Vinyl chloride

Ten Cases of Angiosarcoma of the Liver in Shawinigan, Quebec

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Ten cases of angiosarcoma of the liver have been diagnosed in Shawinigan, Quebec since 1955. All have occurred in men who worked in a vinyl chloride polymerizing plant. Cigarettes and alcohol do not seem to be associated with this tumor. The amount of vinyl chloride to which these people were exposed, according to information obtained through questionnaires, appears elevated. Angiosarcoma of the liver is accompanied by a fibrosis of the liver which may precede its appearance. In describing the Canadian cases of angiosarcoma, this study attempts to shed more light upon the causal relationship between vinyl chloride monomer and angiosarcoma of the liver and thus to provide some clues to understanding the pathogenesis of this disease.

In January 1974, three cases of angiosarcoma of the liver were discovered among workers of a chemical plant.[1] This finding appeared abnormal and the agent suspected of being responsible for the disease was identified as vinyl chloride monomer (VCM). Since then, many reports on the occurrence of this cancer among vinyl chloride workers have appeared around the world[2-5] and the United States Occupational Safety and Health Administration has enacted a new threshold limit value for concentration of this chemical in the air of the working environment.[6]

Ten cases of angiosarcoma of the liver were diagnosed among workers of a vinyl chloride polymerizing plant in Shawinigan, Quebec. This is the largest number of cases ever to take place in a single plant. The present study describes occupational history, drinking and smoking habits and some histological features of these Canadian cases. Data on some of these Canadian cases jointly with cases of angiosarcoma from the United States have already been described in another article by one of the authors.[7] Since more accurate and complete information was retrieved on the Canadian cases, it is being presented separately in the present article.

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Methods

Case Finding. — A search for cases of angiosarcoma of the liver beginning as far back as 1955 and extending over two decades was carried out by scrutinizing files of the regional hospitals in the Shawinigan vicinity. All cases of primary tumors of the liver were collected and the histological material (slides, biopsy reports, autopsy reports) were reviewed for the presence of angiosarcoma. To confirm the diagnosis of angiosarcoma of the liver, the cases were submitted to consultants from the United States familiar with this disease.

Occupational History. — The questionnaires used to obtain a detailed occupational history of each case culled information concerning past and present residence, medical history, smoking and drinking habits along with past occupations and employers in chronological order. The answers to most of questionnaires were given by spouses of the men who died from the disease. In one instance, however, the answers were given by the sister and brother-in-law, and in another, by the worker himself. Two former co-workers of the men who died of an angiosarcoma of the liver confirmed and completed the information obtained through the families.

Plant Description. — The Shawinigan vinyl chloride plant started operating in 1943. At that time, it produced and polymerized vinyl chloride monomer. Later in the 1950s, it stopped producing VCM and kept operating the polymerization unit. The workforce varied from 100 to 350 workers. At the moment, it employs 250 men. Production of PVC has fluctuated with time. Present production is estimated at 50 million pounds annually. Exposure to VCM in the working atmosphere, though not documented, is believed to have been very high in the past. Sharp improvement has taken place in recent years and it is estimated at less than 3 ppm at the moment.

Results

Table 1 shows the age at death, the smoking habits and alcohol consumption for the ten cases of angiosarcoma of the liver diagnosed in the Shawinigan region over the last two decades. All

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Vinyl Chloride

Original Articles

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Effect of Occupational and Nonoccupational Factors on the Respiratory System of Vinyl Chloride and Other Workers

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There are suggestions in the literature that vinyl chloride (VC) acts as a lung irritant. Respiratory questionnaires and lung function tests were administered to 174 chemical (VC) workers, 81 polyvinyl chloride (PVC) workers, 72 former VC workers, and 136 rubber workers, and 68 maintenance workers with exposure to VC, PVC, and rubber. Except for small airways obstruction associated with rubber, increased respiratory symptoms and decreased pulmonary function were not associated with working in chemicals, plastics, or rubber. Some increases in baseline pulmonary function were associated with VC exposure. Acute reductions in pulmonary function were observed in smokers working in chemicals, plastics, and rubber. Heavier cigarette smokers over 40 years of age had the most adversely affected respiratory system.

Work was not associated with chronic respiratory effects, but all exposure groups experienced some acute respiratory insult.

At high exposures, vinyl chloride (VC) is a nervous system depressant, and in fact was investigated as a possible anesthetic, but was not used because of circulatory and cardiac effects at concentrations of 10-20 vol. %.[1] In the late 1960's, acroosteolysis was associated with the polymerization of VC to form polyvinyl chloride (PVC).[2-4] Early in 1974, four fatal cases of angiosarcoma of the liver were reported in reactor operators working in a VC-polymerization plant.[5] Subsequently the disease has been discovered among VC workers all over the world. Experimental and epidemiologic studies suggest that exposure to VC may carry an increased risk of respiratory impairment.[6-14] As a result, the Occupational Health Studies Group (OHSG) at the University of North Carolina and the National Institute of Occupational Safety and Health (NIOSH) and CDC jointly carried out an epidemiologic study of VC-PVC workers. A part of this study was the investigation of respiratory function and symptoms in currently employed VC and PVC workers, former VC workers, and a sample of control rubber workers employed in the same plant.

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Methods and Materials

The plant under study has three major divisions. The chemical plant produces primarily polyvinyl chloride (PVC) resin, although some copolymers such as vinylidene chloride and styrene-butadiene are also produced. The polymers are either shipped or used in the Film and Sheeting division of this same plant in the production of plastic products. Film and Sheeting division (plastics) is in a building adjacent to the Chemical Plant, which also contains the Rubber Products division manufacturing primarily tires and tubes. All workers currently employed in the VC-PVC plants were invited for examination. A sample of 136 rubber workers from cleaner areas of the rubber division (i.e., tire building, final inspection, shipping and receiving) and without prior exposure to either VC or PVC, were selected and group-matched with the VC workers on age and sex. A total of 71 former VC workers and 68 maintenance workers were also examined. The response rate varied from a low of 62% in rubber workers to 77% in chemical workers. Clinical, smoking and occupational histories, complete physical examinations, chest roentgenograms, sputum cytology, symptoms, blood and urine chemistries were obtained on all 531 workers, and will be reported elsewhere.

The British Medical Research Council respiratory questionnaire was administered by trained medical interviewers. Each worker performed a minimum of five forced exhalations, seated and with a noseclip. The three best performances were selected on the basis of forced expiratory volume in 1 second (FEV) and forced vital capacity (FVC) within 10% of each other, and acceptable reproducibility of the flow-volume curve. In addition to FEV and

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FVC, expired flow at 25% (FEF_{25}), 50% (FEF_{50}), and 75% (FEF_{75}) of exhaled FVC were obtained. At least three single-breath nitrogen tests were also performed. Recommended procedures and selection criteria were followed for obtaining closing volume (expressed as ratio of closing volume to vital capacity, CV/VC).[15] In addition, a random sample of fifty-six VC, PVC and rubber workers were administered lung function tests before work and again after work. The difference in flow rates is calculated as after - before/mean with afterwork flow rates measured using the maximum pre-exposure FVC.

The following questions were of interest in this study:

1. What are the effects of work on respiratory symptoms and function? Symptoms and baseline lung function were analyzed according to three work exposure categories: (a) current job (hourly VC salary VC, PVC, rubber, maintenance, former chemical); (b) all jobs, past and present (only in VC, only in PVC, only in rubber, or in a combination of the three). In this mixed exposure group an analysis of covariance was used to sort out the contributions of the VC, PVC, and rubber work experience to baseline pulmonary function; (c) man-months of exposure to VC: All VC jobs were given a high (10), medium (3) or low (1) exposure rating. Time (in months) spent in each job multiplied by the exposure index provided a cumulative exposure to VC. This cumulative exposure score (CES) was then compared to baseline pulmonary function.

The association of dose (years worked in the exposure categories or CES) and baseline lung function were assessed by calculating lung function regression equations for each smoking category of the total population. Then, within each exposure group, actual values of each smoking category were expressed as a percentage of expected values for all workers in that same smoking category. In this way, the effect of work exposure on lung function was adjusted for differences in age, height and smoking between exposure categories.

2. What are the potential hazards of work exposure as measured by changes in pulmonary function over a work shift (ΔPF)? A reduction in lung function suggests the likelihood of some harmful exposure in the working environment.

3. Are symptoms rates and lung function parameters comparable to other occupation groups? Because the PVC and rubber control groups were themselves exposed to varied levels of dust and fumes, comparisons with other studies are made.

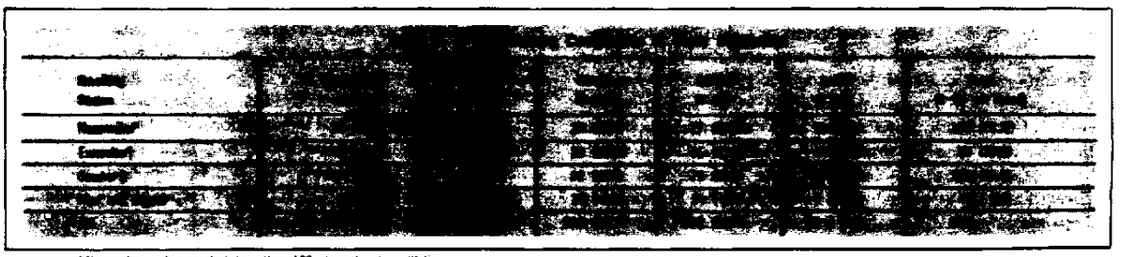
Results

The age-smoking distribution of the population is shown in Table 1. Slightly over half of the population were smokers, 20% nonsmokers, and 16% exsmokers. The exsmokers were older than the other smoking categories, with proportionally fewer exsmokers in the $\leq$39 year age group. Smokers and nonsmokers had approximately the same distribution in all age groups, although a higher proportion of nonsmokers were older, and a higher proportion of smokers were in the middle age groups. None of the light smokers (< 1 pack/day) smoked more than 25 pack-years, and they were equally distributed in the < 25 pack-years category. Most (61%) of the heavy smokers ($\geq$1 pack/day) were in the > 25 pack-year category; 25% smoked 10-25 pack-years, and 14% < 10 pack-years.

Table 2 shows the distribution of symptoms related to smoking and age. Prevalence of cough, phlegm, and persistent cough and phlegm did not increase with age. Breathlessness increased slightly but steadily with age, with the oldest age group reporting a rate of breathlessness 2.5 times greater than the youngest age group. Smoking had a strong effect that was dose-related for all respiratory symptoms. Light smokers (< 1 pack/day) had the same symptom rate for cough, phlegm, and persistent cough and phlegm as exsmokers and pipe or cigar smokers. Exsmokers, pipe, cigar, and < 1 pack/day smokers had similar rates of breathlessness.

Because of the potential confounding effects of age and smoking, comparison of symptoms in each exposure category were adjusted for smoking and age differences. Table 3 shows the prevalence of respiratory symptoms according to current job. The salaried chemical workers consistently had the lowest prevalence for all symptoms. Plastics, former chemical, and maintenance workers reported the highest rates for cough, phlegm, and persistent cough and phlegm; rubber and hourly chemical workers were intermediate for these symptoms. All workers except the salary chemical workers observed similar rates of breathlessness.

Table 4 reports the age and smoking adjusted prevalence of respiratory symptoms in workers working only in the rubber division, only in plastics, and only in the chemical plant. Maintenance workers move back and forth among chemical, plastics, and rubber, with no epidemiologically appropriate records kept of time spent in any of these areas. The mixed group comprised those who had worked in two or more exposure categories. The plastics only and chemical plant only workers had marked reductions in reported symptoms when compared to all currently employed workers in these same categories. Symptom rates for the mixed group were slightly higher than observed in the total population, and similar to the former chemical group. Those working only in chemical, plastics, or rubber appear to be a select group of healthier workers. A high proportion of those with symptoms in current job categories had a mixed exposure of rubber, chemicals and/or plastics.



*Nonsmoker = has smoked less than 100 cigarettes in a lifetime.

†Exsmoker = has stopped smoking for more than 1 year, and does not now smoke a pipe or cigar.

‡Smoker = has smoked more than 100 cigarettes in a lifetime, and has smoked within the last year. Pipe or cigar smokers who also smoke cigarettes are included in this category

§Pipe and Cigar = all those who smoke a pipe or cigar now, but do not smoke cigarettes or have not smoked cigarettes for a year or more.

Percentages in the margenals are % of totals, percentages in cells are column percentages.

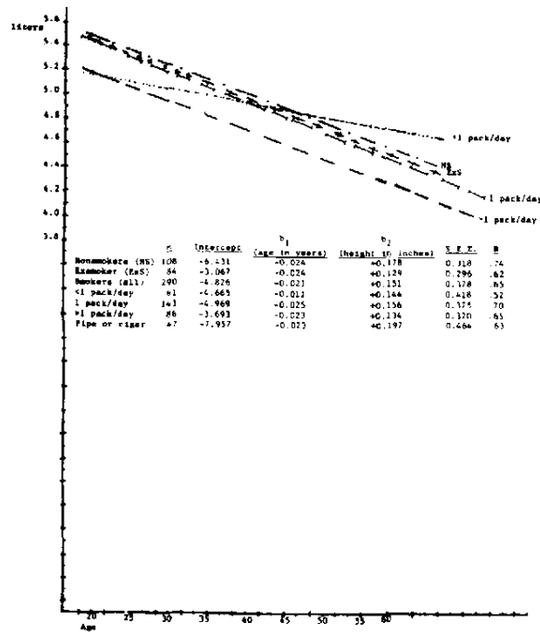
Smoking Category	N	Cough 1 & 2 %	Phlegm 1 & 2 %	Persistent Cough & Phlegm %	Breathlessness %
Nonsmoker	108 (20.3%)	5.6	8.3	2.8	11.1
Exsmoker	84 (15.8%)	7.1	13.1	6.0	19.3†
All smokers	292 (55.0%)	21.6	26.4	13.7	26.5†
< 1 pack/day	61 (11.5%)	9.8	13.1	1.6	23.3†
1 pack/day	143 (26.9%)	18.9	23.8	11.2	18.9
>1 pack/day	88 (16.6%)	34.1	30.8	26.1	40.9
Pipe and Cigar	47 (8.9%)	8.5	19.6	2.1	15.2†
All	531	14.9	19.2	9.2	21.2‡
Age Category					
< 29	107 (20.2%)	14.0	20.6	9.3	12.5‡
30-39	88 (16.6%)	15.7	15.7	9.0	19.1
40-49	162 (30.5%)	15.4	28.8	10.5	21.6
50-59	151 (28.4%)	14.6	18.5	7.9	26.5
> 60	22 (4.1%)	13.6	22.7	9.1	31.8

* = Scored by criteria from British Medical Research Council Respiratory questionnaire.
† = 1 missing
‡ = 3 missing

Figures 1-6 display the regressions of pulmonary function tests for the different smoking categories. Age and height significantly affected FEV and FVC values; age, but not height, was a statistically significant predictor of flow rates and closing volume (CV/VC). Heavy smokers (≥1 pack/day) had markedly reduced ventilatory capacity compared to other smoking groups (except for FVC where smoking did not significantly affect lung volume). Lung function values of exsmokers decreased at a rate intermediate between the heavy smoker and nonsmoker groups. Pipe or cigar smokers resembled nonsmokers for FEV, FEF_{50}, and FEF_{75}, but resembled exsmokers for FEF_{25-75} and closing volume (CV/VC). Except for CV/VC, the least reduction of ventilatory capacity was observed in the light smoker (< 1 pack/day) group. All smokers had similar functional reductions of CV/VC with increasing age. Current smoking behavior showed a better correlation with pulmonary function than did pack-years of smoking, and for this reason regressions based on current smoking categories were used in calculating predicted lung function values.

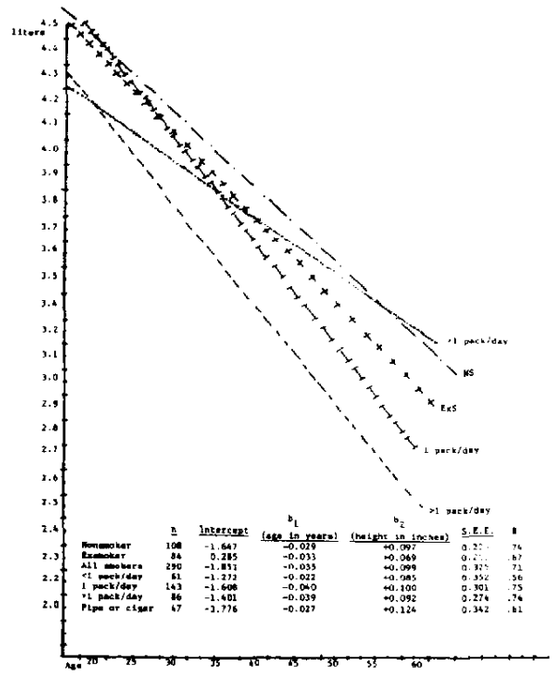
Table 5 summarizes the prevalence of impaired lung function as related to age and smoking. Except for FVC and CV/VC, pulmonary function impairment (see Table 5 for definitions) consistently increased with age; and for all parameters consistently increased with increased smoking. Impairment rates for FEF_{25-75}, FEF_{50}/FVC and CV/VC were significantly higher for smokers than nonsmoking categories; the smaller number of pipe or cigar smokers precluded them from achieving statistically significant differences. Age and smoking were then analyzed simultaneously. Regressions of pulmonary function with age (Figs 1-6) suggested that after about age 40, smokers of ≥1 pack/day clearly had lower lung function values than the other categories of smokers. As there was little difference in prevalence of impairment among exsmokers, nonsmokers and pipe or cigar smoker categories, they were combined into a nonsmoker category, divided into age groups above and below 40 years of age, and compared with cigarette smokers. Smokers and nonsmokers in the younger age group had similar rates of lung function impairment. Smokers over

* = 1 missing
† = 3 missing



	n	Intercept	b_1 (age in years)	b_2 (height in inches)	S.E.E.	R
Nonsmokers (NS)	108	-6.431	-0.024	+0.178	0.318	.74
Exsmoker (ExS)	84	-3.067	-0.024	+0.129	0.296	.62
Smokers (all)	290	-4.826	-0.021	+0.151	0.378	.65
<1 pack/day	61	-6.665	-0.011	+0.144	0.418	.52
1 pack/day	143	-4.969	-0.025	+0.156	0.375	.70
>1 pack/day	86	-3.693	-0.023	+0.134	0.320	.65
Pipe or cigar	47	-7.957	-0.023	+0.197	0.484	.63

Fig 1. — Prediction Equations for FVC in Total Population by Smoking.



	n	Intercept	b_1 (age in years)	b_2 (height in inches)	S.E.E.	R
Nonsmoker	108	-1.647	-0.029	+0.097	0.2[illegible]	.74
Exsmoker	84	0.285	-0.033	+0.069	0.[illegible]	.67
All smokers	290	-1.851	-0.035	+0.099	0.325	.71
<1 pack/day	61	-1.272	-0.022	+0.085	0.352	.56
1 pack/day	143	-1.608	-0.040	+0.100	0.301	.75
>1 pack/day	86	-1.401	-0.039	+0.092	0.274	.74
Pipe or cigar	47	-3.776	-0.027	+0.124	0.342	.61

Fig 2. — Prediction Equations for FEV_1 in Total Population by Smoking.

40 years of age had significantly increased impairment compared to their nonsmoking counterparts. A synergistic effect of age and smoking was not observed for FVC (impairment was not affected by age or smoking) and CV/VC (both young and old smokers had rates of impairment higher than nonsmokers at any age).

To preclude confounding effects of age, height, and smoking in assessing the importance of occupational exposure, mean percent pulmonary function for each job group was calculated by dividing individual pulmonary function values by predicted values derived from the appropriate smoking category, and calculating the mean. Smoking-adjusted impairment rates were directly adjusted using the smoking distribution of the standard (total) population.

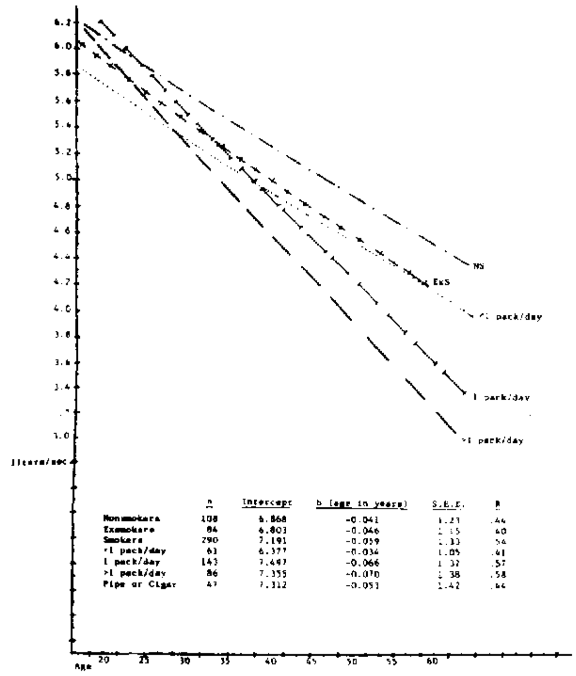
Baseline lung function as measured by mean percent predicted was the same in all current job groups. Table 6 summarizes the prevalence of impaired pulmonary function by current job. Former chemical workers tended to have the highest impairment, salary chemical workers the lowest. The other job categories generally had impairment rates between these extremes.

The effect of duration of exposure on lung function was then analyzed. Age, height, and smoking variables were adjusted in the manner previously described. Predictive equations were

Table 4. [illegible]

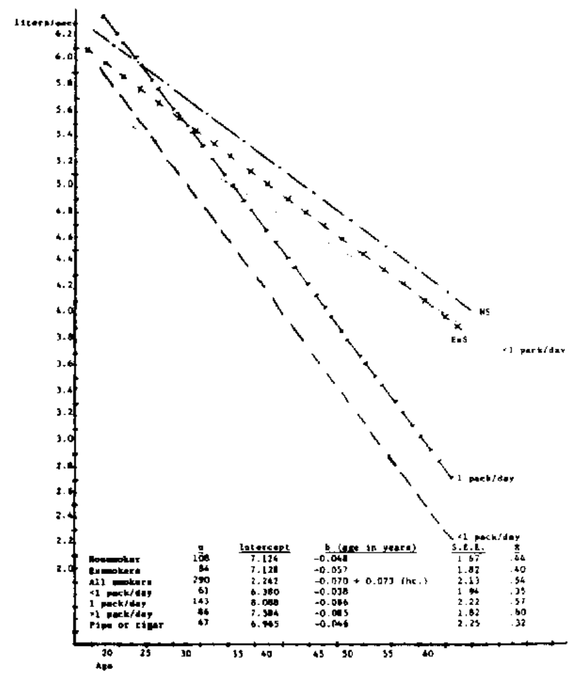
Symptom	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	All
	%	%	%	%	%	%
Cough 1 and 2	20.2	[illegible]	[illegible]	[illegible]	8.9	15.6
Phlegm 1 and 2	21.8	[illegible]	[illegible]	[illegible]	7.9	16.2
Persistent Cough and Phlegm	11.2	[illegible]	[illegible]	[illegible]	2.8	9.2
Bronchitis[illegible] (Grade 2, 3 4)	27.6*	21.3*	19.2	[illegible]	1.9*	21.2
N	217	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Age (years)	44.3	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	(11.8)					(12.3)
Height (in.)	69.5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	(2.5)					(2.5)
Weight (lbs.)	184.0	175.2 [illegible]	[illegible]	[illegible]	174.2 [illegible]	183.0
	(28.6)					(26.8)

* = 1 missing
† = 3 missing



	n	Intercept	b (age in years)	S.E.E.	R
Nonsmokers	108	6.868	-0.041	1.23	.44
Exsmokers	84	6.803	-0.046	1.15	.40
Smokers	290	7.191	-0.059	1.33	.54
<1 pack/day	61	6.377	-0.034	1.05	.41
1 pack/day	143	7.497	-0.066	1.32	.57
>1 pack/day	86	7.355	-0.070	1.38	.58
Pipe or Cigar	47	7.312	-0.053	1.42	.44

Fig 3. — Prediction Equations for FEV25-75 in Total Population by Smoking.



	n	Intercept	b (age in years)	S.E.E.	R
Nonsmoker	108	7.124	-0.048	1.67	.44
Exsmokers	84	7.128	-0.057	1.87	.40
All smokers	290	2.242	-0.070 + 0.073 (ht.)	2.13	.54
<1 pack/day	61	6.380	-0.038	1.94	.35
1 pack/day	143	8.088	-0.086	2.22	.57
>1 pack/day	86	7.584	-0.085	1.82	.60
Pipe or cigar	47	6.965	-0.046	2.25	.32

Fig 4. — Prediction Equations for FEF50 in Total Population by Smoking.

Table 5. — Prevalence Rate of Impaired [illegible]

Smoking Category	N	FEV/FVC %	FVC %	[illegible]	[illegible]	[illegible]/FVC %	CV/VC %
Nonsmoker	108	25.9	4.6	[illegible]	[illegible]	[illegible]	0.9
Exsmoker	84	[illegible]	7.4	[illegible]	[illegible]	[illegible]	7.3
Smoker	[illegible]	43.8	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Pipe or Cigar	47	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	4.3
All	531	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	10.5
Age Category							
<29	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	7.5
30-39	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
40-49	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	11.3
50-59	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	13.7
>60	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
*Nonsmokers, ≤ 39	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Smokers, ≤ 39	[illegible]	22.7	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
All, ≤ 39	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Nonsmokers*, ≥ 40	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Smokers, ≥ 40	178	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	17.3
All, ≥ 40	335	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	11.6
All, *Nonsmokers	239	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
All, Smokers	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

*Nonsmokers = nonsmokers, exsmokers and pipe or cigar smokers

†Impaired Pulmonary Function =

FEV/FVC < 0.75

FVC/0.148 (height) - 0.025 (age) - 4.241 < 0.80 (from Reference 31)

FEF25-75/0.040 (height) - 0.050 (age) + 4.139 < 0.75 (from this population)

FEF50/FVC < 0.56

FEF75/FVC < 0.30

CV/VC/0.562 + 0.357 (age) > 8.30 above predicted (from Reference 34)

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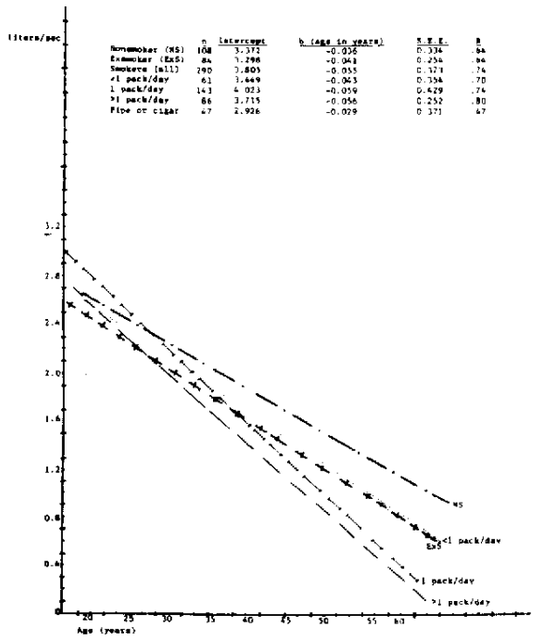


Fig 5. — Prediction Equations for FEF_{75} in Total Population by Smoking.

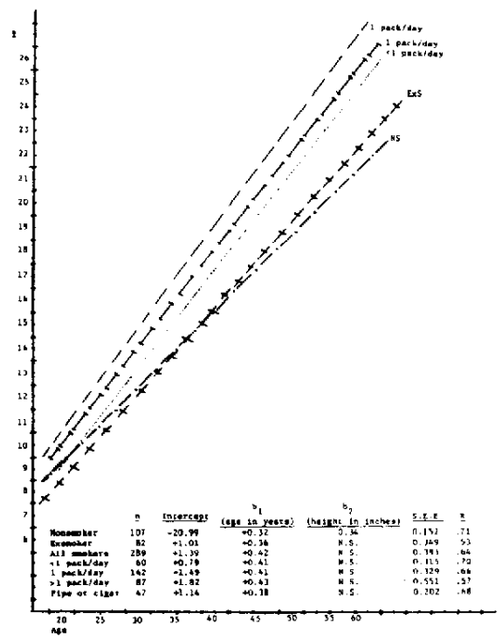


Fig 6. — Prediction Equations for Closing Volume/Vital Capacity (CV/VC) in Total Population by Smoking.

calculated using length of work in years as the independent variable, i.e., predicted pulmonary function = % predicted + % change in pulmonary function/year spent in exposure category. Table 7 summarizes regression for which a significant change occurred. For exposure category 1 (rubber only, chemical only, plastics only), rubber workers observed a significant decrease of -0.8%/year in FEF_{75}, plastics workers a decrease of -1%/year. All other significant changes were increases in lung function.

Health-related selective migration of workers is a potential source of bias in a cross-sectional study. In an attempt to take account of this, the effects of working in rubber and chemical, rubber and plastics, chemical and plastics, rubber, chemical, and plastics, or any one alone, were examined by analysis of covariance (Table 7). By backwards elimination method, exposure variables not statistically significant ($p > 0.05$) were sequentially removed until only the most significant exposure variables remained in the model. The analysis was done first on the total population (No. 2), then on the mixed exposure group (No. 3) and finally on the combination of categories within the mixed exposure group (Nos. 4-6). For the total population, working in chemicals was associated with increased FEV, FEF_{25-75}, FEF_{25}, and FEF_{50}. The only reductions in ventilatory capacity were observed in FEF_{75}, a highly significant reduction associated with rubber, and increased CV/VC, a functional decrease associated with plastics. The analysis of the mixed exposure groups (exposure categories 3-6) tended to support the results observed in the total population.

*Definition of Impaired PF in Table 5.
1 = 1 missing
2 = 2 missing
6 = 6 missing
9 = 9 missing

Exposure Category*	Ventilatory Function	= % Predicted	+ % Change	For Each Year Spent in Exposure Category	% Change for
1	FEV	98.4%	+0.47%	Salary Chemical Only	0.02
2		99.2	+0.15	Chemical	0.05
3		100.8	-0.25	Rubber	0.10
1	FVC	93.3	+0.36	PVC Only	0.04
6		98.3	+0.52	PVC	0.06
1	FEF25-75	93.6	+0.86	Hourly Chemical Only	0.002
2		98.0	+0.33	Chemical	0.009
4		107.3	-0.94	Rubber	0.04
6		94.4	+0.86	Chemical	0.03
1	FEF50	91.0	+0.89	Hourly Chemical Only	0.009
2		98.6	+0.36	Chemical	0.005
3		96.8	+0.35	Chemical	0.10
4		105.0	-0.65	Rubber	0.07
6		94.8	+0.99	Chemical	0.02
1	FEF75	94.8	+0.99	Hourly Chemical Only	0.03
2		98.2	+0.99	Chemical	0.08
1	FEF75	100.2	-0.77	Rubber Only	0.01
1		111.8	-1.8	PVC Only	0.07
2		100.5	-0.87	Rubber	0.0001
3		94.8	-0.97	Rubber	0.005
4		100.9	-2.89	Rubber	0.004
5		96.8	-1.0	Rubber	0.04
2	CV/VC	98.3	+0.83	PVC	0.04
3		97.8	+0.45	PVC	0.09
5		107.9	-0.75	Chemical	0.08
6		92.7	+1.56	PVC	0.05

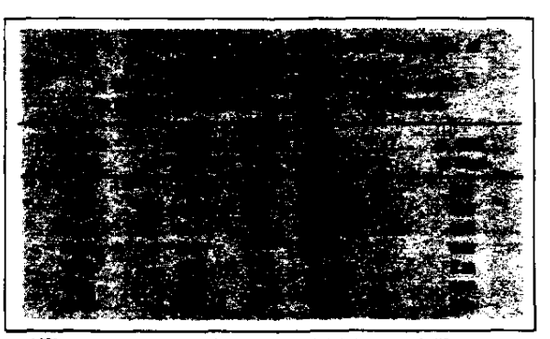
*Exposure Category
1 = Rubber Only, PVC Only, Chemical (H & S) Only.
2 = Total Population (Rubber, Chemical, PVC)
3 = Mixed Exposure (Rubber & Chemical; Plastics & Chemical; Rubber & Plastics; Rubber, Chemical & Plastics)
4 = Rubber & Plastics (N = 52)
5 = Rubber & Chemical (N = 86)
6 = Rubber, Chemical & Plastics (N = 61)

Work in the chemical plant was associated primarily with increased flow measured over mid vital capacity. Work in plastics was associated with functional reductions of from 0.4 to 1.2%/year in CV/VC. The most consistent and greatest changes were reductions of from -0.7 to 2.3%/year in expired flow rates at low lung volumes (FEF_{75}), associated with work in rubber.

Table 8 summarizes the relation of pulmonary function and cumulative exposure to vinyl chloride (see Table 8 for definition of CES-cumulative exposure score). Increasing exposure to VC in all workers *ever* exposed to VC was not associated with any significant reduction in pulmonary function. The general tendency was for pulmonary function to *improve* with increasing exposure. Only reductions in FVC approached statistical significance. Dividing the group into those with current VC exposure, and those that worked in chemical or plastics in the past (former chemical) and repeating the analysis produced the same results.

The relation between respiratory symptoms and baseline pulmonary function is summarized in Fig 7. All respiratory symptoms were significantly associated with reduction in expiratory flow (FEF_{25-75}, FEF_{25}). Cough, phlegm, and persistent cough and phlegm were significantly associated with reductions in FEF_{50}. Those with cough 2, phlegm 2 and persistent cough and phlegm had reduced percent predicted CV/VC. Reduced FEF_{75} was associated with symptoms of cough and persistent cough and phlegm.

In addition to baseline pulmonary function, 56 workers were tested before work and again after work. Since the workers were also taking physical exams, actual working time averaged about 4-hours. As there were about twice as many smokers (82%) among chemical workers as plastics (36%) and rubber (41%) workers, acute effects were compared in cigarette smokers and all others combined (nonsmokers). Current smokers observed significant



*CES = cumulative exposure score. All jobs in the chemical plant were rated for VC exposure as high (TWA = approximately 250 ppm), medium (TWA approximately 75 ppm), and low (TWA approximately 25 ppm). CES was calculated by multiplying months worked times a relative exposure rating (high = 10, medium = 3, low = 1) for that job, and summing over all jobs. Range = 0 - 2877 exposure-months.

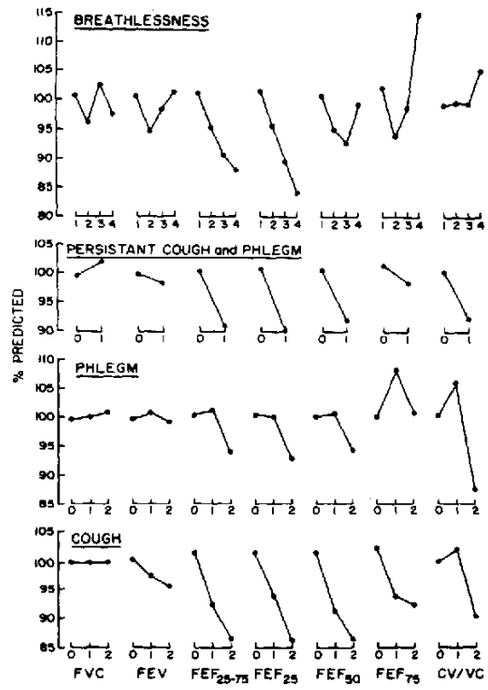


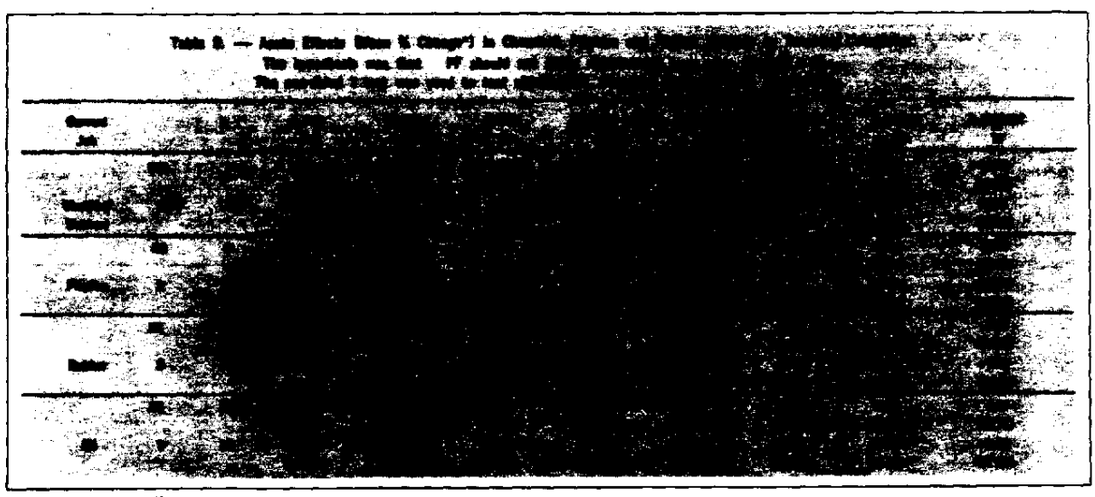
Fig 7. — Percent Predicted Pulmonary Function in Workers With and Without Respiratory Symptoms Adjusted by Age, Height and Smoking.

reductions in both flows and volumes. Nonsmokers observed increases in FVC and peak flow, but other lung function parameters decreased, significant only for FEF_{50} (Table 9). Smokers in all job groups had reductions in ventilatory capacity, the greatest decrement occurring in flows at low lung volumes. The reductions were of the same order of magnitude for all three exposure groups, but were significant only for vinyl chloride and rubber workers. Except for reductions over the shift of FEF_{50} and FEF_{75} in nonsmoking rubber workers, ventilatory capacity of nonsmokers did not change significantly from zero.

Discussion

This study was stimulated by the finding of an increased incidence of liver angiosarcoma in vinyl chloride (VC) workers. Experimental studies, case histories, and epidemiologic studies all suggest VC acts as a lung irritant. This literature is briefly summarized.

Patty, Yant and Waite[6] exposed guinea pigs for 30 minutes to 10-40% VC. The principle gross pathological effect was congestion and edema of the lungs, and hyperemia of the kidneys and lungs. Exposure to 10% VC resulted in slight signs of lung hyperemia while hemorrhages, edema, and severe damage to the tracheal epithelium were observed at the higher concentrations in animals dying from the initial exposure. Pulmonary congestion was present after two weeks in surviving animals. Lower exposures for longer time periods (50-500 ppm for six months) resulted in no change in lung weight in rats, guinea pigs, rabbits and dogs. Exposures at concentrations greater than 100 ppm produced reversible liver injury in the more sensitive species.[7] Lester, et al.[8] exposed rats to 20,000 ppm (2% VC) for three months, and 50,000 ppm (5% VC) for 19 days. They observed increases in liver weight and decreases in white blood cells, but concluded that the observed



*p = < 0.05
**p = < 0.025
***p = < 0.005
****p = < 0.005
†NS = nonsmoker, exsmoker, pipe or cigar smoker
‡S = smoker
‡ = A positive sign indicates a decrease in performance as the after work CV/VC ratio is larger than the before work CV/VC ratio.
*Mean % change = $\frac{\text{after work PF} - \text{before work PF}}{\text{mean PF}}$; mean PF = $\frac{\text{after} + \text{before}}{2}$

lung edema and congestion could not be attributed to the irritating effects of VC, and the pneumonia observed was probably due to secondary infection. Keubler[10] exposed rats, mice, and guinea pigs to 5,000, 15,000 and 25,000 ppm VC for 2-hours a day for 100 days without observing any histological damage. In a report of a case of VC gassing in a plant in Great Britain, a worker washing out a polymerization vessel with water collapsed and was given artificial respiratory. Subsequent symptoms included chest tightness.[16]

Boytsov[9] reports (without giving the number of species or animals, length or amount of exposure) that inhalation and intratracheal administration of PVC resin produced a "development of peribronchitis in the lungs" and local thickening of interalveolar septa. Two studies of PVC workers in Russia and Germany conclude that the respiratory system was affected.[11, 12] A "considerable number" of 96 PVC workers in Russia had a "changed bronchovascular pattern and increased pulmonary ventilation at rest".[11] Eight of thirteen German PVC workers employed for 1.75 to 18 years showed partial pulmonary insufficiency with signs of predominantly restrictive changes of the lungs.[12] This latter finding is in agreement with the case described by Szende, et al.[11] A 31 year old male had shoveled PVC dust in a drafty place for 1-year prior to being examined for severe dyspnea. The possibility of pneumoconiosis elicited by inhalation of PVC resin was suggested.

There are a number of problems with the experimental studies of animals. Only at very high VC concentrations are effects observed, and these are anatomical changes from gross pathology or histology. More sensitive functional measurements at lower, more realistic, VC exposure concentrations have not been reported. The foreign studies are only suggestive, and do not provide enough information to evaluate.

There is only one reported epidemiologic study of VC and PVC workers in the U.S.[14] Cough and sputum production for most of 1-year or more clinical signs of emphysema were reported in 31% of the 348 currently and previously employed VC and PVC workers. Smokers and nonsmokers over 40 years of age had similar rates of flow impairment. In the age group under 40 however, smokers had about twice the prevalence of flow impairment as nonsmokers. The higher prevalence of flow impairment in smokers compared to nonsmokers converged slightly with increasing duration of exposure; nonsmokers and smokers with more than 20 years exposure had the same prevalence of flow impairment. The authors conclude that the etiologic agents producing the reduced air flow in workers over 40 years of age or with > 20 years exposure is unclear but is not due to smoking. Exposure was to VC monomer, PVC resin dust, and pollution in a heavily industrialized city.

The effect of smoking on respiratory symptoms has become common knowledge following the report of the Surgeon General on the Health Consequences of Smoking (1964) and its subsequent supplements.[17] The results of this study confirm these reports, with the possible exception that light smokers (<1pack/day) in this study resembled exsmokers more than heavier smokers (≥1 pack/day). Pipe or cigar smokers have been less studied, although it has been suggested that pipe smokers are to be distinguished from cigar smokers.[18] Because of small numbers this has not always been done, and in this study these smokers were combined. They generally resembled light smokers and exsmokers in both symptoms and lung function.

The effects of smoking on symptoms have generally shown cough and phlegm to be higher in smokers, with prevalence relat-

Table 10. — Comparison of Respiratory Symptom Prevalence

Population	N	Cough %	Phlegm %	Persistent %	Breathlessness %
This Study (All	531	14.9			21.2*
Nonsmokers	169	5.6			11.1*
Smokers	362	21.6			26.5*
Mining Community					
West Virginia[8]					
Nonsmokers		15.6			5.0†
Smokers		40.2			19.3†
Random Sample, Males					
Berlin, N. H.[9]					
Nonsmokers	76	10.7	6.6	7.1	3.8‡
Smokers	172	18.1	16.2	17.6	10.9‡
Stratified Sample,					
Industrial town in England[10]					
Nonsmokers	40	—		9.0	5.1
Smokers	359	—		43.4	8.9
White, male nonsmokers					
35-64[7]					
Maryland	487	9.5		1.5	22.6‡
NYC Postmen[6]					
Nonsmokers	555	7.9			21.6‡
Smokers	2007	27.6			34.0
NYC Transit Workers[5]					
Nonsmokers	1662	6.4		8.6	18.4‡
Smokers	3745	23.5		15.2	23.3

*Grade 2, 3, 4 breathlessness
†Grade 3 and 4 breathlessness
‡Grade 2 and 3 breathlessness

ed to the amount of smoking, a relationship supported by this study. Breathlessness, while generally higher in smokers, is often not related to the amount of smoking. This is hypothesized as due to selective reduction of smoking in those developing symptoms of breathlessness, a more severe and disabling condition than "smokers cough".[19] Although movement of less fit heavy smokers into lighter smoking or nonsmoking categories seems a plausible explanation, selection does not appear to be a strong factor in this population as there was a high prevalence of breathlessness on the heavy smoker category.

A trend for breathlessness to increase with increasing age is commonly observed,[19] and was apparent in this study. The association of cough and phlegm with increasing age has not been as consistent. Some studies report an increase with age;[19 20] others (including this study) find little tendency for cough and phlegm to increase with age.[19 21]

Two studies in West Virginia have observed an association between educational level and prevalence of respiratory symptoms and ventilatory lung function capacity, with the lower prevalence of symptoms partly attributed to fewer smokers in the higher educational categories.[22 23] Stebbings[27] in 469 white male nonsmokers found no effect of social class (based on occupation, education, and income) on most respiratory symptoms; only dyspnea was significantly less common in the upper social class. Lower pulmonary function was also associated with lower socioeconomic status in these nonsmoking males.[27] Salaried chemical workers in this study resemble the upper social class in that they smoke less than hourly workers, and are probably more educated. Exposure to VC and PVC resin is generally less than that of the hourly workers. It is not known from this study whether social class, exposure, smoking, or some combination of these factors can explain the lower symptom rates of salaried chemical workers when compared to hourly workers. The same argument applies to the slightly better pulmonary function of salaried chemical workers compared to hourly workers. Among hourly workers, no consistent or convincing differences in respiratory symptoms or function were observed.

When workers were divided into exposure categories of working *only* in plastics or chemicals, the respiratory symptom rate was reduced considerably. Workers with more job mobility were less healthy in the sense that they reported more symptoms. This could be due to a greater susceptibility, to having a more unfavorable job experience in terms of exposure, to self-propelled movement to less symptom producing jobs, or some combination of these factors. Although the reasons are unknown, the fact remains that the less mobile "pure" exposure groups had lower symptom rates than control rubber workers, maintenance, and the mixed exposure workers.

Are the symptom rates observed in this population comparable to those in other populations? Table 10 compares the prevalence of respiratory symptoms in this study with other studies. There is considerable variation between reported symptoms in the various populations. The workers in this study compare favorably except for perhaps breathlessness.

The effects of age and smoking on pulmonary function observed in this population are comparable to other reported studies. There were no significant statistical differences in the intercepts of the smoking regression equations. Heavier smokers in this cross-sectional analysis had significantly greater reductions of FEV, FEF_{25-75}, FEF_{50}, and FEF_{75} with increasing age. Two points are of interest with regard to the effect of smoking. Before the age of 40, smoking had no apparent effect on pulmonary function. Secondly, light smokers were obviously less affected than moderate and heavy smokers. In the analysis of smoking, one should examine this dose response relation, and not arbitrarily lump together all smokers.

Careful consideration of possible smoking-exposure interactions is also required. For example, in a group of workers exposed to asbestos dust, smokers reported worse lung function than nonsmokers when a single regression was used for height and age adjustment.[29] The inference was that smoking increased the effect of dust exposure. Using only a single regression equation for standardization is misleading however, as smokers pulmonary function decreases more rapidly than exsmokers and nonsmokers. Rossiter and Weil[29] point out that an apparent synergism between dust and age may instead be a smoking-age interaction. When separate regression equations were used for standardization, i.e., one each for nonsmokers, exsmokers, and smokers, they observed no difference in pulmonary function related to dust exposure. In fact, the asbestos dust exposure had a more detrimental effect on nonsmokers than smokers. We know there was a smoking-age interaction in this study. Since we are primarily interested in the effect of VC exposure on pulmonary function, age and smoking adjustments were made using the regression equations of the various smoking categories (Figs 1-6). As there was no difference in pulmonary function between current job categories, and no nonexposed group of workers was available, the regression equations used for standardization were derived from the smoking categories of the total population.

After standardization, increasing duration of exposure in chemicals, plastics, and rubber was not associated with large changes in pulmonary function. Reductions in FEF_{75}, the most sensitive measure of small airways obstruction, was consistently and significantly associated with working in rubber; less significant reductions in FEF_{75} were associated with hourly chemical and plastics workers, and FVC in hourly chemical workers. Other pulmonary function parameters generally remained the same or improved with increasing duration in chemicals or plastics, and with increasing cumulative VC exposure. The reported case of pneumoconiosis on exposure to PVC resin[13] is suggestive that high exposure to PVC resin may result in a restrictive type of respiratory disease. Baggers in the chemical plant are exposed to from 1-5 mg/m^3 of particulate (measured by area Hi-volume samplers); respiratory particulate is 1/10 to 1/20 these levels. Exposure to the PVC resin in plastics appears higher for Banbury operators but lower for workers in milling, and negligible for other plastics workers. The low prevalence of FVC impairment in both chemical and plastics workers does not support the hypothesis of PVC resin exposure producing volume restriction.

What difference is there between the workers in this study and those reported on by Miller, et al? Pulmonary function impairment for FEV/FVC, FVC, and FEF_{75}/FVC in this study employed the same definition as Miller, et al.[14] in their study of VC-PVC workers. The prevalence of impairment for FEF_{25-75}, using the same criteria, was essentially zero, and thus far below the 53% they observed. The cutoffs for impaired flow as measured by FEF_{50}/FVC and FEF_{75}/FVC have been shown to be reasonably effective in distinguishing normal subjects from those with obstructive lung disease.[32] The highest prevalence (almost 50%) of impairment was for FEF_{75}/FVC and supports the observed association of reduced FEF_{75} with increasing duration of work. All VC-PVC nonsmokers less than 40 years of age, and all workers in this study less than 40 years of age, had about a 20% prevalence of impairment for FEV/FVC and FEF_{75}/FVC. The prevalence of impairment increased for non-

smokers over 40 in both populations, but more so in the Miller study. The rates of flow impairment in both studies are the same for smokers over 40. In both studies the prevalence of impaired FVC (< 10%) is considerably lower for flow impairment (18-75%) and much lower than expected from exposure to asbestos.[31]

The association of increased pulmonary function performance with increasing exposure and work duration, particularly in chemicals, suggests that selection is occurring in this population. The reason for the lack of association between VC exposure and respiratory effects may be due to differential migration of more susceptible workers out of chemicals. Note that the mixed exposure group reported a higher symptom rate than chemical and rubber workers who had never moved. The current plastics worker had symptom rates comparable to or higher than this mixed exposure group, suggesting that net migration of "susceptibles" may have been into plastics. The association of small airways obstruction with exposure may be more informative than symptoms because (1) small airways may be more sensitive to the effects of environmental agents; and (2) small airways obstruction is probably not noticed by the individual to the same extent as symptoms and FEV reductions, and would therefore not be affected as much by selective migration.

Several conclusions emerge concerning factors that affect baseline pulmonary function in this population: (1) age and smoking were the two most important factors reducing pulmonary function; smoking was associated with obstruction only (no significant effect on FVC). (2) small airways function as measured by FEF_{75} was affected by both smoking *and* work exposure, primarily rubber worker exposure. (3) work, whether measured by duration or estimated cumulative exposure to VC and after adjustment for smoking effects, was not associated with reduced baseline pulmonary function (except for FEF_{75}). (4) although prevalence rates of impairment are not often reported, the air flow impairment (FEV/FVC, FEF_{75}), rates appeared elevated only in the older smoker.

Respiratory symptoms and measurement of pulmonary function are two somewhat independent and yet overlapping methods for investigating the risk of environmental exposures to the respiratory system. Symptomatology suffers from the disadvantage of being subjective, can show interobserver variation, and requires adequate recall on the part of the person being interviewed; symptomatology is useful in diagnosis, particularly chronic bronchitis. Independent validation of symptoms in practice turns out to be pulmonary function measures, despite the fact that different, albeit overlapping, parameters are being measured. The observed association of reduced pulmonary function with increasing severity of symptoms increased the validity of respiratory symptom information. The conclusion that VC exposure did not constitute a significant respiratory hazard in this population was strengthened by similar results for both symptoms and pulmonary function.

While one methodologic strength of this present study is the ability to make internal comparisons between work groups, it must be stressed that none of the groups can be regarded as having worked in hazard-free conditions. Both rubber and plastics workers are exposed to varied levels of dust and fume, and it could be that reduction in lung function among chemicals workers (whether due to vinyl chloride exposure, or to some other agent) are being obscured because of similar reductions in the other job groups. The results of FEF_{75}/FVC impairment (pertaining to that part of the respiratory tract thought to be first affected by harmful exposure — the small bronchioles) suggest increased abnormality rates in *all* workers. Indeed, for several of the pulmonary function tests the chemical workers had better results than rubber and plastics workers. To assess the potential respiratory hazard of each exposure category, before-and-after shift tests were carried out on some workers. Any reduction in respiratory function over the shift suggests the likelihood of some harmful exposure in the working environment.[34]

Smokers overall had statistically significant reductions for all ventilatory tests; nonsmokers showed little reduction. The most obvious reductions were flow rates at low lung volumes, i.e., measures of small airways performance. Chemical workers who were smokers had significant reductions for five of the seven tests, predominantly reflecting small airways obstructive change; both plastics and rubber workers who smoked showed reductions of similar magnitude. No clear picture emerges suggesting one job group faced greater daily respiratory insult than the others. Reduction in small airways performance among nonsmokers in each job group suggests that all workers were exposed to agents with adverse respiratory effects. In a clean environment the average result for these nonsmokers would have been a slight increase in test performance. Whether these acute reversible changes have any permanent effect is not known. The significance of these findings is unclear. The small airways obstruction associated with work in the rubber division, i.e., the control group, could be related to a number of environmental agents. The complexity of the industry and the heterogeneity of the control group does not allow for determining the etiologic agents. The rubber worker group was selected on the basis of lower particulate exposure and never having worked in chemical or plastics. But they could have, and probably did, work in other jobs with higher exposures within the rubber division. A complete work history for each rubber worker would be required to investigate further the association of reduced small airways function with work in rubber.

Fundamental and more difficult questions remain. What is the biological significance of acute reversible reductions in small airways function over a shift? What is the biological significance of statistically significant reductions in baseline pulmonary function over a longer time period? For FEF_{75}, the reduction is on the order of -1%/year. Over a 40 year period, this would amount to a 40% decrease. However, some individuals have a reversible change of 40% in the course of a day. The association of working in rubber with a downward slope of the percent predicted FEF_{75} is a finding that requires further investigation of workers in other areas of the rubber plant, an investigation currently underway.

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