

Angiosarcoma of the liver: annual occurrence and aetiology in Great Britain

P J BAXTER,¹ P P ANTHONY,² R N M MACSWEEN,³ AND P J SCHEUER⁴

From the Health and Safety Executive, Employment Medical Advisory Service,¹ London NW1 5DT, the Area Department of Pathology,² Exeter EX2 5DY, Western Infirmary,³ Glasgow G11 6NT, and Royal Free Hospital,⁴ London NW3 2QG, UK

ABSTRACT The annual occurrence of angiosarcoma of the liver (ASL) in Britain from 1963 to 1977 was studied, including clinical and occupational details for those cases agreed as ASL by a panel of histopathologists. Thirty-five cases (28 men, six women, and one infant girl) were agreed as ASL. The increase in the incidence of ASL observed in recent years was attributable to Thorotrast (thorium dioxide) usage (eight cases) and exposure to vinyl chloride (two cases) in the past. In its clinical presentation and prognosis ASL resembled primary liver carcinoma, except that extrahepatic metastases were found in only eight (23%) cases, and haemoperitoneum was more common in those cases due to Thorotrast. The results suggested a possible increased risk of ASL in the electrical and plastics fabrication industries, but information on exposure was inadequate to implicate specific chemicals. The clinical features of one case were indicative of arsenical intoxication, but medications in the other patients did not appear to be of aetiological importance.

We present our findings on the annual occurrence of angiosarcoma of the liver (ASL) in Britain during a 15-year period, 1963-77, and the clinical details of those cases agreed as ASL by a panel of pathologists. The role of known or suspected aetiological factors,¹ including vinyl chloride, Thorotrast (thorium dioxide), inorganic arsenic and copper, and haemochromatosis, is also discussed. Many other chemicals occurring in the environment naturally or from industrial sources have been linked with liver tumours in animal studies,² but the role of these substances in man remains to be resolved. The advantage of monitoring a tumour as rare in the general population as ASL is that it may be used as a marker tumour to identify human carcinogens, and we have adopted this approach.

Method

In 1974 an ASL register was set up in Britain by the Employment Medical Advisory Service (EMAS) of the Health and Safety Executive, and a preliminary report on the incidence of ASL in 1963-73, with details of the method of working of the panel, has been published.¹ EMAS, in collaboration with the

Office for Population Censuses and Surveys (England and Wales) and the General Register Office (Scotland), identifies recorded cases by the regular review of death certificates. The underlying cause of death is routinely coded by the Registrar General's staff under the International Classification of Diseases, 8th revision, as primary, secondary, or unspecified neoplasms of the liver and intrahepatic bile ducts (ICD numbers 155.0, 155.1, 197.7, 197.8, 211.5); neoplasms of unspecified nature of the liver and biliary passages (230.5); and haemangioma or lymphangioma (227). Additional sources of notifications are hospital pathologists, publications, and cancer registries (England and Wales only). Recorded cases are identified if any of the following diagnoses are mentioned: haemangio or angiosarcoma, Kupffer cell sarcoma, haemangioendothelioma, haemangioblastoma (adults only), or malignant angioma.

For all the recorded cases the hospital pathologists concerned are requested to send histological material from the tumour for review by a panel of three histopathologists (PPA, RNMMS, and PJS). Material for control purposes in the study of the 1974-7 cases of ASL was obtained from cases recorded as dying from other liver tumours (selected randomly from death certificates) or because the diagnosis was of special interest—for example, angioma, haemoperitoneum—or mentioned Thoro-

Received 4 June 1979
Accepted 3 July 1979

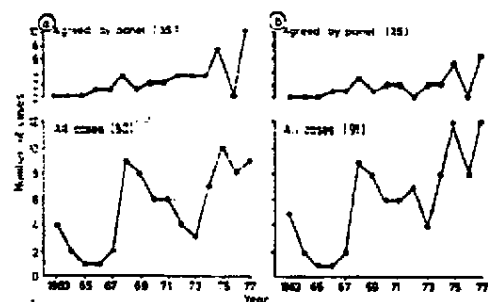


Fig 1(a) Annual incidence of all recorded cases (including three controls), and numbers of cases agreed as ASL by panel, 1963-77.

Fig 1(b) As in fig 1(a), but excluding cases of known aetiology.

until 1975 and 1977, when it rose to 12 in both years. The numbers of cases agreed by the panel remained at two to three a year until 1975 and 1977, when they rose to seven and nine respectively. If the cases of known aetiology (vinyl chloride and Thorotrast, to be described below) were removed from consideration an increasing incidence was not so apparent (fig 1b), suggesting that the rise had been due to a real increase in the number of cases rather than an improvement in case finding after publicity of the vinyl chloride problem in 1974. This interpretation is supported by the annual numbers of death certificates for ASL (figs 2a and b). These did not

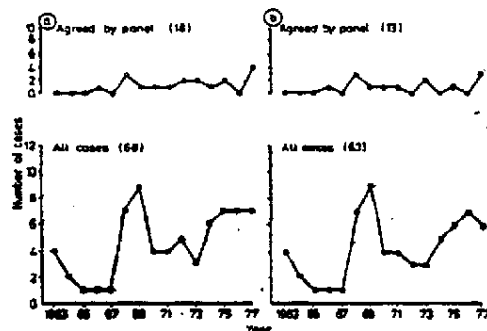


Fig 2(a) Annual incidence of all cases identified by death certificate search, and numbers of cases agreed as ASL by panel, 1963-77.

Fig 2(b) As in fig 2(a), but excluding cases of known aetiology.

show the increase expected if national awareness had led to more recording of ASL. Also, in the prospective studies of Thorotrast patients²⁸ and British workers exposed to vinyl chloride⁷ deaths from ASL have occurred only in recent years.

Taking the ten-year period 1968-77 as being most representative, the annual number of cases in which no causal agents had been positively identified was fairly constant, both for the recorded cases and those agreed by the panel (figs 1b and 2b). On average, seven cases a year were recorded from all sources, and among those for whom histological sections were obtainable, about two cases a year were agreed as ASL. For death certificate cases only, the average number of cases reported was five a year, with about one a year agreed by the panel.

AGE DISTRIBUTION

The distribution of the ages at death of the agreed cases of ASL is shown in fig 3; there was no apparent difference between cases of known and unknown aetiology, though the numbers of both were small. The mean age (and range) for men was 58.3 (30-78) years, and for women 65.2 (44-84) years; the infant girl died aged 8 months.

SOCIAL CLASS

For the male cases agreed as ASL, the occupations recorded on the death certificates were assigned to the appropriate social class according to the scheme of the Registrar General⁸ by a statistician who was not provided with any other information about the cases. The social class distribution was then compared with that obtained by a proportional analysis of male deaths aged 15-64 in England and Wales, 1970-2,⁹ and also of the male population of Britain

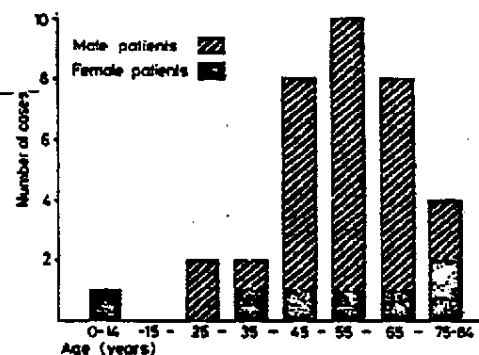


Fig 3 Age-distribution of male and female cases agreed by panel as ASL, 1963-77.

Table 4 Industries employing at least two of the agreed adult cases of ASL according to aetiology. (No of cases in parentheses)

Aetiology	Industry	No of patients
Unknown, or doubtful (24) Men (19)	Electrical	6
	Plastics fabrication	3
	Transport	3
	Construction	3
	Coal mining	3
	Farming	2
	Coke-ovens (gas and steel)	2
	Cable making	2
	Catering	2
	Domestic service	2
Women (5)		
Vinyl chloride (2) Men (2)	PVC manufacture	2
Thorotrast (6) Men (7)	Transport	2
	Construction	2
	Coalmining	2

death certificates, as mentioned in the results of the social class analysis. Unfortunately, no further information was obtainable for two of these cases; according to the death certificates they had been an electronic testing engineer and power station engineer. The two others, the first a construction and design engineer at a power plant and the second a Post Office engineer supervising telephone and postal power plant, had been in the industry for most of their lives. One of the two remaining cases had been a self-employed electrical fitter all his life, and the other a boilerman and odd job man for the electricity board. It was not possible from the histories obtained to derive a specific exposure which these six men may have had in common. At least three of them, however, probably handled or repaired electrical components for some period in their careers, but more precise information was not available.

Of special interest in relation to vinyl chloride is the finding of three cases among plastics fabricators. According to the death certificates the occupation of two of these men was "machine fitter." The three men had been employed in factories that manufactured goods from raw plastic, including, at some time, PVC; two factories had also produced rubber articles (the use of chloroprene, a possible cause of ASL,¹⁴ was excluded in one of these firms). The records were inadequate, however, for confirming whether or not these men had come into contact with PVC.

In the construction industry two men had been building labourers and one a clerk. All three men in the transport industry had been road vehicle drivers. Three men had worked in collieries, one as a clerk, another as a "colliery worker" for one year, and the

third as a haulage worker for most of his working life.

In the remainder of the industries shown in table 4, farming is noteworthy because of the known use of arsenical pesticides. Both men who had held farming jobs had been labourers at the beginning of their working lives, but details of pesticide usage were unobtainable. Information was provided for one of the two men who had worked in cablemaking; he had been an inspector of brass-plated wire in an entirely non-rubber part of a tyre factory, and was not directly exposed to chemicals or PVC. The other man had been employed in this industry from 1941 to 1946, before PVC was generally used in cable manufacture. The two men employed in coke ovens had held this occupation for five years and over 30 years.

Of the five women, four had either worked in catering or domestic service for at least five years.

Vinyl chloride cases

The two men in this category had been process workers in the manufacture of PVC for three and a half years⁸ and 20 years¹⁴; their ages at death were 37 and 71. Both had worked in autoclaves, where exposure to VCM would have exceeded 200 ppm. Neither had been employed in occupations where heavy exposure to PVC dust could have occurred.

Thorium dioxide cases

Transport and construction industries also feature in this category. The two men in coalmining had been faceworkers, and an injury at work to one had resulted in his receiving Thorotrast during further medical investigations.

Other cases

Occupations mentioned only once did not show any aetiological pattern. In the infant case, occupational histories were obtained from both parents to study the possible role of transplacental carcinogens. The father had worked for three years in market gardening, followed by three years as a mechanic and painter of old vehicles. He then worked as a refuse collector a year before and after the child was born. The mother had worked as a hairdresser since leaving school until she was seven months' pregnant. She admitted having received heavy exposures to hair lacquer from hand-pumped sprays, and had rarely used canned aerosols at work.

MEDICATIONS

Of the agreed cases, seven men and one woman had been neurosurgical patients investigated with intra-arterial Thorotrast 28-36 years before their deaths. Another woman, who died aged 70, was suspected,

cases, the sites being the spleen in four cases, the lungs in two, and the left ovum and porta hepatis in each of the remaining two. In two of the cases with splenic involvement, distant metastases were found in the bone, peritoneum, and adrenal gland.

In most patients the liver was enlarged by the presence of vascular tumour tissue. Tumour nodules, sometimes raised above the liver surface and containing cavernous or honeycombed areas were often described, as were varying amounts of fibrotic tissue, and macro- or micro-nodular cirrhosis of the liver. In two cases in which the liver was cirrhotic, the presence of a tumour was not confirmed until histological examination. In five Thorotrast cases the spleen was small and fibrotic. The liver of the infant was enormously enlarged and contained multiple umbilicated nodules of tumour tissue on its surface; there were areas of small, thick-walled channels filled with blood surrounded by normal liver tissue, but no extrahepatic metastases, and the immediate cause of death was congestive cardiac failure. In none of these cases was haemochromatosis found.

Discussion

Excluding the cases of confirmed aetiology, the incidence of ASL during a representative ten-year period was seven a year for all recorded cases, and two a year for cases agreed by the panel, in a British population of about 50 million. Surveys from elsewhere have also shown the rarity of ASL, but they have been undertaken in industrialised countries where the incidence of primary cancer is low, though in Britain it has probably increased slightly over recent decades.^{18, 19}

Necropsy surveys indicate that ASL accounts for less than 3% of primary liver tumours and less than 15 per 100 000 of all necropsies.^{20, 21} Epidemiological data in the USA²² and the Netherlands²³ show much the same rate of recorded cases as found in the present study. Infant cases are extremely rare. Out of four recorded infant deaths, tumour tissue was obtained for two, and one of these was agreed as ASL.

The use of data solely from death certificates seemed to provide an insensitive measure of incidence compared with that from all sources, including hospital pathologists, published reports, and cancer registries. The rising trend for all recorded cases for the last years of the study period was not seen for the death certificate cases. Evidently data from death certificates alone cannot be relied on to detect those moderate increases in incidence that may be a clue to new environmental agents. In 17 cases agreed as ASL the death certificate gave a different underlying

cause; thus reliance on death certificates could underestimate the true incidence by at least half. In the Thorotrast study²² six cases of ASL were eventually identified whereas only three were recorded as ASL on the death certificates; this finding in a virtually complete follow-up of patients with an above-average necropsy rate also suggests that the true incidence could be underestimated by half. On the other hand the panel agreed the diagnosis in under half of all the cases seen, so that incidence rates based on death certificates might not be too far removed from the true incidence, at least among hospital deaths. In Britain about half of all deaths occur in hospital, and on average 20-30% of these undergo necropsy.²⁴ Hepatic cirrhosis and primary liver cancer were the commonest misleading diagnoses, but we have no evidence to suppose that many more cases of ASL were being overlooked in these categories.

The age distribution of the adult cases resembled that of primary liver carcinoma in Britain.^{18, 25} There was no conspicuous social class gradient, but surprisingly all four cases in social classes I and II were engineers in the electrical industry. The male:female ratio for adults was 5:1 for all cases, and 4:1 for "idiopathic" cases only. This male preponderance has been shown for primary liver carcinoma²⁶ as well as ASL,⁴ suggesting that occupational factors may be responsible. Male susceptibility has been observed in animal studies of primary liver carcinoma,²⁸ however, so the importance of occupational agents in these sex differences awaits further elucidation.

The commonest presenting symptom was upper abdominal pain, and in this respect, and also in the time between onset of symptoms and death, ASL resembled primary hepatic carcinoma.¹⁸ The median survival time of three weeks after admission to hospital emphasises the difficulties in obtaining occupational histories for survey purposes and the necessity of relying on the relatives for this information.

Thus in its incidence and presentation ASL resembled primary hepatic carcinoma, though the number of cases of ASL on which to base these comparisons was small. Extrahepatic metastases, however, were found in only 23% of cases; this figure should be compared with 47% obtained by MacSween for primary liver carcinoma in Scotland,¹⁸ and 69% reported by Popper *et al.*⁴ in their cases of ASL, which were mostly drawn from the USA. The reason for our low figure is not clear, but may relate to differences in diagnostic criteria or aetiology.

Rupture of the tumour resulting in intra-abdominal haemorrhage caused or contributed towards death in 26% of adult cases, and was significantly more common in those patients who

- ¹ Preussman R. Hepatocarcinogens as potential risk for human liver cancer. In: Remmer H, Bolt HM, Bannasch P, Popper H, eds. *Primary Liver Tumours*. Lancaster: MTP Press, 1979:11-29.
- ² MacSween RNM, Vickers JM, Ross SK, Ferguson J, Johnstone JM, Sandison AT. Haemangioendothelial sarcoma of the liver. *J Pathol* 1973;109:39-44.
- ³ Popper H, Thomas LB, Telles NC, Falk H, Selikoff IJ. Development of hepatic angiosarcoma in man induced by vinyl chloride, Thorotrast and arsenic. *Am J Pathol* 1978;92:349-70.
- ⁴ Smith PM, Williams DMJ, Evans DMD. Hepatic angiosarcoma in a vinyl chloride worker. *Bull NY Acad Med* 1976;52:447-52.
- ⁵ Syed S, Jung RT. Cardiac tamponade caused by metastasising haemangioendothelial sarcoma of the liver. *Brit Heart J* 1978;40:697-9.
- ⁶ Fox AF, Collier PF. Mortality experience of workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain. *Br J Ind Med* 1977;34:1-10.
- ⁷ Office of Population Censuses and Surveys. *Classification of Occupations, 1970*. London: HMSO, 1970.
- ⁸ Office of Population Censuses and Surveys. *Registrar General's Decennial Supplement for England and Wales, 1970-2*. London: HMSO, 1978.
- ⁹ Office of Population Censuses and Surveys. *Census 1971, Great Britain, Economic Activity Part IV*. London: HMSO, 1975.
- ¹⁰ Tarring T, ed. *Non-Ferrous Metal Works of the World*. 2nd ed. London: Metal Bulletin Books, 1974.
- ¹¹ Aston SR, Thornton I, Webb JS, Milford BL, Purves JB. Arsenic in stream sediments and waters of South West England. *Sci Total Environ* 1975;4:347-58.
- ¹² Colbourn P, Alloway BJ, Thornton I. Arsenic and heavy metals in soils associated with regional geochemical anomalies in South West England. *Sci Total Environ* 1975;4:359-63.
- ¹³ Infante PF. Mutagenic and carcinogenic risks associated with halogenated olefins. *Environ Health Perspect* 1977;21:251-4.
- ¹⁴ Lee FI, Harry DS. Angiosarcoma of the liver in a vinyl-chloride worker. *Lancet* 1974;1:1316-8.
- ¹⁵ Donald D, Dawson AA. Microangiopathic haemolytic anaemia associated with malignant haemangio-endothelioma. *J Clin Pathol* 1971;24:436-9.
- ¹⁶ Pollard SM, Milward-Sadler GH. Malignant haemangio-endothelioma involving the liver. *J Clin Pathol* 1974;27:214-21.
- ¹⁷ MacSween RNM. A clinicopathological review of 100 cases of primary malignant tumours of the liver. *J Clin Pathol* 1974;27:669-82.
- ¹⁸ Burnett RA, Patrick RS, Spill WGS, Buchanan WM, MacSween RNM. Hepatocellular carcinoma and hepatic cirrhosis in the West of Scotland: A 25-year necropsy review. *J Clin Pathol* 1978;31:103-10.
- ¹⁹ Alrenga DP. Primary angiosarcoma of the liver. *Int Surg* 1975;60:198-203.
- ²⁰ Rein FR, Huth F. Sechs spontane primäre maligne Gefäßgeschwülste der Leber in einem Kollektiv von 30,000 Obduktionen. *Int Arch Occup Environ Health* 1975;34:237-46.
- ²¹ Heath CW, Falk H, Creech JL. Characteristics of cases of angiosarcoma of the liver among vinyl chloride workers in the United States. *Ann NY Acad Sci* 1975;246:231-6.
- ²² Dalderup LM. Angiosarcoma of the liver in Great Britain. *Br Med J* 1977;3:1149-50.
- ²³ *British Medical Journal*. Reviving the hospital necropsy. *Br Med J* 1977;3:1560.
- ²⁴ Johnson PJ, Krasner N, Portmann B, Eddleston ALWF, Williams R. Hepatocellular carcinoma in Great Britain: Influence of age, sex, HBsAg status, and aetiology of underlying cirrhosis. *Gut* 1978;19:1022-6.
- ²⁵ Da Silva Horta J, Da Motta LC, Tavares MH. Thorium dioxide effects in man: Epidemiological, clinical and pathological studies (experience in Portugal). *Environ Res* 1974;8:131-59.
- ²⁶ Ong GB, Taw JL. Spontaneous rupture of hepatocellular carcinoma. *Br Med J* 1972;4:146-9.
- ²⁷ Doll R, Vessey MP, Beasley RWR, et al. Mortality of gasworkers—final report of a prospective study. *Br J Ind Med* 1972;29:394-406.
- ²⁸ Health and Safety Executive. *Mortality in the British Rubber Industries*. London: HMSO (in press).
- ²⁹ Milby TH, ed. *Vinyl Chloride: an information resource*. United States: DHEW, 1978.
- ³⁰ Ministry of Agriculture, Fisheries and Food. *Survey of vinyl chloride content of polyvinyl chloride for food contact and of foods*. London: HMSO, 1978.
- ³¹ Baxter PJ, Langlands AO, Anthony PP, MacSween RNM, Scheuer PJ. Angiosarcoma of the liver: a marker tumour for the late effects of Thorotrast in Great Britain. *Br J Cancer* (in press).