Air Products

Date 13 September 1983

INTEROFFICE MEMORANDUM

Subject Edwards Case

To G. Bays — Insurance (Location, Organization, or Department)

From J. T. Barr — Regulatory Response (Location, Organization, or Department)

I enclose 2 copies of an article by Evans, et al, from Histopathology, 7 377 (1983) which I just obtained, and which you may wish to pass on to Ed Edelstein. These authors state that they found carcinoma in two of five cases of angio among BP workers. They also reference other supporting reports. See especially the discussion on page 386. This may be of interest in the Edwards Case.

J. T. Barr

JTB:csb

Enclosure

(320)

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Histopathology 1983, 7, 377–388

Angiosarcoma and hepatocellular carcinoma in vinyl chloride workers

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Angiosarcoma and hepatocellular carcinoma in vinyl chloride workers

The livers from five vinyl chloride workers are described. They show angioformative and hepatocellular growth disturbance in varying proportions: angiosarcoma in four cases, liver cell hyperplasia in all, hyperplastic nodules in three cases and hepatocellular carcinoma in two cases. In one case the transition between hyperplastic nodule and hepatocellular carcinoma is demonstrated. The relationship between these changes and vinyl chloride exposure is discussed, with evidence that they are causally related.

Keywords: liver tumours, angiosarcoma, hepatocellular carcinoma, vinyl chloride, occupational cancer

Introduction

Polyvinyl chloride (PVC) had been produced commercially for 40 years by polymerization of vinyl chloride before it was discovered that the latter substance was carcinogenic (Creech & Johnson 1974). Although many different tumour types have been described in animals (Viola, Bigotti & Caputo 1971, Maltoni & Lefemine 1975, Keplinger *et al.* 1975) angiosarcoma of the liver has been the main type described in humans following vinyl chloride exposure (Heath, Falk & Creech 1975, Lee & Harry 1974, Makk *et al.* 1976, Popper *et al.* 1978).

Angiosarcoma of the liver (ASL) is so rare that only about 200 cases have been reported in the world literature (*British Medical Journal* 1981). However, a number of papers have now been published indicating that hepatocellular carcinoma (Gokel, Liebezeit & Eder 1976) and cancers at other sites (Monson, Peters & Johnson 1974, Tabershaw & Gaffey 1974, Nicholson *et al.* 1975, Duck & Carter 1976, Waxweiller

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et al. 1976, Byrén *et al.* 1976, von Reinl, Weber & Greiser 1977), may also result from vinyl chloride exposure.

It is of some importance to determine whether angiosarcoma is the only type of liver cancer to be produced by vinyl chloride. As an industrial disease it has medico-legal implications. We accordingly report our investigations into the histological characteristics of liver tumours occurring in five vinyl chloride workers to demonstrate the diversity of histological types. One of the cases has been previously reported (Smith, Williams & Evans 1976).

Materials and methods

The study is based on liver biopsy and autopsy material obtained at Llandough Hospital between 1973 and 1981 from five male workers who had been exposed to vinyl chloride before it was known to be a health hazard.

An autopsy was performed on every case. The degree of exposure was assessed from the very complete works records of the continuous monitoring for vinyl chloride in the atmosphere where the men were working. The tissues obtained were fixed in 10% buffered formalin, processed and embedded in paraffin. Sections were stained by H & E, Van Gieson and reticulin stains. In addition glutaraldehyde fixed material from two cases was examined by electron microscopy.

Results

The results are summarized in Table 1 which gives details of vinyl chloride exposure.

CASE 1

From the age of 29 years this worker was exposed for a period of only 3½ years to vinyl chloride at a constant working level of over 200 parts/10^6. At the age of 35 years liver biopsy revealed a vascular lesion consistent with angiosarcoma. Alpha-fetoprotein was not detectable in his serum 10 days before death. He died at the age of 37 years from liver failure. Autopsy disclosed a multifocal vascular haemorrhagic liver tumour showing the characteristic histological features of angiosarcoma (Smith *et al.* 1976). One part of liver not affected by tumour showed portal tract fibrosis and liver cell hyperplasia, characterized by twin cell plates. The lobular architecture on the whole was still preserved. There was no nodule formation and no liver cell dysplasia could be found. Angiosarcoma cells were present in lung vessels but no metastatic tumour deposits were seen.

CASE 2

From the age of 44 years this worker was exposed to vinyl chloride over a period of 21 years. No record of serum alpha-fetoprotein estimation was found. At the age of

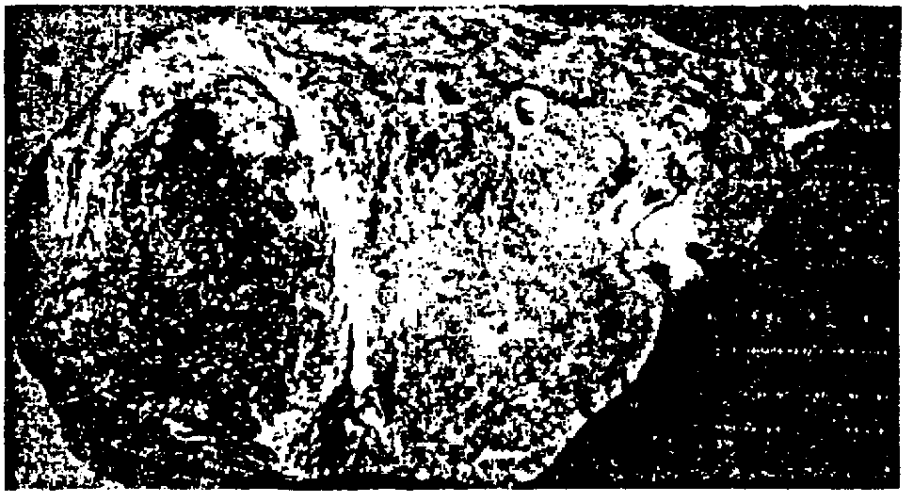
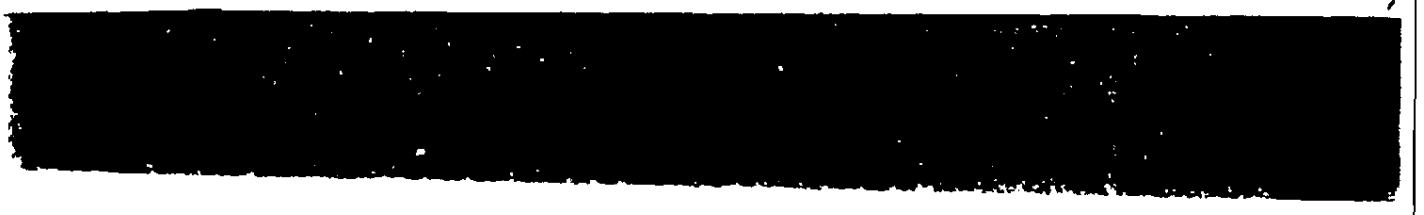


Figure 1. Case 3. Liver with multifocal haemorrhagic vascular tumour (angiosarcoma) mainly occupying right lobe.

65 years he died with spontaneous haemoperitoneum from a liver tumour. The liver at autopsy contained multiple large masses of vascular haemorrhagic liver tumour. Deposits of haemorrhagic tumour tissue were present in lymph nodes of the porta hepatis. On light microscopy the tumour was found to be an angiosarcoma. The rest of the liver showed features similar to Case 1, displaying portal tract fibrosis and diffuse regenerative hyperplasia of hepatocytes with preserved lobular architecture and no nodule formation. However, an occasional focus of liver cell dysplasia was observed. On electron microscopy malignant vascular endothelial cells were clearly distinguished from dysplastic hepatocytes.

CASE 3

From the age of 26 years this worker was exposed to vinyl chloride for a period of 24 years. Four months before his death at the age of 57 years he developed lethargy, anorexia and weight loss, followed by jaundice and evidence of increasing liver failure from which he died. Serum alpha-fetoprotein 10 days before death was 19 mg/l (normal 30 mg/l). At autopsy the liver was enlarged (2900 g) and contained multiple masses of vascular haemorrhagic tumour with large blood-filled spaces, mainly in the right lobe (Figure 1), which was shown histologically to be an angiosarcoma. Blocks from the liver far away from the tumour again showed portal fibrosis. Liver cell hyperplasia was more exuberant than in the two previous cases. Hyperplastic hepatocytes formed nodules (Figure 2) which encroached upon pre-existing lipofuscin-laden liver cells. The general microanatomy of the liver was still well maintained, precluding the diagnosis of cirrhosis. Small foci of liver cell dysplasia (Figure 3) were readily detectable. No metastatic tumour deposits were found.



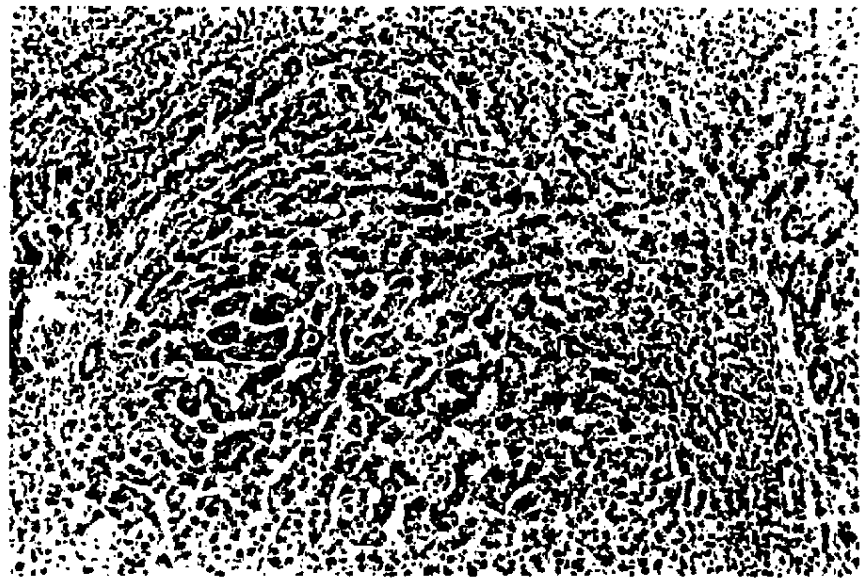


Figure 2. Case 3. Hyperplastic nodule in liver. It has an ill-defined circular outline. Twin cell plates can be seen towards the bottom and left of the picture. H & E. × 100.

CASE 4

From the age of 30 years this worker was exposed to vinyl chloride over a period of 12 years. No record of alpha-fetoprotein estimation was found. Shortly before his death at the age of 48 years he developed portal hypertension with bleeding varices which were controlled by sclerotherapy. Death was from haemoperitoneum due to spontaneous rupture of an apparently single vascular haemorrhagic liver tumour which replaced nearly all the right lobe of the liver. Histological sections from different areas of this lesion however disclosed two different tumours, an angiosarcoma (Figures 4 & 5) and a hepatocellular carcinoma (Figure 6). No alpha-fetoprotein was detected in paraffin sections. In the tumour-free areas of the liver, hyperplastic nodules similar to those seen in Case 3 were again recognized, in addition to portal tract fibrosis. No metastatic tumour deposits were found.

Figure 3. Case 3. Liver cell dysplasia. There is considerable variation in nuclear size, shape and chromatin pattern. H & E. × 225.

Figure 4. Case 4. Angiosarcoma. The tumour tissue contains large vascular spaces. H & E. × 40.

Figure 5. Case 4. Angiosarcoma, showing characteristic pattern of tumour extending between liver cell plates. H & E. × 225.

Figure 6. Case 4. Hepatocellular carcinoma. The tumour cells can be recognized as hepatocytic. The pattern is partly trabecular (*upper right*) and partly more irregular, with much cellular pleomorphism. H & E. × 144.

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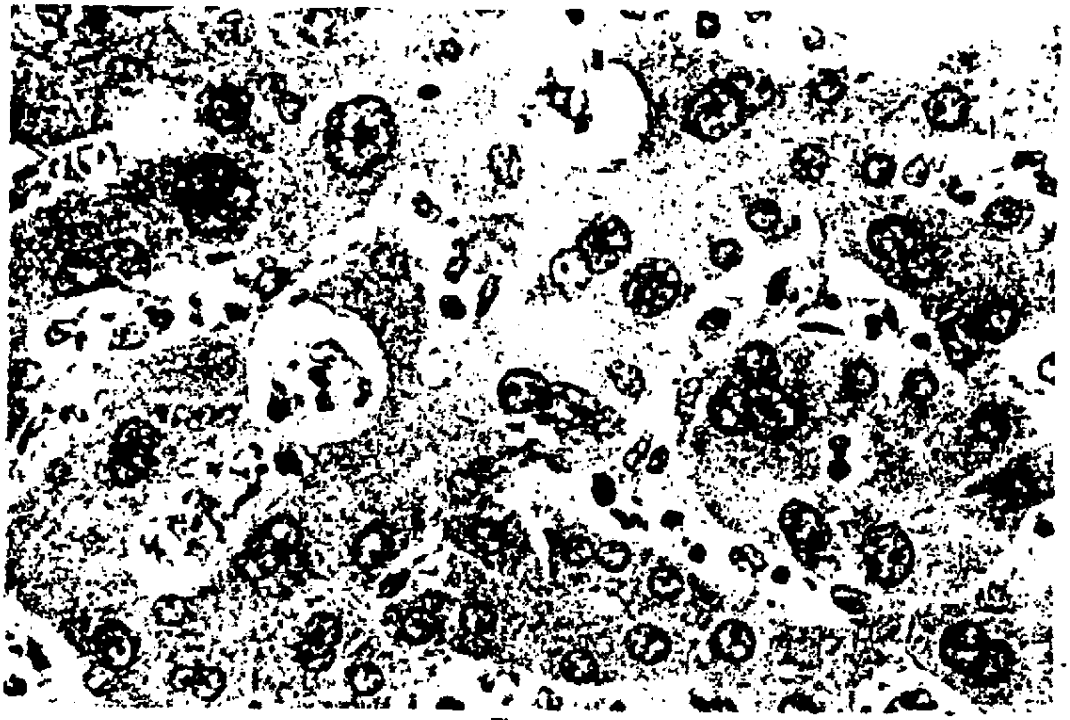

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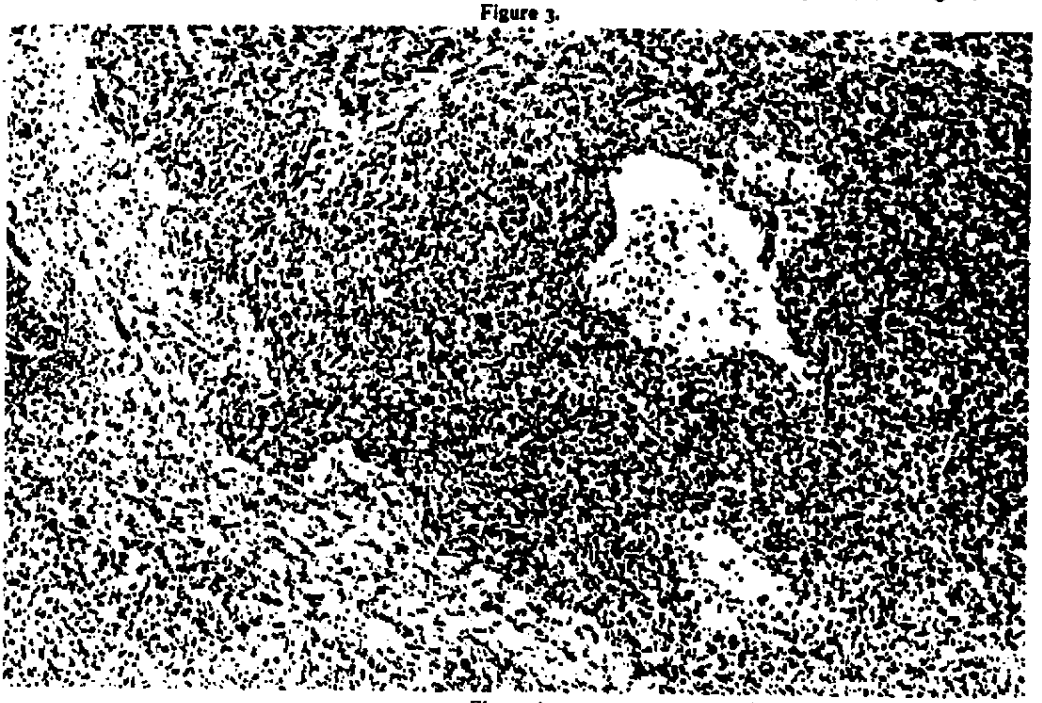

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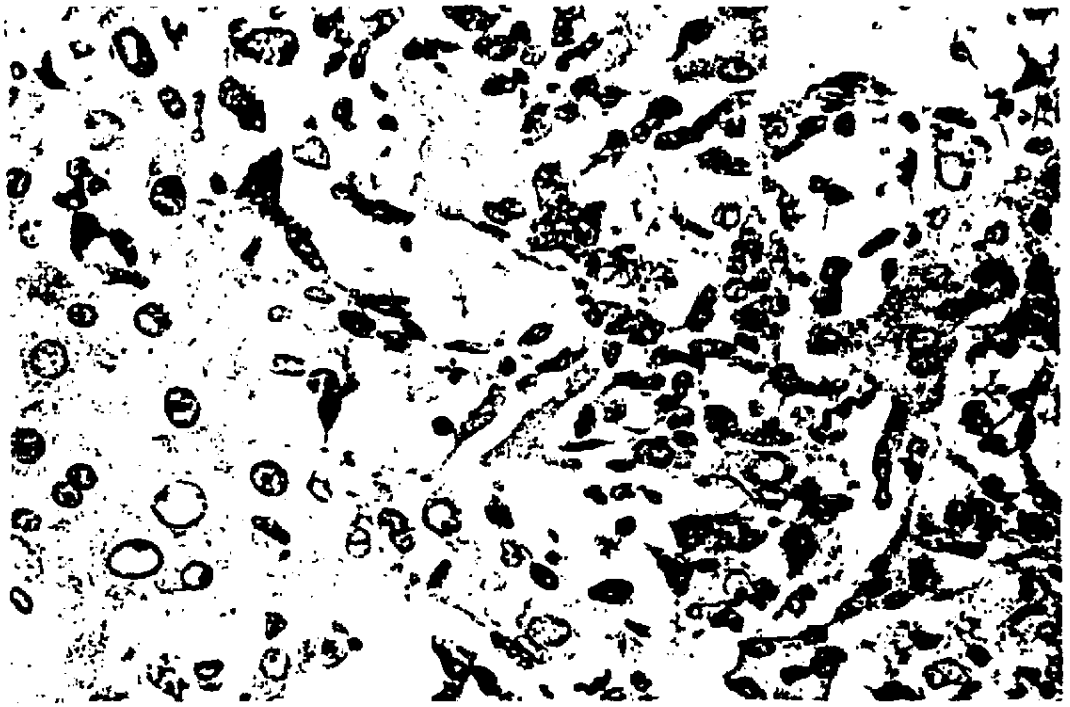

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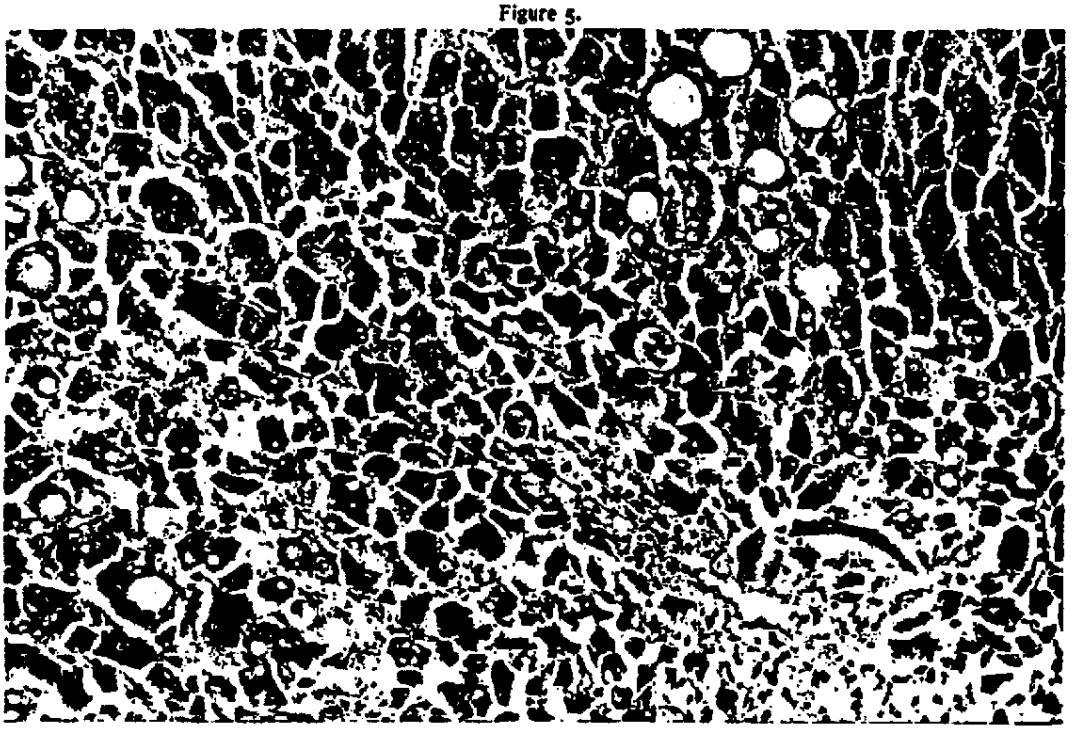

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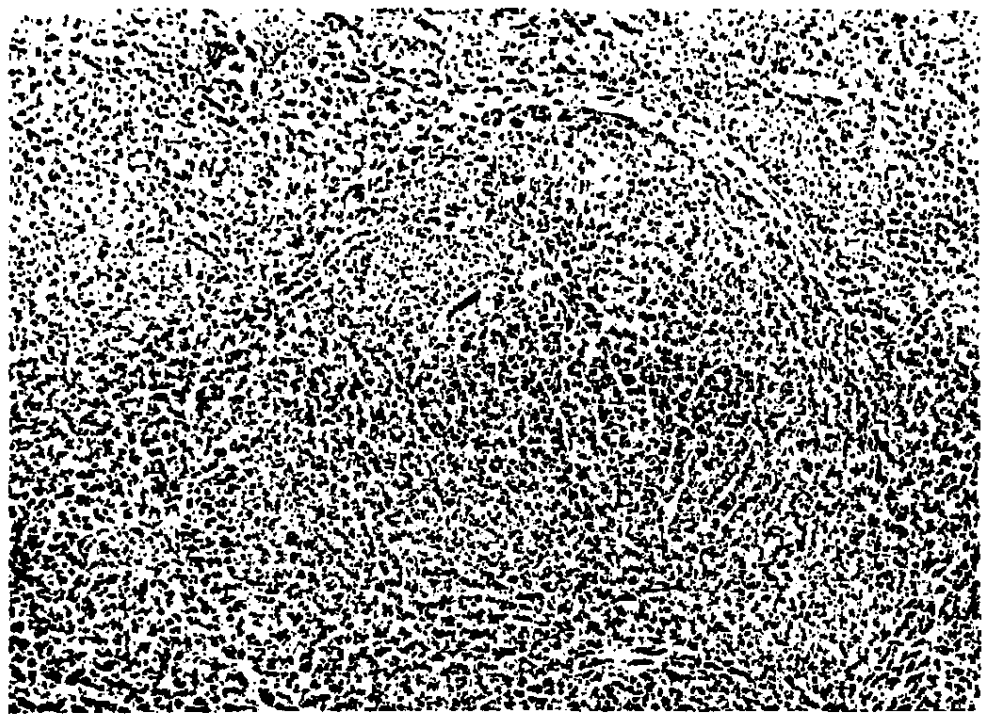

Figure 7. Case 5. Hyperplastic hepatocytic nodule. Twin cell plates are frequent. The nodules are more numerous and well-defined than in case 3, illustrated in Figure 2. H & E. × 25.

CASE 5

From the age of 37 years this worker was exposed to vinyl chloride over a period of 8 years. He developed portal hypertension which was relieved by a portocaval shunt. At the age of 48 years liver biopsy revealed non-cirrhotic portal fibrosis and he eventually died from liver failure, aged 54 years. No alpha-fetoprotein was detected in his serum 6 years before death and the test was not repeated. At autopsy the liver contained multiple foci of tumour tissue, some of which appeared vascular. Histological sections revealed once again portal tract fibrosis and liver cell hyperplasia. Hyperplastic nodules were more numerous, more discrete and, more easily discernible than in the two previous cases (Figure 7), in some instances showing malignant transformation (Figure 8). The tumour was a hepatocellular carcinoma with a solid pattern in some areas and a trabecular pattern elsewhere (Figure 9). The immunoperoxidase test for alpha-fetoprotein on paraffin sections gave a minimal reaction. No metastatic tumour deposits were found.

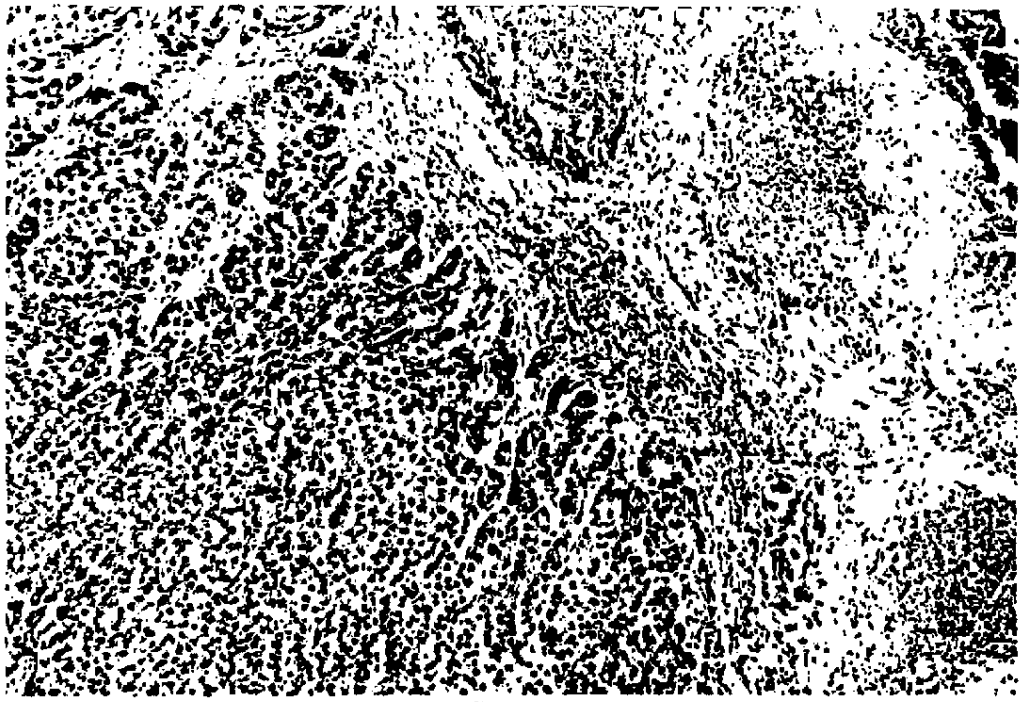

Figure 8.

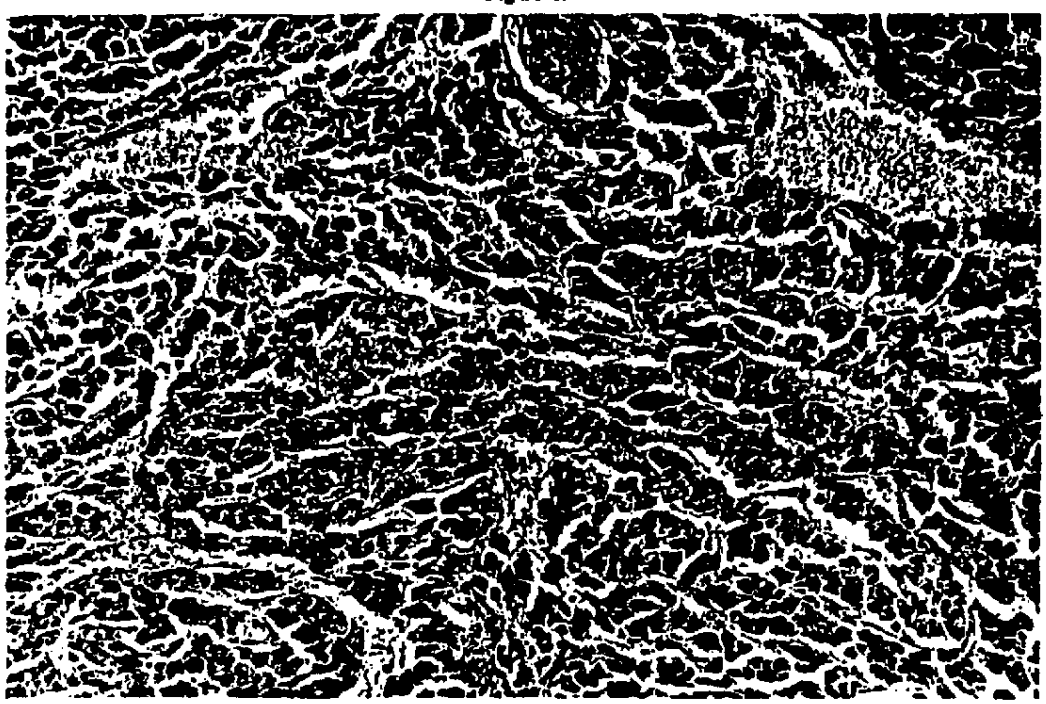

Figure 9.

Table 1. Vinyl chloride exposure

Case	Age at death (yr)	Survival after 1st exposure (yr)	Exposure to vinyl chloride: Duration Total (yr)	Duration Period (yr)	Level (parts/10^6)	Constancy	Cause of death	Histology
1	37	8	3½	3½	200+	Constant	Hepatic failure	Angiosarcoma. Regenerative liver cell hyperplasia
2	65	28	21	1	200+	Constant	Haemoperitoneum	Angiosarcoma. Liver cell regerative hyperplasia and dysplasia
				18+	50–200	Constant		
				1+	0–20	Intermittent		
3	57	31	24	18	200+	Constant	Hepatic failure	Angiosarcoma. Hyperplastic liver cell nodules and liver cell dysplasia
				6	50–200	Constant		
4	48	18	12	8	50–200	Intermittent	Haemoperitoneum	Angiosarcoma. Hepatocellular carcinoma and hyperplastic nodules
				3	10–25	Constant		
				1	25–50	Intermittent		
5	54	17	8	2½	200+	Constant	Hepatic failure	Hepatocellular carcinoma and hyperplastic nodules and liver cell dysplasia
				5½	50–200	Constant		

Discussion

The great rarity of angiosarcoma facilitates the recognition of a clustering effect due to carcinogens such as Thorotrast (thorium dioxide), arsenic and vinyl chloride. In 1963 an angiosarcoma of liver (ASL) panel, set up by the Employment Medical Advisory Service (EMAS), commenced to monitor the occurrence of this tumour in

Figure 8. Case 5. Malignant hepatocytic nodule (*lower left*) with necrotic tumour tissue (*upper right*). H & E. × 100.

Figure 9. Case 5. Hepatocellular carcinoma showing trabecular pattern, in places becoming irregular. H & E. × 108.

the British population. In the 15-year period 1963–1977 the ASL panel (Baxter *et al.* 1980) found only two cases of angiosarcoma in which there was a history of significant exposure to vinyl chloride out of a total of 35 cases; one of the two was Case 1 above, leaving only one other such case in Britain. Four additional cases had been exposed to only minimal levels of vinyl chloride, suggesting that even low level exposure could be significant in susceptible individuals, a possibility envisaged in a leading article (*British Medical Journal* 1974).

In animal studies more than one cell type has been shown to be affected by exposure to vinyl chloride. Maltoni & Lefemine (1975) found angiomas, angiosarcomas, hepatomas, hepatoblastomas, zymbal gland carcinomas, neuroblastomas, skin carcinomas and mammary gland carcinomas in rats, mice and hamsters exposed to vinyl chloride. Keplinger *et al.* (1975) exposed animals of the same species to vinyl chloride and produced various tumours, including angiosarcoma of the liver and liver cell carcinoma. Gokel (1976) ascribed a case of human liver cell carcinoma to vinyl chloride exposure. A number of workers in different countries have reported an increased incidence of various types of cancer in vinyl chloride workers, particularly of liver, pancreas, alimentary tract, lung, brain, lymphatic and haemopoietic systems. (Monson *et al.* 1974, Tabershaw & Gaffey 1974, Nicholson *et al.* 1975, Duck & Carter 1976, Waxweiller *et al.* 1976, Byrén *et al.* 1976, von Reinl *et al.* 1977).

The livers from the five vinyl chloride workers in the present series show angioformative and hepatocellular growth disturbance in varying proportions. Angiosarcoma is present in cases 1 to 4. Liver cell hyperplasia is present in all five cases, with hyperplastic nodules in the last three. Hepatocellular carcinoma is present in cases 4 and 5.

There is evidence that hyperplastic nodules are precursors of hepatocellular carcinoma. This is most commonly seen in animal experiments employing chemical carcinogenesis, e.g. nitrosamines to induce liver cell cancer (Medline & Farber 1981).

It is well known that tissues with a high turnover rate stand an above average chance of developing malignancy. The same applies to tissue that has become hyperplastic. Cirrhosis of liver with subsequent hepatocellular carcinoma is a relevant example. Liver cell hyperplasia, in addition to portal fibrosis has been seen regularly in livers affected by vinyl chloride, although cirrhosis as such is not a commonly described feature (Berk *et al.* 1976). It is therefore not surprising that these livers should be prone to develop hepatocellular carcinoma (HCC). The finding of hyperplastic nodules strengthens the link between HCC and vinyl chloride; lending more support to our belief that the two are causally related and not just the result of coincidence.

Further evidence is provided by the liver cell dysplasia which was seen in four of the present cases. Liver cell dysplasia has been recognized as a premalignant change associated with liver cell cancer (Anthony, Vogel & Barker 1973). This is a common phenomenon in HBsAg positive livers with HCC, whether cirrhosis is present or not (Ho, Wu & Kung 1981). It is therefore entirely possible that vinyl chloride can induce liver cell dysplasia and hyperplastic nodule formation, both terminating in HCC.

There is thus a growing body of evidence that vinyl chloride is a carcinogen affecting not only the endothelial cells of the liver, but also a variety of other cell types. It is

of note that angiosarcoma was originally thought to be the most common type of liver cancer produced by Thorotrast, a carcinogen which, like arsenic and vinyl chloride, can also cause a lesion resembling non-cirrhotic portal fibrosis (Patrick & McGee 1980). However in the more recent cases of Thorotrast-induced liver tumours, hepatomas have exceeded angiosarcomas (Baserga, Yokoo & Henegar 1960, Ishak 1976, Battifora 1976). This is attributed by Baserga *et al.* (1960) to the longer mean induction period for liver carcinomas (19.4 ± 4.0 yr) than for liver sarcomas (12.6 ± 4.3 yr).

We should therefore have an open mind to the possibility that vinyl chloride may eventually be found to promote not only angiosarcoma of the liver and hepatocellular carcinoma but also other tumour types comparable in range to those caused by Thorotrast.

Acknowledgements

We wish to acknowledge the help given by B.P. Chemicals Ltd, Sully, and in particular Dr David Williams for information on vinyl chloride exposure; Dr Paul Smith and Dr Peter Beck for access to clinical information; Dr Barrat Jasani for undertaking immunoperoxidase tests for alpha-fetoprotein; Mr Brendan Cleary for assisting in the photo-micrography; Mr Robert Boothby and Mr David Llewellyn for processing the photo-micrographs; and Mrs Andrea Holloway for typing the manuscripts.

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