Vinyl Chloride-induced Liver Disease

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At present, the world annual production of vinyl chloride monomer (VCM) is in excess of 12 million tonnes and approximately 6 million tonnes of polyvinyl chloride (PVC) are produced. The polymer has a considerable range of uses, e.g. roofing, food and liquid containers, footwear, rainproof clothing, piping, etc. In the past, VCM was manufactured by the acetylene process in which mercuric chloride was used as an activator. This was the source of the Minamata disaster in which, from 1953 onwards, a scattered community of Japanese fishermen and their families along the shores of Minamata Bay suffered an outbreak of organic mercury poisoning. The illness was traced to fish poisoned by effluent in the bay. At present, VCM is produced almost exclusively by the ethylene route in which ethylene dichloride is ‘cracked’ by heating to vinyl chloride and hydrochloric acid. In some of the older plants exposure to VCM used to be high but for many years it has been low. PVC manufacture is carried out in autoclaves at high pressure. The autoclaves or ‘pots’ may be large—up to 200m³. The process is exothermic and the autoclaves are surrounded by a cooling jacket. As it forms, PVC coats the inside of the autoclave, which interferes with cooling. Production, therefore, takes place in batches, the surface polymer being removed between batches. In the past, men entered the autoclaves to remove the polymer and were exposed to high levels of VCM trapped in the polymer; there are many stories of narcotic episodes. At room temperature, VCM is a slightly sweet-smelling gas, not readily detectable at levels below 250 ppm. Serious acute toxicity, in the form of dizziness and progressive narcosis, only develops at 5,000–10,000 ppm.

There are six PVC producing plants in the UK—two large old plants and four more modern ones. A modern PVC-producing factory is shown in Fig. 1. There has been a massive world-wide investment, estimated at £500,000,000, in plant adaptation and development, with the object of improving industrial hygiene in the wake of health problems associated with the industry.

Early Occupational History

Apart from the risk of fire, vinyl chloride was first noticed to be an occupational hazard in the 1960s. A report from Rumania[1] attributed Raynaud’s syndrome, a skin lesion resembling scleroderma, and hepatomegaly to exposure to vinyl chloride. Cordier et al.[2] from Belgium described a syndrome in autoclave workers which consisted of acro-osteolysis of the terminal phalanges with widespread changes in the skeletal system and again Raynaud’s syndrome and scleroderma-like skin changes. Reports from the USA[3] and the UK[4] confirmed the widespread occurrence of such symptoms in these workers. When the workers left the manufacturing plant the skin and vascular changes improved and bone lesions healed.

Torkelsen et al.[5] described hepatic changes in rats and rabbits and recommended a lowering of occupational exposure levels. Further work in Italy showed tumours at various sites in rats[6]. Subsequently, an investigation sponsored by four PVC manufacturers[7] reported tissue and skeletal changes and, in addition, a variety of tumours, including angiosarcoma of the liver.

Angiosarcoma

The scene was set for the observation[8] in December 1973 that angiosarcoma of the liver had occurred in three autoclave workers in a large PVC-producing factory in Louisville, Kentucky. Within a short time large surveys of men involved in the industry were carried out. Death
certification surveillance revealed a few cases[9]. In Blackpool[10] we were reminded of a 72-year-old man who had died in 1972, having been employed for the last 22 years of his working life in VCM and PVC manufacture; for 13 of those years (1948–61) he had been an autoclave operator. He presented with progressive oedema, ascites and breathlessness. Both liver and spleen were enlarged. There were minor liver enzyme changes and hepatic scintiscan showed patchy uptake in a diffusely enlarged liver with splenomegaly. After initial improvement he deteriorated and died. Autopsy showed considerable enlargement of the liver which consisted of irregular interconnecting reddish-brown honeycombed areas separated by pale brown liver tissue (Fig. 2). These appearances are typical of angiosarcoma and the diagnosis was confirmed on histological examination.

Since 1974 a further six cases of occupationally-related angiosarcoma have occurred in the UK[11]. Most of them conform to international experience, with a prolonged exposure and long latent interval between first exposure and development of the tumour[11]. At a recent count 98 cases of occupationally related angiosarcoma have been reported[11]. The majority have occurred in older plants in North America and Western Europe[11] (Table 1). Other known environmental causes for angiosarcoma include thorotrast[12], and arsenic used either as a pesticide[13] or for chronic skin disease[14].

There have been reports of an association with the use of androgens[15], an oral contraceptive agent[16], and phenelzine[17].

The clinical features of angiosarcoma are very much those of severe tumour involvement of the liver[18]. Abdominal pain and swelling, fatigue, anorexia and gastrointestinal haemorrhage are usual presenting features. Physical examination may show enlargement of the liver and spleen, abdominal tenderness and swelling. A bruit may be audible over the liver. Rapid clinical deterioration is usual, with increasing fluid retention, gastrointestinal haemorrhage and hepato-cellular failure contributing to the picture. Occasionally, haemoperitoneum may occur terminally, secondary to rupture of a blood-containing tumour area[18]. The lesions produce characteristic angiographic and radionuclide abnormalities[19] but histological proof of the diagnosis is difficult to obtain by needle biopsy. Indeed, in a patient in whom the occupational and clinical picture suggests hepatic angiosarcoma, needle biopsy of the liver is contra-indicated in view of the possibility of severe haemorrhage into the peritoneum[18,20]. In the Louisville experience, diagnosis was mainly confined to biopsy material obtained at laparotomy. In some instances, metastatic manifestations may be prominent.

The pathology of the tumour is distinctive. The liver is usually enlarged and brown in colour, with characteristic haemorrhagic nodules of varying size. The residual liver tissue is distorted by fibrosis and infiltrating tumour tissue. Microscopic appearances are variable but three main patterns are described[21,22]. The most common pattern is a sinusoidal one in which dilated hepatic sinusoids are lined with enlarged proliferating tumour cells with easily recognisable hepatocyte plates. The second most common pattern is termed the papillary type, in which papillary formations of tumour cells are borne on a core of connective tissue that may include recognisable surviving hepatocytes, often with canaliculi containing inspissated bile pigment. The third is the cavernous type in which blood-filled spaces appear enlarged and are surrounded by thick fibrous walls lined by tumour cells. Cells may be difficult to distinguish from reactive cells or they may be quite unusual, showing irregular, bizarre giant cell forms. A helpful diagnostic feature seems to be their close relationship to hepatocyte plates and obvious blood-filled spaces. The tumours are multicentric. Spread outside the liver is predominantly local, involving lymph nodes, diaphragm, abdominal wall, gall-bladder and bowel. Spread may also occur to lungs and other organs although it is unusual for these distant deposits to have clinical importance. There are also changes in the remaining liver, which take the form of increased sinusoidal reticulin. Doubt about the cells that are involved in these tumours is reflected in the variable terminology used in the past. It has been suggested that the cell concerned is the endothelial cell, as opposed to the Kupffer cell. Factor VIII, a known endothelial cell marker, has been demonstrated by an immunofluorescent technique in the cells and the term 'endothelial cell' sarcoma has been proposed in preference to 'angiosarcoma'[23]. The clinico-pathological fea-

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Table 1. Distribution of vinyl chloride related hepatic angiosarcoma cases, January 1982[11].

| Country       | Cases |
|---------------|-------|
| USA           | 28    |
| Canada        | 10    |
| West Germany  | 21    |
| France        | 14    |
| Sweden        | 5     |
| Yugoslavia    | 4     |
| Italy         | 3     |
| UK            | 7     |
| Czechoslovakia| 2     |
| Japan         | 2     |
| Norway        | 1     |
| Belgium       | 1     |
| North America | 38    |
| Western Europe| 52    |
| Rest of World | 8     |
| Total         | 98    |
tures of hepatic angiosarcoma do not indicate the cause of the disease; environmental causes such as vinyl chloride, arsenic and thorotrust produce the same changes as are seen in cases with no known aetiological agent[24].

Other Hepatic Changes

The observation that the livers from some workers exposed to vinyl chloride had marked changes not due to tumour had already been made, particularly in reports from Bonn, West Germany[25,26]. The concept of 'vinyl chloride disease' was introduced. A variety of changes was described in monomer plant and, more particularly, in autoclave workers. These changes included the sclero-derma-like skin changes, Raynaud's phenomenon and acro-osteolysis previously described; in addition, thrombocytopenia, hepatic bromsulphthalein retention, abnormal hepatic enzyme tests, splenomegaly and oesophageal varices secondary to portal hypertension were recognised. In a few patients liver biopsy showed perportal fibrosis. Further investigation confirmed the presence of hepatic fibrosis as an integral part of the syndrome. At laparoscopy capsular fibrosis was found to be prominent but unevenly distributed on the surface. Capsular vessels were variably increased. Splenomegaly was observed in association with capsular fibrosis. This laparoscopic picture, although characteristic, was not diagnostic of vinyl chloride liver involvement. Following observation of the obvious capsular changes, liver biopsy material showed less pronounced changes, even in cases in which laparoscopy had suggested advanced liver cirrhosis. The principal histological features were described—portal and slight sinusoidal fibrosis, cytoplasmic and nuclear changes in the hepatocytes and proliferation of the sinusoidal lining cells.

Case Report

In 1974 a man aged 52 who had been a PVC autoclave worker for 15 years, presented with ascites and oedema. The liver and spleen were enlarged. His haemoglobin was 9.9 g/dl and there was minor elevation of serum alkaline phosphatase and aspartate transaminase enzymes. Tests for mitochondrial and smooth muscle antibodies and hepatitis B antigen were negative. Diuretics produced an effective response but he declined further investigation and returned to his previous employment. One year later, however, he presented with severe gastrointestinal bleeding which was found to be due to oesophageal varices. After transfusion of 13 units, a percutaneous trans-splenic venogram confirmed the varices and a patent portal system. The intrasplenic pulp pressure was 32 mm Hg. A portacaval shunt was carried out but, unfortunately, further bleeding occurred and a spleno-renal shunt was performed following the demonstration of an occluded portal vein and splenic pulp pressure of 40 mm Hg. At operation (Fig. 3) the liver showed the capsular changes described in Bonn, and histological examination confirmed the presence of dense collagen (Fig. 4). He recovered but has had to give up manual work. On clinical review, in 1982, he was fairly well but suffering occasional episodes of hepatic encephalopathy. Studies at Cardiff[27,28] have been carried out in five workers, in whom splenomegaly or thrombocytopenia was detected during screening, to elucidate the mechanism of the portal hypertension. Intrasplenic pressures were between 20–29 mm Hg, with normal wedged hepatic venous pressures, but the gradient between the wedged and free hepatic vein pressures was increased. Splenic blood flows were increased in both hypertensive and normotensive subjects. There was no correlation between the splenic blood flow and the portal pressure or the presence of portal fibrosis. The portal hypertension was considered to be mainly pre-sinusoidal in type, and was possibly attributable to an abnormality of the portal vein radicals or hepatic sinusoids. Vinyl chloride, therefore, takes its place with other causes of pre-sinusoidal portal hypertension such as schistosomiasis, congenital hepatic fibrosis, myeloproliferative disorders, primary biliary cirrhosis and arsenic poisoning.
Screening Programmes

As a result of these observations, various screening programmes were set up to diagnose early liver involvement and to identify workers at risk. Some of the findings of these studies are interesting.

ICI Hillhouse[29]

PVC manufacture started in 1940. Four hundred and twenty-two vinyl chloride workers were screened and the findings compared with those of 202 control workers not exposed to VCM. There were no significant differences in the liver function tests. Further investigations were carried out in men with abnormal tests. Splenomegaly was found in four exposed workers and no controls. Liver biopsies showed minor increases in portal and sinusoidal fibrous tissue. No overt cases of vinyl chloride disease were discovered and, if such cases were present, liver function tests did not provide a sensitive screening test.

There had been a 93 per cent response rate in this programme but in 1974 the autoclave worker described previously had presented initially with ascites and later with bleeding oesophageal varices. In 1979 another man died from angiosarcoma. He had left occupational exposure in 1972, after having worked in PVC manufacture for 18 years.

British Petroleum, Barry[30]

PVC manufacture started in 1948. Four hundred and eighty seven men with variable degrees of exposure, including 129 considered to be at high risk, were investigated. Two men were found to have splenomegaly and portal hypertension associated with hepatic fibrosis. Thrombocytopenia provided the first diagnostic evidence, as liver function tests were normal. The occurrence of many abnormal liver function tests without detectable liver disease raised questions about the value of such screening programmes. In particular, concern was expressed about causing anxiety in the work force. It was suggested that ultrasound examination might be of value in detecting splenomegaly[30,31].

Louisville, Kentucky

Approximately 1,200 employees in a plastics and rubber manufacturing factory were examined, following the discovery of three employees with angiosarcoma of the liver[32]. An initial retrospective study revealed eight cases, which included five angiosarcomas. Portal fibrosis was present in all the livers. Scintiscans detected two more angiosarcomas and 55 workers with splenomegaly but there was no difference in incidence between high and low exposure groups. In addition, liver biopsies showed fatty damage, portal fibrosis and two more angiosarcoma cases. Splenomegaly was not a useful predictor of hepatic histology. A later comprehensive assessment of the findings[33] was reported in which greyscale ultrasoundography of the liver, microvascular skin capillary assessment, urinary analysis of glycosaminoglycan secretion and standard 99mTc sulphur colloid radionuclide liver/spleen scan were compared with biochemistry and liver histology. There was no significant correlation. Within the assessment, indocyanine green clearance, aspartate transaminase, pyruvate transaminase and gamma glutamyl transferase were the most sensitive tests, but alkaline phosphatase was the most specific.

Sequential Hepatic Lesions in Vinyl Chloride Workers

Screening programmes have provided a great deal of information. In particular, the opportunity has been taken to assess the sequence of early and late changes. Observations in man and animals have shown that there is a gradation of changes and that there are three groups of lesions involving hepatocytes, sinusoidal lining cells and fibrosis[34].

Hepatocytic Changes. Foci of enlarged hepatocytes with increased cytoplasm and large hyperchromatic nuclei occur, intermingled with normal sized and small cells, creating focal indistinct nodular areas. Slight sinusoidal dilatation is observed, with an increase in the reticulin framework, best illustrated by silver impregnation. This lesion is termed ‘focal hepatocytic hyperplasia’ (FHH).

Sinusoidal Lining Cell Changes. These are most conspicuous in areas of sinusoidal widening and consist of nuclear and cytoplasmic changes in Kupffer and Ito cells. Some cells may have elongated, almost rectangular, nuclei with a moderate amount of cytoplasm. There is a range of abnormal cells, some of which are bizarre with huge hyperchromatic nuclei, whose polymorphous changes and clustering suggest early focal angiosarcomatous transformation. These changes, with those of FHH, are termed ‘mixed focal hyperplasia’ (FMH) (Fig. 5).

Fibrotic Changes. The fibrosis is most conspicuous in the capsule and the periportal zones are also involved.

Fig. 5. Histological section of liver showing mixed focal hyperplasia (FMH). Features include sinusoidal widening, hepatocyte hyperplasia and nuclear variation, and endothelial cell hyperplasia. (Haematoxylin and Eosin × 500).
most important lesion may be the excess of connective tissue in the dilated sinusoidal spaces.

It has been suggested that the precursor lesion of FMH may be of predictive value in detecting some initial environmental lesions. At some stage in the sequence, progression to angiosarcoma may perhaps be inevitable. Indeed, there are cases in whom the demonstration of fibrotic changes was followed some years later by angiosarcoma[20,35].

**Conclusion**

The vinyl chloride story has unfolded over the last few years and there have been changes in manufacture, hygiene and health surveillance. It may be seen as a watershed in the history of occupational medicine, leading to new attitudes to occupational hazards[36]. The recognition of the problem by factory medical officers was only the beginning. Epidemiological studies and observations on the clinico-pathological findings coincided with massive plant investment designed to reduce the occupational risk to a minimum.

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