Low Exposure to Asbestos

Gas Exchange in Ship Pipe Coverers and Controls

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In a previous survey of shipyard pipe coverers and controls, clinical criteria were used to define pulmonary asbestosis. This second survey focused on physiologic abnormalities.

Pipe coverers had significantly reduced vital capacities (FVC) as well as single breath (D_LSB) and exercise steady state (D_LSS-Ex) diffusing capacities. Resting steady state diffusing capacity (D_LSS-R), fraction carbon monoxide removed (F_{CO}), and the diffusing constant (K) differed from selected normals but not from all controls. Airways resistance, specific conductance, minute ventilation, arterial carbon dioxide pressure (P_{CO_2}) and dead space were not significantly abnormal. Obstructive disease was equally common in both groups. All workers with clinical "asbestosis" also had severely reduced D_L and F_{CO}.

The significance of isolated reduction of D_L requires further study. However, in a third survey three years later, D_L in exposed workers had deteriorated more rapidly than FVC; some with initially isolated reduction of D_L had developed other signs of disease.

In a shipyard survey in 1965, we felt confident of a "positive" diagnosis of asbestosis based on clinical criteria.[1] We were less certain that a "negative" diagnosis indicated absence of interstitial lung disease. It has been suggested that tests of respiratory gas exchange may be more sensitive in detecting early, or subclinical asbestosis,[2-6] but their importance remains controversial.[7,8]

Our defined population presented an opportunity for evaluation of such tests. Exposure had varied from 1 to 30 years, and therefore we expected all gradations from slight to advanced disease. While in the past, quantitative dust exposure histories have been difficult to obtain, exposure in our pipe coverers had been monitored.[1] Finally, a control group, comparable except for dust exposure, has not been available previously. Accordingly, this second survey was planned to explore the usefulness of tests of respiratory gas exchange in assessing the spectrum of pulmonary asbestosis.

Population Studies

In the first survey, we studied all 101 pipe coverers employed in a New England shipyard. An equal number of controls, matched for duration of employment and age, were selected from among shipfitters and pipe fitters without known exposure to asbestos. Participation among the latter was voluntary and seven refused, leaving 94 controls. In this survey, one year later, three of the pipe coverers with "asbestosis" had died, and 14 others had left for lack of work; the latter were younger men, none of whom had been diagnosed as asbestotics. Among the

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controls, lack of work, vacations, retirements, and three refusals accounted for 24 losses so that there remained 84 pipe coverers and 70 controls for this second survey.

Smoking habits were similar: 66.4% of the pipe coverers and 68.1% of the controls were present smokers.[1] Dust exposure, under surveillance for 20 years, had been at or near the then recommended threshold limit value of 5 million particles per cubic foot (mppcf).[1]

In the first survey, asbestosis was defined by the presence of three or more of five clinical abnormalities including (1) moderate dyspnea (on climbing one flight of stairs or less, approximately equivalent to Fletcher grade III); (2) crepitant basilar rales in two or more sites; (3) clubbing of the fingers (a hyponychial angle of 198° or greater); (4) a vital capacity of less than 80% of predicted; and (5) a roentgenogram consistent with moderately advanced (code 5) or advanced asbestosis (code 6). These codes 5 and 6 correspond to the new UICC/Cincinnati classification of profusion 2 and 3.[9] By this definition, asbestosis was diagnosed in 11 pipe coverers and one control; it was found first after 13 years of exposure or 60 mppcf-years; with more than 20 years of exposure, the prevalence was 38%.[1]

Among the three of 11 pipe coverers with clinical asbestosis who were not seen in the second survey, one had died of coronary occlusion and postmortem examination showed asbestosis; autopsy in another showed asbestosis and cor pulmonale; and the third died of bronchopneumonia without autopsy. Four pipe coverers had to be classified as new cases of asbestosis on the basis of our clinical criteria.

Methods

The vital capacity (FVC) and the volume exhaled during the first second (FEV_1) were measured in both surveys.[1] Methods of plethysmography and measurement of diffusing capacity have been described[10-15] and were modified as follows.

Body Plethysmography.—The functional residual capacity (FRC_{BP}), airways resistance (R_A), and specific conductance (G_A/L_V) were measured with a constant volume, variable pressure box.[10] Calibration and loops during panting were displayed on a storage oscilloscope, and the angles of the slopes were read directly.

Steady State Observations.—The breathing circuit consisted of an Otis-McKerrow valve with a baffle to reduce dead space to 40 ml. Subjects inspired humidified 0.1% CO in air and expired into a balloon within a 200 liter steel drum with a window. This drum was connected to a spirometer with a kymograph to monitor minute ventilation ($\dot{V}e$) and respiratory frequency (f). End-tidal CO_2 partial pressure ($P_{ET_{CO_2}}$) was monitored at the mouth. Mixed expired gas was analyzed after each run while a small blower emptied the balloon within the drum.

At rest, subjects were seated on a treadmill, adequate relaxation, and a steady state were indicated by steady ($P_{ET_{CO_2}}$) and f. Then, the CO mixture was breathed for six minutes, with expired gas collection for the last three minutes.

For exercise, the breathing assembly was raised and the workers walked at 2 mph at an 8% incline for six minutes, breathing the CO mixture for the last four minutes, and with gas collection for the last two minutes. This moderate exercise increased O_2 uptake about fourfold.

Calculations.—Minute ventilation ($\dot{V}_E$) and tidal volume (V_T) corrected to BTPS, O_2 uptake ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$), and CO uptake ($\dot{V}CO$) all corrected to STPD. The ventilation equivalent for O_2 ($\dot{V}_EO_2$) and the respiratory exchange ratio (R) were all calculated in the usual manner. Physiologic dead space (V_D), alveolar ventilation ($\dot{V}_A$), and the alveolar O_2 pressure ($P_{A_{O_2}}$) were calculated from the alveolar equation, substituting $P_{ET_{CO_2}}$ for $Paco_2$. Alveolar CO pressure ($P_{A_{CO}}$), the steady state diffusing capacity (D_{LSS}), and the fraction of CO removed from alveolar ventilation (F_{CO}) were calculated according to Filley et al.[11]

The single breath diffusing capacity (D_{LSB}) was measured in duplicate according to Forster et al[12] with a special instrument.[13] The original procedure was modified by using an alveolar volume (V_A) calculated from the single breath helium dilution ratio[14] instead of V_A calculated by addition of the inspired volume to a residual volume measured separately by a rebreathing technique.[12] Each subject had a dry run with air; the inspiratory circuit was then flushed with balloon gas. A buzzer signaled the ten-second breath-holding period, and an interval of at least five minutes was allowed between duplicate studies. When the inspired volume was less than 90% of the FVC, the procedure was repeated. A predicted D_{LSB} was calculated from regression equations derived from 100 normal subjects.[15,16]

Gas Analysis.—Carbon monoxide and CO_2 were measured with nondispersion infrared spectrometers which were calibrated with four gases of known composition before and after each run. Oxygen was analyzed with a paramagnetic instrument, and He with a temperature compensated thermistor catharometer. These linear instruments were calibrated with nitrogen and one gas of known concentration before and after each run.

Switching of gases, valves, sample pumps, and meters was accomplished with a solenoid-controlled instrument designed for this survey so that one individual could control the entire procedure.

Carboxyhemoglobin (COHb) saturation and CO "back pressure" were estimated by breath holding[17] before and after each test in ten randomly selected nonsmokers and ten smokers. Initial COHb saturations ranged from 1% to 2% in nonsmokers and up to 6% in heavy smokers in the afternoon. Each DLSB, steady state diffusing capacity at rest and exercise (DLSS-R and DLSS-Ex) raised COHb saturation by about 1%, 2%, and 4% respectively. Neglect of back pressure may have resulted in an underestimation of DL of up to 4% in some cases.

Results

Respiratory Function of Pipe Coverers and Controls.—The two groups were virtually identical with respect to age, stature, present smoking, and pack-years of cigarette consumption (Table 1). "Restrictive" impairment was more common in the pipe coverers in that their FVC, FEV_1, and total lung capacity (TLC_{He}) was significantly lower ($P < .01$).

From the measurements cited in Table 1, there was no evidence that obstructive airways disease was more common in the pipe coverers than in the controls. Their mean $FEV_1\%$ was 72.1 ± 8.9 compared to controls with 73.7 ± 8.1%; there was no significant difference in airways resistance, specific conductance, or functional residual capacity.

In Fig 1, the subjects are arranged in order of their $FEV_1\%$; nine pipe coverers (10.7%) and five controls (7.1%) had an $FEV_1\%$ which was more than 2 standard deviations below the predicted mean, an insignificant difference. The presence of clinical asbestosis, shown in relation to $FEV_1\%$, was not particularly related to obstructive lung disease; only one such pipe coverer had a significantly reduced $FEV_1\%$. A reduction of DL may be caused by obstructive airways disease, particularly with emphysema.[7] However, only four pipe coverers and two controls had a significant reduction of both DL and $FEV_1\%$.

Among the tests of respiratory gas exchange, the largest difference between pipe coverers and controls was found concerning DLSB and DLSS-Ex ($P < .01$). Not significantly different were DLSS-R and Fco-Ex. Discriminant function analysis confirmed these observations.

Definition of a Normal Control Group.—The control group was selected to match the pipe coverers solely by age and duration of employment, and therefore it included workers with significant cardiopulmonary impairment. It was thought that this represented the expected background of nonasbestos related disease prevalent in men working in the same locality for the same number of years in related occupations.[1] However, it was also of interest to compare the pipe coverers to individuals without known cardiorespiratory disease because, for several of our tests, regression equations for normal performance are not available. Therefore, we selected a "normal" control group by excluding from the 70 controls 30 persons who had symptoms or a history of cardiorespiratory illness with confirmatory evidence by physical examination, chest roentgenogram or both (Table 3).

In Table 1, we compared the pipe coverers not only to all controls but also to those 40 normal controls. The latter were about three years younger and smoked slightly less, but these differences were not significant. Predictably, the respiratory function of the pipe coverers differed in the same respects from the normal controls as from all controls. In addition, the new comparison showed the pipe coverers to have significantly increased $P_{ET}CO_2$ and $\dot{V}EO_2$ during exercise, and significantly reduced DLSS-R, diffusing constant K, and Fco both at rest and during exercise. A number of other variables was virtually the same for all three groups including $\dot{V}O_2$, VCO_2, f, VT and a residual volume obtained by subtracting FVC from the total lung capacity calculated from the single breath He dilution.

Table 1.—Respiratory Function of

	40 Normal Controls		All 70 Controls	
	Mean	± SD	Mean	± SD
1. Stature and smoking				
Age, yr	40.3	9.9	44.0	10.3
Weight, kg (lb)	77 (171)	13 (28)	78 (174)	13 (28)
Height, cm (in)	175 (68.7)	6 (2.5)	173 (68.0)	6 (2.5)
Body surface area, sq m, (BSA)	1.92	0.17	1.92	0.16
Smoking, pack years	17.2	16.5	25.4	24.4
2. Mechanics and lung volumes				
Vital capacity, liter (FVC)	4.60	0.58	4.28	0.78
Timed FVC, liter in 1 sec (FEV_1)	3.47	0.47	3.15	0.65
(FEV_1/FVC) × 100 = FEV_1%	75.5	6.1	73.7	8.1
Airway resistance, cm/liter/sec (R_A)	1.97	0.69	2.11	0.75
Specific conductance, liter/sec, cm/liter (G_A/V_L)	0.191	0.047	0.183	0.054
Functional residual capacity (plethysmography), liter (FRC_{BP})	2.96	0.59	2.94	0.73
Total lung capacity, (He) liter (TLC_{He})	5.86	0.74	5.59	0.86
3. Steady state studies				
Ventilation, liter/min/sq m ($\dot{V}_E$) rest	5.38	1.00	5.59	1.43
Ventilation, liter/min/sq m ($\dot{V}_E$) exercise	16.31	3.32	17.06	3.53
O_2 uptake, ml/min/sq m ($\dot{V}O_2$) rest	166	22	165	22
O_2 uptake, ml/min/sq m ($\dot{V}O_2$) exercise	667	120	662	105
Ventilatory equivalent for O_2, liter/100 ml ($\dot{V}_EO_2$) rest	3.26	0.52	3.40	0.72
Ventilatory equivalent for O_2, liter/100 ml ($\dot{V}_EO_2$) exercise	2.45	0.26	2.59	0.43
Respiratory exchange ratio (R) rest	0.85	0.10	0.85	0.10
Respiratory exchange ratio (R) exercise	0.87	0.05	0.88	0.07
End-tidal CO_2 tension, mm Hg ($P_{ET}CO_2$) rest	37.5	3.0	36.5	3.8
End-tidal CO_2 tension, mm Hg ($P_{ET}CO_2$) exercise	43.2	3.3	41.9	3.7
Physiologic dead space, ml (V_D) rest	209	49	208	52
Physiologic dead space, ml (V_D) exercise	423	117	421	108
Fraction CO removed, % (F_{CO}) rest	46.5	5.7	44.8	7.2
Fraction CO removed, % (F_{CO}) exercise	39.5	4.9	37.4	6.0
Diffusing capacity, ml/min/mm Hg (D_LSS) rest	18.8	5.7	17.3	5.6
Diffusing capacity, ml/min/mm Hg (D_LSS) exercise	30.4	6.1	28.6	6.4
4. Single breath				
Diffusing capacity, ml/min/mm Hg (D_LSB)	36.8	6.0	34.3	6.3
Krogh's diffusion constant (K)	4.6	0.8	4.5	0.8

* Pipe coverers significantly different ($P < .01$) from normal controls only.
† Pipe coverers significantly different ($P < .01$) from normal controls and all controls.
‡ Pipe coverers significantly different ($P < .01$) from all controls only.

In the subsequent analysis of results and discussion, this special group of normal controls was not further considered.

Relationship of Clinical "Asbestosis" to Abnormalities of Respiratory Gas Exchange.—Figure 2 illustrates that mean values for the three D_L tests decreased with an increasing number of clinical abnormalities; even the pipe coverers with none or only one of the clinical criteria had lower D_L values than the controls. Individual clinical findings also correlated with tests of gas exchange; radiologic abnormalities corresponded most closely; even the readings of questionable (code 3 or UICC 0/1) and slight (code 4 or UICC 1/1) asbestosis had meaning in statistical terms while they had been of little importance in individual cases. Clubbing was least related, reflecting perhaps the nonpulmonary causes of this abnormality or the difficulties in accurate assessment.

A principal objective of the D_L and Fco studies was to discover individuals with impaired lung function, perhaps due to asbestosis, who were considered "borderline" or "negative" by our clinical criteria. For this purpose we defined abnormal values as those that were more than 2 standard deviations below the mean of all controls. Figure 3 shows that workers with a "positive" clinical diagnosis also had abnormal D_LSB, D_LSS, and Fco at rest and during exercise, or were unable to exercise.

Of greater interest were workers with impaired gas exchange and only two positive clinical findings. Three such pipe coverers had no abnormalities suggesting any other diagnosis than asbestosis, while among the three controls, two had bullous emphysema, and one a lobectomy for carcinoma. This suggests that inclusion of diffusion tests among the criteria for diagnosis might define additional individuals with lung disease.

There were eight pipe coverers with impaired D_L and Fco who had no clinical

Pipe Coverers		
84 Pipe Coverers		
Mean	± SD	Significance
43.2	11.0	
76 (168)	10 (23)	
171 (67.4)	6 (2.2)	*
1.88	0.14	
24.8	20.2	
3.87	0.70	†
2.78	0.59	†
72.1	8.9	
1.96	0.73	
0.213	0.069	‡
2.77	0.66	
5.15	0.90	†
5.74	1.37	
17.72	3.86	
170	25	
668	98	
3.36	0.62	
2.66	0.47	*
0.83	0.12	
0.87	0.07	
36.4	3.6	
40.9	4.4	*
222	53	
394	115	
42.8	6.7	*
35.5	6.9	*
15.9	4.9	*
25.8	5.8	†
30.5	6.6	†
4.2	0.8	*

abnormalities and a normal FVC. Only follow-up examinations will show whether such isolated impairment of gas exchange has meaning in terms of detecting early asbestosis.[2-6] There is support for this possibility. Four of the pipe coverers with isolated D_L reduction were restudied three years later. At that time, one had developed dry rales and dyspnea, one had finger clubbing, and one had emphysematous bullae and a markedly reduced $FEV_1\%$.

Follow-up Studies.—In 1970, a third visit was made to the shipyard, 3½ years after the second survey. Eight surviving workers with asbestosis and 24 other pipe coverers were reevaluated. Among the latter, two additional individuals now fitted our clinical criteria for asbestosis. The mean FVC of these 32 workers had decreased from 3.70 to 3.53 liters or 4.5%. This is significant ($P < .01$), but amounts to only 47 ml/yr, compared to a 20 to 100 ml/yr reduction predicted for aging alone.[18,19] The mean D_LSB had decreased much more, from 26.9 to 23.5 ml/min/mm Hg, or 12.6%; this was 0.96 ml/yr, nearly four times the predicted decrease of 0.26 ml/yr.[20] The number of workers with a reduced FVC had increased from 12 to 14, and those with reduced D_LSB from 12 to 19 (Fig 4). None of those who were abnormal in these respects in 1966 had improved.

Correlations Among Physiologic Tests for All Subjects.—Many tests correlated significantly with others ($P < .01$ if $r > .21$) because they reflected the same type or location of functional impairment (Table 3). In some instances, close correlations suggested simplifications for future surveys.[21] Forced vital capacity corresponded well to the maximal inspiratory effort preceding the D_LSB test ($r = .94$), an observation that indicates adequate performance by most subjects. Correlation of $FEV_1\%$ with airways resistance and with specific conductance was poor ($r = .09$ and .37), because in this study nearly all values fell within the broad range of normal (Fig 1), whereas previous studies showing good correlations contained many patients

Table 2.—"Normal" Controls and Controls Cardiopulmonary Disease

Normal controls	
1. Asymptomatic, or no more than 1+ dyspnea, 1+ cough, or 1+ sputum with negative history	
2. Positive history but without symptoms and without residual verified by physical examination and roentgenogram	
Total	40
Controls with cardiopulmonary disease	
1. Cardiac	
Acquired heart disease, symptomatic	4
Congenital heart disease, symptomatic	2
2. Pulmonary obstructive	
Chronic bronchitis with obstructive syndrome	5
Bullous emphysema with or without obstruction	5
Bronchial asthma with signs and symptoms	3
Emphysema and mid thigh amputation	1
3. Pulmonary restrictive	
Healed tuberculosis with radiologic residua	3
Marked pleural thickening, old empyema	2
Chest trauma with marked radiologic residua	2
Lobectomy for bronchogenic carcinoma	1
Pneumonectomy for pulmonary arteriovenous aneurysm	1
"Diffuse interstitial fibrosis" from smoke inhalation (asbestosis by our clinical criteria)	1
Total	30

Table 3.—Correlation Coefficients (r) Among Physiologic Tests*

	FVC	D_LSS Rest	D_LSS Exercise	D_LSB	F_{CO} Rest
FVC, liter		0.39	0.52	0.52	
DLSS-R			0.76	0.57	0.68
DLSS-Ex				0.72	0.61
F_{CO}-R				0.51	
F_{CO}-Ex				0.61	
V_E-R		−0.09			−0.63
V_E-Ex			−0.23		
$P_{ET}CO_2$-R		0.37			0.53
$P_{ET}CO_2$-Ex			0.49		
Maximal IC preceding D_LSB maneuver	0.94				
Total lung volume from SB He dilution	0.74				

* For 154 (pipe coverers and controls combined) subjects: any $r > .16$: $P < .05$; and $r > .21$: $P <$.

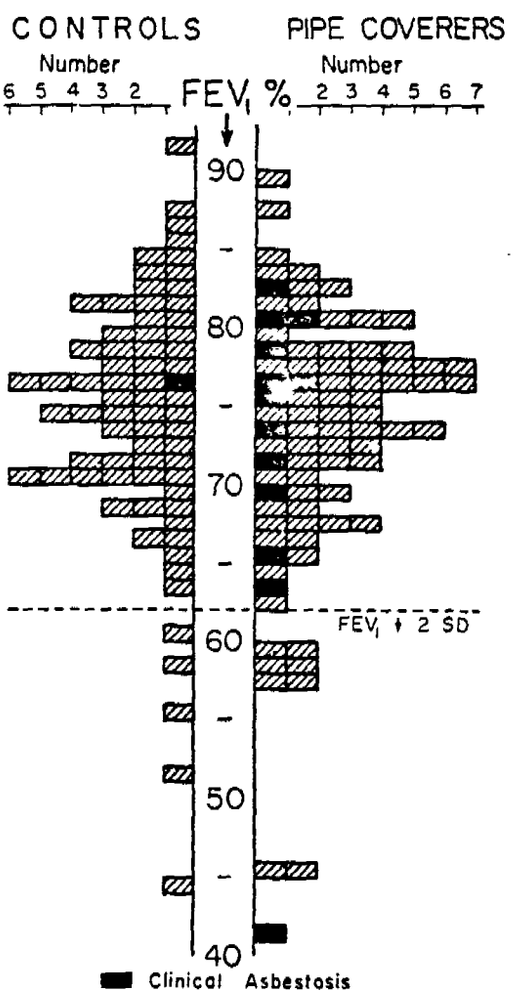
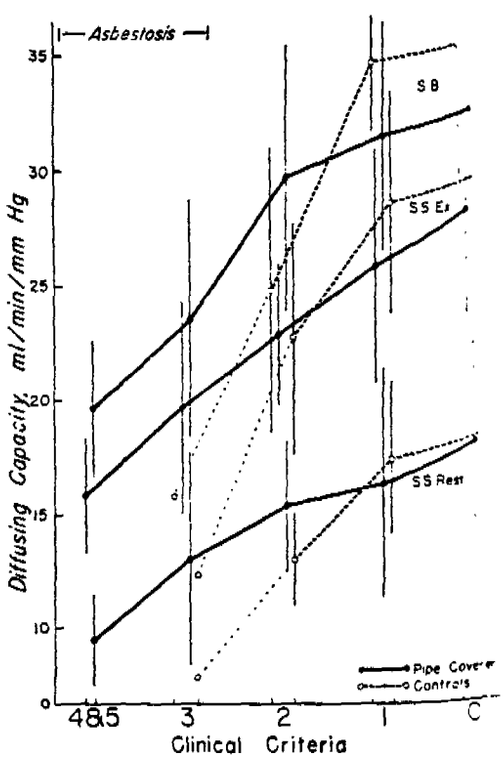


Fig 1.—Pipe coverers and controls arranged according to decreasing FEV_1%. Subjects with clinical asbestosis are indicated in black. The frequency distribution of FEV_1% was about the same for both; asbestosis was not significantly related to FEV_1%.

Fig 2.—The mean steady state rest, exercise and single breath diffusing capacities decreased with increasing number of clinical criteria for asbestosis. There was only one control with as many as three clinical criteria. The vertical lines represent 2 standard deviations.



with severe obstructive disease.

Concerning the relationship between FVC and D_L, it has been said that DLSS is more affected by ventilation-perfusion discrepancies, while DLSB is related more to lung volume; nevertheless, here FVC related equally well with both (Table 3).

All three D_L measurements were closely related, particularly DLSS-R with DLSS-Ex ($r = .75$) and DLSS-Ex with DLSB ($r = .72$). The scattergram of Fig 5 shows that all individuals with an abnormal DLSS-Ex also had an abnormally low DLSB, but the reverse was not true. There was a good correlation between Fco and DLSS (Fig 6) but with considerable scatter. This was largely because Fco was inversely related to minute ventilation ($r = -.63$ at rest, $-.76$ during exercise), while DLSS was only slightly affected by ventilation ($r = .09$ and .23, respectively) (Table 3). As a corollary, $P_{ET_{CO_2}}$ was much more related to Fco than to DLSS (Table 3). In other words, Fco was very sensitive to voluntary or pathologic hyperventilation while DLSS was much less affected by this.

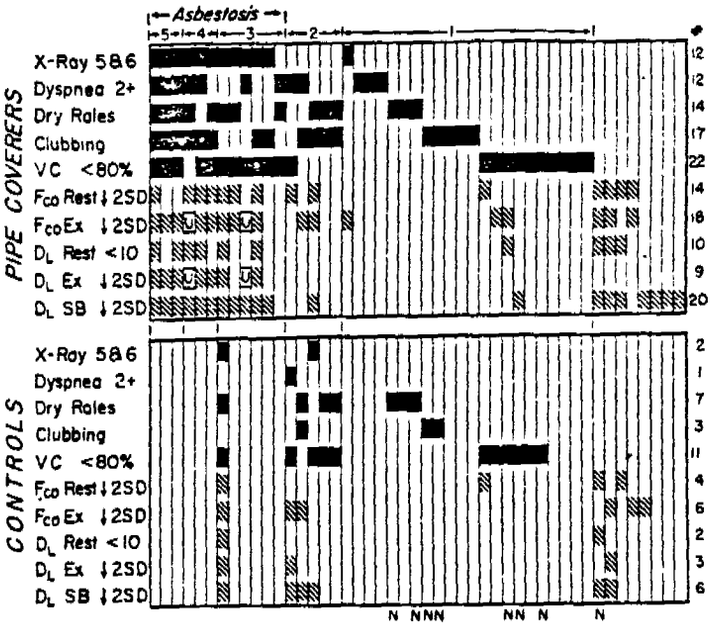
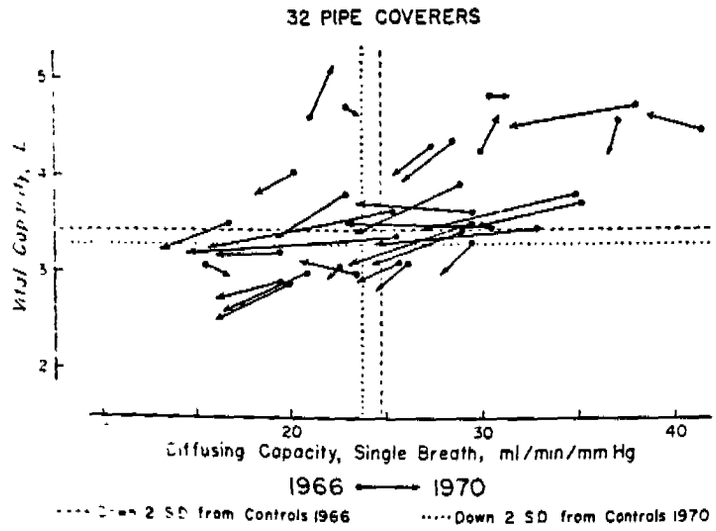


Fig 3.—Pipe coverers and controls arranged from left to right according to the number of positive clinical criteria; three or more signified asbestosis. Abnormalities of gas exchange are also shown. U signifies unable to exercise; N indicates normal controls (Table 2).

Fig 4.—Comparison of FVC and DLSB in 32 pipe coverers studied three years later. Eight had asbestosis in 1966, and ten in 1970. Solid dots indicate performance in 1966 and arrow for 1970. The lines indicate 2 standard deviations down from the mean of controls. The number of workers with a significantly decreased FVC increased from 12 to 14, and those with a reduced DLSB from 12 to 19 during the interval.



Comment

Respiratory abnormalities in advanced asbestosis have been well described. Reduction of lung compliance[1,22-25] is reflected by restriction of

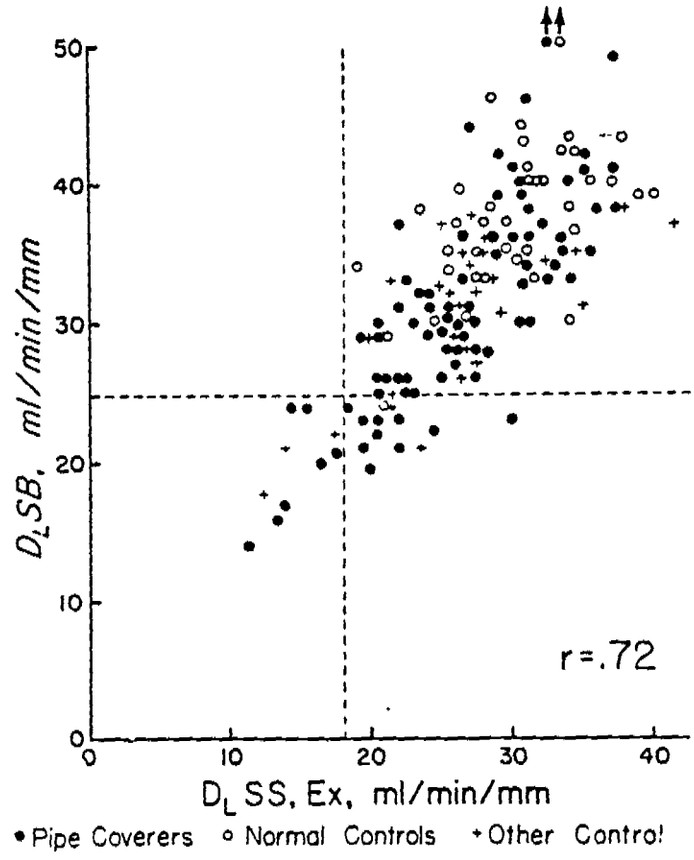


Fig 5.—Correlation between steady state exercise (DLSS-Ex) and breath holding (DLSB) diffusing capacities. Broken lines indicate 2 standard deviations down from the mean for all controls.

vital capacity.[1-8,22-29] This has been attributed to pulmonary fibrosis while the added effects of pleural complications have been considered more recently.[8,24,30,31] Hyperventilation, especially during exercise, is common.[3,4,8,24,26,27] Wright[2] has pointed out that dyspnea in asbestosis is more the result of an increased ventilatory requirement than of a reduced ventilatory capacity. Such hyperventilation, stimulated by slight hypoxemia and increased lung and chest wall reflexes, has been thought to occur early, but this was not borne out by our studies (Table 1).

Impaired O_2 exchange was first inferred from "oxygen debt," reduced ventilation on O_2 breathing[28] and oximeter studies[26,27] and eventually was confirmed by demonstration of increased A-a O_2 gradients.[2,5,13,29,31] This "alveolar-respiratory insufficiency" has been ascribed to alterations in the thickness and size of the pulmonary membrane.[2,26-28] With demonstration of a reduced D_L,[13] the term "alveolar-capillary block" was used to characterize the principal impairment resulting from asbestosis.[2-8,13,23,29,30] It is now recognized that the concept of alveolar-capillary block is an oversimplification because ventilation-perfusion discrepancies contribute, or may be largely responsible, for the A-a O_2 gradient. In asbestosis, uneven ventilation and perfusion have been demonstrated whenever refined techniques were used.[5,29,33] In such a "mixed impairment of O_2 transport mechanism,"[5] the theoretical and practical difficulties of separating "diffusion gradients" from "venous admixture gradients" are considerable.[24] At any rate, neither the pathologic changes nor the physiologic and clinical alterations of asbestosis differ from those associated with "usual interstitial pneumonitis."[34]

The Physiologic Alterations of Early Asbestosis.—Definition of such changes would be of greatest interest for monitoring of exposed workers. Wright[2] first reported functional abnormalities in asbestos workers without clinical or radiographic manifestations and such cases have been recognized subsequently.[3-7,22,30,32,35] Interpretation of these abnormalities is difficult because they may not be caused by asbestos.[36] Among our pipe coverers without clinical or radiologic signs of asbestosis, 18 had one or more physiologic alterations (Fig 3).

The discriminant value of function tests has been evaluated by comparing cases of asbestosis certified by the British Pneumoconiosis Medical Board with workers in asbestos-using industries without certifiable disease.[3,7,23,36] Even though the "diagnosis of the Medical Board is reliable,"[36] the significance of impaired function in the absence of clinical evidence of disease obviously cannot be evaluated in this way. Few serial examinations are available. Leathart[36] selected 12 laggers initially free of

disease; over a three- to nine-year period, five showed a drop of DLSS to less than 80% of their original reading. Among these, three developed rales, one emphysema, and one convincing evidence of asbestosis. More persuasive data come from Hunt.[6] He followed 36 workers with a DLSB below 60% but without clinical signs of asbestosis for four to five years. During this time, four died of neoplasia and had asbestosis at death, and 14 others developed clinical and radiological signs of asbestosis. Our own three-year follow-up included 24 pipe coverers with fewer than three clinical criteria for asbestosis; among those with initially reduced FVC and DLSB as the only abnormality, two developed dyspnea, dry rales, and clubbing, and one emphysematous bullae.

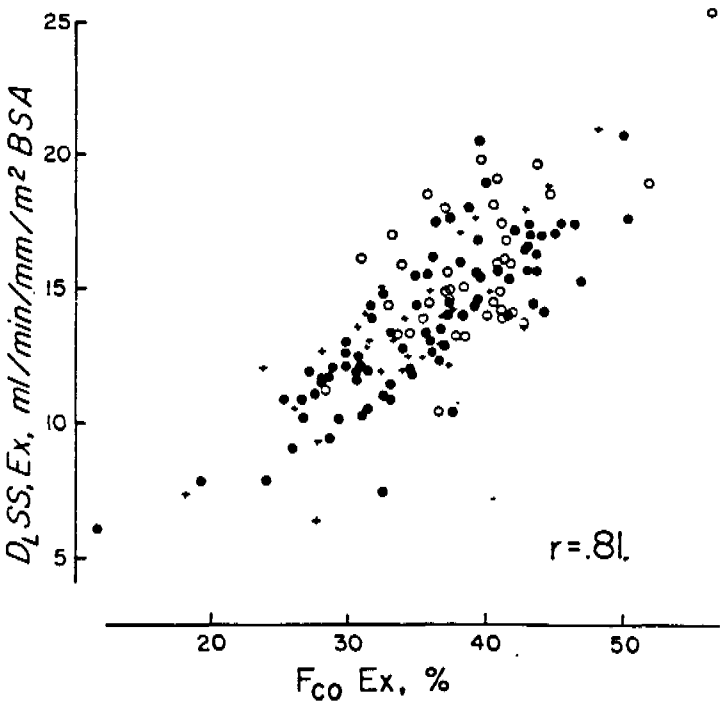


Fig 6.—Correlation between steady state exercise (DLSS-Ex) diffusing capacity per square millimeter of body surface area and fraction of carbon monoxide removed (FCO-Ex). The code is the same as in Fig 5.

The question of sensitivity of individual function tests has been considered. Williams and Hugh-Jones[3] and Leathart[4] suspected that DL might be the most sensitive index of impairment; and it is now recognized that reduced DL may be found in exposed individuals who have normal FVC.[6,7,23,31,32,36] Becklake and associates,[8] on the contrary, concluded from a population-oriented study that reduced FVC and inspiratory capacity (IC) are the earliest signs of asbestosis. Their data are difficult to interpret because they chose as controls asbestos workers without radiographic abnormalities. Also, their series purposely was weighted with older individuals[8]; indeed, before these older individuals were included, both FVC and DL were significantly reduced in early disease.[37] In our series, the mean DL was reduced even among workers with roentgenograms revealing questionable asbestosis. Prevalence surveys may be misleading on the question of which type of examination gives the earliest evidence of impaired function. The answer can come only by following a defined population over a period of years.[8] Unfortunately, no such studies have been reported.

The best estimate of disease prevalence in this group with uniform exposure, in our opinion, was the duration of exposure. Accordingly, we calculated correlation coefficients between this variable and our clinical criteria as well as selected tests of respiratory gas exchange. Pipe coverers and controls were combined for these analyses. Significant correlations were found for DLSB (−0.395), VC (−0.386), x-ray (0.356), dyspnea (0.320), and DLSS-Ex (−0.318) (Table 4). Discriminant function (multiple r^2) for the clinical variables excluding VC was 0.246; adding VC it was 0.299 and increased to a maximum of 0.311 when DLSB was the only test of respiratory gas exchange added to the clinical variables (Table 4). These associations are not as high as those reported by Regan et al[38] most likely because our inclusion of controls tended to lower these values. However, we believe that this represents a more accurate assessment of the true association.

Chronic Obstructive Lung Disease.—In early studies of severe asbestosis, emphysema and chronic bronchitis were prominent[26-29]; later, obstructive lung disease with reduced maximal breathing capac-

Table 4.—Simple Correlation Coefficients and Discriminant Function Analysis for Clinical Variables and Selected Tests of Pulmonary Function vs Duration of Exposure*

1. Simple correlation coefficients vs duration of exposure	
	r
Age	+.333
Dyspnea	+.320
Paronychial angle	+.086
Rales	+.229
VC	−.386
X-ray	+.356
DLSS-R	−.175
FCO-R	−.203
DLSS-Ex	−.318
FCO-Ex	−.309
DLSB	−.395
2. Discriminant function	
	Multiple r^2
Clinical variables (dyspnea, rales, paronychial angle, and x-ray films)	
Without VC	.246
With VC	.299
Clinical variables with VC plus	
(a) DLSS-R	.299
(b) FCO-R	.301
(c) DLSS-Ex	.301
(d) FCO-Ex	.299
(e) DLSB	.311

* Pipe coverers and controls combined.

ity and $FEV_1\%$ and increased R_A and residual volume (RV) was demonstrated in up to one half of patients.[4,24,31,33] Recent observers, however, have thought that this is not an important complication.[2,3,23,29,32] Furthermore, such tests as the $FEV_1\%$ and peak flow may be misleading[31] because, with increased elastic recoil of pulmonary fibrosis, this value may be larger than normal.[8] Most recently, it has been suggested on physiologic grounds that early asbestosis may result in obstructive disease of small airways.[39] However, this is not borne out by our pathologic studies of lung biopsies in early disease.[40]

Chronic bronchitis and emphysema are common particularly among older male smokers; therefore, comparison of large groups of exposed workers must be made with controls living in the same area, matched for sex, age, duration of employment, and smoking habits. Only three surveys have included controls,[6,32,35] and actual data were shown only by Kleinfeld et al,[32] who compared 56 asbestos workers with 50 men without dust exposure. They found more individuals with reduced $FEV_1\%$ and increased RV in the exposed group, but it contained twice as many smokers. In our clinical study, chronic obstructive lung disease was equally common among exposed workers and controls,[1] and this was confirmed by physiologic data (Fig 1); moreover the prevalence of obstructive impairment was no greater among pipe coverers with asbestosis than among those without clinical or radiologic manifestations of the disease.

Critique of Methods.—Determination of DLSS requires knowledge of the effective alveolar CO partial pressure, $P_{A_{CO}}$. Usually, this is calculated with the alveolar equation from arterial and expired P_{CO_2}.[11] To obviate arterial puncture, Leathart[36] used a rebreathing technique to estimate arterial P_{CO_2}. This was done as a separate procedure and without steady state and caused poor-reproducibility. Bates et al[41] and others[8] have used end-tidal sampling for CO, while we have preferred to sample $P_{ET_{CO_2}}$ because the latter can be done directly while the much larger sample needed for CO analysis requires a special and capricious end-tidal sampler. In 102 normal volunteers studied in our laboratories, $P_{ET_{CO_2}}$ averaged 2.1 mm less than $P_{A_{CO_2}}$ at rest, and 2.9 mm less during exercise. For eight asbestotics studied by both methods, the arterial-end-tidal CO_2 difference was similar: P_{aCO_2} averaged 37.5 mm and $P_{ET_{CO_2}}$ was 35.4 mm; while during exercise, these means were 38.2 and 35.3 mm, respectively. We concluded that our method, compared with the original Filley technique,[11] resulted in slightly lower values for DLSS and tended to accentuate the differences between normal subjects and those with lung disease. The same may apply to end-tidal CO sampling.

For calculation of DLSB, we used an alveolar volume, V_A, calculated from single breath He dilution instead of a volume obtained separately by He rebreathing. Aside from saving much time, this has been advocated as a better method because the distribution of He during breath-holding is said to be more relevant to the "effective V_A" to which CO is distributed during the same deep breath.[14] In normal subjects, the two

volumes should be the same. Actually, in 102 normal subjects in our laboratory, the mean rebreathing V_A of 4.19 liters (STPD) was virtually the same as the single breath V_A of 4.48 liters; and in seven of the pipe coverers with asbestosis, the mean D_L calculated from conventional rebreathing V_A was 17.1 ml/min/mm Hg while the mean from single breath He was 19.0 ml. With uneven lungs, as in emphysema, the single breath V_A may be smaller than the rebreathing V_A,[7,14] and hence the D_L would be underestimated by the simplified technique. Again, this would tend to exaggerate the differences between normal and abnormal subjects.

Conclusions

Tests of respiratory gas exchange gave corroborative evidence that some pipe coverers had asbestosis despite the low level of their exposure. All workers with three or more clinical criteria of asbestosis had markedly reduced D_L and F_{CO}. In addition, several with only two clinical criteria also had impaired gas transfer suggesting that inclusion of such data might improve our diagnostic acumen.

Among the several tests employed, D_LSS-Ex and D_LSB were reliable and reproducible methods of assessing interstitial lung disease, while D_LSS-R and particularly F_{CO}-R were sensitive to minor variations in minute ventilation.

A unique feature of this study as a detailed analysis of the cardiopulmonary status of controls selected on epidemiologic grounds. Although their mean FVC was normal, 30 of the 70 had cardiopulmonary abnormalities. This suggests that surveys looking at a single or only a few factors may be misleading. In spite of these abnormalities among the controls, the pipe coverers had significantly lower FVC, FEV_1, TLC, D_LSS-Ex, and D_LSB ($P < .01$) indicating the major effect of interstitial lung disease on these measurements. The presence of an equal number of cigarette smokers in the two groups, as well as their equal $FEV_1\%$, argues for the overriding importance of the dust exposure in producing the manifestations of lung disease herein described.

The earliest changes of interstitial pneumonitis, consisting of cellular infiltration and regenerating or metaplastic epithelium, probably cannot be detected by any method other than tissue examination.[30,31,36,40] Possibly, characteristic dry rales may be heard at this time.[36] Decrease of D_L and FVC cannot be appreciated until later because of the large standard error of normal range and because of the large pulmonary reserve. The geometric limitations of radiographic techniques are such that interstitial pneumonitis cannot be detected with some certainty until the disease is moderately advanced[34,40]; dyspnea, finger clubbing, and cyanosis are late manifestations.

No definitive studies provide an answer to the relative importance of individual criteria in detecting early asbestosis. Our results (Fig 3) support the impression of Thomson et al[7] that in some patients restriction of lung volume is the earliest manifestation of disease while in others abnormalities of gas exchange appear earlier. In our longitudinal studies, D_LSB deteriorated more rapidly than VC, suggesting that this measurement may prove more sensitive.

Asbestosis is a serious disease which is irreversible when advanced. It can occur with exposure to low levels of dust, and such exposure is increasingly common. Information on the diagnosis and early detection of asbestosis therefore is important and timely.

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