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INTEROFFICE
MEMORANDUM

Subject Angiosarcoma in Great Britain

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From J. T. BARR

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I enclose a copy of a report paper on angiosarcoma in Great Britain, and an associated press release, which I received today from Dr. John Stafford of I.C.I. Although written very cautiously, it would seem to support the absence of risk to the general population from vinyl chloride.

As a side light, an incidence of a little over one case per year for 50 million persons is a lower rate than the estimated 25 per year per 200 million in the U.S.

JTB:djm



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(320)

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Angiosarcoma of the liver in Great Britain, 1963-73

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Summary

Deaths attributed to primary angiosarcoma of the liver (ASL) in Great Britain between 1963-73 were reviewed by submitting available histological material to a panel of histopathologists and by obtaining full occupational and residential histories for the cases agreed as ASL by the panel. On average four recorded cases of ASL occurred a year, but in only one-third of the cases submitted did the panel agree with the original diagnosis. Only one of the agreed cases could be confidently associated with exposure to vinyl chloride.

Introduction

Studies of polyvinyl chloride (PVC) workers have been set up in several industrialised countries after the recognition in 1974 of the association between primary angiosarcoma of the liver (ASL) and occupational exposure to vinyl chloride monomer (VCM), the chemical used to manufacture PVC. In Great Britain the Employment Medical Advisory Service (EMAS) agreed to undertake a mortality study¹ of workers engaged in PVC manufacture and a case-control study² of all known cases of ASL occurring from 1974 onwards. As a preliminary study, we reviewed deaths attributed to ASL in 1963-73, in which available histological material was examined by a panel of pathologists, and full occupational and residential histories were obtained in those cases agreed as ASL by the panel.

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Material and methods

In 1974 the Registrars General of England and Wales and of Scotland were requested to send to EMAS a copy of all death certificates from 1963-73 (Scotland 1965-73 only for administrative reasons) that recorded any type of primary sarcoma or angioma of the liver as a cause of death. These certificates were sorted by one of us (PJB) into two groups—namely, ASL and other liver sarcomas. Certificates were categorised as ASL if any of the following diagnoses were mentioned, irrespective of whether the cases were infants or adults: haemangio- or angiosarcoma, Kupffer-cell sarcoma, haemangioendothelioma, haemangioblastoma, or malignant angioma.

Other cases of ASL were sought by placing notices in medical journals and in the news-sheet of the Royal College of Pathologists, and by undertaking a search of the published reports. Hospital pathologists were invited to forward to the panel of pathologists histological material from the cases of ASL and other liver sarcomas, which were to be used as controls.

The panel regarded the following histological features as being helpful in making a diagnosis of ASL: (1) an essentially intrasinusoidal pattern of growth, though solid and cystic areas may also be present; (2) cytological findings compatible with Kupffer-cell or endothelial-cell origin; (3) characteristic reticulin pattern of dense intrasinusoidal network; (4) diffuse involvement of the affected part of the liver. Other

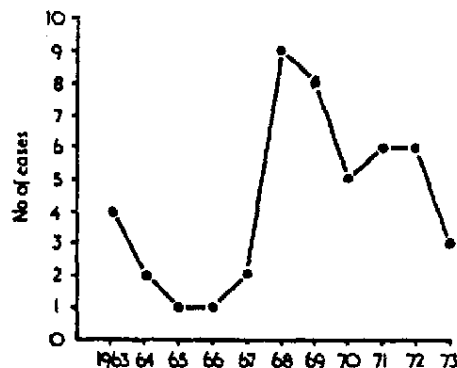


FIG 1—Annual incidence of all recorded cases of angiosarcoma of the liver (ASL) in England and Wales 1963-73 and Scotland 1965-73.

less important features were extramedullary haemopoiesis, erythrophagocytosis, a tendency to thrombosis, infarction, and scarring.

The panel was asked to classify the histological material as follows.

ASL—if the reader was confident about the diagnosis of ASL.

Not ASL—if the reader was confident that the sections were from a control or from a case wrongly labelled as ASL.

Doubtful—if the reader thought the section might be ASL, but was not confident that other diagnoses could be excluded.

Unclassifiable—cases in which the material was inadequate or unsatisfactory, or cases in which the reader considered that additional data would not enable a definite histological diagnosis to be made.

The same slides were circulated in turn initially to four, subsequently to three working members of the panel, who examined them independently and without knowledge of the original diagnoses. If all the members of the panel agreed on the diagnostic category then this was accepted. When there was disagreement sections were projected at a joint meeting of panel members and discussed without knowledge of the previous diagnoses, after which the consensus view was taken. Occupational histories, including places of residence, were sought for all the agreed cases. These were obtained, when possible, from an interview with the next of kin by an employment medical or nursing adviser using a standard questionnaire, and from factory medical officers.

Results

CASES

For the periods 1965-73 in England and Wales and 1965-73 in Scotland 41 death certificates were received which mentioned a diagnosis of ASL. There were 27 males and 14 females, including one female and two male infants. Two patients, both men, died in Scotland. The search revealed nine published cases¹⁻⁷ and a further case was reported to BMAS. All these patients had died between 1967-72. The reported case and five of the published cases would otherwise have gone undetected because the diagnoses mentioned on the death certificates were other than ASL. The annual incidence of all the recorded cases rose to a peak of nine cases in 1968, falling to three cases by 1973 (fig 1).

Histological sections were obtained for 36 (77%) of the recorded cases. The panel agreed the diagnosis of ASL in only 14, and classified seven as doubtful and twelve as not ASL (table 1). Three other cases were regarded as unclassifiable either because the tumour was poorly

differentiated or, in one case, because of insufficient material. Sections were received for one of the infants only and were classified as not ASL.

As the panel classified so few cases as ASL it seemed that the diagnoses as recorded on the death certificates might not accurately reflect the necropsy findings. To assess this we studied the necropsy details available for 25 of the 30 cases notified by death certificate that the panel saw. All the necropsy diagnoses had been based on histological examination (five on biopsy specimens only) and were found to correspond to those on the death certificates with only two exceptions.

CONTROLS

Twenty controls, 15 cases of sarcoma to which five of carcinoma were added, were also seen by the panel. All of these were confirmed as not ASL with one exception, which was classified as "doubtful." The cause of death for this control according to the death certificate was primary haemangioma of the liver, whereas the necropsy diagnosis was "anaplastic primary cancer of the liver."

CASES AGREED BY THE PANEL

The death certificate diagnoses and other details of the 14 cases of ASL agreed by the panel are given in table 11. There were only two women. In three published cases the underlying causes of death were recorded as ovarian cyst, hepatic failure, and ischaemic heart disease respectively, indicating that cases of ASL will be missed if reliance is placed solely upon data from death certificates. The recorded diagnoses for the other cases show that confusion may arise over the nomenclature of ASL, as six different terms for ASL are shown.

Occupational histories were obtained for 12 of these cases. One had been a process worker in PVC manufacture exposed to levels of VCM exceeding 200 parts per million (ppm) for over 20 years.⁸ The glass-fibre worker who died aged 56 in 1970 had been employed for 11 years until the age of 43 in a factory which manufactured rubber components and coated fabric with PVC. The latter process took place in a small part of the factory, and although there was no evidence that he had actually worked there, the possibility could not be excluded. There was no indication that any of the other cases had worked in the manufacture or fabrication of PVC or with other chemicals.

Commercial production of PVC began in Britain in 1941. Four main sites were in commercial production before 1954, and two others in 1959 and 1971. The locations of these factories and their relation to the last place of residence of the 14 cases are shown in fig 2. Eleven cases had either been born or had worked for many years in the area in which they were recorded as dying, but this information was not known for the other three. The cases were widely scattered except for two in the north-west of England. One of these was the process worker described above; within half a mile of the factory where this man had worked, the other patient had lived for seven years before his death in 1970, having spent 40 years as a bus driver before becoming a cashier.

One case, who had been a hospital attendant, had undergone a carotid angiogram in 1939 in which thorium dioxide (Thorotrast, had been used.⁹ Other medical details—for example, drug usage—were not

TABLE 1—Classification by panel of pathologists of cases of ASL occurring in England and Wales (1965-73) and Scotland (1965-73)

	Death certificate cases		Other cases*		Total
	Male	Female	Male	Female	
No. of patients	27	14	3	3	47
Not seen by panel	20	10	3	3	36
Panel classification:					
ASL	11		1	2	14
Doubtful	2	2	2	1	7
Unclassifiable	2	1			3
Not ASL	5	7			12

*Published cases or those not obtained from death certificates.
ASL, primary angiosarcoma of the liver.

TABLE 11—Details of all cases classified by the panel as angiosarcoma of the liver

Diagnosis according to death certificate	Year of death	Sex	Age at death (years)	Occupation according to death certificate	Exposure to VCM
Angiosarcoma	1966	M	54	Electronics engineer	Not known
Ovarian cyst	1967	F	20	Housewife	No
Haemangioendothelioma	1968	M	59	Electrical engineer	Not known
Malignant haemangioma	1968	M	64	Bricklayer	No
Haemangioblastoma	1968	M	20	Machinery fitter	No
Haemangioendothelioma	1969	M	70	Railway porter	No
Haemangioendothelioma	1970	M	61	Cashier	Lived near PVC plant
Hepatic failure	1970	M	56	Fibre glass worker	Possibly PVC pest
Haemangioendothelioma	1971	M	70	Rubber planter	No
Ischaemic heart disease	1971	F	84	Housewife	No
Haemangioendothelioma	1972	M	71	Process worker	Yes
Haemangioendothelioma	1972	M	69	Hospital attendant	(Thorium dioxide)
Angiosarcoma	1972	M	66	Tailor	No
Angiosarcoma	1973	M	49	Lorry driver	No
Kupffer-cell sarcoma	1973	M	49		No

VCM, vinyl chloride monomer. PVC, polyvinyl chloride.

TO: MR N LEM
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CLASS: 100
REF: 100

FROM: DEPARTMENT
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News Release



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October 7, 1977

RISK OF LIVER CANCER FROM VCM COULD HAVE BEEN OVERSTATED SAYS REPORT

A preliminary report published today suggests that the hazard from the chemical VCM to workers employed in the manufacture of PVC or PVC products and to the general public living around the plants involved might not be as great as was first supposed. VCM (vinyl chloride monomer) is the gas used in the manufacture of polyvinyl chloride (PVC). The report, published today (October 7) in the British Medical Journal, is written by Dr. Peter Baxter of the Health and Safety Executive's Employment Medical Advisory Service (EMAS) and three other medical experts.

In 1974, medical findings from the US indicated for the first time that workers engaged in the manufacture of PVC were at risk from developing liver cancer (angiosarcoma). Urgent action by the Health and Safety Executive in collaboration with both sides of the chemical industry resulted in levels of exposure to VCM being drastically reduced in the six British plants involved.

The report says that out of a total of 47 reported cases of angiosarcoma of the liver in the ten-year period 1963-73, in only 14 was the diagnosis verified and out of these only one could be confidently associated with workplace exposure to VCM. It also says that the overall incidence of angiosarcoma did not appear to be geographically linked with the location of factories dealing with the chemical, although there was one confirmed case of angiosarcoma in a man who had lived within half-a-mile of a PVC factory for six years before his death. There was no indication of angiosarcoma having arisen through swallowing minute amounts of VCM, for example, from plastic food wrappings.

Out of 47 deaths in the period which were attributed to angiosarcoma, says the report, 37 had sufficient information supplied by hospitals for the data to be scrutinised by the panel of medical experts. Where the cause of death could be definitively agreed as angiosarcoma (14 cases), full occupational and residential case histories were obtained and analysed in 12 whose next-of-kin could be traced. In the one case where workplace exposure could be associated with the worker's fatal illness, he had been exposed to VCM levels probably exceeding 200 parts per million in air for over 20 years. (The current agreed level in this country for worker exposure which is enforced by the Factory Inspectorate is ten parts per million in air over an eight-hour day.)

The authors of the paper point out that their findings are generally reassuring in that not only does the annual incidence of angiosarcoma appear to be in single figures, in a population of about 50 million, but exposure to VCM seems to have been responsible for only one death over the whole ten-year period. However they say that there remains a possibility that angiosarcoma may be associated with VCM at low exposures so a close watch on the occurrence of this tumour should be maintained.

The paper, "Angiosarcoma of the liver in Great Britain, 1963-73", gives the results of a preliminary study, which is now being extended to include all known cases of angiosarcoma occurring from 1974 onwards. This survey is being undertaken by EH&S, as is a full survey of all causes of death among workers engaged in PVC manufacture. This work parallels studies set up in a number of industrialised countries since 1974.

An EH&S spokesman commented: "These findings give us grounds to hope that this chemical will turn out to be less of a cancer risk than was originally supposed when the American findings were announced. The single case of a man living near a PVC factory who died from angiosarcoma is insufficient evidence to draw any conclusions at this stage."

NOTES TO EDITORS:

1. The text of the report is attached.
2. The period 1963-73 was chosen for study in order to discover the frequency of angiosarcoma of the liver and to evaluate any trends on its incidence before the time when a relationship between occupational exposure to VCM and liver cancer became known in 1974.
3. A first report of the full survey of all causes of death in men engaged in PVC manufacture in Great Britain was published in the British Journal of Industrial Medicine in February 1977. It showed that up to the end of 1974 there were two deaths from angiosarcoma of the liver involving workers exposed to VCM: one, a man who died in 1971, is included in the present report; the other occurred in 1974 and is outside the study period of the present report. Since then no other cases of angiosarcoma are known to have occurred among British workers engaged in PVC manufacture.

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FIG 2—Main sites of PVC manufacture in Great Britain and last place of residence of the cases classified as ASL by the panel.

sought for the 1963-73 cases, but EMAS intends to obtain these for all cases occurring from 1974 onwards.

Discussion

ASL is a rare tumour, and we expected that there might be a fairly wide discrepancy between the original diagnoses and those reached by the panel. Our findings show that between 1963-73 an average of four cases were recorded annually, and in only one-third of the cases submitted did the panel agree with the diagnosis. Undoubtedly the histological material seen by the panel may sometimes have been inadequate compared with that available when the diagnosis was first made by the hospital pathologist. Nevertheless, in one-third of the cases the panel was confident that the diagnosis was not ASL, showing that this explanation was inadequate for these cases at least.

We know of only nine published cases in which ASL was reported as the cause of death in Britain before 1963 (Scotland 1965).¹² One of these was attributed to gamma radiation received from a radium needle that had accidentally become lodged in the myocardium of a patient,⁹ and another case was of suspected idiopathic haemochromatosis.¹³ Thorium dioxide (Thorotrast), a radioactive contrast material introduced in 1928 for angiographic studies, has been the agent most often associated with ASL, but we came across only one such case in this study. By 1950 thorium dioxide was used infrequently in Britain; it had a place in the radiography of cerebral abscesses until the late 1960s, usually remaining localised to the site of injection, and rarely entering the circulation.¹⁴ In other countries ASL has been associated with arsenic exposure—in vineyard workers contaminated from the use of arsenical sprays,¹⁵ and in patients with chronic arsenic intoxication after prolonged taking of arsenical drugs.¹⁶ ASL has also been recorded in a vineyard worker who had worked with copper-containing sprays (Bordeaux mixture) for many years.¹⁷ In Britain the use of arsenic in pesticides and agriculture generally has diminished considerably since 1960, and the use of arsenical drugs was largely discontinued after 1950.

Since 1950, however, the PVC industry has developed rapidly, the material having become one of the most widely used plastics. About 8000 people have been employed at some time in PVC manufacture, over half of whom have been exposed to VCM levels exceeding 25 ppm in the factory atmosphere.¹ Present mean levels of VCM in the atmosphere up to half a mile away from the factory where the neighbourhood case of ASL occurred are considered to be between 0.01 to 0.03 ppm, and may have been several times higher in the past, indicating the order of exposure of people living close to factories manufacturing PVC. (In 1975 a code of practice was introduced, and this was accompanied by a major reduction of VCM levels in and around factories manufacturing PVC.) About 35 000 people in England and Wales are currently working in factories making PVC products, where exposures have been much less than the current hygiene standard of 10 ppm (HM Factory Inspectorate's Records). In addition the general population has ingested extremely small amounts of VCM which have entered foodstuffs from PVC wrappings.¹¹

Despite these observations, only one case of ASL occurring in 1963-73 could be confidently attributed to VCM. One patient was suspected, but not proved, to have worked on a process which used PVC as a raw material, and another had lived for six years within half a mile of a plant manufacturing PVC. These cases had been diagnosed as ASL by hospital pathologists several years before the association between VCM exposure and ASL in man had become known. Although our findings are generally reassuring, in that the annual incidence of ASL in a population of about 50 million seems to be in single figures, the possibility remains that ASL may be associated with VCM at low exposures. Thus more people may be at risk than is currently supposed. Our data provide no reason to suppose that most of even those few cases that have occurred are produced in this way, but a close watch on the occurrence of this tumour should be maintained.

We gratefully acknowledge help from the Registrars General for England and Wales and Scotland; the Medicines Division, Department of Health and Social Security; HM Factory Inspectorate, and HM Alkali and Clean Air Inspectorate. We thank the factory doctors and the employment medical and nursing advisers, who obtained the occupational histories; Prof H K Weinbrein, who was a member of the panel of pathologists at the beginning; Drs S Gauvain and M Greenberg for their advice; and Mr G Sparks for administrative support. We are especially grateful to hospital pathologists for sending histological material.

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