PREVALENCE OF DISEASE AMONG VINYL CHLORIDE AND POLYVINYL CHLORIDE WORKERS

Ruth Lilis, Henry Anderson, William J. Nicholson, Susan Daum, Alf S. Fischbein, and Irving J. Selikoff

Mount Sinai School of Medicine
City University of New York
New York, New York 10029

The emergence in January 1974, of vinyl chloride as a new occupational carcinogen producing hemangiosarcoma of the liver focused attention on the toxicologic effects of this chlorinated hydrocarbon.[4]

A considerable number of studies had been published on the rather puzzling and unique syndrome of "acroosteolysis" (TABLE 1) describing mainly the bone lesions in the distal phalanges of the fingers, but also the associated scleroderma-like skin lesions and the striking vascular (arterial and arteriolar) changes, pathologically the main lesion, leading to secondary bone and skin changes (TABLES 2 and 3).

Much less attention had been given to the hepatotoxic effects of vinyl chloride, although convincing experimental evidence had been produced[16, 23] and scattered reports of ill-defined liver changes were included in some of the studies of vinyl chloride-exposed workers (TABLE 4).

There was evidence that liver damage occurred in workers exposed to higher levels of vinyl chloride. In some studies the liver changes (hepatomegaly, tenderness on palpation, abnormal liver tests) were found to be reversible after cessation of exposure. On the other hand, some observations mentioned the progressive nature of the liver changes, when toxic exposure continued, to what was stated to be "chronic hepatitis."

Recent work from Germany[15] reporting a detailed study of 20 polyvinyl chloride (PVC) workers brought a very important contribution to our present knowledge on the liver changes induced by this toxic exposure. The authors were alerted to the problem by the occurrence of upper gastrointestinal bleeding in several workers of a PVC-producing plant. Esophageal varices, splenomegaly, hepatomegaly, fibrosis of the liver capsule (by laparoscopy), delay in the secretion of bromsulphalein, and thrombocytopenia were the most prominent findings. The pathologic changes encompassed collagenous transformation of the liver sinusoids, focal activation of Kupffer cells, increased collagen deposition in the portal spaces, portal fibrosis, and septal and intralobular fibrosis.

There are a few cases in the literature of lung changes in PVC workers. One case of pneumoconiosis in a 30-year-old worker who had inhaled PVC dust was reported.[29] The lung biopsy showed granulomatous lesions (foreign body type) to be present. Fibrotic changes and altered pulmonary function tests were reported in 96 workers exposed to polyvinyl chloride dust; the changes were more pronounced in persons with long exposure.[25]

In the available literature on vinyl chloride and polyvinyl chloride adverse health effects there were no accurate data on the prevalence of disease in exposed workers, the relative prevalence of the various pathologic changes, their possible association and time sequence.

We have undertaken clinical studies of a number of groups of vinyl chloride-

TABLE 1
ACROOSTEOLYSIS

Year	Author*	Finding
1957	Filatova and Gronsberg	"Angioneurosis of spastic character"
1963	Suciu *et al.*	Raynaud's syndrome (hands and feet), 6% of 168 exposed workers
		Scleroderma-like skin changes (hands, feet, face, neck, thorax), 3.6% of examined
1966	Cordier *et al.*	Raynaud's syndrome
		Scleroderma-like skin changes
		Lytic lesions of terminal phalanges in hands and feet
1967	Harris and Adams	The same changes and also pseudoclubbing of fingers
		Involvement of sacroiliac joints and patella
1967	Wilson *et al.*	Bone changes and Raynaud's syndrome
1971	Dinman *et al.*	Epidemiology of acroosteolysis
1972	Markowitz *et al.*	Skin biopsy and pathology data
1972	Jühe and Lange	Arteriography
		Occlusion of interosseous arteries
1973	Misgeld *et al.*	Arteriography → spastic arteries visualized only after Priscol

* See also References 2, 6, 8, 12, 13, and 17.

TABLE 2
ACROOSTEOLYSIS: BONE CHANGES

Marginal and/or cortical defects in distal phalanges
Loss of cortex in tufts of the distal phalanges
"Half-moon" defects or cuts
Transverse defects or fractures
Complete resorption of tufts and part of shafts
Involvement of the larger bones
  Cystic lesions and increased radiolucency (ulna, radius, humerus, os calcis, patella)
Erosive and sclerotic changes in sacroiliac joints

TABLE 3
ACROOSTEOLYSIS: SKIN BIOPSY PATHOLOGY

Thickening of dermis
Nonfibrillary homogenization of collagen and thickened collagen bundles
Disorganization of elastic fibers, which are split and broken
Inflammatory infiltrates, predominantly perivascular (lymphocytes, few histiocytes)
Thickening of the media of dermal arterioles
Uneven endothelial thickening
Marked swelling of dermal nerve fibers and vacuolization of axones
Intersitital edema
Dilatation of lymphatics

exposed workers in order to assess the prevalence of vinyl chloride-induced changes and to define the natural history of this occupational disease. We are reporting the results of a survey (March 1974) of 267 workers currently employed in a VC polymerization plant, including virtually the entire current production

TABLE 4
EVIDENCE OF LIVER DAMAGE IN PVC-EXPOSED WORKERS

Year	Finding	Author (Country)
1949	"Hepatitis-like liver changes"	Tribukh *et al.* (Russia)
1965	"Chronic epithelial hepatitis" in 15% of cases; hepatomegaly, increased bilirubin and prothrombin time, abnormal Takata-Ara test	Pushin (Russia)
1963	Hepatomegaly in 30% of 168 examined workers, splenomegaly (6%); liver biopsy in 2 cases: "chronic hepatitis"	Suciu *et al.* (Romania)
1967	Hepatomegaly; persistent raised bilirubin	Harris *et al.* (England)
1972	Increased BSP retention, raised icterus index—related to degree of exposure	Kramer and Mutchler (U.S.)
1972	Pain in RUQ and abnormal liver tests (in 2 out of 7 patients with scleroderma-like skin changes)	Jühe *et al.* (Germany)
1973	RUQ discomfort; abnormal liver changes.	Misgeld *et al.* (Germany)

TABLE 5
DURATION OF VC EXPOSURE AMONG 354 WORKERS IN NIAGARA FALLS

Duration of Exposure (yr)	Currently Employed	Formerly Employed	Total
≤2	36	25	61
2.1–5	62	13	75
5.1–10	47	15	62
10.1–20	77	27	104
20+	45	7	52
Total	267	87	354

TABLE 6
AGE DISTRIBUTION OF 354 VC-EXPOSED WORKERS (NIAGARA FALLS)

Duration of Exposure (yr)	Age Groups (yr)					Total
	21–30	31–40	41–50	51–60	60+	
≤2	39	9	8	4	1	61
2.1–5	45	17	9	1	3	75
5.1–10	17	18	24	3	0	62
10.1–20	0	50	30	21	3	104
20+	0	4	14	27	7	52
Total	101	98	85	56	14	354

workforce. Eighty-seven former workers were examined as well. In both groups, exposure for some had started in 1946, when the plant opened. Altogether 354 men were examined.

TABLE 5 shows the duration of exposure for the group and TABLE 6 the age distribution of the men. More than half were under 40 years, 20 percent were 51 or older.

Methods

The medical examination included detailed occupational history, past medical history, and complete physical examination, with special attention to the skin, hands, and feet, arteries accessible to palpation, liver, and spleen.

An Allen test for the assessment of the peripheral circulation in the areas supplied by the radial and ulnar arteries was performed. Each examined worker also had the following:

X-rays of the chest, hands, and feet; pulmonary function tests; complete blood cell counts including platelets; blood chemistries including bilirubin, SGOT, SGPT, LDH, alkaline phosphatase, total protein, electrophoresis of serum proteins, fibrinogen split products; α-fetoprotein, antinuclear antibodies, antimitochondrial antibodies, antismooth muscle antibodies, Australia antigen B by radioimmunoassay and liver antibodies; urinalysis, including microscopic examination of the sediment was done. All examined workers were also tested for carcinogenic embryonic antigen. In a limited number, studies for chromosome breaks in circulating lymphocytes were undertaken.

Results

Unfortunately, appropriate VC measurements had not been made in the past. We have findings which suggest, however (Table 7), that VC levels may have been considerable at times, sufficient to produce symptoms of acute overexposure; for example, 14 of the 354 workers had had loss of consciousness at one time or another.

In any case, our data indicate that measured levels would be of limited utility, unless integrated over time, since both total exposure and duration from onset of exposure seem to be of importance in relation to likelihood of abnormality. The influence of these variables may be demonstrated in a number of areas.

This was so insofar as abnormal peripheral circulation was concerned (Table 8).

Numbness and tingling of the fingers, along with increased sensitivity to cold were early symptoms. They were often associated with pain and cyanotic discoloration sometimes also involving the toes. Classical Raynaud's syndrome, characterized by cold-induced, marked, sudden and sharply demarcated pallor of the fingers followed by cyanotic discoloration in the same area, was found only

Table 7
Symptoms of Acute Overexposure among 354 VC Workers

Duration of Exposure (yr)	No. of Examined Workers	Symptoms				Total	%
		Headache	Lightheaded-ness	Dizziness	Loss of consciousness		
≦2	61	12	21	9	3	28	46
2.1–5	75	13	30	30	3	43	57
5.1–10	62	8	25	20	0	33	53
10.1–20	104	17	40	44	7	56	53
20+	52	7	26	32	1	36	69
Total	354	57 (16%)	142 (40%)	135 (38%)	14 (4%)	196	55

TABLE 8
CLINICAL SIGNS AND SYMPTOMS OF ABNORMAL PERIPHERAL CIRCULATION AMONG 354 VC-EXPOSED WORKERS

Duration of Exposure (yr)	Total No.	Numbness, Tingling	Excessive Sensitivity to Cold	Pain	Cyanosis	Involvement of Toes	Raynaud's Syndrome*
≤2	61	2 (3%)	2 (3%)		2 (3%)		
2.1–5	75	16 (21%)	11 (15%)	4 (5%)	4 (5%)	1 (1%)	2 (2.6%)
5.1–10	62	11 (18%)	11 (18%)	3 (5%)	10 (16%)	5 (8%)	4 (6.4%)
10.1–20	104	36 (35%)	26 (25%)	11 (11%)	19 (18%)	11 (11%)	9 (8.6%)
20.1	52	20 (38%)	13 (19%)	10 (19%)	11 (21%)	8 (15%)	5 (9.6%)
Total	354	85 (24%)	63 (18%)	28 (8%)	46 (13%)	25 (7%)	20 (5.7%)

* Prevalence in workers with more than 10 years of exposure significantly higher than in those with less than 10 years of exposure. $\chi^2 = 5.783$; $p < 0.02$.

in 5.6 percent of the cases. In general, the effect of vinyl chloride exposure on the peripheral vessels of hands and feet appears to produce a wider range of symptoms than those characteristic of Raynaud's syndrome.

As noted, the prevalence of these changes rose with duration of exposure. Typical Raynaud's syndrome was found in almost 10 percent of cases with more than 20 years of exposure. *The prevalence of Raynaud's syndrome was significantly higher in workers with more than 10 years of exposure, than in those with less than 10 years of exposure.* Symptoms of abnormal peripheral circulation (TABLE 9) were more frequent in workers currently exposed than in those with past exposure.

An abnormal Allen test indicating delayed arterial circulation in the areas supplied by the ulnar and/or radial arteries, was found in 94 (26.6 percent) of the examined workers (TABLE 10).

The percentage of persons with abnormal Allen tests increased with their length of exposure. *The prevalence of an abnormal Allen test in workers with more than 5 years of exposure was significantly higher than in those with less than 5 years of exposure.*

Pseudoclubbing of the fingers (FIGURE 1) was also found with increasing frequency as the duration of employment increased; the overall prevalence was 8.7 percent; in the group with more than 20 years of exposure it was 17.3 percent (TABLE 11). However, the difference in the prevalence of pseudoclubbing between workers with less and more than 5 years of exposure did not quite reach the level of statistical significance ($\chi^2 = 3.602$). Pseudoclubbing was almost always associated with signs and/or symptoms of abnormal peripheral circulation and was a more frequent finding than typical Raynaud's syndrome. In some cases, especially in persons with past exposure, there was a history of Raynaud's syn-

TABLE 9
RAYNAUD'S SYNDROME AMONG 354 VC WORKERS

Exposure	No.	Raynaud's
Active	267	17 (6.4%)
Prior	87	3 (3.4%)
Total	354	20 (5.6%)

TABLE 10
ABNORMAL ALLEN TEST AMONG 354 VC WORKERS

Duration of Exposure (yr)	Abnormal Test Results		Total*
	Current exposure	Prior exposure	
≤2	7/36	2/25	9/61 (14.7%)
2.1–5	11/62	7/13	18/75 (24.0%)
5.1–10	16/47	7/15	23/62 (37.1%)
10.1–20	22/77	5/27	27/104 (26.0%)
20+	12/45	5/7	17/52 (32.7%)
Total	68/267 (25.5%)	26/87 (29.9%)	94/354 (26.6%) †

* Prevalence of abnormal Allen Test in workers with more than 5 years of exposure significantly higher than in those with less than 5 years of exposure. $\chi^2 = 5.084$; $0.02 < p < 0.05$.

† Radial, 10; ulnar, 38; both, 46.

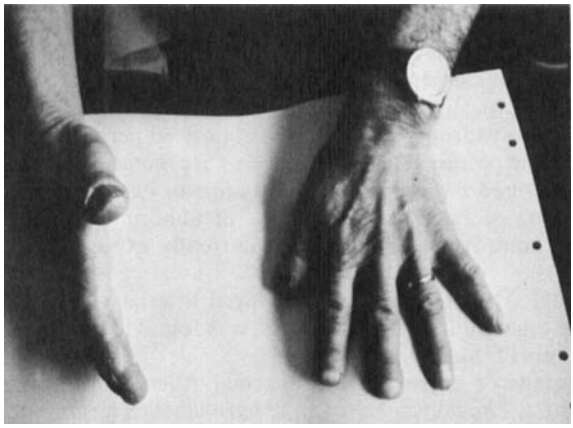


FIGURE 1. Finger shortening and pseudoclubbing in vinyl chloride worker.

TABLE 11
PSEUDOCLUBBING OF FINGERS AMONG 354 VC WORKERS

Duration of Exposure (yr)	Pseudoclubbing of Fingers		Total
	Current exposure	Past exposure	
≷2	2/36	2/25	4/61 (6.5%)
2.1–5	3/62	0/13	3/75 (4.0%)
5.1–10	3/47	3/15	6/62 (9.7%)
10.1–20	7/77	2/27	9/104 (8.6%)
20+	7/45	2/7	9/52 (17.3%)
			31/354 (8.75%)*

* In 25 cases, signs/symptoms of peripheral vascular disease; in 8 cases, typical Raynaud's syndrome.

TABLE 12
SKIN CHANGES IN 354 VC-EXPOSED WORKERS

Duration of Exposure (yr)	Total No. Examined	Skin Changes*
≷2	61	4 (6.5%)
2.1–5	75	2 (2.6%)
5.1–10	62	3 (4.8%)
10.1–20	104	8 (7.7%)
20+	52	6 (11.5%)
Total	354	23 (6.4%)

* Raynaud's syndrome was present in 9 cases.

drome which had gradually faded, while pseudoclubbing had persisted or even progressed.

Skin changes (TABLE 12) involving the fingers, hands, forearms, and sometimes face, were found in 23 examined workers. The fingers and hands appeared to be slightly edematous, the skin was thickened, tense and stiff, with decreased elas-

TABLE 13
PAIN IN JOINTS OF FINGERS AND HANDS*

Duration of Exposure (yr)	Total No. Examined	Fingers, Hands	Wrists
≤2	61	5 (8.1%)	1 (1.6%)
2.1–5	75	5 (6.7%)	
5.1–10	62	2 (3.2%)	1 (1.6%)
10.1–20	104	8 (7.7%)	3 (2.9%)
20+	52	8 (15.4%)	1 (2.0%)
Total	354	28 (8.0%)	6 (1.7%)

* Note: difference in prevalence not significant for workers with less than 10 years or more than 10 years of exposure.

TABLE 14
PAIN IN THE JOINTS OF FINGERS AND HANDS

	Total No. Examined	Pain in Finger and Hand Joints
Current exposure	267	24 (9.0%)
Past exposure	87	4 (4.6%)
Total	354	28 (8.0%)

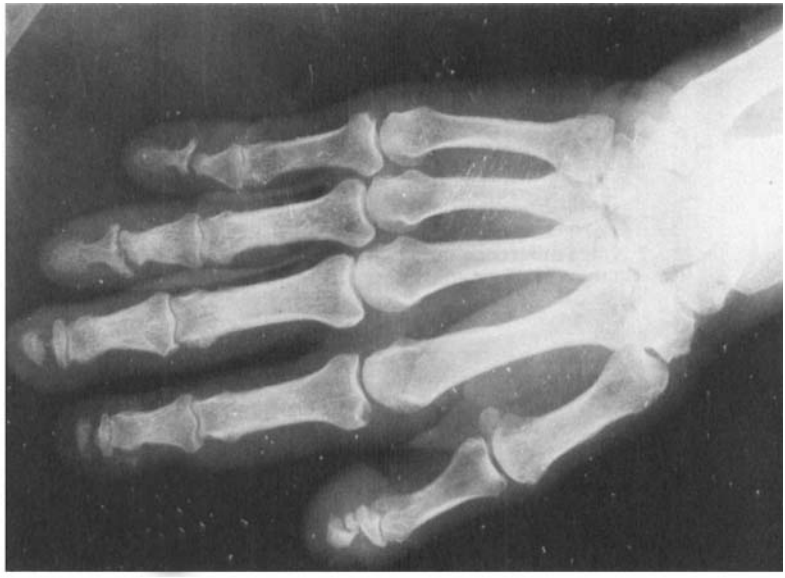
ticity and sparse folding. Well circumscribed plaque or band areas of scleroderma-like skin changes, as described by others, were not found. In 9 of the 23 cases in which skin changes were found, Raynaud's syndrome was also present.

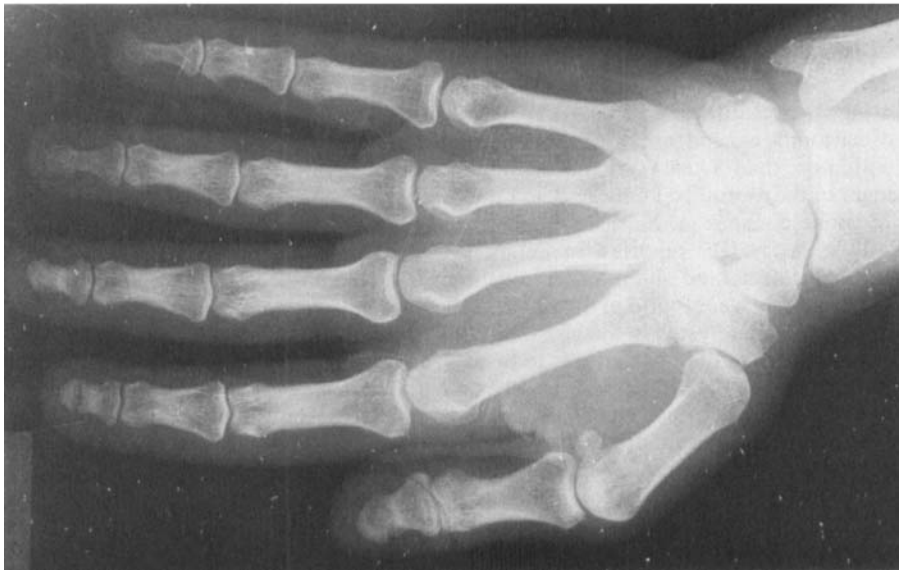
Pain in the small joints of the fingers and hands (TABLE 13), was a complaint in 28 (8 percent) of cases and was found mainly in workers with current exposure, even of short duration (TABLE 14). There was no special trend regarding pain in other joints, except for the wrists, where most of the cases were found in workers with more than 5 years of exposure. There were no symptoms suggesting involvement of the sacroiliac joints, and no radiologic evaluation was undertaken.

Bone changes in the distal phalanges (FIGURES 2 and 3) of fingers and toes will be separately reported in detail. While slight changes, such as marginal cortical defects and slight tuft resorption were seldom seen, transverse defects and fractures were found in only 4 cases.

We were interested in the possibility that hypertension (TABLE 15) might be of importance. We did not find this to be so. The overall prevalence of hypertension (as defined by WHO criteria) was 12 percent. There was no correlation with peripheral vascular impairment in the hands and feet. Abnormal urinary findings were not prominent either (TABLE 16).

The *liver* was found to be slightly or moderately enlarged in 15 percent of the cases [1 to 2 finger breadth below the right costal margin; 11 to 13 cm vertical span (TABLE 17)]; this finding was more frequent in workers with longer duration of exposure. Only in one case was the liver found to be markedly enlarged. The inferior pole of the spleen was palpable in 12 (3.4 percent) cases; again, only one person had *marked* splenomegaly. *There was a highly significant difference in the prevalence of enlarged liver in workers with more than 5 years of exposure as compared with those with shorter exposure.* The same comparison for splenomegaly did not show a statistically significant difference. According to the past medical history, a diagnosis of cirrhosis of the liver had been made previously in 5 cases. Esophageal





FIGURES 2 AND 3. X-ray views of hands of vinyl chloride workers, demonstrating bone alterations of distal phalanges.

TABLE 15
HYPERTENSION AMONG 354 VC WORKERS*

Duration of Exposure (yr)	Exposure	Hypertension			Total
		Systolic	Diastolic	Systolic and diastolic	
≦2	36 Current	0	0	2	2
	25 Prior	0	1	2	3
2.1–5	62 Current	1	0	2	3
	13 Prior	1	0	0	1
5.1–10	47 Current	1	0	2	3
	15 Prior	0	1	1	2
10.1–20	77 Current	3	2	4	9
	27 Prior	3	1	2	6
20+	45 Current	3	5	4	12
	7 Prior	0	0	2	2
Total	354	12	10	21	43 (12%)

* Note: workers with hypertension had no greater prevalence of peripheral vascular changes in hands and feet. Elevated BUN present in only 3 instances.

TABLE 16
ABNORMAL URINE FINDINGS AMONG 354 VC WORKERS

Duration of Exposure (yr)	Current Exposure	Protein 1+	RBC	Casts
≦2	36 Current	1	0	2
	25 Prior	2	0	0
2.1–5	62 Current	2	0	2
	13 Prior	1	0	0
5.1–10	47 Current	1	1	1
	15 Prior	0	1	0
10.1–20	77 Current	1	6	0
	27 Prior	1	1	1
20+	45 Current	1	3	0
	7 Prior	0	0	0
Total	354	10	12	6

TABLE 17
HEPATOSPLENOMEGALY AMONG 354 VC WORKERS

Duration of Exposure (yr)	Total No. Examined	Enlarged Liver*	Enlarged Spleen†
≦2	61	4 (6.5%)	1 (1.6%)
2.1–5	75	5 (6.7%)	2 (2.7%)
5.1–10	62	7 (11.3%)	2 (3.2%)
10.1–20	104	20 (19.0%)	3 (2.9%)
20+	52	17 (32.7%)	4 (7.7%)
Total	354	53 (15.0%)	12 (3.4%)

* Difference in prevalence of enlarged liver in workers exposed for less than 5 years as compared to those exposed for more than 5 years. $\chi^2 = 12.107$; $p < 0.001$.

† For enlarged spleen $\chi^2 = 0.945$; N.S.

TABLE 18
ABNORMAL LIVER FUNCTION TESTS AMONG 354 VC WORKERS

Duration of Exposure (yr)	Total No. Examined	Bilirubin >1.1	SGOT >50	SGPT >36	LDH >225	AP* >86
≤2	61	2	3	5	0	9 12.6%
2.1–5	75	5	4	7	0	7 9.3%
5.1–10	62	7	3	5	4	11 17.7%
10.1–20	104	2	6	8	3	19 18.2%
20+	52	5	4	6	1	13 25.0%
Total	354	21 (6%)	20 (6%)	31 (9%)	8 (2.3%)	59 (16.6%)

* Prevalence of elevated alkaline phosphatase (AP) significantly higher in workers with more than 5 years of exposure than in those with less than 5 years of exposure. $\chi^2 = 3.84$; $p = 0.05$.

varices had been diagnosed in 1 patient who had undergone surgery, including portocaval shunt, 12 years before the present examination, with good clinical result.

Abnormal liver function tests (TABLE 18) were found in small percentages (6 percent for bilirubin and SGOT, 9 percent for SGPT), *except* for *alkaline phosphatase* which was elevated in 59 (16.6 percent of cases). Duration of exposure correlated with an increase in the prevalence of elevated alkaline phosphatase, especially in workers with more than 5 years of exposure.

There was a higher percentage of abnormal liver tests in workers with current exposure than in those with past exposure (TABLE 19). Alkaline phosphatase was an exception, since similar proportions of abnormal tests were found in persons with current *or* prior exposure.

The best correlation between clinical findings of hepatomegaly and/or splenomegaly and abnormal liver function tests was found to be that with elevated alkaline phosphatase (TABLE 20); 41 percent of those with such clinical abnormalities had increased alkaline phosphatase.

Hematologic abnormalities were scant in our study. Thrombocytopenia, a frequent finding in the German studies, was present in only one of the examined workers (TABLE 21).

The possible contributory effect of significant ethanol intake was carefully considered (TABLE 22); no trend as related to duration of exposure could be found for ethanol intake.

In one-third of the cases with clinical liver and/or spleen changes significant ethanol intake could have been a factor (TABLE 23), and in 25 percent of the cases

TABLE 19
ABNORMAL LIVER FUNCTION TESTS AMONG 354 VC WORKERS CURRENTLY OR PREVIOUSLY EMPLOYED

Liver Function Test		Current Employment (267)	Prior Employment (87)	Hepatosplenomegaly, Hepatic Tenderness (66)
Bilirubin	>1.1	18 (6.7%)	3 (3.6%)	—
SGOT	>50	17 (6.4%)	3 (3.6%)	6/20 (30.0%)
SGPT	>36	26 (9.7%)	5 (5.7%)	8/31 (26.9%)
LDH	>225	6 (2.4%)	2 (2.3%)	—
Alkaline phosphatase	>86	43 (16.0%)	16 (18.0%)	27/59 (45.8%)

TABLE 20
RELATION OF HEPATO- AND/OR SPLENOMEGALY TO ELEVATED ALKALINE PHOSPHATASE AMONG 354 VC WORKERS

Duration of Exposure (yr)	No.	Enlarged Liver and/or Spleen or Hepatic Tenderness	Elevated Alkaline Phosphatase
≦2	61	7	3 (43%)
2.1–5	75	7	1 (14%)
5.1–10	62	10	4 (40%)
10.1–20	104	20	10 (45%)
20+	52	20	9 (45%)
Total	354	64	27 (41%)

TABLE 21
HEMATOLOGIC CHANGES IN 354 VC WORKERS

Duration of Exposure (yr)	Total No. Examined	Thrombocytopenia <150,000	Leucopenia		Hemoglobin <14 g
			<4,000	4,000–5,000	
≦2	61		1	8	1
2.1–5	75		3	6	1
5.1–10	62		1	2	
10.1–20	104			6	4*
20+	52	1		6	2*
Total	354	1 (0.3%)	5 (1.4%)	28 (7.8%)	8 (2.2%)

* Persons with past history of gastrointestinal bleeding.

TABLE 22
ALCOHOL INTAKE IN 354 VC-EXPOSED WORKERS

Duration of Exposure (yr)	Total No. Examined	Alcohol Intake			Total
		++ (1–2 qt/wk)	+++ (2–3 qt/wk)	++++ Known alcoholic	
≦2	61	10	5	0	15 (24.6%)
2.1–5	75	11	4	1	16 (21.2%)
5.1–10	62	13	0	0	13 (21%)
10.1–20	104	9	4	0	13 (12.5%)
20.1+	52	10	1	1	12 (23%)
Total	354	53 (15%)	14 (3.9%)	2 (0.6%)	69 (19.5%)

TABLE 23
SIGNIFICANT ALCOHOL INTAKE AND LIVER CHANGES (CLINICAL)

Duration of Exposure (yr)	Total No. Examined	Enlarged Liver and/or Spleen or Hepatic Tenderness	Cases with Significant Alcohol Intake
≦2	61	7 (11.5%)	2 (3.3%)
2.1–5	75	7 (9.4%)	3 (4.0%)
5.1–10	62	10 (16.0%)	4 (6.5%)
10.1–20	104	21 (20.0%)	4 (3.8%)
20+	52	20 (38.0%)	8 (15.0%)
	354	65 (18.2%)	21 (6.2%)

TABLE 24
ELEVATED ALKALINE PHOSPHATASE AND SIGNIFICANT ALCOHOL INTAKE

Duration of Exposure (yr)	Total Examined	Elevated Alkaline Phosphatase	Significant Alcohol Intake
≦2	61	9 (12.6%)	1 (1.6%)
2.1–5	75	7 (9.3%)	1 (1.3%)
5.1–10	62	11 (17.7%)	6 (9.7%)
10.1–20	104	19 (18.2%)	2 (1.9%)
20+	52	13 (25%)	4 (7.7%)
Total	354	59 (16%)	14 (3.9%)

TABLE 25
HEPATO- AND/OR SPLENOMEGALY AND SIGNIFICANT ALCOHOL INTAKE*

Duration of Exposure (yr)	Total No. Examined	Significant Alcohol Intake		No Significant Alcohol Intake	
		Total no.	Enlarged liver and/or spleen	Total no.	Enlarged liver and/or spleen
≦2	61	15	2 (13.4%)	46	7 (15.0%)
2.1–5	75	16	2 (12.5%)	59	4 (6.8%)
5.1–10	62	13	4 (30.5%)	49	5 (10.2%)
10.1–20	104	13	4 (30.5%)	91	17 (18.7%)
20+	52	12	8 (75.0%)	40	12 (30.0%)
Total	354	69	20 (29.0%)	285	45 (16.0%)

* Difference in prevalence of enlarged liver and/or spleen between the group with alcohol intake and those without alcohol intake nonsignificant for workers with less than 10 years of exposure. $\chi^2 = 1.951$; N.S. Significant for workers with more than 10 years of exposure. $\chi^2 = 7.248$; $p < 0.01$.

with increased alkaline phosphatase was there a history of significant intake (TABLE 24). Further, the prevalence of an enlarged liver and/or spleen in persons with and without significant ethanol intake was compared (TABLE 25). Although there was no statistically significant difference in workers with less than 10 years of exposure, in those with more than 10 years of exposure, there was a higher prevalence of enlarged liver and/or spleen in persons with a significant ethanol intake. A multiple factor additive interaction may be considered.

Liver function tests were also analyzed in relation to ethanol intake (TABLE 26). There was no significantly higher prevalence of elevated alkaline phosphatase, bilirubin, or LDH in the group with significant ethanol intake. However, high SGOT or SGPT values were significantly more frequent in this group. *It is of interest that elevated alkaline phosphatase, the most frequent biochemical abnormality found, did not correlate with ethanol intake, while there was a significant correlation with duration of vinyl chloride exposure.*

Many of the examined workers (TABLE 27) gave a past medical history of "gastritis," ulcer (gastric and duodenal), upper gastrointestinal bleeding (most often attributed to ulcer), and gallbladder disease. However, it is difficult to know whether such symptoms were more common than might be expected in a similar group without VC exposure.

Out of the 112 workers with such past medical history, there were 28 (25 percent) who were found to have enlarged liver and/or spleen (TABLE 28): the

TABLE 26
ALCOHOL INTAKE AND ABNORMAL LIVER FUNCTION TESTS

	Total No. Examined	Alkaline Phosphatase	Bilirubin	SGOT	SGPT	LDH
Significant alcohol intake	69	14 (20.3%)	1 (1.4%)	9 (13.0%)	11 (16.0%)	2 (2.9%)
Nonsignificant alcohol intake	285	45 (15.8%)	20 (7.0%)	11 (3.9%)	20 (7.6%)	6 (2.1%)
Total	354	59 (16.0%)	21 (6.0%)	20 (6.0%)	31 (9.0%)	8 (2.3%)
		$\chi^2 = 0.810$; N.S.	$\chi^2 = 3.087$; N.S.	$\chi^2 = 8.790$; $p < 0.01$	$\chi^2 = 5.537$; $p < 0.01$	N.S.

TABLE 27
GASTROINTESTINAL DISEASE (BY HISTORY) IN 354 VC-EXPOSED WORKERS

Diagnosis	No.	%
"Gastritis"	47	13
Ulcer (gastric or duodenal)	31 } 52	9 } 15
Ulcer and upper GI bleeding	21 }	6 }
Gallbladder disease	13	3.6
Total	112	

TABLE 28
GASTROINTESTINAL DISEASE (BY HISTORY) AND ENLARGED LIVER AND/OR SPLEEN (CLINICAL EXAMINATION)

Diagnosis	Total No.	Enlarged Liver and/or Spleen
"Gastritis"	47	8 (17.0%)
Ulcer (gastric or duodenal)	31	7 (22.6%)
Ulcer and upper GI bleeding	21	8 (38.0%)
Gallbladder disease	13	5 (38.4%)

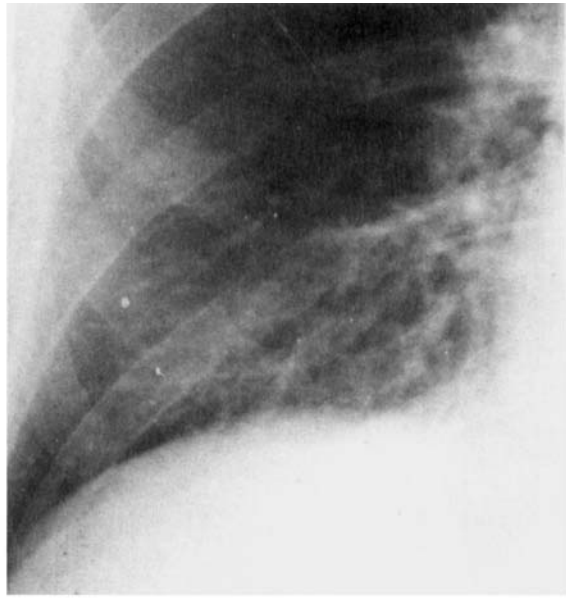
TABLE 29
CHEST X-RAY ABNORMALITIES* AMONG 142 VC WORKERS

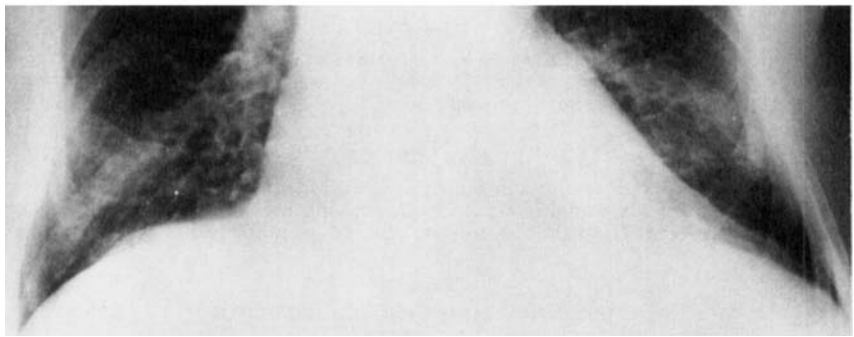
Duration of Exposure (yr)	Current Exposure	X-Ray Findings	
		Normal	Abnormal
≤2	13 Current	12	1 (5.2%)
	6 Prior	6	0
2.1–5	32 Current	25	7 (23.0%)
	3 Prior	2	1
5.1–10	19 Current	18	1 (11.0%)
	8 Prior	6	2
10.0–20	32 Current	17	15 (48.6%)
	5 Prior	2	3
20+	23 Current	15	8 (33.3%)
	1 Prior	1	0
Total	142	104	38 (27.0%)

* Data incomplete.

percentage was 38 percent for those with past upper gastrointestinal bleeding and 38.4 percent for those with a history of gallbladder disease. In the other 242 workers without such a past medical history, 29 (12 percent) were found to have an enlarged liver and/or spleen.

Chest x-rays of 142 examined workers were available at the time that this report was prepared. In some of the cases linear reticular and less often nodular changes were found in the middle and lower lung fields (TABLE 29; FIGURES 4–6). No relationship was observed with smoking or chronic bronchitis (TABLES 30 and 31). The significance of these changes is difficult to evaluate at this point since most of the workers had been exposed to *particulate polyvinyl chloride resin* as well as to vinyl chloride. Three of those with abnormal chest x-ray findings had





FIGURES 4 AND 5. X-ray views of lung bases of vinyl chloride workers, showing increased linear markings and small irregular opacities.

had previous dust exposure (in coal mines for periods ranging from 4 to 9 years). There was not relationship between chest x-ray changes and liver changes, but signs and symptoms of peripheral vascular impairment (Raynaud's syndrome, cyanosis, pseudoclubbing, positive Allen test) (TABLE 32) were found in more than half (53 percent) of the cases with abnormal chest x-ray findings. The prevalence of Raynaud's syndrome was significantly higher in the group with abnormal chest x-rays.

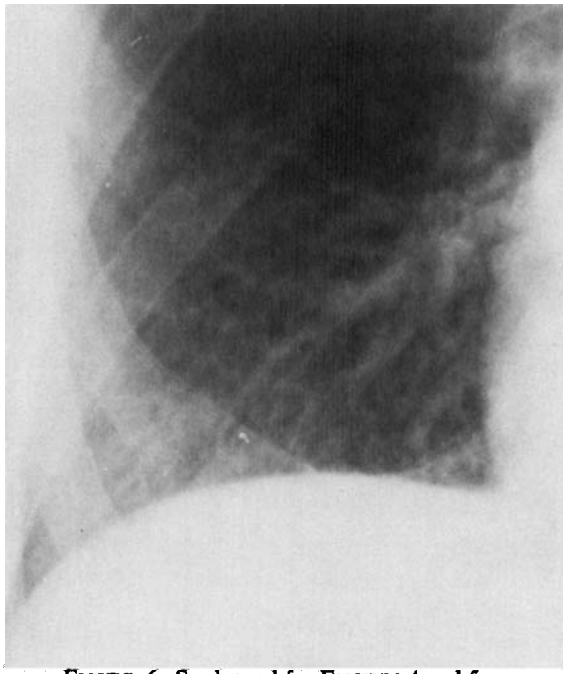


FIGURE 6. See legend for FIGURES 4 and 5.

TABLE 30
CHEST X-RAY AND SMOKING

Chest X-Ray	Total No.	Smokers	Ex-smokers	Nonsmokers
Normal	104	53 (51%)	23 (22%)	28 (27%)
Abnormal	38	25 (66%)	6 (16%)	7 (18%)

* Prevalence of abnormal chest x-ray in persons with history of smoking not significantly different from that in nonsmokers. $\chi^2 = 1.083$; N.S.

TABLE 31
CHEST X-RAY AND CHRONIC BRONCHITIS

Chest X-Ray	Total No.	History of Chronic Bronchitis	No History of Chronic Bronchitis
Normal	104	20 (21%)	84 (79%)
Abnormal	38	8 (19%)	30 (81%)

TABLE 32
ABNORMAL CHEST X-RAY AND ABNORMAL PERIPHERAL CIRCULATION

Chest X-Ray	Total No.	Raynaud's Syndrome	Cyanosis	Pseudo-clubbing	Abnormal Allen Test
Normal	104	5 (4.8%)	9 (8.6%)	8 (7.7%)	20 (19%)
Abnormal	38	7 (18.4%)	6 (16.0%)	7 (18.4%)	13 (34%)
		$\chi^2 = 6.667$; $p < 0.01$			$\chi^2 = 3.501$) N.S.

Discussion and Conclusions

Our findings confirm the broad outlines of the clinical syndromes reported by other investigators.

In the examined group relatively high VC exposure had occurred in the past, and symptoms of acute prenarcotic effects were reported by more than half of the examined workers.

Clinical signs and symptoms of abnormal peripheral circulation in the fingers and toes were quite frequent, with cyanosis present in 13 percent, excessive sensitivity to cold in 18 percent and numbness and tingling of the fingers in 24 percent of cases. A typical Raynaud's syndrome was present in 5.7 percent of cases. An abnormal Allen test, indicating delayed arterial circulation in the areas supplied by the ulnar and/or radial arteries was found in 94 (26.6 percent) of the examined workers. The prevalence of all these abnormalities increased with length of VC exposure.

Hepatomegaly was a finding in 15 percent of the examined workers, while splenomegaly was found in 3.4 percent. Cirrhosis of the liver had been previously diagnosed in 5 workers, and in one esophageal varices with upper gastrointestinal bleeding had led to surgery including portocaval shunt.

Alkaline phosphatase was the test which was most frequently found to be abnormal and showed the best correlation with clinical findings.

Hepatomegaly and elevated alkaline phosphatase were significantly more frequent in workers with longer VC exposure.

Radiologic pulmonary changes, linear reticular and nodular opacities in the lower and middle lung fields were found in a number of cases; the prevalence of these changes was higher with longer duration of exposure, and there was a significant association with peripheral circulation abnormalities. The evaluation of these pulmonary changes is still in progress.

Our results indicate that liver involvement and probably lung involvement in PVC workers are significant and should be given full attention in the medical surveillance of workers with past exposure.

Future exposure to vinyl chloride should be controlled in order to prevent development of all adverse effects, including the carcinogenic effect.

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DISCUSSION

MR. J. SNYDER (*Hoffmann-LaRoche Company, Nutley, N.J.*): We had the opportunity to do carcinoma embryonic antigen (CEA) levels on the same group that was examined by Dr. Lilis. The report we will make now is very preliminary; a complete report will be made later.

In our study of CEA levels in a "normal, healthy" population of 1,747 individuals, we observed 9.2 percent with levels over 2.5 ng/ml. A value above 2.5 ng/ml is considered abnormal. Further analyzing this group by smoking habits, we found 3 percent of nonsmokers had levels above 2.5 ng/ml, 7 percent of former smokers and 19 percent of current smokers also had elevations over 2.5 ng/ml.

In a separate study, CEA titer elevations in a group of smokers were positively correlated with atypical sputum cytology.

In contrast with the CEA levels in our normal, healthy study group, we observed in the polyvinyl chloride production workers so far examined (all actively working) 15 percent of nonsmokers, 17 percent of former smokers, and 39 percent of current smokers with CEA levels above 2.5 ng/ml. These differences between the normal group and the PVC workers are statistically significant at the $p < 0.005$ level for nonsmokers, $p < 0.01$ for former smokers, and $p < 0.005$ for current smokers.

We further analyzed the PVC group by the duration of their PVC work experience. We divided the workers into 2 groups: 10 years or less of PVC exposure and 10.1 years or more of exposure. Of the nonsmokers who had been exposed to PVC 10 years or less, 11 percent had levels above 2.5 ng/ml, whereas in the group of nonsmokers who had greater than 10.1 years of exposure, 25 percent had elevations above 2.5 ng/ml. Among the former smokers, the respective elevations for less than and more than 10 years of exposure were 16 percent and 17 percent (obviously no difference). In the current smokers, 26 percent of those with less than 10 years of exposure had CEA elevations above 2.5 ng/ml, and 34 percent of those with greater than 10 years had levels above 2.5 ng/ml.

There are other things besides cancer that will cause elevation of CEA, including alcoholic cirrhosis and active inflammatory bowel disease.

Due to the small number of PVC workers so far examined, and the limited data available, we cannot draw any positive conclusions. However, these preliminary results are interesting. We are continuing to gather and analyze data as they become available and will make a more definitive report at a later date.