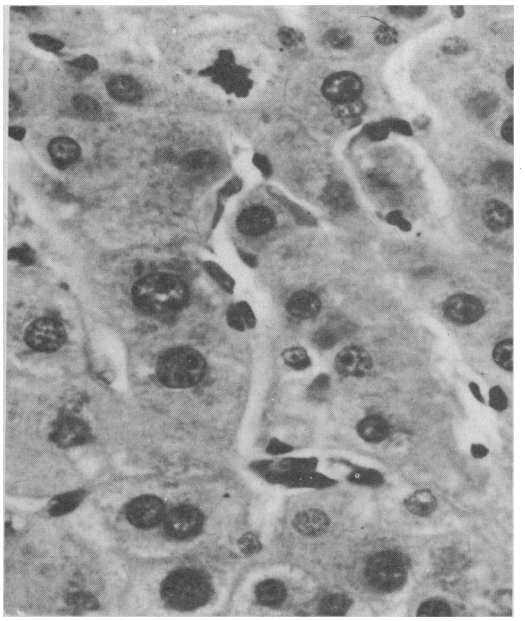

Fig 9 *Bizarre and enlarged sinusoidal lining cells and hepatocyte mitotic abnormality in same patient as Fig 8. H & E. ×600*

to be striking hepatocyte involvement, even with mitotic abnormalities (Figs 8–9).

The question whether these lesions are significant as premalignant changes is unanswered, as many of the alterations can be found in other conditions such as congestive cardiac failure, endothelial cell hyperplasia in cases of lymphoma, and of hepatocyte and other changes in many drug toxicity situations. Other pathogenetic questions also have to be posed, such as what is the primary lesion, which cell is involved in the formation of the tumour, what is responsible for the curious fibrosis and survival of the hepatocytes. Understanding these processes would probably enable us to make a better assessment of individual risk factors and perhaps to work out whether there is a tolerable exposure.

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Epidemiological Studies of Vinyl Chloride Health Effects in the United States

The vinyl chloride (VC) problem has had a considerable impact in the United States during the past year and a half. Perhaps related to the age and conditions of the VC industry, or simply to the sheer size of it, the United States has so far had the largest share of cases of VC-induced hepatic angiosarcoma (HAS); at the present time there have been 17 known cases in polymerization workers (Lloyd 1975). The finding of the initial cases was a dramatic event, and unlike what has occurred with many other proven or suspect carcinogens, the confirmatory experimental evidence arrived almost simultaneously with the epidemiologic results (Maltoni & Lefemine 1974). The widespread industrial applications and uses by the consumer were instantly appreciated, and since the VC problem also arrived at a time of growing awareness and concern among workers and consumers about environmental and occupational hazards, it served to focus these concerns.

Within the first few months after the initial cases were described a number of worrisome reports appeared. Investigators in Louisville, Kentucky, and also at Mount Sinai Hospital in New York demonstrated a high percentage of liver function abnormalities in polymerization workers, suggesting a broad problem (Makk *et al.* 1974, Lilis *et al.* 1975), and, in addition to this, the earliest mortality studies (Monson *et al.* 1974, Tabershaw & Gaffey 1974) suggested increased rates for nonhepatic tumours, parallelling the multiplicity of tumour types seen in experimental studies (Maltoni & Lefemine 1974). Review of records at the Connecticut Tumor Registry, started in 1935, revealed 5 definite cases of HAS; 4 cases were clustered in one industrialized area and had occurred since 1967; 3 of these (and possibly a fourth case where the diagnosis was uncertain after review of slides) occurred in workers at two polyvinyl chloride (PVC) fabricating plants or in residents living nearby (Landrigan & Heath 1976). Further concern was generated by

reports of the potential carcinogenicity of chemicals structurally related to VC, e.g. chloroprene (Lloyd *et al.* 1975) and trichloroethylene (National Cancer Institute 1975, unpublished data), and by the knowledge that VC workers in many instances have been exposed to multiple related chemicals, including vinylidene chloride and acrylonitrile (vinyl cyanide).

As part of the United States Public Health Service response to the VC problem, the National Institute of Occupational Safety and Health (NIOSH) and the Bureau of Epidemiology, Center for Disease Control (CDC), have worked on a number of VC-related epidemiologic projects during the past year and a half; in this paper we will briefly review some of the early results of three of these studies.

HAS Surveillance

A death certificate search for all cases of HAS recorded under ICD Code 197.8 (8th Revision), which encompasses various miscellaneous forms of liver tumour including most cases of HAS, was undertaken by CDC for the years 1966–73 in the United States. This search is almost completed, with only data for New York City not yet available at the time of this review.

Table 1 shows the number of cases of HAS and non-angio hepatic sarcomas by year of death for 1966–73; there is no evidence for an increase in the incidence of these malignancies during this period.

A review of the relative occurrence of hepatic sarcomas recorded under ICD Code 197.8 showed angiosarcoma to be the largest group (35% of total hepatic sarcomas), followed by sarcoma of unspecified type (31%), leiomyosarcoma (12%), fibrosarcoma (7%), and a grouping of miscellaneous sarcomas (15%).

Table 1

Hepatic sarcoma in the United States● by reported histology and year of death, 1966–1973

Year of death	*All sarcoma*	*Angiosarcoma*	*Non-angio sarcoma*
1966	31	9	22
1967	40	13	27
1968	23	9	14
1969	14	7	7
1970	31	15	16
1971	23	5	18
1972■	9	1	8
1973	25	9	16
	196	68	128

● From death certificates, ICD Code 197.8 (8th Revision). Data from New York City not included
■ Half year sample

Table 2

Hepatic angiosarcoma in the United States● by age at death and sex, 1966–1973

Age at death (years)	*Male*	*Female*	*Total*
0–9	2	2	4
10–19	1	1	2
20–29	1	1	2
30–39	5	4	9
40–49	7	2	9
50–59	13	2	15
60–69	5	5	10
70–79	11	3	14
80+	1	2	3
	46	22	68

● From death certificates, ICD Code 197.8 (8th Revision). Data for New York City not included

There was approximately 1 case of HAS for every 300 death certificates reviewed.

Table 2 demonstrates a male to female ratio of 2:1 for HAS. Sixty-two percent of cases occurred in the group aged 50 or more, with 26% in the 30–49 year age group. Non-angio hepatic sarcomas differed in having a male to female ratio of only 1:1, and an altered age grouping with 78% of cases aged 50 or more and only 9% in the 30–49 year age group. These differences are consistent with a hypothesis that occupational exposure may be a more significant factor in the causation of HAS than of non-angio hepatic sarcoma.

Only 2 of the patients with HAS in the death certificate review were recorded as having worked in PVC or plastics plants (1 PVC polymerization worker and 1 accountant in a PVC fabrication plant); both were cases which had been identified prior to this study. No other occupation is recorded more than twice except for the occurrence of 5 printers. Although all were subsequently confirmed as printers, a preliminary review of pathology records and specimens suggests that 4 of the 5 cases may have been incorrectly diagnosed as HAS.

CDC has supplemented the death certificate survey with an intensive case-finding effort, including a national mailing to all pathologists, state epidemiologists, and major cancer referral centres and tumour registries, seeking information on as many cases of HAS as possible diagnosed in the US during the years 1964–74. At the present time approximately 240 cases have been identified. Pathology specimens for about two-thirds of these are currently under review at the National Cancer Institute and the Armed Forces Institute of Pathology. An epidemiologic evaluation of all cases to obtain more detailed histories regarding

past occupations, toxic exposures, and places of residence is underway.

Medical Screening of VC Workers

Together with the Occupational Health Studies Group of the University of North Carolina, NIOSH-CDC recently concluded a cross-sectional medical screening examination of 530 workers at a plant in Pennsylvania which contains both a large tyre-building facility as well as one of the oldest PVC polymerization plants in the United States. Included in the study were approximately 130 current PVC polymerization workers and a similar number of control workers from the tyre plant who had never worked in the polymerization facility. The 2 groups were comparable in age, alcoholic intake, and socioeconomic background; the controls were chosen from those areas of the tyre plant where exposure to solvents and dusts was least.

Preliminary review of the results shows no significant differences between the 2 groups for any of the 6 liver function tests performed (SGOT, bilirubin, alkaline phosphatase, LDH, GGTP, and ornithine carbamyl transferase). Additional analyses based on levels of VC exposure, duration and type of job, and other subgroupings are being done; these preliminary results however do not suggest the occurrence of liver function abnormalities on a broad scale secondary to VC exposure. One should of course be cautious about generalizing from the results at a single plant, and it will be important to compare these findings to studies at other PVC plants. It is also important to realize that since liver function tests are relatively insensitive to the early finding of VC-induced hepatic disease (i.e. fibrosis), the results of this type of testing are not a reliable estimate for the prevalence of VC-induced disease. Liver scans were also performed on all workers with more than 10 years duration of work in the PVC polymerization plant, and no cases of HAS were detected. Some increase in frequency of palpable livers on physical examination was found, however, among VC workers. A full report of findings from this comprehensive medical screening study is in preparation and will be available shortly.

Cohort Mortality Study at Four PVC Polymerization Plants

One of the results of this NIOSH-CDC study was the demonstration of an increased SMR for respiratory system cancer among members of the cohort (Waxweiler *et al.* 1976). On preliminary pathologic review, it was also noted that of the 12 lung cancer cases all 8 for which pathologic specimens were available were either large cell undifferentiated or adenocarcinoma of the lung; if confirmed, this unusual cell type distribution may support the association between VC exposure and occurrence of lung cancer.

Table 3

Lung cancer among workers at PVC polymerization plants in the United States by histologic type and extent of VC exposure

	Extent of VC exposure			
Histologic type	*None*	*Less than one year*	*More than one year*	*Total*
Epidermoid	1	1	0	2
Small cell undifferentiated	0	3	0	3
Adenocarcinoma	1	1	4	6
Large cell undifferentiated	4	0	6	10
Unclassified	1	0	0	1
	7	5	10	22

There are, however, two additional features which should be considered in evaluating this potential relationship. When all of the workers at these 4 plants are considered, including those who were not part of the defined VC-exposed cohort, a total of 22 cases of lung cancer (out of 48) were available for pathologic review. The increased incidence of large cell undifferentiated and adenocarcinoma of the lung was seen in VC workers with more than 1 year of exposure, while a distribution more closely resembling the expected small cell predominance was seen for VC workers with less than 1 year of exposure. Interestingly, however, cases of lung cancer in non-VC workers at these plants, although small in number, appeared to have a cell type distribution which was also predominantly large cell undifferentiated (Table 3). In addition, unlike the situation for HAS in these plants where all but one of the cases were long-term reactor cleaners and operators, the workers with large cell undifferentiated and adenocarcinoma of the lung were distributed in a number of different job categories. As a result, cases of lung cancer seem not to correlate as tightly with VC exposure as cases of HAS and it is conceivable therefore that some additional chemical exposure at these plants may be working together with VC (or even separately) to produce this effect. Further studies are currently underway in an effort to confirm these preliminary pathologic findings.

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DISCUSSION

Dr Mitchell R Zavon (*Baton Rouge, Louisiana*) asked whether the clinical examiners at Pottstown knew whether or not the person being examined worked in vinyl chloride.

Dr H Falk replied that none of the clinical examiners were aware of the occupational status of the workers at the time of the examination.

Dr R I McCallum (*University of Newcastle upon Tyne*) asked Dr Falk to give in more detail the way in which histological diagnosis was made in the case of lung cancer shown in his slide. Was this done by one individual or by a panel of pathologists? How were the specimens of tissue obtained: by biopsy, surgical resection or at autopsy? It was remarkable that in none of the cases was an oat cell carcinoma diagnosed, as this was the type often considered a characteristic result of exposure to a chemical carcinogen.

Dr H Falk replied that the WHO lung cancer classification scheme of Kreyberg (1967) was used. Four pathologists reviewed the slides and agreed on the interpretation (Dr Louis B Thomas and Dr T Powell, National Institutes of Health; Dr M Kuschner, State University of New York; and Dr Laszlo Makk, St Anthony Hospital, Louisville, Kentucky). All available pathological material for each case was reviewed.

The expanded pathological review currently underway would include the selection of multiple control cases of lung cancer from the same hospitals (with similar age and date of diagnosis to the study cases) and a blind review by a panel of pathologists in a more detailed evaluation of available pathology material.

To Dr Falk's knowledge large cell undifferentiated carcinoma of the lung had not been related to exposure to chemical carcinogens, which made the findings in the VC cohort even more intriguing.

Dr A J Fox (*Employment Medical Advisory Service, London*) asked how many factories had been studied individually in the USA. What proportion of these had indicated vinyl-chloride-associated disease?

Dr H Falk replied that cases of hepatic angiosarcoma had been seen at 5 of the 8 PVC polymerization plants opened prior to 1950.

There was some confusion in this area in that a number of the VC worker mortality studies had been overlapping. Three separate studies, for example, (the NIOSH-CDC study, the Tabershaw study, and the Monson-Peters study) had all looked at the Louisville, Kentucky plant where the initial angiosarcoma cases occurred as well as at a varying number of additional plants. Compounding the problem was the fact that the definitions for entrance into the cohorts studied differed from study to study, so that the results even at the same plant were not identical.

Dr J A Bonnell (*Central Electricity Generating Board*) asked whether, since vinyl chloride monomer was a carcinogenic agent, there was any evidence in experimental animals or in human clinical experience that the skeletal or skin changes described might be premalig:.ant conditions.

Dr H Falk said that cases of angiosarcoma in the USA did not have a history of acro-osteolysis or skin problems, although they did not have the multiple tests for early changes of acro-osteolysis. It would seem, therefore, that the skin changes were not premalignant conditions.

Professor I J Selikoff (*Mount Sinai School of Medicine, City University of New York*) said that a review of known details of identified cases of vinyl-chloride-associated angiosarcoma of the liver by Dr Lloyd (1975) of the National Institute for Occupational Safety and Health had demonstrated that the median duration from onset of exposure was approximately seventeen years. These cases were derived from the rather small number of polymerization workers employed during the establishment and initial growth of the vinyl chloride industry. Attempts were underway to identify and trace the initial groups of workers, employed during the years 1938–55, since analysis of their experience would allow evaluation of the risks which might be suffered by the very much larger group of vinyl chloride workers exposed more recently, in a period during which PVC production was increasing at the rate of approximately 10% per annum.

Limited data bearing on the problem had been obtained. In one polymerization process studied, 257 men had been employed for five years or more in the period between 1946, when the plant opened and 1964. Each man had been traced to 1 July 1974, with 25 deaths from all causes: 3 of the deaths were due to angiosarcoma of the liver (Nicholson *et al.* 1975), each confirmed on review of autopsy material (Thomas & Popper 1975); in addition there was one death due to ruptured œsophageal varices. Another worker, examined during the clinical survey at this facility (Lilis *et al.* 1975) had had a successful portacaval shunt operation for the same condition. These experiences suggested that vinyl-chloride-associated disease would be an important hazard for vinyl chloride workers in the future, unless control of exposure resulted in at least some reversal of the risk.

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