶⁸⁻⁷¹ and after infection of hamsters by polyomavirus.⁷²

Materials and Methods

This study is based on review of material which became available primarily for consulta-

tion at the Laboratory of Pathology of the National Cancer Institute and at the Mount Sinai School of Medicine. Most of the material was submitted as a result of an extensive epidemiologic investigation of angiosarcoma in the United States from 1964 to 1974 by the Center for Disease Control, Atlanta, Georgia. Additional material came from the Environmental Sciences Laboratory of the Mount Sinai School of Medicine. Some material of vinyl-chloride-related cases was provided for study directly by pathologists in Louisville, Kentucky; other material came from many pathologists from this country and Europe. Eight of the Thorotrast cases were obtained from the Armed Forces Institute of Pathology.⁷⁸

In addition, cases were pulled from the files at the National Cancer Institute and at Mount Sinai Hospital. In all instances, histologic slides were studied, and, in some, blocks or wet tissue were also available. Where possible, additional special stains were performed such as Mallory's trichrome, chromotrop aniline blue, silver for reticulum (mainly collagen Type III)⁷⁴ without toning to leave hard collagen (Type I) yellow-brown (otherwise stained by conventional connective tissue stains of the aniline blue variety), PAS reaction after removal of glycogen by diastase to identify increased phagocytosis, iron reaction, and Shikata stain to demonstrate elastic tissue and the s component of hepatitis B antigen.

The material studied as well as sex and age distribution are listed in Table 1.

In the vinyl-chloride-associated material is a series of cases in which multiple biopsies or biopsies and subsequent autopsies could be studied. The fibrotic precursor lesion was identified in biopsies and occasionally in autopsy specimens in areas sufficiently removed from the angiosarcoma to reasonably exclude mechanical or other effects. These were male patients, and the estimated exposure to vinyl chloride varied from 12 years to 28 years; the average exposure was 19.6 years. The latent period between first exposure and diagnosis of angiosarcoma ranged from 12 to 38 years; the average latent period was 22.3 years.

The arsenic-associated lesions were the result of exposure to Fowler's solution for many years for psoriasis or asthma; in the 4 cases for which detailed information is available, the duration of exposure ranged from 10 to 17 years, with a mean of 14 years. Thorotrast had been given for radiologic visualization of, primarily, brain lesions many years ago. When Thorotrast administration could be verified, records indicated that it had been given 16 to 40 years before the patient sought medical care for a hepatic disease.⁷⁸

The patient material designated "unknown" represents the histologically completed part of a survey of cases of hepatic angiosarcoma of unknown etiology retrospectively reviewed after death certificate, autopsy, or surgical biopsy recorded the above diagnosis. Among 117 cases, 4 were children. In this survey the cases not conforming to this diagnosis were eliminated, and in the confirmed cases a search for etiologic factors was initiated but is not complete.⁷⁸ Among the factors under consideration are previous liver disease, other chemicals, and various sources of exposure to known etiologic agents such as arsenic.

Results

Features Distinguishing Etiologic Factors

The same pattern and evolution were encountered in all the cases studied, independent of the etiology, with hardly any exceptions. The most prominent feature of the Thorotrast-associated lesions was deposition of large amounts of Thorotrast in dense connective tissue in the capsule and in the portal tracts but often also within the parenchyma. Proliferation of bile ductules was absent or only rarely seen in the Thorotrast-associated cases, in contrast to the vinyl chloride and arsenical as well as cryptogenic cases, in which marked bile duct proliferation was common. Hematopoietic foci were found in cases of each etiology. Therefore,

in the following presentation of the observations, little reference will be made to etiology. The same holds true with few exceptions for the legends of the illustrations.

Precursor Stage

This stage was characterized by hepatocytic proliferation associated to varying degrees with sinusoidal lining cell proliferation and with focal sinusoidal dilatation. The hepatocytic hyperplasia was observed in two forms which varied in size and degree of demarcation, uniformity of hepatocellular hyperplasia, and extent of associated sinusoidal lining cell activation and fibrosis.

In the first form, multiple, poorly circumscribed foci of hepatocytes exhibited variations from the surrounding parenchyma. The cells varied in size and formed two-cell-thick plates with their nuclei adjacent to the sinusoidal border. Binucleated and even multinucleated hepatocytes were seen (Figure 1). The bile canaliculi were sometimes dilated but devoid of bile plugs. Lipofuscin pigment was often increased. The sinusoidal lining cells in these foci were increased in number and varied in morphologic appearance. They included normal endothelial cells, plump cells with spindle-shaped nuclei and with diffuse PAS-positive diastase-resistant reaction of the cytoplasm, a few macrophages, and many lipocytes, identified by small fat droplets. The silver-impregnated reticulum framework was barely increased.

The second form was observed when transformation to angiosarcoma was present or subsequently established. A uniform, conspicuous hyperplasia and hypertrophy of hepatocytes in contiguous, almost nodular areas, was associated with an even more conspicuous increase in various sinusoidal cells (Figure 2). The sinusoidal cell proliferation included normal and enlarged endothelial cells, macrophages with PAS-positive diastase-resistant granules, lymphocytes, and occasionally plasma cells or segmented leukocytes (Figure 3). This sinusoidal cell reaction differed from that seen in hepatitis in that it was not associated with degeneration and necrosis of hepatocytes. The reticulum framework was increased in silver stains and showed an excess of both longitudinal and cross fibers. The irregular areas with increased reticulin were recognized under low-power magnification (Figure 4). The areas of hepatocytic and sinusoidal cell hyperplasia and hypertrophy distorted the lobular architecture. The areas usually involved only part of the lobule but occasionally extended into a neighboring one. They were usually closer to the portal tract than to the central zone and were not round but garland-shaped. The surrounding parenchyma, also curved, was either normal or compressed (Figure 5). The hepatocytes in the compressed areas often revealed degeneration,

and PAS-positive macrophages accumulated while the reticulin framework was condensed. Sometimes these compressed zones were hyperemic or hemorrhagic. After Thorotrast exposure, Thorotrast granules were found in the macrophages of the compressed areas; they were absent or infrequent in the hyperplastic areas. Bile plugs were noted on the border between the hyperplastic and the compressed areas.

The mixed hyperplastic areas differed from nodules in multiple nodular hyperplasia of humans and from the hyperplastic areas and neoplastic nodules of rodents by a) proliferation of various sinusoidal cells, b) increase of the reticulin framework, and c) garland-shaped outline.

Focal sinusoidal dilation observed frequently in the precursor stage involved in part portions of the mixed hyperplastic areas and in part the surrounding parenchyma, without relation to lobular topography. The cells lining the irregularly dilated sinusoids were increased in number (Figure 6) and the surrounding reticulin framework was thickened.

Nonspecific alterations in the surrounding parenchyma included occasional focal steatosis and clumping of hepatocytic cytoplasm. The portal tracts showed varying degrees of fibrosis which sometimes disrupted the limiting membrane and extended into the periportal parenchyma. Portal fibrosis was occasionally associated with proliferation of bile ductules and, in a few instances, with accumulation of lymphoid cells around bile ducts (Figure 7). This pericholangitis was usually accompanied by diffuse canalicular cholestasis.

Where it was possible to study the capsule, it showed focal capsular and subcapsular fibrosis in vinyl-chloride-associated cases. In the Thorotrast cases, these fibrotic areas contained Thorotrast deposits. Inflammatory cells were not noted in the areas of capsular fibrosis.

Transition to Angiosarcoma

Five processes participated to varying degrees in the transition to angiosarcoma: 1) proliferation with increasing anaplasia of intralobular endothelial cells; 2) initial hyperplasia of hepatocytes followed by atrophy and disappearance; 3) increasing fibrosis in perisinusoidal spaces; 4) progression of sinusoidal dilatation to peliosis; and 5) sarcomatous transformation of lining cells of sinusoids and of portal capillaries. The combination of the processes resulted in three pathways to angiosarcoma:

1. *Intralobular growth with fibroplasia.* The number of sinusoidal cells in the hyperplastic areas increased further so that they were in places arranged in more than one layer, although flat endothelial cells lined part of the sinusoidal spaces. The conspicuous hepatocytic hyperplasia might result in hepatocytic trabeculae lined by increased sinusoidal cells (Figure

8). The Disse space was widened and filled with many reticulum fibers in layers of variable thickness since cross fibers were also irregularly increased. It contained fibroblasts and many lipocytes. Some sinusoidal lining cells had a bulky cytoplasm and hyperchromatic nuclei; similar cells were found also in the Disse spaces and indented adjacent hepatocytic plates. The sinusoids were either narrowed or somewhat dilated in places and contained an increased number of inflammatory cells. Eventually, spindle-shaped lining cells predominated, while lymphocytes, macrophages, and other inflammatory cells disappeared. Atypical cells formed multiple uniform layers lining the sinusoids and, because of increasing atypia and anaplasia, were considered to be angiosarcoma cells. Further progression was reflected in several features which occurred coincidentally with the previously described changes: a) Hard connective tissue (Type I collagen) associated with elastic fibers increased conspicuously around angiosarcoma cells within and around vascular spaces and compressed adjacent hepatic plates which atrophied and resembled bile ductules (Figure 9) and finally also disappeared. Fibrotic areas often became hyalinized and replaced many lobules. b) The angiosarcoma cells filled and extended the sinusoidal spaces to interfere with microcirculation, and the hepatic parenchyma showed anoxic necrosis (Figure 10). c) The angiosarcoma cells formed large clusters and, occasionally, solid nodules (Figure 11) composed mostly of spindle-shaped and sometimes of polyhedral cells.

2. *Intralobular growth with sinusoidal dilatation.* This pattern was an accentuation of the sinusoidal dilatation which was noted mainly in the mixed hyperplastic areas. It was characterized by further proliferation of sinusoidal and perisinusoidal cells. With increasing dilatation, adjacent hepatic plates were disrupted so that small cystic spaces formed by confluence of dilated sinusoids. These irregular spaces were separated by plates of hyperplastic hepatocytes (Figure 12) and the surrounding framework was remarkably thickened (Figure 13). Often, hematopoietic cells accumulated in the dilated sinusoids. Into larger spaces, blindly ending spurs of hepatocytes extended, covered by atypical sinusoidal or angiosarcoma cells. Eventually, the diffuse irregular loosening of the parenchymal architecture by some uniform and some irregular sinusoidal dilatation produced a plexiform, trabecular arrangement of the hepatocytes, with great variations in the quantitative relation between hepatocytes and sinusoidal cells. Initially the hepatocytes appeared hyperplastic and arranged in two and more cell layers around bile canaliculi which often contained bulky bile thrombi (Figure 14). When the hyperplastic hepatocytes predominated, the picture resembled the trabecular type of he-

patocellular carcinoma although the hepatocytes were not anaplastic. The considerably widened Disse spaces around the trabeculae contained a variety of mesenchymal cells, including segmented leukocytes, macrophages, lipocytes, and lymphocytes, as well as spindle-shaped angiosarcoma cells (Figure 15) and a significantly increased, irregularly arranged reticulum framework. The angiosarcoma cells, often in two layers, did not contain PAS-positive glycogen-resistant granules indicative of phagocytosis, nor iron granules or Thorotrast, even when the latter was found in other locations. The destruction of the lobular architecture by the described loosening need not involve the portal and the central canals. They remained as beam-like trabecular structures containing vessels and bile ducts and traversed the enlarging blood spaces. They were covered by layers of angiosarcoma cells, which also infiltrated these beams which underwent hyalinizing fibrosis (Figure 16). Bile ductules were similarly initially preserved and appeared also as trabeculae. The blood spaces eventually became grossly visible blood cysts in which fibrin clots formed.

Another variant of the trabecular form of angiosarcoma was gradual fibrosis in the hepatocytic cords while inflammatory cells disappeared (Figure 17). Hard, Type I collagen, intermixed with elastic fibers, formed in the reticulin matrix and predominated in later stages.

A third variant was relatively thin fibrotic stalks lined by spindle-shaped angiosarcoma cells, presenting a papillary arrangement (Figure 18).

In all three variants, angiosarcoma cells also formed solid clusters and, eventually, nodules.

3. Portal growth. Mainly spindle-shaped angiosarcoma cells lined capillaries or lymphatics of the portal tracts or appeared single or in small nests in their connective tissue (Figure 19). This was associated, even in small lesions, with involvement of the periportal parenchyma. Only in few instances was angiosarcoma restricted to the portal tracts. Thus, portal involvement appeared to be caused by spread of intralobular angiosarcoma. This growth pattern was accompanied by proliferation of bile ductules surrounded by inflammatory cells intermixed with angiosarcoma cells. Considerable fibroplasia, mainly of reticulin character, but, subsequently, also hyalinized collagen, produced masses of fibrous tissue, with varying amounts of either ductules or angiosarcoma cells together with occasional solid nests of predominantly spindle-shaped angiosarcoma cells.

Portal angiosarcoma was accompanied in a few instances by connective tissue septums containing proliferated bile ductules, some venules and arterioles, and angiosarcoma cells intermixed to various degrees with inflammatory cells. These septums formed bridges connecting portal

tracts with each other or with central canals. They subdivided the lobules to create the picture of a cirrhosis (Figure 20). In the thus formed parenchymal nodules the hepatocytic plates were rearranged, usually in layers two and more cells thick, but, in contrast to common cirrhosis, they had an increase in reticulin and in sinusoidal cells surrounding the hepatocytes.

Variations in Angiosarcoma Pattern

Clusters and nodules were composed of angiosarcoma cells of two types. One type was spindle-shaped and had large nuclei and distinct cytoplasmic extensions (Figure 11). The nuclei were often hyperchromatic and sometimes multiple, but nucleoli were small. Few vascular spaces were lined by angiosarcoma cells but, occasionally, by flat endothelial cells. The other type of cell was large and had abundant cytoplasm. These polyhedral cells were often multinuclear and showed greater tendency for anaplasia than the spindle-shaped cells (Figure 21). The polyhedral cell nodules had few vascular spaces, while necrosis and hemorrhage were common. Transitions between and admixtures of both types of cells were frequent. The polyhedral cells were not intermixed with inflammatory cells except following necrosis. Sometimes they formed multiple layers lining blood-filled cystic cavities (Figure 22).

Both types of nodules, which also were grossly visible, compressed the surrounding parenchyma and had often a connective tissue pseudocapsule. They were frequently associated with invasion of veins by tumor cells, mainly of branches of the portal vein. Extensive necrosis was common with or without vein invasion. With silver stains, some areas of necrosis showed persisting hepatic trabeculae and portal tracts, while others failed to reveal remnants of hepatic structure.

Specific developmental patterns were distinguished to trace the evolution of the multicentric angiosarcomas to sinusoidal, trabecular, papillary, portal, and nodular end stages.⁶ Combinations, however, of several patterns were usually seen in different parts of the same liver. For instance, fibrosing areas around hepatocytes, presumably derived from intralobular lesions, merged with others around proliferated ductules originating in portal tracts. Two cases of unknown etiology had a combination of both angiosarcoma and hepatocellular carcinoma. In one of them, nodules of these two types of malignant growth were separated by a fibrous pseudocapsule (Figure 23).

Additional Features

Foci of hematopoietic cells, mainly nucleated red cells but also mega-

karyocytes, were frequent in all forms of angiosarcoma (Figure 24). The hematopoietic cells were also in the perisinusoidal space but more frequently in the spaces lined by the angiosarcoma cells. The portal tracts showed variable amounts of lymphocytic infiltration. Bile ducts and ductules showed not only proliferation of their epithelial cells, associated with hyperchromasia and formation of several layers, but also excess mucus formation, irregular dilatation, and out-pouching of epithelium into the surrounding, often hyalinized, connective tissue.

Extrahepatic metastases (although multicentric origin is not excluded) of either spindle-shaped or polyhedral cell character were reported in 69% of the cases (Table 1). There was a lower percentage of metastases in those of known etiology, notably Thorotrast, than in those of unknown etiology, but the differences are probably not significant. The autopsy records of the entire series list involvement of other organs as follows: lung and pleura (35%), spleen (28%), lymph nodes (25%), bone (23%), adrenal glands (14%), diaphragm (9%), heart (8%), and brain (8%). Many other organs were involved rarely. Spleen involvement was recorded far more frequently (36%) in the group of unknown etiology than in the vinyl chloride (13%) or Thorotrast group (11%).

Diagnosis

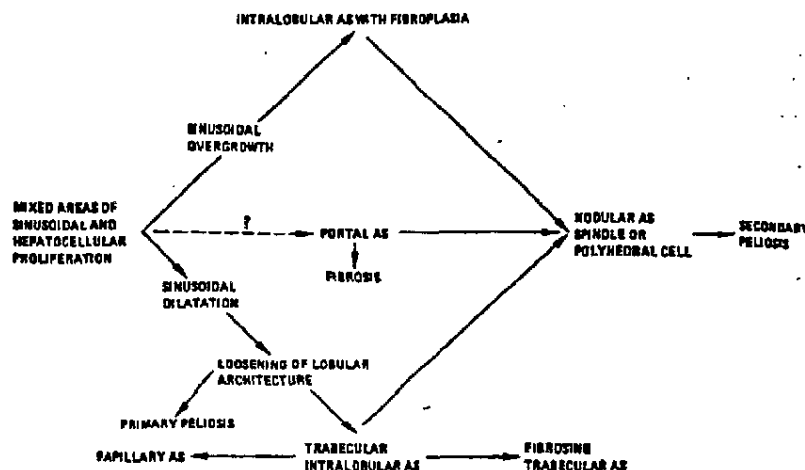
Diagnostic criteria are particularly important in the evaluation of biopsy specimens. The following features proved useful in the survey of the material. The trabecular pattern with sinusoidal dilatation was most diagnostic when plates of hyperplastic hepatocytes were covered by single or multiple layers of angiosarcoma cells and hepatocytic spurs extended into blood-filled spaces. A second diagnostic feature was anaplasia of sinusoidal lining cells with or without an associated inflammatory reaction, especially when accompanied by sinusoidal dilatation and perisinusoidal fibrosis. The diagnosis of angiosarcoma was more difficult when only a few anaplastic cells were observed in the sinusoids since lymphoma, myeloma, or single metastatic carcinoma cells had to be excluded. The association with inflammation is characteristic for angiosarcoma. A third feature, more readily overlooked especially in small biopsy specimens, is angiosarcoma cells mixed with inflammatory cells and proliferated bile ductules in portal spaces. Solid tumor nodules offered the greatest differential diagnostic problem; particularly, polyhedral cells are difficult to distinguish from hepatocellular carcinoma and other types of sarcoma. Connective tissue stains, including silver stains, assist in the distinction from hepatocellular carcinoma. Frequent misdiagnoses were encountered in the material available for study because lymphoma, heman-

Table 1—Reviewed Hepatic Angiosarcoma Material

Etiology	No.	Sex		Age at death (yrs)		Race		Specimens			No. of cases with metastases
		M	F	Average	Range	W	B	Biopsy	Autopsy	Biopsy and autopsy	
Vinyl chloride	19	19	—	52	36-67	19		13	17	11	10/18*
Thorotrast	28	19	7	54	32-73	25	1	9	19	2	8/19
Fowler's solution	5	4	1	49	41-58	5		2	5	2	3/5
Unknown				4 mo							
Children	4	1	3	3	—	4		4	4	4	3/4
Females	28	—	28	57	18-82	23	3	13	18	3	16/18
Males	85	85	—	61	18-89	81	3	22	70	7	50/68*
Total	167†	128	39	—	—	157	7	63	133	29	90/130

* Information about metastases not available for 1 vinyl chloride and 2 male cases.

† Includes 2 orientals and 1 whose race was unknown.



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.⁸ This suggests that in cryptogenic cases, environmental factors are responsible, the nature of which is being sought by intensive epidemiologic studies.¹⁶ The available surveys^{18,20} 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 and in the areas where polyvinyl chloride is pro-

essed.^{41,76} Presumably no additional instances of initiation will occur. However, in view of the long period of promotion of tumors, additional cases of angiosarcoma, unfortunately, have to be expected in the future. The differential diagnostic criteria may have practical importance if other environmental and industrial hazards produce the same morphologic sequences.

The diagnostic significance of the characteristic precursor stage of mixed hyperplasia and hypertrophy of hepatocytes and sinusoidal cells, frequently associated with sinusoidal dilatation, may be helpful in screening, although its specificity requires further study. It is best recognized in silver stains even with low-power examination.

The second purpose of this paper is an attempt to better understand the development of hepatic angiosarcoma (Text-figure 1). Characteristically it entails, at least in early stages, a proliferation and hyperplasia of both hepatocytes and sinusoidal cells. The metabolic factors accounting for this interplay remain to be established. The appearance points to a proliferative, potentially carcinogenic stimulus for the hepatocytes. This is supported by occasional primary hepatocellular carcinomas seen after arsenic and Thorotrast and, in rare cases, after vinyl chloride exposure. In young rats with less-developed microsomal biotransformation, including lesser metabolite degrading activity,⁷⁷ vinyl chloride exposure leads more frequently to hepatocellular carcinoma than in adult rats.¹⁰ This observation points to the possibility that variations in enzymatic biotransformation may determine the type of tumor that develops. In experimental animals, both angiosarcoma and hepatocellular carcinoma have been produced, sometimes simultaneously.⁷⁸ In human hepatocellular carcinoma, varying degrees of sinusoidal cell activity are noted, also expressed in variations of the reticulum framework around the trabecular form of this tumor. This suggests variable stimulation of sinusoidal cells even in frank hepatocellular carcinoma. Cases of both tumors in humans have been seen very rarely. Thus, the interaction between carcinogenic effects on sinusoidal cells and hepatocytes is a promising area for further study. Peculiarly, in Thorotrast-induced epithelial tumors, bile duct carcinoma may be more frequent than hepatocellular carcinoma.⁷⁹ The described alterations of the bile ducts in the angiosarcomas studied in this series suggest a carcinogenic stimulus on bile duct cells, but the possibility that this is only a secondary reaction to the presence of a tumor in the liver cannot be excluded.

Reports of intensive investigations of the metabolism of vinyl chloride are available.^{41,80-82} It is transformed by hepatic microsomal action to mutagenic⁸⁴⁻⁸⁶ and potentially oncogenic⁸⁷ metabolites which covalently bind to DNA^{84,88} and are injurious to hepatocytes in animals exposed to

very large doses of vinyl chloride.⁶⁰ These metabolites are then rendered inactive by enzymatic or nonenzymatic action or by binding to glutathione.⁶¹

In the precursor stage, significant degenerative alterations of the hepatocytes, such as steatosis, focal necrosis, and lipofuscin deposits which are not age-dependent, have only been recognized histologically after short intervals between exposure and biopsy; these features subsequently regress.⁶¹ This explains why conventional liver function tests are of little diagnostic value in this stage. Only with progression of the process to tumor formation appear measurable alterations of hepatic function. Angiographic⁶² and scintigraphic⁶³ demonstration of the lesion has greater diagnostic value and the lesions are also reflected in hemodynamic alterations.⁶⁴

A predominant early alteration is the sinusoidal cell proliferation associated with sinusoidal dilatation and fibrosis. While in such stages these cells are intermixed with various inflammatory cells, a transformation to angiosarcoma cells is associated with a disappearance of the other mesenchymal cells in all growth patterns. Hypothetically, the inflammation may have a suppressing effect from which the angiosarcoma cells seem to escape. Azoxymethane-induced angiosarcoma growth is stimulated by antilymphocytic serum which has no effect on the hepatocellular carcinoma produced by this agent.⁶⁵ An immune complex disorder has been claimed as the basis of the vinyl chloride injury.⁶⁶ This could explain the inflammatory reaction in both parenchyma and portal tracts.

Transition to angiosarcoma cells from the sinusoidal lining cells could be traced. They appeared to be derived from endothelial cells, not only because they were devoid of any phagocytic activity but also because they were clearly distinguished from phagocytic macrophages. Their origin from endothelial cells was also confirmed by electron microscopic study.⁶⁷ However, better confirmation by use of histologic markers of endothelial cells, for instance, Weibel-Palade bodies,⁶⁸ or of catalase and peroxidases⁶⁹ is desirable. The angiosarcoma cells exhibited various forms of arrangement to include a) lining or tectorial, b) enveloping hepatocytes or bile ductules, c) vasoforming, or d) solid. They were either spindle-shaped with relatively little cytoplasm or polyhedral. The latter sometimes resembled epithelial cells and thus created differential diagnostic problems. The solid or nodular forms developed from almost any growth pattern, including the intralobular, the portal, and the trabecular.

Angiosarcoma may develop in the lobular parenchyma and in the portal tracts. The primary growth in the parenchyma appears to be far more frequent, with the invasion of the portal tracts being secondary. In the

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fibrotic stages particularly, both growth patterns are combined, reflected in the presence of both hepatocytes and ductules.

The sinusoidal dilatation found in the majority of instances is not explained by passive congestion because of its irregular location in the lobule. Similar forms of sinusoidal dilatation without angiosarcoma have been reported in women taking oral contraceptive drugs¹⁰⁰ and in men and women receiving large doses of anabolic steroids.¹⁰¹ In the latter cases, the peliosis may be sufficiently advanced to produce hepatic failure. In these instances, it has been explained by injury to the sinusoidal lining¹⁰² and this was also demonstrated in vinyl-chloride-intoxicated mice.⁹⁷ The observations here are in keeping with this assumption of a sinusoidocidal effect. In contrast to this, primary peliosis, the progression of which to large bloody cysts is associated with persistence of hyalinized connective tissue beams, best seen in silver stains, is a secondary peliosis occurring within angiosarcoma nodules undergoing extensive central necrosis and hemorrhage. In these instances no septums remain in the silver stains. Necrosis with hemorrhage is the predominant gross manifestation of these tumors.

The relation of the sinusoidal cell hyperplasia to fibroplasia represents an interesting problem. The excess of perisinusoidal and sinusoidal cells of several types, accompanied at least initially by hepatocytic hyperplasia, was regularly associated with excess reticulum fibers. This reticulin increase was also found in the presence of sinusoidal dilatation and was a useful diagnostic criterion. The morphologic appearance suggests a fibroblastic activity of some of the perisinusoidal cells.¹⁰³ Increased and enlarged Ito cells¹⁰⁴ or lipocytes,¹⁰⁵ small fat droplets containing perisinusoidal cells, were observed in light and in electron microscopic studies,^{91,97,106,107} particularly in the fibrotic precursor stage. They are considered precursors of fibroblasts.^{108,109} Their transformation to fibroblasts is associated with formation of collagen Type III, mainly reticulum.¹⁰⁹ Also, the splenic enlargement after vinyl chloride exposure results partially from proliferation of fibroblastic cells.¹¹⁰ Subsequent stages of the hepatic lesion are associated to a varying degree with desmoplasia, either in the form of a creeping fibrosis around hepatocytes, often in pseudoductular arrangement or around bile ductules, or as massive hyalinized fibrosis. Then hard, collagen Type I, a different gene product than collagen Type III, develops within the reticulum and eventually replaces it. This implies a significant desmoplastic potential of the tumor, although the role of the fibroblasts in the later stages has not been established. A peculiar form is the septal fibrosis which leads to an almost cirrhotic picture.

The characteristic abundance of hematopoietic cells, including megakaryocytes, in the developing angiosarcoma, both intrasinusoidal and perisinusoidal, may reflect a local formation of these cells in the activated mesenchyme¹⁰³ or bone marrow irritation.

The great variability in appearance of the tumor is accounted for by the variable growth potential of hepatocytes and sinusoidal cells and by the irregular tendency for fibrosis and sinusoidal dilatation. However, in virtually all cases a multicentric angiosarcoma of variable type results.

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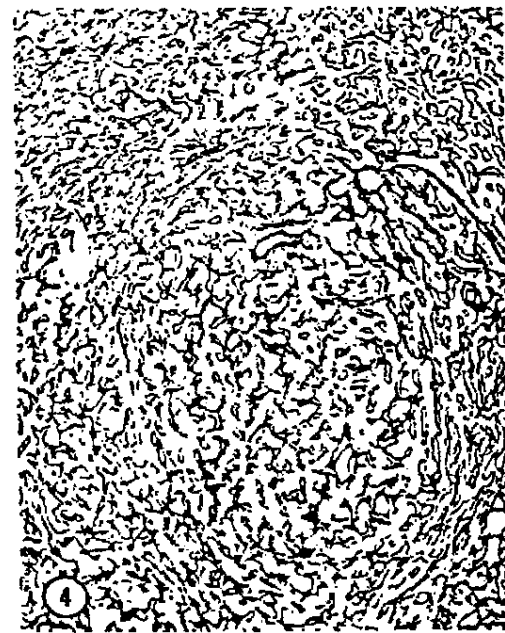
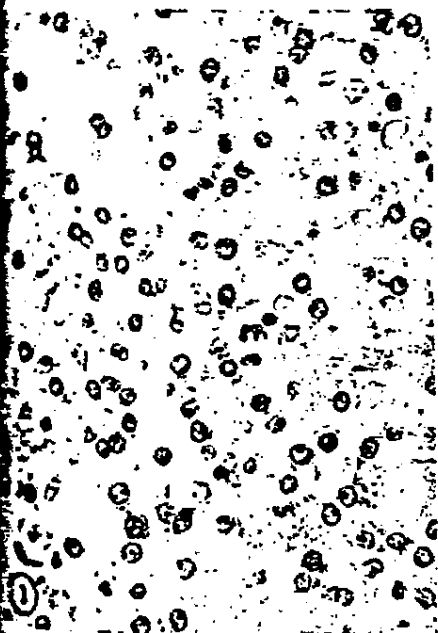
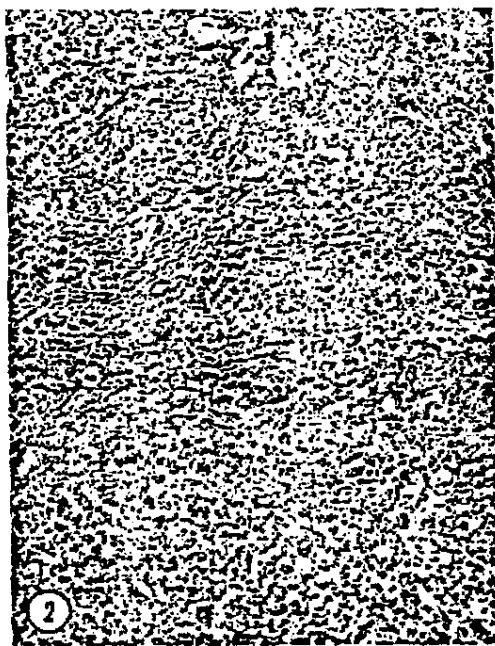
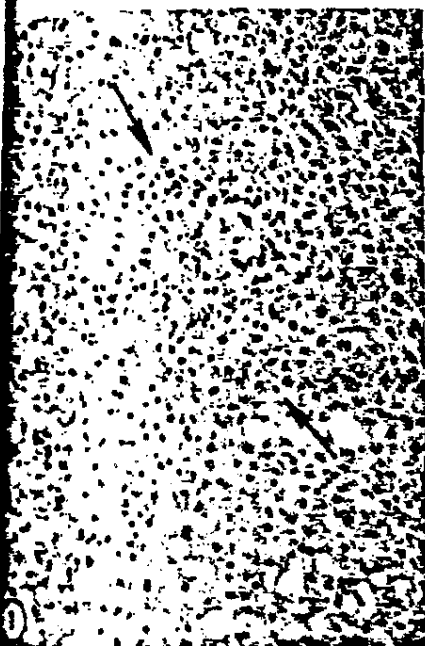
Acknowledgments

Particular gratitude is expressed to Dr. John Herbert, Center for Disease Control, for his enthusiastic support in the conduct of this study. The authors also wish to thank Mrs. Sue Hostler for typing the manuscript and Mr. Ralph Isenburg for photographic services.

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[Illustrations follow]



1—Focal variation in size of hepatocytes within lobular parenchyma (between arrows). Note small and large cells and droplet steatosis in surrounding parenchyma. Liver biopsy (S74-415) from worker exposed to vinyl chloride. (H&E, X100)
 2—Hepatocytes in more than one-cell-thick plates surrounded by increased sinusoidal cells. Almost nodular area which exerts pressure on the surrounding parenchyma. Autopsy (L7374) specimen from worker exposed to vinyl chloride. (H&E, X40)
 3—Mixed hyperplastic area. Hepatocytes, usually in two-cell-plates, indicated by sinusoidal position of nuclei and excess of sinusoidal cells of various types. Autopsy (L7208) from worker exposed to vinyl chloride. (H&E, X250)
 4—Increased reticulin in mixed hyperplastic area. Autopsy (A74-183). (Silver stain, X60)



Figure 5—Mixed cellular area in left lower corner. Increased size of hepatocytes. Autopsy (A75-75). (H&E, X100). Note hepatocytic nuclei near limiting plate. Note accumulation of cells in right lower aspect. At times containing bile in a variety of cells, some becoming multinucleated. (H&E, X100)

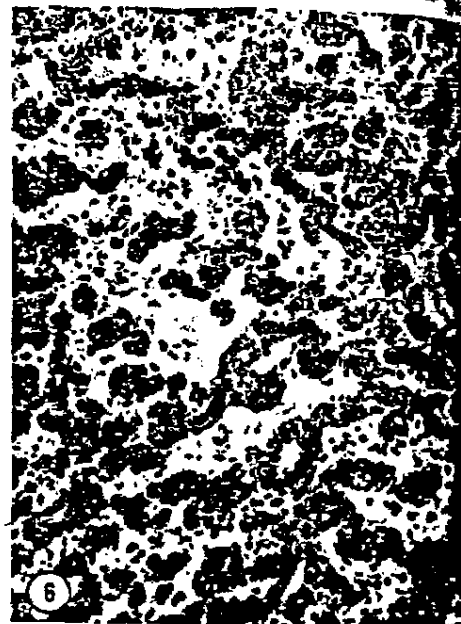


Figure 6—Hepatocytes in two-cell-thick plates. The plates appear compressed. There is irregular dilatation of sinusoids. The overall architecture is somewhat disorganized, suggesting early cirrhotic changes. (H&E, X100)

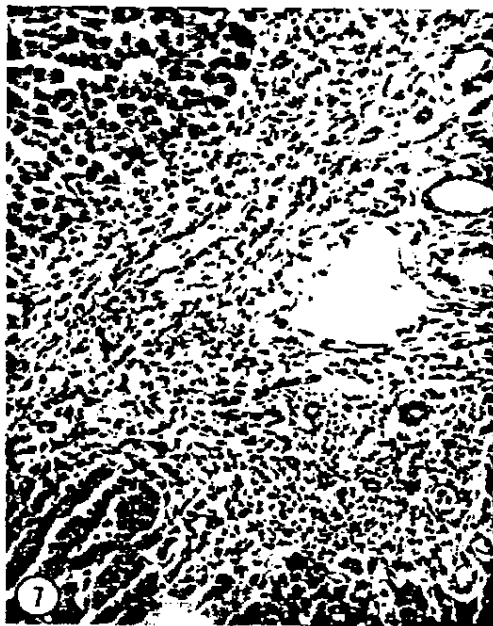


Figure 7—Limiting plate. Note accumulation of cells in right lower aspect. At times containing bile in a variety of cells, some becoming multinucleated. (H&E, X100)

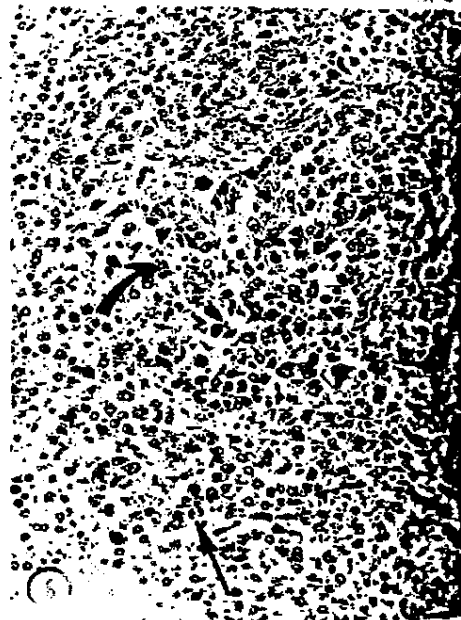


Figure 8—Hepatocytes in two-cell or more cell-thick plates. There is a curved arc of multiple layers of cells, indicating early cirrhotic changes. (H&E, X100)

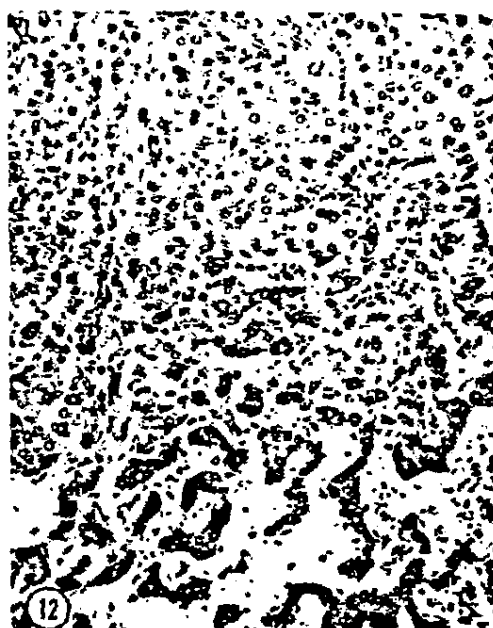
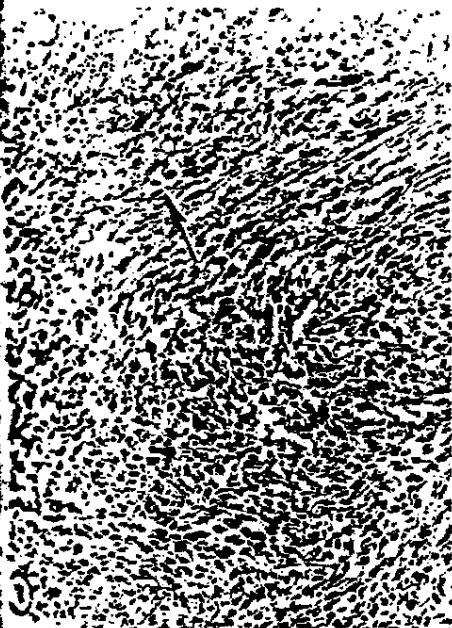
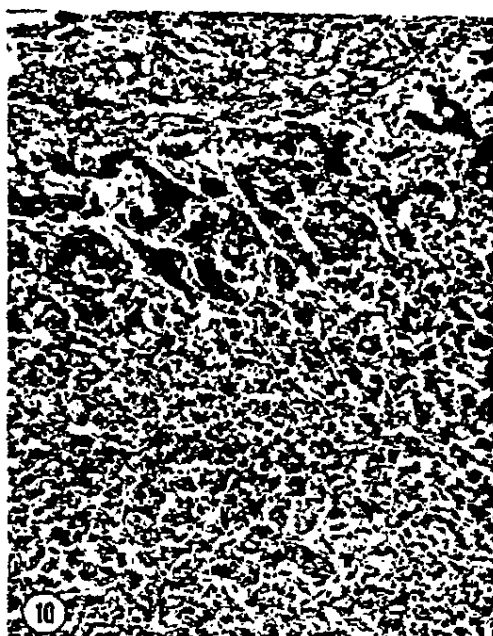


Figure 9—Hepatocytes in pseudoductular arrangement surrounded by excess fibrous tissue and vascular spaces lined by angiosarcoma cells, often in multiple layers (arrows). Accumulation of lymphocytes on lower border. Autopsy (A74-287). (H&E, X100) Figure 10—Angiosarcoma cells filling sinusoids, in upper aspect between hyperplastic and in lower aspect between necrotic hepatocytes. Autopsy (A77-341). (H&E, X100) Figure 11—Nodule composed of nodular-shaped angiosarcoma cells in places lining vascular spaces which are also lined by nontumorous endothelial cells (arrow). Biopsy (S74-816). (H&E, X160) Figure 12—Loosening of lobular architecture by irregular dilatation of sinusoids containing angiosarcoma cells intermixed with sinusoidal lining cells of other types. Note conspicuous hypertrophy and hypertrophy of hepatocytes in upper aspect. Autopsy (A74-287). (H&E, X100)

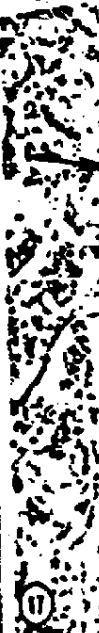


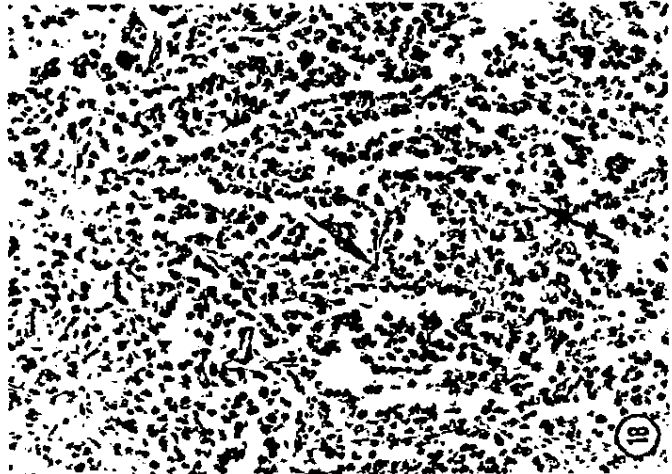
Figure 13—

used reticulum framework around hyperplastic hepatocytes in places associated with sinusoidal spaces (arrow). Autopsy (A74-11). (Silver stain, X250). Figure 14—Trabeculae, in part around thick bile plugs (arrow) are widened and contain a variety of cells. (H&E, X160). Figure 15—Trabecular spaces lined by angiosarcoma cells. Autopsy (A74-11). (H&E, X250). Figure 16—Trabecular spaces (primary peliosis) traversed by fibrous central canals. Fibrosing, trabecular angiosarcoma. (H&E, X40).

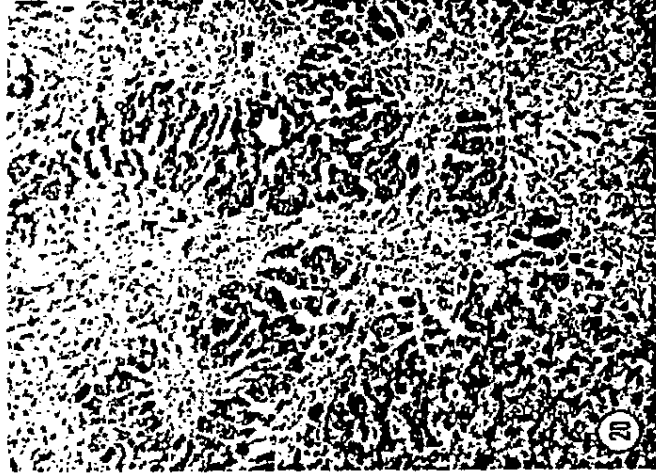
Figure 14—Trabeculae, in part around thick bile plugs (arrow) are widened and contain a variety of cells. (H&E, X160). Figure 15—Trabecular spaces lined by angiosarcoma cells. Autopsy (A74-11). (H&E, X250). Figure 16—Trabecular spaces (primary peliosis) traversed by fibrous central canals. Fibrosing, trabecular angiosarcoma. (H&E, X40).



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Figure 17—Progressive fibrosis of trabecular angiosarcoma with compressed, atrophic hepatocytes (arrows). Autopsy (A74-37). (H&E, X100). Figure 18—Pagillary angiosarcoma. Note tumor cells around thin connective tissue stalks within stalks (arrows). Autopsy (A74-89). (H&E, X160). Figure 19—Angiosarcoma filling sinusoids of lobular angiosarcoma and in and around vascular spaces in portal tracts (arrows). Autopsy (A74-31). (H&E, X100). Figure 20—Angiosarcoma containing angiosarcoma cells and connecting nodules consisting of hyperplastic hepatocytes, in part separated by angiosarcoma, to produce the nodules of cirrhosis. Autopsy (A74-123). (H&E, X40).

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Figure 21—M
x400) Fi
Autopsy (A
H&E, x40)
Nodules composed of polygonal angiosarcoma cells surrounding hepatocytes. Autopsy (A74-31) and
Figure 23—Solid angiosarcoma above and trabecular hepatocellular carcinoma (secondary nodules)
H&E, x40) Autopsy (A74-31) and
Figure 24—Accumulation of hematopoietic cells within sinusoids in angiosarcoma (megakaryocytes
H&E, x25) straight at

Figure 22—M
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Autopsy (A
H&E, x40)
Nodules composed of polygonal angiosarcoma cells surrounding hepatocytes. Autopsy (A74-31) and
Figure 23—Solid angiosarcoma above and trabecular hepatocellular carcinoma (secondary nodules)
H&E, x40) Autopsy (A74-31) and
Figure 24—Accumulation of hematopoietic cells within sinusoids in angiosarcoma (megakaryocytes
H&E, x25) straight at

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ANESTHESIA XXVII. NARCOSIS WITH VINYL CHLORIDE*

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Jr., PH.D., with the technical assistance of MARY JANE BAUERWALD, B.A.

Baltimore, Md.

Received for publication December 12, 1944

In our studies on various volatile organic compounds available as inhalation anesthetics, our attention was directed to vinyl chloride. Vinyl chloride is an industrial chemical used in the synthesis of many organic compounds. The substance is a gas which boils at -18°C . It is soluble in the etheral solvents and its vapors are combustible.

Vinyl chloride was suggested as an anesthetic by Patty, et al. (1) and tried on human subjects by Schaumann (2). Patty's experiments on guinea pigs revealed that the action of vinyl chloride was similar to that of ethyl chloride and less harmful than either chloroform or carbon tetrachloride. According to Schaumann the narcotic limiting concentration for man is 7 to 10 per cent; 12 per cent is dangerous. In our studies, planned to give a first approximation of the anesthetic syndromes of vinyl chloride, we suggest that this compound not be used as an anesthetic in man.

Chemotherapeutic Considerations: There is a dictum in pharmacology (3) that potency and unsaturation parallel each other among analogous organic compounds. This holds for ethane and its more potent analogue, ethylene. It is also true for ethyl ether and its more potent analogue, divinyl ether. Therefore, one might expect that vinyl chloride would be a more potent anesthetic than its analogue, ethyl chloride. This relationship, however, appears not to obtain between these two chlorinated hydrocarbons. With ethyl chloride, 3.6 to 4.5 volumes per cent (4) are required for anesthesia with 20 mg. per cent in the blood. Schaumann (2) used 7 to 10 volumes per cent of vinyl chloride to produce anesthesia and found 17 to 20 mg. per cent in the blood. Our observations in dogs conform well to the indication of these data, namely, that there is little difference in potency between the saturated and the unsaturated analogues, and actually ethyl chloride appears to be the more potent.

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† The expense of this investigation was defrayed partially by a grant from the Ohio Chemical and Manufacturing Company of Cleveland, Ohio.

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For the information of anesthesiologists who are contemplating application for certification by the American Board of Anesthesiology, Inc., or who are training physicians for the specialty, the following questions have been employed for Part I (written) examination in the past in Physiology:

1. Describe inhalation therapy that is indicated in the presence of pulmonary edema.
2. Discuss the important points to be thought of in connection with cyanosis in the anesthetized patient. (Cover all ordinary methods of anesthetizing patients.)
3. What are the approximate normal values for oxygen and for carbon dioxide, expressed in either millimeters or tension, or percentage, in:
(a) Inspired air (c) Arterial blood (e) Venous blood
(b) Pulmonary (d) Tissue spaces
alveoli
4. What physiological functions of the liver are of particular interest to the anesthesiologist and why?
5. (a) Assuming that they are available, under what circumstances during anesthesia would you recommend the intravenous use of whole citrated blood, plasma, solutions of glucose, physiologic saline solution, or solutions of acacia, gelatin, pectin or isinglass (agar agar)?
(b) Under what circumstances would you use vasopressor substances with these substances and with which substances and in what dose?
6. Concerning the article, "Absorption, Distribution and Elimination of Ethyl Ether": who wrote it, where and when was it published, and what important contributions to knowledge of the clinical use of ether did it contain?

University of Pittsburgh

Library, School of Medicine

Observation Anesthesia in Dogs: Two dogs were anesthetized with vinyl chloride* using mixtures of the gas and oxygen. For induction the concentration of the gas momentarily was allowed to run to 50 volumes per cent and then reduced to 7 volumes per cent. Induction was rapid. There was continuous "crowing" even under deep anesthesia. There was much salivation. Abdominal relaxation was good, but the legs showed rigidity and incoordinated leg movements throughout the anesthesia. The recovery period was prompt but accompanied by violent excitation.

In a third dog anesthesia was produced using 25 volumes per cent momentarily, and a similar syndrome ensued.

Blood Pressure in Dogs: Four dogs were prepared for blood pressure tracings by cannulating the femoral artery. The operation was performed under monocaïne hydrochloride local anesthesia. After a normal blood pressure tracing had been obtained, the animals were anesthetized with vinyl chloride-oxygen mixtures, using 10 volumes per cent of the former. In all 4 cases the magnitude of the blood pressure remained within normal limits during anesthesia. There was definite evidence of cardiac irregularity, however, such as intermittent tachycardia, extrastricular systoles and vagal beats. These irregularities disappeared upon changing the anesthetic to ethyl ether. These cardiac disturbances confirmed our stethoscopic observations on the unoperated dogs.

Electrocardiographic Studies in Dogs: Six dogs were anesthetized with vinyl chloride-oxygen mixtures, using 10 volumes per cent of the former. Electrocardiographic records, lead II, were made at light surgical anesthesia, surgical anesthesia and threatened respiratory collapse. All of the animals manifested marked changes in cardiac rhythm in surgical anesthesia. Marked tachycardia followed by bradycardia was typical. In 2 of the 6 animals the R-spike was inverted during surgical anesthesia and in 1, evidence of incipient ventricular fibrillation obtained. Inversion of the R-spike with bradycardia is shown in the record from dog 6, lead II, chart 1.

Abnormalities in the QRS complex were found in all 6 dogs varying from sinus arrhythmia and transitory extreme left axis deviation to very serious conditions including auriculoventricular block, ventricular

* The vinyl chloride used in these studies was prepared for us especially purified by H. R. Smith of Petroleum Chemicals, Inc., Baltimore, Md. It was stabilized with 0.5 per cent of tertiary butyl alcohol. The compound was purified as follows:

"Vinyl chloride of 94%, by weight purity containing 5.6% by weight trichloroethylene, 2.5 ppm. of acetylene, and no free acidity was carefully distilled to remove trichloroethylene. The distilled vinyl chloride was washed with cuprous ammonium chloride, phosphoric acid, and dried over purified potassium hydroxide. The purified vinyl chloride was found to have the following specifications:

Acetylene: None by cuprous ammonium chloride test.
Free Acidity: None.
Ammonia: None.
Trichloroethylene: Trace."

tachycardia, ventricular multifocal extra systoles, and inversion of the T-wave with elevated ST segments in lead II. As anesthesia progressed toward respiratory failure, most of the QRS abnormalities disappeared but the R amplitude was greatly reduced.



Normal
Lead II

Vinyl Chloride Anesthetized
Lead II

CHART I

Two dogs under ethyl chloride anesthesia and the same experimental conditions showed a lowering of blood pressure and progressive bradycardia without arrhythmias. In 1 animal a brief period of left axis deviation appeared during the induction phase.

SUMMARY AND CONCLUSIONS

1. Vinyl chloride has been studied as an anesthetic in the dog.
2. The anesthetic syndrome is marked by incoordinated muscular activity in the extremities.
3. In 6 dogs cardiac arrhythmias of a serious nature were observed.

It is our opinion that, as an anesthetic in the dog, vinyl chloride is unsafe and that its use in man is unwarranted.

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mit häufiger Abbildung einer intratumoralen Cholelithiasis. Nicht nur die bestehende Leberinvasion per continuitatem, sondern auch die zum Zeitpunkt der computertomographischen Diagnose bereits vorliegende hämatogene und lymphogene Metastasierung des biliären Karzinoms erklärt, jedoch unverändert das therapeutische Dilemma und die ungünstige Prognose dieser Tumoren.

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Fortschr. Röntgenstr. 134, 3 (1981) 283-290

Das vinylchloridinduzierte Leberangiosarkom und hepatozelluläre Karzinom

Von D. Koischwitz, W. K. Lebach, K. Lackner und D. Hermanutz

3 Abbildungen

Radiologische Klinik (Direktor: Prof. Dr. P. Thurn) und Medizinische Klinik (Direktor: Prof. Dr. H. J. Dengler) der Universität Bonn

Es wird über drei Patienten eines PVC-herstellenden Betriebes berichtet, die an Angiosarkomen der Leber, in einem Fall kombiniert mit einem multilokulären primären hepatozellulären Karzinom, erkrankten. Epidemiologie, Klinik und Diagnostik unter besonderer Berücksichtigung der angiographischen, sonographischen und computertomographischen Befunde werden diskutiert. Dabei erweisen sich die nicht-invasiven Untersuchungsverfahren Computertomographie und Sonographie als Mittel der Wahl, wenn nach einer VCM-Langzeitexposition ein Angiosarkom der Leber angenommen wird.

Die Toxizität des Vinylchlorids ist erst in jüngster Zeit (1970-1974) erkannt worden, obwohl seit über 40 Jahren Polyvinylchlorid (PVC), einer der am häufigsten verwendeten Kunststoffe, durch Polymerisation des gasförmigen Monomers (VCM) großtechnisch hergestellt wird. Erste Berichte aus Rußland über Leberschäden, als „chronische epitheliale Hepatitis“ bezeichnet (Tribukh et al. 1949), sowie weitere Hinweise auf die Toxizität des Vinylchlorids aus Rumänien (Sudu et al. 1963) fanden anfangs wenig Beachtung. Ein größeres Interesse setzte erst ein, als seit 1966 aus verschiedenen Ländern über ein vorwiegend bei Autoklavenreinigern beobachtetes Krankheitsbild berichtet wurde, das auf eine VCM-Langzeitexposition zurückgeführt wird und sich zunächst mit der Trias von

Akroosteolysen, Raynaud-Syndrom und sklerodermieartigen Hautveränderungen präsentierte (Chatelain und Motillon 1967, Cordier et al. 1966, Marin et al. 1967, Wilson et al. 1967).

Tierexperimentelle Untersuchungen mit genügend langer Laufzeit, die der Erforschung der Veränderungen an den Akren dienen sollten, deckten erstmals die onkogene Potenz des VCM auf (Viola 1970, Maltoni und Lefemine 1975, Keplinger et al. 1976). Seither folgten zahlreiche Mitteilungen, die sich teils anhand tierexperimenteller Untersuchungen, teils anhand klinischer Beobachtungen mit dem Auftreten VCM-induzierter Tumoren befaßten (Cresch und Johnson 1974, Lange et al. 1974, Makk et al. 1974, Gedigh et al. 1975). Insbesondere

Vinyl chloride-induced angiosarcoma and hepato-cellular carcinoma of the liver

Three patients with industrial exposure to PVC are described, who developed angio-sarcomas of the liver; in one patient this was combined with a multi-locular primary hepato-cellular carcinoma. The epidemiology, clinical features and diagnosis are discussed, with particular reference to angiography, sonography and computerized tomography. The non-invasive methods, such as computerized tomography and sonography, are the techniques of choice if an angio-sarcoma is suspected after long exposure to PVC.



Abb. 1a Zöliakographie, arterielle Durchströmungsphase.

Abb. 1 Angiosarkom der Leber bei VCM-Krankheit.



Abb. 1b Spätvenöse Durchströmungsphase. Leberverkleinerung mit geschlängelter Verlauf der intrahepatischen Arterien. Bereits in der arteriellen Phase beginnende (▲) und in der venösen Phase lang persistierende, fleckige Kontrastierung eines Angiosarkoms im rechten Leberlappen.

wurde beim Menschen über das Auftreten von Angiosarkomen der Leber, sehr selten auch von hepatozellulären Karzinomen berichtet (Creech und Johnson 1974, Lloyd 1974, Delorme 1978, Gokel et al. 1976, Popper et al. 1978), wohingegen aufgrund tierexperimenteller Untersuchungen von Viola (1970, 1974) auch mit dem Auftreten von Geschwülsten der Nieren, des Gehirns, des Skeletts, der Haut, des lymphatischen und hämatopoetischen Systems gerechnet werden muß. Seit der ersten Mitteilung über 4 Patienten mit VCM-induziertem Angiosarkom der Leber in den USA (Creech und Johnson 1974) hat das National Institute for Occupational Safety and Health (NIOSH) bis Herbst 1978 weltweit Daten über insgesamt 76 Patienten mit VCM-induziertem Angiosarkom der Leber zusammengetragen, davon 68 bei Arbeitern aus der unmittelbaren PVC-Produktion (Spiras und Kamiński 1977, 1978). In der Bundesrepublik Deutschland sind bis Ende 1978 16 Patienten mit VCM-induziertem Angiosarkom der Leber beobachtet worden (Reinl et al. 1978). Sieben dieser Patienten stammen aus einer Gruppe von Arbeitern eines PVC-herstellenden Betriebes, die sich seit 1970 in klinischer Betreuung der Bonner Universitäts-Kliniken befinden. Über klinische und histologische Befunde bei zwei Patienten dieser Gruppe wurde bereits früher berichtet (Lange et al. 1974, Gedigk et al. 1974). Bei drei weiteren Patienten dieser Gruppe konnte bereits zu Lebzeiten durch radiologische Untersuchungen der Tumornachweis in der Leber geführt werden. Deshalb soll hier insbesondere über die angiographischen, computertomographischen und sonographischen Befunde der VCM-induzierten Tumoren der Leber berichtet werden.

Kasuistik

1. Patient, E. U., 57 Jahre

Arbeitsanamnese: 21 Jahre VCM-Exposition.

Klinik: Im Januar 1975 erstmals Untersuchung in der Medizinischen Universitätsklinik Bonn. Leichte Heparomegalie. Normale Milzgröße. Deutliche Thrombozytopenie. Diabetes mellitus seit 1967.

Laborbefunde: Deutliche Aktivitätserhöhung der alkalischen Phosphatase. 45-Minuten-Bromsulfaleinretention 20,6%.

Leberszintigramm: Speicherdefekte im lateralen Teil des rechten Leberlappens.

Laparoskopie: Bräunliche, flachhöckerige bis kleinknotige, zirrhoseartige Leberoberfläche mit ausgedehnter flächenhafter, weißlicher Kapselfibrose. Zeichen der portalen Hypertension. Keine umschriebenen tumorverdächtigen Areale. Histologisch (linker Leberlappen) teils septale, teils postnekrotische Zirrhose mit mäßiger Parenchymsiderose. Perisinusoidale Fibrose. Kettenförmige Proliferation sinusoidaler Uferzellen.

Verlauf: Im Juli 1975 erstmaliger Nachweis geringer Ösophagusvarizen. In den folgenden Monaten Entwicklung einer Splenomegalie und Zunahme der portalen Hypertension. Im Dezember 1975 rasche Entwicklung von Ikterus und Aszites.

Zöliakographie: (5. 12. 1975) (Abb. 1a und b): Kleine Leber. Geschlängelter Verlauf der intrahepatischen Arterien. Keine auffälligen Tumorgefäße. In der parenchymatösen Durchströmungsphase fleckige Kontrastierung des polyzyklisch begrenzten Tumors im lateralen Teil des rechten Leberlappens.

Weiterer Verlauf: Exitus letalis infolge Leberinsuffizienz nach Varizenblutung am 15. 12. 1975. Autopsisch multizentrisch wachsendes Hämangiosarkom im rechten Leberlappen*.

2. Patient, W. F., 54 Jahre

Arbeitsanamnese: 10 Jahre als Autoklavereiniger und weitere 9 Jahre (bis 1974) als Vorarbeiter am selben Arbeitsplatz VCM-exponiert tätig.

Klinik: Seit 1972 Diabetes mellitus bekannt. Heparomegalie, als „Fettleber“ gedeutet. Mäßige Splenomegalie. Seit 1974 progrediente Thrombozytopenie. Im Februar 1975 erstmalige Untersuchung in der Medizinischen Universitätsklinik Bonn. Allgemeines Krankheitsgefühl. Teerstühle. Bräunliche Hautpigmentation.

Laborbefunde: Lediglich grenzwertige Erhöhung von Gesamtbilirubin, SGOT, SGPT, Gamma-GT und BSP-Retention.

Laparoskopie: Gemischtförmige, mikro- und makronoduläre Zirrhose mit zahlreichen flachen, postnekrotischen Narben. Kapselfibrose.

* Die pathologisch-morphologischen Befunde verdanken wir Prof. Dr. P. Gedigk, Direktor des Pathologischen Institutes der Universität Bonn, der gesondert berichten wird.

Bräunliche Verfärbung des Leberparenchyms. Zeichen der portalen Hypertension. *Histologisch*: teils septale, teils postnekrotische Zirrhose. Bedeutende Siderose. Fokale Verfettung. Kein Nachweis von Sinuszellatypen, keine Sinuspektasie. Kein Malignomnachweis. *Explorative Laparotomie*: Keilbiopsien aus beiden Leberlappen. Ebenfalls kein Malignomnachweis. Histologie identisch mit Punktionsbiopsiebefund.

Röntgenbefunde

Ösophagogramm (22. 2. 1975): Varizen im unteren Ösophagus.

Selektive Hepatikographie und indirekte Splenoporthographie

(24. 2. 1975) (Abb. 2a): Stark vaskularisierter Tumor mit zahlreichen arteriovenösen Shunts, der den gesamten rechten Leberlappen einnimmt. Linker Leberlappen unauffällig. Retrograde Durchströmung der V. portae und der V. mesenterica superior bei regelrechter Durchströmung der V. lienalis als Zeichen eines intrahepatischen Blocks mit hepatofugalem Kollateralkreislauf.

Sonographie der Leber (Gerät mit bistabiler Speicherröhre) (31. 3. 1975): Keine Lebervergrößerung. Scharfkantige Margo inferior hepatis. Zentral im rechten Leberlappen 8 cm im Durchmesser messender Tumor, der bei stufenweiser Schallintensitätsverstärkung ein zunehmendes irreguläres Reflexbild zeigt.

Sonographie der Leber (20. 10. 1977) (Abb. 2b und c): Lebervergrößerung unter Bevorzugung des linken Leberlappens. Verplumpung des Lobus caudatus. Abrundung der Margo inferior hepatis. Diffuse Leberparenchymveränderung bei Verstärkung des Leberstrukturechomusters. Verstärkung der Schallabsorption. Multiple, verstärkt reflektierende Tumoren innerhalb des rechten und linken Leberlappens. Diffuse Pankreasvergrößerung mit Verstärkung des Strukturreflexmusters.

Selektive Hepatikographie und indirekte Splenoporthographie (5. 11. 1977) (Abb. 2d und e): Bogige Verlagerung des rechten intrahepatischen Hauptastes der A. hepatica propria durch einen 8 cm im Durchmesser messenden, hypervaskularisierten Tumor zentral im rechten Leberlappen. Multiple weitere, 1 bis 3 cm im Durchmesser messende Tumoren mit ausgeprägter Kontrastmittelanreicherung und langer -speicherung. Keine Darstellung der früher nachgewiesenen retrograden Pfortaderdurchströmung.

Computertomographie (7. 11. 1977) (Abb. 2f und g): Im rechten und linken Leberlappen multiple, 2 bis 4 cm im Durchmesser messende, teilweise konfluierende, hypodense Areale mit einer Dichte von nativ 40 bis 45 Hounsfield-Einheiten, die nach i.v. Kontrastmittelanreicherung (100 ml Telebrix 300) teilweise hypodens bleiben, teilweise, bei einer Dichte des Leberparenchyms von 65 bis 70 Hounsfield-Einheiten, isodens werden. In der Differentialdiagnose wird ein multilokulärer Tumor oder aber multiple Leberregeneratknoten erwogen.

Weiterer Verlauf: Computertomographische und sonographische Kontrolluntersuchungen zeigen eine weitere Zunahme der Lebergröße, eine Progredienz der Lebertumoren sowie einen zunehmenden Aszites. Am 23. 3. 1978 röntgenologischer Nachweis einer Osteolyse im Margo lateralis scapulae rechts. Palliative Strahlenbehandlung der rechten Schulterregion und deutliche Besserung der Schmerzen. Die Osteolyse bestätigt letztlich die Diagnose eines metastasierenden Malignoms, das aufgrund der sonographischen, computertomographischen und angiographischen Befunde in der Leber diagnostiziert worden war. Unter weiterer Größenzunahme der Leber, insbesondere deutlicher Vergrößerung des linken Leberlappens, Zunahme des Aszites und Entwicklung eines auf der Abdomenoberfläche sichtbaren Kollateralkreislaufes, progrediente Verschlechterung des Allgemeinzustandes des Patienten. Anhaltende Blutstühle mit erheblichem Hb-Abfall. Die Ursache der Blutungen kann endoskopisch nicht eruiert werden (Hämophilie). Exitus letalis am 7. 8. 1978. Die *Autopsie* bestätigt das röntgenologische und klinisch diagnostizierte metastasierende Lebermalignom; es fand sich ein multizentrisch wachsendes Angiosarkom, kombiniert mit einem multizentrisch wachsenden primären hepatozellulären Karzinom der Leber.

3. Patient, B. K., 54 Jahre

Arbeitsanamnese: 18 Jahre VCM-exponiert (bis 1973) in der PVC-Polymerisation.

Klinik: 1969 erstmals Teerstühle; die Ursache wird in einem blutenden Ulcus duodeni angenommen. Erneut Melena 1970 und 1972. Des-

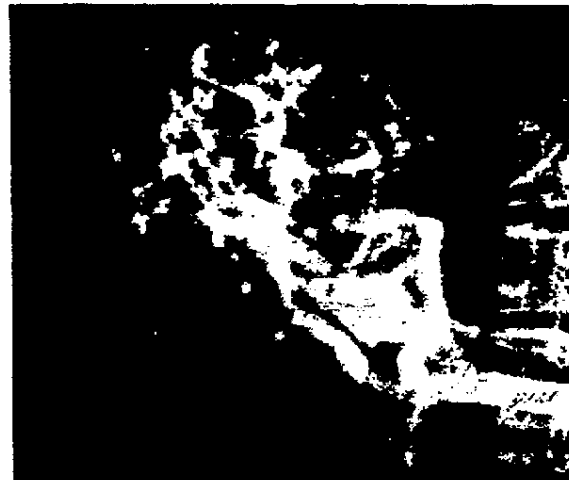


Abb. 2a Selektive Hepatikographie (24. 2. 1975). Stark vaskularisierter solitärer Tumor im rechten Leberlappen mit irregulärem Gefäßbild. Zahlreiche AV-Shunts mit verstärktem Kontrastmitteldurchsatz durch den Tumor und retrograder Pfortaderdurchströmung.

halb 1972 Magenresektion nach Billroth II. Intraoperativ Feststellung eines Aszites sowie einer vergrößerten, „zirrhoseartigen“ Leber. *Histologisch* lediglich geringe portale Fibrose. Postoperativ erstmals Ikterus. Im Februar 1973 erstmalige Untersuchung in der Medizinischen Universitätsklinik Bonn. Dabei Druckgefühl im rechten Oberbauch. Kälteempfindlichkeit an Händen und Füßen. Raynaud-Syndrom. Splenomegalie. Leichte Leukopenie und Thrombopenie.

Laborbefunde: Grenzwertige Hyperbilirubinämie. Geringe Aktivitätserhöhung der alkalischen Phosphatase. Alle übrigen Laborwerte im Normbereich.

Gastroskopie und Laparoskopie: Nachweis von Ösophagus- und Magenfundusvarizen. Fein- bis grobknotige Leberzirrhose. Zeichen der portalen Hypertension. *Histologisch* lediglich geringe septale und portale Fibrose.

Verlauf: Trotz Beendigung der VCM-Exposition Progredienz der Ösophagus- und Magenfundusvarizen. Im März 1975 massive Varizenblutung. Konservative Therapie. Eine angeratene splenorenales Shuntoperation wird abgelehnt. Im September 1976 erneute Varizenblutung. Endoskopische Ösophaguswandsklerosierung und Wiederholung der Sklerosierung im März 1977. Progredienz der Splenomegalie. Im August 1979 rezidivierende Epistaxis. Schmerzen im rechten Oberbauch und Epigastrium. Derber, der Leber angehörender Tumor tastbar. Starke Kopfschmerzen rechts parietal. Optische Halluzinationen. Verdacht auf Hirnmetastasen.

Röntgenbefunde

Computertomographie des Gehirns (12. 1. 1980): Multiple Hirnmetastasen mit perifokalem Ödem in beiden Hirnhemisphären.

Sonographie des Oberbauches (1. 2. 1980) (Abb. 3a und b): Ausgedehnter, 12 x 15 cm im Durchmesser messender reflexarmer Tumor zentral intrahepatisch zwischen linkem und rechtem Leberlappen gelegen, der aus multiplen, rundlichen Strukturen konglomeratähnlich zusammengesetzt ist. Keine Lebervergrößerung. Mäßige Splenomegalie. Portale Hypertension mit Erweiterung der Pfortader auf 1,5 cm im Durchmesser.

Computertomographie des Abdomens (6. 2. 1980) (Abb. 3c und d): Großer, solitärer, intrahepatischer Tumor von 15 cm Durchmesser, zentral in der Leber gelegen, sowohl den rechten wie den linken Leberlappen betreffend, der sich nativ hypodens mit Dichtewerten um 40 Hounsfield-Einheiten darstellt und nach i.v. Kontrastmittelanreicherung (100 ml Telebrix 300) dem Lebergewebe mit 55 bis 60 Hounsfield-Einheiten isodens erscheint. Mäßige Splenomegalie. Lymphkno-

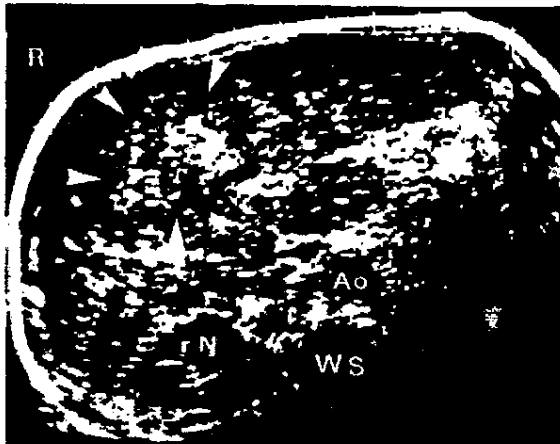


Abb. 2b Transversalsonogramm der Leber. Lebervergrößerung. Multiple, stark reflektierende intrahepatische Tumoren. WS = Wirbelsäule, Ao = Aorta, rN = rechte Niere.

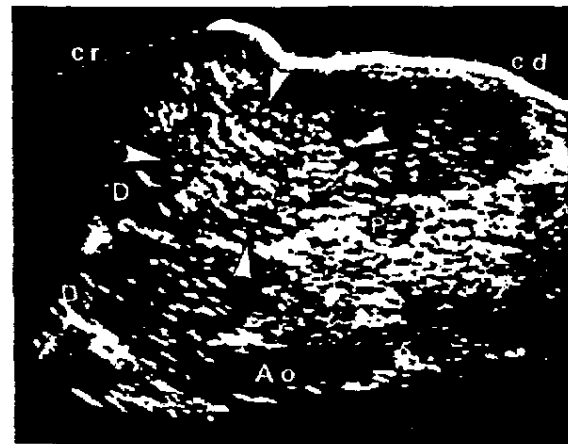


Abb. 2c Longitudinalsonogramm des linken Leberlappens. Bevorzugte Vergrößerung des linken Leberlappens und des Lobus caudatus. Abrundung der Leberkante. Multiple intrahepatische Tumoren. D = Diaphragma, P = Pankreas, Ao = Aorta.

Abb. 2 Kombination von multikulärem Angiosarkom der Leber und multikulärem primärem hepatozellulärem Karzinom der Leber bei VC-Krankheit.



Abb. 2d Selektive Hepatikographie, arterielle Phase (5. 11. 1977). Bogige Verlagerung des rechten intrahepatischen Hauptastes der A. hepatica propria. Großer hypervaskularisierter Tumor im rechten Leberlappen. Weitere stark kontrastanreichernde Tumoren im linken Leberlappen.



Abb. 2e Selektive Hepatikographie, venöse Phase (5. 11. 1977). Verzögerter Abfluß des Kontrastmittels aus den peritumoralen Leberveinen im rechten Leberlappen. Lange Kontrastmittelspeicherung in multiplen Tumoren, insbesondere links.

tenvergrößerung paraaortal im Hiatus diaphragmatis und im hinteren unteren Mediastinum.

Verlauf: Schnelle Verschlechterung des Gesamtzustandes des Patienten. Desorientiertheit. Bewußtlosigkeit. Exitus letalis am 22. 2. 1980. Die Autopsie bestätigt die angenommene Diagnose eines metastasierenden Lebermalignoms (Angiosarkom der Leber) mit Hirn-, Lungen- und Lymphknotenmetastasen*.

Diskussion

Das primäre Angiosarkom der Leber wird im Schrifttum unter einer Vielzahl von Synonyma aufgeführt, so als angioblastisches Sarkom, angioplastisches Retikulosarkom, Endotheliom, Endothelioblastom, Hämangioblastom, Hämangioendothe-

liom, hämangioendotheliales Sarkom, Kupffer-Zell-Sarkom, malignes Hämangiom, metastasierendes Hämangiom, retikuloendotheliales Sarkom, primäres Sarkom der Leber (Zimmermann und Eck 1975, Popper und Thomas 1975, Leibel und Marsteller 1981). Die zahlreichen Synonyma erschweren es, die Zahl der bisher mitgeteilten Beobachtungen exakt zahlenmäßig anzugeben. Zweifellos handelt es sich um ein außerordentlich seltenes Malignom, das seinen Ausgang von den sinusoidalen Uferzellen, Gefäßendothelien mesenchymalen Ursprungs, nimmt. In großen Autopsiestatistiken fand sich ein Angiosarkom der Leber auf 20 000 bis 100 000 Autopsien, und 165 aus dem Schrifttum zusammengefaßte Angiosarkome der Leber stellten lediglich 1,8% aller innerhalb dieser Gruppe

nachgewiesenen primären Lebermalignomen dar (Alrenga 1975).

Das erwartete spontane Auftreten von Angiosarkomen der Leber in den USA wird mit 0,014 auf 100 000 Einwohner oder 25 bis 30 Erkrankungen pro Jahr für die gesamten USA errechnet (Heath et al. 1975). Deshalb kam der Beobachtung von 4 Patienten mit Angiosarkomen der Leber unter 270 Arbeitern einer PVC-herstellenden Fabrik in Kentucky, USA, zwischen 1967 und 1973 eminente Bedeutung zu, da sie eine neue, schwere Berufserkrankung aufdeckte (Creach et al. 1974, Creach und Johnson 1974). Die Entstehung von Angiosarkomen der Leber beim Menschen war bis zu diesem Zeitpunkt nur im Zusammenhang mit zwei anderen Substanzen beobachtet worden, einem Thoriumdioxidpräparat (Thorotrast), das als Kontrastmittel verwendet worden war (Da Silva Horta 1967), sowie dem im Weinbau als Insektizid verwendeten Arsenitoxid (Roth 1957). Heath et al. (1975) zeigten für die VCM-exponierten Arbeiter der PVC-Polymerisationsindustrie ein 400fach höheres Risiko auf an einem Angiosarkom der Leber zu sterben, als es der Spontanentwicklung entsprechen würde.

Obwohl tierexperimentelle Untersuchungen (Viola et al. 1971, Maltoni und Lefemine 1975, Popper et al. 1978) belegen, daß neben Angiosarkomen auch hepatozelluläre Karzinome bei VCM-Exposition auftreten, wurden bisher nur 3 Patienten mit solitären hepatozellulären Karzinomen (Gokel et al. 1976, Fox und Collier 1977) und 3 weitere Patienten mit einer Kombination von Angiosarkom und hepatozellulärem Karzinom ange- troffen (Byren und Holmberg 1975, Delorme 1978, Tamburro et al. 1978), denen wir einen weiteren Patienten (W. F.) hinzu- fügen können. Es ist bisher nicht geklärt, warum die Hepatozy- ten im Gegensatz zu den sinusoidalen Uferzellen von der kanzerogenen Wirkung des VCM in geringerem Maße betrof- fen scheinen.

Die klinische Symptomatik des Angiosarkoms der Leber ist uncharakteristisch. Zunehmende Verschlechterung des Allge- meinbefindens, Gewichtsverlust, einhergehend mit uncharak- teristischen Oberbauchbeschwerden oder geringen Schmerzen, sind gewöhnlich die ersten jedoch vieldeutigen Symptome. Gelegentlich kann ein geringer Ikterus bestehen. Die laborche- mischen Parameter der Leber sind nicht oder nur gering, meistens jedoch uncharakteristisch verändert (Williams et al. 1975, Leibach und Marsteller 1981). Auch hat sich die Bestim- mung des Alpha-Fetoproteins nicht als hilfreich für die Dia- gnosestellung erwiesen. Im fortgeschrittenen Stadium fallen Lebervergrößerung und Blutung aus dem Intestinaltrakt auf (Thomas und Popper 1975, Roche et al. 1978, Konetzke et al. 1978), zu denen im weiteren Verlauf Aszites, Ödeme und Marasmus hinzukommen, wie es auch bei allen von uns beob- achteten Patienten der Fall war. Während die Leber von den meisten Autoren als stark vergrößert bezeichnet wird (Thomas und Popper 1975), fand sich nur bei einem der von uns beobachteten Patienten eine relativ große Leber mit 3200 Gramm, während sie bei den beiden restlichen Patienten mit 1350 und 1150 Gramm eher verkleinert war.

Mittels Laparoskopie und Leberbiopsie gelingt es zwar mit hoher Treffsicherheit, die diffusen, VCM-induzierten Leber- veränderungen zu erkennen, wie subkapsuläre und portale Fibrose, sinusoidale Dilatation und atypische proliferierende sinusoidale Uferzellen, wobei letzteres als Tumorstufe zu werten ist (Marsteller et al. 1973, Creach et al. 1974, Falk et al. 1974, Thomas und Popper 1975). Die umschriebenen tumorö- sen Läsionen können jedoch verborgen bleiben (Smith et al. 1976), wie es auch bei einem der hier vorgestellten Patienten



Abb. 2f Computertomogramm der Leber, Natvuntersuchung. Multiple hypodense intrahepatische Tumoren, im rechten Leberlappen bis zu 8 cm im Durchmesser messend (▲) und von geringerer Größe auch im linken Leberlappen (▲), mit Dichtewerten von 40 bis 45 HE. N = rechte Niere, Mi = Milz.



Abb. 2g Computertomogramm der Leber, Kontrastuntersuchung nach i.v. Applikation von 100 ml Telebrix 300. Verschiedene Tumore sind isodens, andere Tumore im rechten (▲) wie im linken (▲) Leberlappen bleiben jedoch hypodens bei multiklokulärem Angiosarkom und hepatozellulärem Karzinom. N = rechte Niere, Mi = Milz.

der Fall war, der unter angiographisch und sonographisch erhobenem Tumorverdacht laparotomiert wurde und trotz multipler tiefer Keilbiopsien eine Tumordiagnose mißlang. Falls das Angiosarkom die Leberoberfläche erreicht, stellt es sich als grobknotige, hypervaskularisierte oder zystisch erscheinende Veränderung dar, ähnlich einer grobknotigen Leberzirrhose oder einer Metastasenleber. Eine transkutane Nadelbiopsie bei Verdacht auf ein Angiosarkom der Leber ist

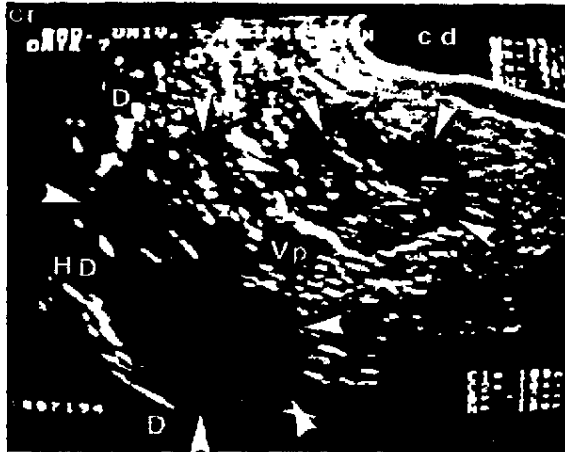


Abb. 3a Longitudinalsonogramm durch den rechten Leberlappen. Konglomeratartig aus multiplen, wenig reflektierenden Arealen aufgebautes Angiosarkom der Leber (▲), weitgehend den rechten Leberlappen ausfüllend. D = Diaphragma, HD = Hiatus diaphragmatis, Vp = Vena portae.

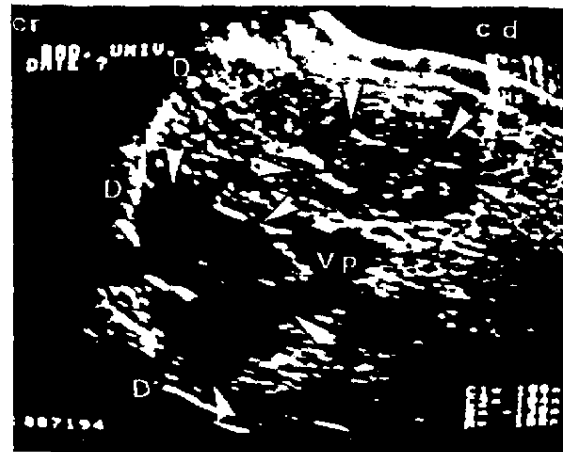


Abb. 3b Longitudinalschnitt durch die Leberpforte. Das Angiosarkom involviert auch den linken Leberlappen (▲). Verplumpung der Margo inferior hepatis. Portale Hypertension. D = Diaphragma, Vp = Vena portae.



Abb. 3c Computertomogramm der Leber, Nativuntersuchung. Großer solitärer hypodenser Tumor von 12 cm Durchmesser, zentral in der Leber gelegen, sowohl in den rechten wie in den linken Leberlappen reichend. Dichte nativ 40 HE. Aszites (▲), Ma = Magen, N = rechte Niere, Mi = Milz.



Abb. 3d Computertomogramm der Leber, Kontrastuntersuchung nach i.v. Applikation von 100 ml Telebrix 300. Das Tumorgewebe wird dem Lebergewebe nahezu vollständig isodens (55 bis 60 HE). Lediglich ein zentraler Rest bleibt hypodens (▲).

Abb. 3 Angiosarkom der Leber bei VC-Krankheit.

aber wegen der zu befürchtenden, nicht kontrollierbaren Nachblutung kontraindiziert.

Deshalb haben sich die radiologischen Nachweisverfahren wie Szintigraphie, Leberangiographie und insbesondere Sonographie und Computertomographie des oberen Abdomens als die diagnostischen Verfahren der Wahl erwiesen, wenn ein Angiosarkom der Leber angenommen wird. Die Leberszintigraphie zeigt zwar isolierte oder multiple Aktivitätsdefekte, die durch die intrahepatischen Tumoren verursacht sind, und gleichzeitig

können auch atypische Aktivitätsanreicherungen in der Milz erkannt werden (Biersack et al. 1975), aber peripher gelegene und multiple Aussparungen der Aktivitätsanreicherung sind schwer zu erfassen, und ihre Interpretation stößt auf Schwierigkeiten (Whelan et al. 1976). Bei der Hepatikographie sind Verlagerung der A. hepatica propria und ihrer Äste durch den Tumor, Hypervaskularisation des Tumors mit irregulärem Gefäßbild und insbesondere mit Kontrastmittelanreicherungen im gesamten Tumor oder nur in der Tumorperipherie, die in

der venösen Phase noch lange, bis über 30 Sekunden persistiert, als typische Befunde des Angiosarkoms beschrieben worden (Abb. 1b, 2d und c) (Whelan et al. 1976). Neben verschiedenen Graden einer Peliosis hepatis wurde einmal über einen portalen Reflux mit hepato-fugalem Kollateralkreislauf beim Angiosarkom der Leber berichtet (Whelan et al. 1976), wie er auch bei einem von uns angiographisch untersuchten Patienten beobachtet werden konnte (Abb. 2a). Die retrograde Pfortaderperfusion stellt beim Angiosarkom der Leber anscheinend ein bisher noch selten beobachtetes Phänomen dar, das beim primären hepatozellulären Karzinom häufiger beschrieben wurde: Okuda et al. (1973, 1977) berichten über eine retrograde Füllung des Pfortaderhauptstammes über den Leberhilus hinaus bei 25,4% von 114 Patienten mit primärem hepatozellulären Karzinom, was als Folge intratumoraler arterioportal Shunts interpretiert wird. Da bei dem von uns beobachteten Patienten mit retrograder Pfortaderperfusion eine Kombination von Angiosarkom und hepatozellulärem Karzinom vorlag, ist die Zuordnung dieses Phänomens zur sarkomatösen oder karzinomatösen Tumorkomponente hier nicht sicher. Auch ist die Reversibilität der retrograden Pfortaderperfusion bei der zweiten, 2½ Jahre später erfolgten angiographischen Untersuchung nicht geklärt.

Trotz hoher Treffsicherheit beim Tumornachweis kann in Einzelfällen die Erstellung der korrekten Diagnose eines Angiosarkoms der Leber auch bei wiederholten Angiographien mißlingen (Roche et al. 1978). Sonographie und Computertomographie bieten sich aber neuerdings als nicht-invasive, den Patienten nicht belastende Verfahren mit hoher Aussagekraft an (Bosnjakovic et al. 1980), insbesondere bei wiederholten Untersuchungen von VCM-exponierten Patienten zur Befundkontrolle oder zur Begutachtung (Taylor et al. 1976). Da viele dieser Patienten bereits zahlreiche, häufig auch belastende und invasive Untersuchungen durchlaufen haben, werden Computertomographie und Sonographie bevorzugt toleriert. Die Sonographie erbrachte bei beiden von uns untersuchten Patienten den Nachweis solitärer oder multilokulärer, entweder reflexarmer oder verstärkt reflektierender, konglomeratartiger intrahepatischer Tumoren. Daneben konnten eindeutig Leber- und Milzgröße, diffuse Leberparenchymveränderungen sowie die Weite der V. portae beurteilt werden. Computertomographisch zeigten die Tumoren bei beiden untersuchten Patienten nativ hypodense Strukturen mit Dichtewerten von 40 bis 45 HE, während sie nach Kontrastmittelinjektion dem Leberparenchym isodens erschienen. Bei einem Patienten (W. F.) jedoch verhielten sich einzelne Tumorateile nach Kontrastmittelinjektion isodens, andere Tumorateile blieben hypodens, was entweder Tumornekrosen oder den beiden histologisch unterschiedlichen Tumorarten zuzuordnen ist.

Beide Verfahren können mit annähernd gleich hoher Sensitivität bereits den präklinischen Nachweis intrahepatischer Tumoren erbringen (Snow et al. 1979, Scherer et al. 1979, Stadler et al. 1980, Janson et al. 1980). Gleichzeitig ist die Beurteilung diffuser Leberveränderungen, Beschaffenheit und Größe anderer Oberbauchorgane sowie die Weite des portalen Gefäßsystems möglich (Williams et al. 1976, Taylor et al. 1976). Im Zusammenhang mit der Anamnese einer chronischen VCM-Exposition ist die Spezifität beim Tumornachweis hoch. Deshalb erscheint es gerechtfertigt, die sonographische und computertomographische Untersuchung der Leber in der Reihe der Kontroll- und Überwachungsuntersuchungen bei der Beurteilung der VCM-bedingten Tumorentstehung bevorzugt einzusetzen.

Für die technische Mitarbeit danken wir Fr. M. Smeets.

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Fortschr. Röntgenstr. 134, 3 (1981) 290-292

Internal endoprosthesis as treatment of obstructive jaundice in pancreatitis

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3 Figures

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In five patients with pancreatitis, obstructive jaundice was relieved by internal drainage of the biliary tract with an endoprosthesis inserted by percutaneous transhepatic technique. The average duration of treatment was 3.5 months. The endoprosthesis were removed by means of a duodenoscope, and jaundice did not recur.

Obstructive jaundice occurs in approximately 20% of patients with acute or chronic pancreatitis (1, 5, 8). In the absence of gallstones, hepatocellular disease or pancreatic cancer it is generally attributed to pancreatic oedema or fibrosis, pancreatic cysts or abscesses (1, 7, 8). The obstruction may lead to cholangitis, depletion of bile salts and electrolytes, and if long standing, to biliary cirrhosis (1, 6, 9) making decompression of the biliary system imperative. We report the results of internal biliary drainage by an endoprosthesis in patients without associated biliary tract disease.

Patients and methods

During a 3-year period 135 patients were admitted to the department with pancreatitis. Five of these had obstructive jaundice without associated biliary disease (4%) and were treated with endoprosthesis.

They were all males with an age range from 34 to 68 years (Table 1), and had jaundice with marked elevations of plasma bilirubin and alkaline phosphatase. The pancreatitis was in two patients classified as chronic, in two as acute relapsing and in one as acute. Etiology was in all cases alcohol. Ultrasonic scanning showed diffuse enlargement of the pancreas and in one patient also a small pseudocyst in the head of pancreas (patient 2).

In one case cancer was ruled out by autopsy, and in the others the clinical course made carcinoma extremely unlikely.

Percutaneous transhepatic cholangiography revealed smooth stenoses in the intrapancreatic part of the distal common bile duct and dilation of the biliary tree (Table 1) (Fig. 1).

Because jaundice persisted for more than 3 weeks, and pseudocysts were absent or too small to justify surgery, internal drainage was performed. The endoprostheses were inserted under local anaesthesia according to a technique previously described (2, 3,) (Fig. 2 and 3).

The endoprostheses were removed later by means of a duodenoscope (3).

Interne Endoprothese zur Behandlung des Stauungsikterus bei Pankreatitis

Bei 5 Patienten mit Pankreatitis konnte der dabei aufgetretene Stauungsikterus mittels interner Drainage der Gallengänge durch eine Endoprothese behoben werden, die perkutan-transhepatisch eingesetzt wurde. Die durchschnittliche Behandlungsdauer betrug 3,5 Monate. Die Endoprothese wurde nach Behandlungsende mittels Duodenoskop entfernt, ohne daß Rezidivierung des Ikterus eintrat.