Information solicited from relatives and fellow workers concerning the individual's drinking history indicate only very modest alcohol consumption and suggest that this case, too, may be causally related to the individual's exposure to vinyl chloride. Among the other cancers resulting in death were a glioblastoma, a lymphosarcoma, and a reticulum cell sarcoma. Our observation of a brain tumor and two lymphomas conforms to observations in other vinyl chloride-exposed populations[8] and suggests the possibility that their origin may also be related to vinyl chloride exposures. In addition to the above, other malignancies were the underlying causes of death in this group of 24 workers.

The details of the work histories of the 3 workers who died of hemangiosarcoma and the other possible occupationally related cancers appear in TABLE 6. All but two worked extensively in the polymerization facility.

All of the hemangiosarcomas occurred in individuals who first worked prior to 1951. As the time from onset of exposure increases in cohort members with similar exposures, additional cases of occupational cancer may occur in this group of workers.

SUMMARY

These data are derived from early follow-up of individuals exposed for 5 or more years to vinyl chloride in a polymerization facility. At least 17 percent of the deaths that occurred were causally related to exposure to vinyl chloride. Longer periods of observation are required to provide information concerning the full spectrum of vinyl chloride-induced malignancies and their incidence among exposed workers.

These data speak for the need to prevent exposure to vinyl chloride and for surveillance and early disease detection of those who have experienced vinyl chloride exposures in the past.

REFERENCES

1. MALTONI, C. & G. LEFEMINE. 1974. Carcinogenicity bioassays of vinyl chloride: current results. This monograph.
2. LILLIS, R., H. ANDERSON, W. J. NICHOLSON, S. DAUM, A. S. FISCHBEIN & I. J. SELIKOFF. 1974. Prevalence of disease among vinyl chloride and polyvinyl chloride workers. This monograph.
3. VELTMAN, G., C.-E. LANGE, S. JÜHE, G. STEIN & U. BACHNER. 1974. Clinical manifestations and course of vinyl chloride disease. This monograph.
4. SUCIU, I., L. PRODAN, E. ILEA, A. PADURARU & L. PASCU. 1974. Clinical manifestations in vinyl chloride poisoning. This monograph.
5. CREECH, J. L., JR. & L. MAKK. 1974. Liver disease among polyvinyl chloride production workers. This monograph.
6. HEATH, C. W., H. FALK & J. L. CREECH, JR. 1974. Characteristics of cases of angiosarcoma of the liver among vinyl chloride workers in the United States. This monograph.
7. THOMAS, L. B. & H. POPPER. 1974. Pathology of angiosarcoma of the liver among vinyl chloride-polyvinyl chloride workers. This monograph.
8. TABERSHAW, I. R. & W. GAFFEY. 1974. Mortality study of workers in the manufacture of vinyl chloride and polyvinyl chloride. J. Occupational Med. In press.

CHARACTERISTICS OF CASES OF ANGIOSARCOMA OF THE LIVER AMONG VINYL CHLORIDE WORKERS IN THE UNITED STATES

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The relationship between vinyl chloride exposure and human angiosarcoma of the liver (ASL) first received serious attention in December 1973 when a case of this rare tumor was diagnosed at autopsy in a vinyl chloride (VC) worker from the B. F. Goodrich chemical plant in Louisville, Kentucky. At that time, this case represented the third recognized among VC workers at this plant; prior cases had been diagnosed in May 1970 and March 1973.[1] Although at first the possibility was considered that case occurrence might be unique to the Louisville facility, the subsequent detection of cases at three other plants has shown the problem to be industry-wide. Ten additional cases have subsequently been identified among other VC polymerization workers in the United States (TABLE 1). Workers at a total of four different plants have been involved.

The earliest case recorded to date occurred in 1961, the others being scattered over subsequent years with 5 in the past 2 years (1973–1974). In several instances, the diagnosis of ASL was not specifically made until review of pathologic material during the early months of 1974. Death certificate diagnoses in such cases indicated "primary liver cancer," and in one instance merely "liver cirrhosis." The 3 most recent cases were diagnosed in the course of systematic medical screening, 2 at the Louisville plant in February 1974 and 1 at the South Charleston plant in May 1974. These 3 patients are the only ones of the 13 who are alive currently.

All 13 cases have occurred in white males. About half have been in their 40s with an age range from 36–60 years and a mean age at time of diagnosis of 48.2 years. Length of time between first VC work and diagnosis has ranged from 12–29 years (mean 20.3 years), mean total duration of VC work being 18.0 years.

COMPARISON OF OBSERVED AND EXPECTED INCIDENCE

The reason an etiologic association between VC work and tumor could be inferred so readily on the basis initially of only 3 cases is that ASL is extraordinarily rare. Based on data from the National Cancer Institute's Third National Cancer Survey (1969–1971), expected annual incidence of this tumor is on the order of 0.0014 case/100,000, or about 25–30 cases a year in the entire United States population. Estimating the total VC worker population past and present in the United States at roughly 20,000 persons (an estimate which may be too high), one can calculate that only about 0.03 case of this

TABLE 1
CASES OF ASL AMONG VC WORKERS IN THE UNITED STATES

ame of Company	Location of Plant	Age at Diagnosis, Race, Sex	Month and Year of First VC Work	Month and Year of Diagnosis	Month and Year of Death	No. of Years between First VC Work and ASL Diagnosis	Total Years in VC Work
F. Goodrich	Louisville, Ky.	52 WM	6-44	4-64	4-64	19	18
F. Goodrich	Louisville, Ky.	43 WM	7-52	8-67	1-68	15	15
F. Goodrich	Louisville, Ky.	36 WM	11-55	5-70	9-71	14	13
F. Goodrich	Louisville, Ky.	49 WM	12-48	3-73	3-73	24	16
F. Goodrich	Louisville, Ky.	58 WM	11-45	12-73	12-73	28	28
F. Goodrich	Louisville, Ky.	45 WM	1-62	2-74		12	12
F. Goodrich	Louisville, Ky.	43 WM	5-45	5-73		28	17
F. Goodrich	Louisville, Ky.	40 WM	10-46	4-61	8-61	14	14
odyear	Niagara Falls, N.Y.	54 WM	6-51	5-68	5-68	16	16
odyear	Niagara Falls, N.Y.	60 WM	10-46	3-70	3-70	23	23
odyear	Niagara Falls, N.Y.	45 WM	8-44	3-68	3-68	23	18
ion Carbide	S. Charleston, W.Va.	52 WM	8-44	4-73		29	29
ion Carbide	S. Charleston, W.Va.	50 WM	9-49	5-69	5-69	19	15
estone	Pottstown, Pa.						

expected in such a population over a decade. Since 13 cases have thus far been identified (and it is not unreasonable to think that more cases may be found among other VC workers), one arrives at a risk ratio (a ratio of observed to expected cases) of at least 400:1.

Needless to say, had the situation concerned a common tumor such as lung cancer, the picture would have been much less clear-cut and would have required many more cases and much more elaborate epidemiologic manipulation to associate tumor with industrial VC exposure.

CLINICAL FEATURES

Medical and epidemiologic data have been examined in detail for cases at the Louisville plant in particular. The remainder of this presentation summarizes these and other data concerning VC workers at that plant. For each Louisville case, all available medical records have been reviewed. Interviews have been held with each surviving patient and with close relatives of all deceased patients to obtain specific information concerning work history, toxicologic exposures, and family history. Pathologic material, particularly sections of liver and of tumor, have been reviewed both by local pathologists in Louisville and by Dr. Louis Thomas at the National Cancer Institute and Dr. Hans Popper at The Fogarty International Center.

In most cases the diagnosis of ASL was reached only with difficulty; 3 of the 5 fatal cases were not diagnosed until autopsy. In only 1 of the 2 remaining fatal cases was ASL diagnosed unequivocally prior to death (4 months). In the other case, a diagnosis of "primary liver cancer" was made 5 months before death, but ASL was not clearly identified until recent review of autopsy material.

Presenting signs and symptoms varied widely and were relatively nonspecific. Abdominal mass was a presenting feature in 4 cases, gastrointestinal bleeding in 2 (diagnosed initially in each instance as peptic ulcer), fatigue and weakness in 4, and noticeable weight loss in 1. In 1 case no signs or symptoms referable to cancer or liver disease were present and the diagnosis was made in the course of workup for another health problem.

Duration of symptoms prior to diagnosis ranged from 1–11 months for 5 of the 6 cases displaying symptoms. In the 6th case, symptoms related to liver disease antedated diagnosis of tumor by 8–10 years. In that particular case, a diagnosis of liver fibrosis was made in May 1965 following two episodes of gastrointestinal bleeding in 2 years. A portocaval shunt operation was performed because of varices, splenomegaly, and increased portal vein pressure. Six years later (May 1971) the patient was reevaluated because of progressive symptoms, and at that time, liver scans suggested the presence of tumor. ASL, however, was not unequivocally diagnosed until autopsy in March 1973.

At time of tumor diagnosis, physical findings among the 7 cases varied considerably. In 2 cases, no abnormal findings at all were recorded. Three cases presented with liver enlargement, in each instance accompanied by splenomegaly. In a 4th case, splenomegaly alone was detected. One additional case presented with severe right upper quadrant tenderness in the absence of clear-cut organomegaly. Laparotomy revealed free blood in the peritoneal cavity traced to what was tentatively diagnosed prior to death as "hemangioma of the dome of the liver."

Abnormalities of one or more liver function tests were present in every case at or around the time of diagnosis. In most instances, however, these abnormali-

were at least mildly increased in all 7 cases, total bilirubin in 6, and alkaline phosphatase in 5. LDH was increased in 4 of 6 cases tested and BSP in 1 of 2.

Diagnoses were made with the help of liver-spleen scanning in 6 cases and hepatic angiogram in 2. Esophageal varices were demonstrated in 2 cases, one by x-ray, the other by endoscopy. Efforts at tissue diagnosis were made by open liver biopsy in all 7 cases and by needle biopsy in 3; autopsies were performed in 4 of the 5 deceased cases. Open liver biopsy provided a diagnosis of tumor in 4 cases while in the remaining 3 cases, diagnosis was made at autopsy.

Recent review of pathologic material in all 7 cases has shown evidence of portal fibrosis as well as of tumor. In addition, discrete subcapsular fibrotic areas were described at time of open liver biopsy in one of the 2 cases diagnosed in 1974. In 2 cases, angiosarcoma was present in tissues other than liver. In one the picture was that of local tumor spread.

Epidemiologic Features

The B. F. Goodrich Louisville plant employs about 1200 persons of whom about 270 or 20 percent are engaged in VC polymerization activities. The plant first began polyvinyl chloride (PVC) production in 1942 after pilot operations dating from 1937. The present polymerization work force size was reached in the late 1950's. All 7 patients had worked in jobs directly related to VC polymerization, and in this capacity it can be assumed that all seven have had direct exposure to vinyl chloride monomer (VCM). Initial involvement in VC work occurred from 12–28 years prior to tumor diagnosis (mean 20.0 years) (Table 1). Involvement was essentially continuous during these years (mean duration of VC work 17.0 years). Dates of initial industrial VC exposure ranged from 1944–1945 soon after the plant began production (2 cases), to as recently as 1957 and 1961. Ages at initial exposure ranged from 21–33 years (mean age 27.6 years).

Although the data are far from conclusive, they do suggest a possible dose-response relationship when one tries to compare intensity of VC exposure with latent period. Virtually everyone entering VC polymerization work at the Louisville plant starts as a "helper," a job which includes cleaning the interiors of polymerization vats and hence involves maximum exposure to VCM. When duration of work as a helper (a rough measure of VCM exposure) is correlated with interval between first exposure and diagnosis, an inverse relationship is suggested. For 3 cases who averaged only 5.3 months as helpers, exposure-to-diagnosis intervals averaged 22.0 years; for the 4 remaining cases who averaged 36.5 months as helpers, this interval was 14.5 years.

No evidence was found that exposure to other potentially hepatotoxic materials outside the work place played any consistent role in these particular cases. Only 2 patients had a history of increased alcohol intake, and in one the increase was borderline. One man gave a history of exposure to arsenic insecticides for several years as a teenager. In none was there any suggestion of thorium dioxide exposure. Acroosteolysis, past or present, was not observed in any case.

Nonmalignant Liver Disease

Because 2 of the 3 tumor cases which were initially recognized in Louisville had shown evidence of hepatic fibrosis antedating or coexisting with tumor, medical records at the Louisville plant were reviewed for cases of nonmalignant liver

Table 2
Cases of Nonmalignant Liver Disease among Louisville VC Workers

Age at Diagnosis, Race, Sex	Month and Year of Diagnosis	No. of Years between First VC Work and Diagnosis	Clinical Features			Pathologic Features	
			Enlarged spleen	Enlarged liver	Abnormal liver function test*	Portal fibrosis	Subcapsular fibrosis
46 WM	12-68	24	+	−	AP, BSP, SGOT	+	+
28 WM	1-72	6	+	+	TB, SGOT	+	+
56 WM	9-73	24	+	−	TB, AP	+	−
56 WM	9-73	29	−	−	TB, LDH, SGOT	+	+

* AP, alkaline phosphatase; BSP, bromsulphalein clearance; SGOT, serum glutamic oxaloacetic transaminase; TB, total bilirubin; LDH, lactic dehydrogenase.

disease. A total of 4 such cases have been identified to date, again all among VC workers.

The clinical and epidemiologic features of these 4 cases closely resemble those of the 7 tumor cases (Table 2). All were white males, average age 46.5 years at time of first diagnosis. One was diagnosed in 1968, 1 in 1972, and 2 in 1973. VC work began on the average 20.8 years prior to diagnosis and in every instance was continuous. One patient, however, a 28-year-old man, had worked at the plant for only 6 years. Duration of illness prior to diagnosis ranged from 0–7 months. Although 3 of the 4 patients presented with significant splenomegaly (one with hepatomegaly in addition), in 1 case physical examination was entirely negative. A variety of liver function tests showed abnormalities although none was severe and no consistent patterns were evident. In 2 cases esophageal varices were demonstrated, and in both instances, splenorenal shunt operations were performed. All 3 patients with splenomegaly underwent splenectomy.

Open liver biopsies were performed in all 4 cases. In each instance, a picture of portal fibrosis was seen, and in 3 cases it was accompanied by discrete nodules of subcapsular fibrosis. The latter feature was indistinguishable pathologically from the subcapsular lesions observed in 1 of the 7 tumor cases.

Discussion

In light of recent animal experiments[8] and of clinical observations reported in European VC workers,[9] it seems likely that exposure to VCM in the course of VC polymerization work is responsible for malignant and nonmalignant liver disease in these cases. Epidemiologic features further suggest that either prolonged exposure and/or a long interval from initial exposure is required before liver disease becomes apparent. Although the length of time involved seems quite variable (6–29 years), in all but 1 case the interval was 12 years or longer.

We have no assurance, however, that the actual latency required for development of liver disease (as opposed to latency in relation to clinical recognition) may not be considerably shorter. Unfortunately, if one can judge by the clinical features of the Louisville cases, manifestations of liver disease are quite variable, and in most instances were not detected until the process of hepatic fibrosis was so far advanced that splenomegaly and increased portal pressure were evident. Furthermore, if one envisions angiosarcoma as a late manifestation of the same pathologic process, then it seems even more likely that clinical detection of liver

disease lags considerably behind actual disease onset. At present, therefore, a major concern is to develop more sensitive means for detecting liver disease, not in its late malignant phase (if in fact a single pathologic spectrum is involved), but in the early stages when fibrotic reaction first sets in.

Eventually, nonmalignant liver disease, not ASL, may prove to be the most prominent disease problem associated with VCM exposure in terms of numbers of persons affected. One must also consider the possibility, however, that VCM may produce angiosarcoma at sites other than liver or that tumors of other kinds may also be induced. At present, animal experiments suggest that a wide spectrum of tumors may be involved,[2] although as yet there is no clear human evidence to support the concept. In addition, no human cases of liver disease, whether fibrosis or frank angiosarcoma, have yet been strongly linked to VC exposure outside the industrial setting. Whereas this may mean that risk of disease is greatly reduced or even nonexistent at very low levels of VC exposure, it is obviously too early to draw any conclusions. In view of past experience with other oncogenic chemicals, it will be prudent, until many more data have been assembled, to view any exposure to VCM as potentially harmful.

Summary

A total of 13 cases of ASL have been documented to date among VC workers in four different plants in the United States. In this particular industrial population, this number of cases represents at least a 400-fold increase over expected incidence for this extremely rare tumor. The first case occurred in 1961. Average age at diagnosis is 48.2 years. Average length of time between initial VC work and diagnosis has been 20.3 years.

A detailed review of 7 cases associated with one plant revealed that clinical features varied from little or no overt illness prior to diagnosis to advanced liver disease with portal hypertension and marked splenomegaly. Portal fibrosis was present in all 7 of these ASL cases as well as in 4 additional cases with nonmalignant liver disease among VC workers at the same plant. These findings suggest that exposure to VCM in industrial settings can produce hepatic fibrosis with angiosarcoma as a late manifestation. Conventional liver function tests may not be sensitive indicators of such liver impairment, at least in its early stages.

References

1. Creech, J. L., Jr. & M. N. Johnson. 1974. Angiosarcoma of liver in the manufacture of polyvinyl chloride. J. Occupational Med. 16: 150–151.
2. Maltoni, C. Unpublished observations.
3. Marsteller, H. J., W. K. Lelback, R. Müller, S. Jühe, C. E. Lange, H. G. Rohner & G. Veltman. 1973. Chronisch-toxische Leberschäden bei Arbeitern in der PVC Produktion. Deut. Med. Wochschr. 98: 2311–2314.

FROM MOUSE TO MAN—OR HOW TO GET FROM THE LABORATORY TO PARK AVENUE AND 59TH STREET*

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Introduction

If the title of this paper sounds like a guide to a road map, that is what intended to be, with information about detours, chuckholes, swamps, quagm and dead ends. In fact, our description of the problems may lead some peop conclude that you really cannot get there from here. We think you can, how —perhaps not *exactly* there, but certainly into the neighborhood.

When we extrapolate moderate or high dose animal toxicity data to presu effects in man, we must do it like the animal trainer entering the lion's cage— cautiously. The first caution in this careful operation is to extrapolate from m to mouse from the higher dose levels where it is possible to see some results small or moderate-sized experiments to the very low doses, where even very l experiments are not likely to show much. We really do want to extrapolate an do not want to do these very large experiments because they are so full of p lems that they probably cannot be done well. We will discuss this later. Weinl in his paper on Trans-Science,[1] refers to this sort of difficulty that the meg periment poses as his first kind of trans-science problem.

Models for In-Mouse Extrapolation

The usual way to extrapolate to responses at low doses is to assert the e ence of some mathematical model of dose-response and then compute th sponse at the desired dose or compute the dose for the desired response. V berg suggests this as a possible way out of the mega dilemma.

Presently two classes of mathematical models are advocated for in-m extrapolation. First, there are the models that deal with yes-no data, the dicl mous data models. These are concerned with whether or not an effect occu

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