Asbestos Content of Lung Tissue, Lymph Nodes, and Pleural Plaques from Former Shipyard Workers[1,2]

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SUMMARY Autopsy samples from eight former shipyard workers were collected from lung parenchyma, tracheal lymph nodes, and pleural plaques. The tissue from each respective area was prepared by a modified bleach digestion technique, and the residue was collected on a 0.2-μm pore polycarbonate or 0.22-μm mixed cellulose ester filter.

Quantitation of ferruginous bodies and uncoated fibers was done by light and transmission electron microscopy, respectively. Differences in the asbestos burden were noted for each site. Ferruginous bodies were observed in both parenchyma and nodes but not in plaques. Three subjects were found to have more ferruginous bodies per gram dry weight in their lymph nodes than in their lung parenchyma. Likewise, all subjects were found to have more uncoated fibers per gram in the nodes than in the parenchyma. Amphibole and chrysotile fibers were noted in the lung and extrapulmonary sites, with chrysotile being the predominant asbestiform in plaques. The majority of the uncoated fibers in both the nodes and the plaques were < 5 μm in length. However, some fibers with dimensions conforming to the "Stanton hypothesis" reached both areas.

These residual patterns most likely reflect the impact of clearance on lung burden as opposed to the eventual accumulation and stasis in the extrapulmonary areas.

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Introduction

Attention has been given to the amount of asbestos found in lungs of occupationally exposed workers (1–6) and, to a lesser extent, to the concentrations in lungs of the general population (7–11). These analyses have defined the parenchymal burden not cleared by the mucociliary escalator or relocated into the interstitium and removed by the bloodstream and pulmonary lymphatics (12). This latter route includes a pathway for relocation that could explain the development of granulomatous lesions in extrapulmonary sites (lymph nodes, spleen, and liver) such as has been reported after exposure to fine soot and silica dust (13). In studies involving animals exposed to mixed minerals dusts, McMillan and coworkers (14) found appreciable relocation of titanium dioxide and quartz particles from the lung parenchyma to the lymph nodes.

Although the lymphatics may be involved in only a small fraction of the total particulate removal, they may nevertheless be very significant in the overall pathogenesis of lung diseases since a slow rate of particle movement allows maximal interactions to occur (15).

Much of the inhaled asbestos is in the form of thin fibers, and tissue data obtained by transmission electron microscopy indicate that many of these fibers retained in lung tissue are short, uncoated fibers (≤ 5 μm in length) (1, 16).

These small uncoated asbestos fibers are more easily moved and are thus likely candidates for relocation from lung parenchyma either via airway clearance or through interstitial routes to other tissues. However, most information about asbestos in extrapulmonary sites has been derived by light microscopy, which is selectively restricted by resolution limits (0.2 μm) and which identifies only ferruginous bodies (FB) or longer uncoated fibers. Although the numbers of FB reported in extrapulmonary sites have been low, their occurrence has been noted in tissue from the stomach (17), liver (18), kidney (18, 19), spleen (18–20), lymph nodes (20, 21), and bile duct tumor (22), and in pleural plaques (23). This tissue marker (i.e., FB) is known to represent only a fraction of the total fiber burden in lung tissue and offers no clear insight as to the levels of uncoated fibers in lung tissue, much less in other tissues.

The present study was designed, therefore, to expand the limited quantitative data that exist for total asbestos burdens (FB and uncoated fibers) in lung tissue compared with that in important extrapulmonary sites of relocation—lymph nodes and pleural plaques. The tissue in this study was obtained from occupationally exposed subjects, and the fiber diameter, length, type, and concentration in each area are reported.

Methods

Tissue samples were collected at autopsy from eight shipyard workers with histories of occupational asbestos exposure. The necropsies were performed at the General Hospital of Monfalcone, which is a small industrial town in northeastern Italy and is the site of large shipyards. The tracheal lymph nodes, parietal plaques, and lung parenchyma were fixed in prefiltered formalin (0.22-μm filter). To avoid cross-contamination, each tissue was placed in a separate container. Additionally, the pleural plaques and lymph nodes were carefully rinsed with water and debrided with precleaned scalpels for removal of all adhering tissue before the final samples were taken.

Subjects were 58 to 82 yr of age (mean, 70 ± 9 yr) at the time of autopsy. Seven had work histories indicating 6 to 46 yr of exposure in shipyard activities. The group consisted of smokers as well as nonsmokers (four smokers averaging 35 cigarettes per day, one ex-smoker, and three nonsmokers). Medical histories for the subjects showed multiple diseases. Seven of the eight subjects had cardiovascular disease, four had asbestosis, three had cancer, one had a neoplasm, and two had emphysema (table 1).

Areas of lung parenchyma were collected from beneath the pleura. The regions were carefully dissected to assure sampling of multiple homogeneous areas. Samples of parietal plaque and tracheal lymph nodes were

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TABLE 1

FORMER SHIPYARD WORKERS

Subject No	Sex	Age (yr)	Smoking History	Occupation	Disease	Plaque
1	M	58	15–20 cig/day	Shipyard plumber and painter, 30 yr, miner	Asbestosis; small cell Ca of right lung	Bilateral
2	M	61	20 cig/day	Shipyard welder, 37 yr	Asbestosis; adeno Ca of the right lung; arteriosclerosis	Bilateral
3	M	63	40 cig/day	Shipyard laborer, 6 yr; Navy; oil mill, crane operator	Laryngeal Ca; arteriosclerosis	Bilateral
4	M	70	60 cig/day	Shipyard worker and draftsman, 46 yr	Lung fibrosis; emphysema; arteriosclerosis	Bilateral
5	M	72	Stopped in 1973	Shipyard tracer, 27 yr	Arteriosclerosis; meningioma	Bilateral
6	M	76	No	Shipyard welder, 45 yr	Asbestosis; arteriosclerosis	Left
7	M	78	No	Shipwright, 25 yr; chemical industry	Asbestosis; emphysema; arteriosclerosis	Bilateral
8	F	82	No	Shipyard cleaner for some months; husband shipyard welder	Arteriosclerosis	Bilateral

Definition of abbreviations: Ca = carcinoma.

also carefully dissected. Each sample was halved, with one half used for the determination of the wet weight/dry weight ratio and the other half for digestion in 9.2% sodium hypochlorite. The mean weights of the individual samples were as follows: parietal plaque, 0.3691 ± 0.028 g wet; parenchyma, 0.3899 ± 0.018 g wet; lymph nodes, 0.2053 ± 0.053 g wet. Aliquots from each digest were filtered through either a 0.22-μm Millipore mixed cellulose ester filter for FB counts (Millipore Corp., Bedford, MA) or a 0.2-μm Nuclepore polycarbonate filter for fiber counts (Nuclepore Corp., Pleasanton, CA). This was followed by a further clean-up according to the procedure of Williams and coworkers (24). Reagent blanks were prepared using the same reagents and procedures described above.

Part of the mixed cellulose ester filter was cleared (made transparent) using acetone vapor, and the FB were counted at ×200 by light microscopy. FB per gram wet and dry weight were calculated for each digest. The average detection limits for FB were 55/g wet and 248/g dry.

Carbon extraction replicas were made from the polycarbonate filters, and these were examined at ×16,000 to ×100,000, as required, in a JEOL 100CX Temscan analytical electron microscope equipped with a Tracor Northern TN-2000 energy-dispersive X-ray analyzer. Actual length and width, composition, and electron diffraction pattern were characterized for each fiber encountered. All fibers 0.5 μm in length or greater were counted. The definition of a fiber for these counting procedures included those with ≥ 3:1 aspect ratios and parallel sides for a majority of their lengths. Forty 200-mesh grid squares were examined for each sample, and fibers per gram wet and dry weight were computed. The average detection limits were 41,000 fibers/g wet and 200,000 fibers/g dry.

The following nonparametric statistical tests were used because the data were not normally distributed. Spearman's rank correlation coefficient (25) was used to test for linear relationships between the various fiber and FB concentrations, and Wilcoxon's matched pairs signed rank test (25) was used to test for similarities in the amphibole to chrysotile concentration ratios between sites. It was also used to test for similarities among the median lengths and widths, which had been weighted by the number of asbestos fibers observed per case.

Results

Asbestosis had been diagnosed histologically in four of the subjects; however, all eight subjects had a history of occupational exposure to asbestos (table 1). The distribution of the chrysotile and amphibole concentrations in the tissues is illustrated by site in figure 1. In seven of the eight subjects (table 2), the numbers of FB in the lung parenchymal samples (1,120 to 853,000 FB/g dry) reflected this past exposure. The total number of uncoated asbestos fibers (chrysotile plus amphibole) in these seven subjects ranged from 830,000 to 192,000,000 per gram of dry tissue. No FB were found in pleural plaques; however, in three of the subjects the numbers of FB per gram of dry tissue from the tracheal nodes exceeded the numbers per gram in lung (table 2). There was no linear correlation between FB per gram dry and the chrysotile or amphibole concentrations. In the lung and nodes, the FB mean lengths were 39.2 ± 23.5 and 35.9 ± 23.2 μm, respectively (table 3), and, though surprisingly similar, were statistically different ($p = 0.0018$).

Linear correlations between the concentrations or concentration ratios of amphibole to chrysotile were generally not observed except for a negative correlation between lung and plaque chrysotile ($r = -0.881$; $p = 0.002$). Still, in all eight subjects, the chrysotile concentrations in the plaques exceeded the amphibole concentrations, whereas in the lungs (Subjects 3, 5, 6, and 7) and nodes (Subjects 4, 5, 6, and 8), this was true in only half of the subjects (table 2).

In seven of eight subjects, the amphibole to chrysotile concentration ratios were greater in the lungs than in the plaques ($p = 0.0173$), and in all cases they were greater in the nodes than in the plaques ($p = 0.0117$).

The physical features of the two types of uncoated asbestiforms in the lungs did vary ($p < 0.00005$ for length and width). As shown in table 4, 86% of the chrysotile was ≤ 5 μm in length, whereas 59% of the amphibole was ≤ 5 μm in length. The mean length of chrysotile was 2.87 ± 1.07 μm, whereas that for amphibole was twice that figure (5.82 ± 6.71 μm).

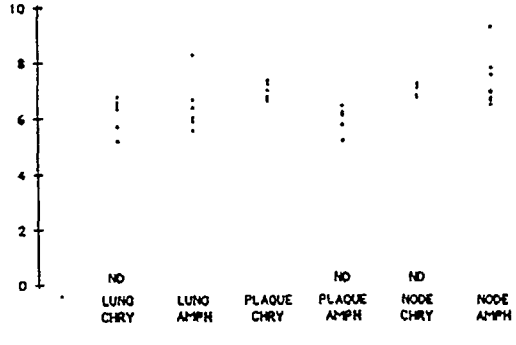

Fig. 1. Log of asbestos concentration by site (fibers/gram dry). ND = none detected.

TABLE 2

FORMER SHIPYARD WORKERS*

Subject No.	Tissue Location	FB/g Wet	FB/g Dry	CHRY/g Wet	CHRY/g Dry	AMPH/g Wet	AMPH/g Dry	ASB/g Dry
1	PL	ND	ND	2.900	9.900	430	1.500	11,400
	LU	154.000	853.000	370	2.000	34.000	190.000	192.000
	NO	17.600	68.600	ND	ND	430.000	1,700.000	1,700,000
2	PL	ND	ND	2.200	5.500	500	1.300	6,800
	LU	1.200	7.080	650	3.800	780	4.600	8,400
	NO	1.170	3.420	5.100	15.000	21.000	62.000	77.000
3	PL	ND	ND	4.800	16.000	850	2.900	18.900
	LU	0.238	1.300	90	500	60	330	830
	NO	2.100	11.100	ND	ND	550	2.900	2.900
4	PL	ND	ND	5.500	17.000	500	1.600	18.600
	LU	0.051	0.269	25	140	64	340	480
	NO	4.160	17.200	3.000	13.000	2.200	9.000	22.000
5	PL	ND	ND	1.400	4.000	480	1.400	5.400
	LU	0.265	3.030	480	5.500	64	720	6.220
	NO	1.030	4.370	2.900	12.000	1.200	5.200	17.200
6	PL	ND	ND	2.100	5.200	250	630	5.830
	LU	1.390	9.340	350	2.400	140	930	3.330
	NO	ND	ND	4.200	18.000	1.900	7.700	25.700
7	PL	ND	ND	1.300	3.900	52	160	4.060
	LU	3.300	22.300	410	2.800	160	1.100	3.900
	NO	2.050	10.200	1.300	6.600	6.700	33.000	39.600
8	PL	ND	ND	6.200	21.000	ND	ND	21.000
	LU	0.232	1.120	ND	ND	490	2.400	2.400
	NO	0.147	0.610	1.700	5.500	1.200	4.100	9.600

Definition of abbreviations: FB = ferruginous bodies; CHRY = chrysotile fibers; AMPH = amphibole fibers; ASB = total asbestos; ND = none detected; PL = plaque; LU = lung; NO = node

* Data × 1,000

TABLE 3

FERRUGINOUS BODY LENGTH*

	Mean	Median	Minimum	Maximum
Plaque†	–	–	–	–
Lung, n = 591	39.2 ± 23.5	34	8	119
Node, n = 241	35.9 ± 23.2	30	9	112

* All dimensions are in micrometers.

† None detected.

TABLE 4

UNCOATED CHRYSOTILE AND AMPHIBOLE FIBERS*

	Average Length	Average Width	Length % > 5 µm	Length % > 10 µm
Chrysotile fibers				
Plaque	1.34 ± 1.50 (0.85)	0.09 ± 0.15 (0.06)	3.1	0.0
Lung	2.87 ± 1.07 (1.51)	0.07 ± 0.06 (0.05)	14.0	4.0
Node	1.27 ± 1.07 (0.94)	0.08 ± 0.06 (0.06)	0.0	0.0
Amphibole fibers				
Plaque	1.98 ± 3.13 (1.05)	0.15 ± 0.07 (0.14)	10.0	8.0
Lung	5.82 ± 6.71 (3.39)	0.19 ± 0.21 (0.14)	41.0	20.0
Node	2.22 ± 3.36 (1.55)	0.21 ± 0.12 (0.18)	6.0	2.5

* All dimensions in micrometers; numbers in parentheses are geometric means.

The mean amphibole width was 0.19 ± 0.21 µm, which was more than 2.5 times the chrysotile width of 0.07 ± 0.06 µm; figures 2 and 3 illustrate the length and width distributions of all uncoated chrysotile and amphibole fibers found at each of the three sites.

The process involved in relocating asbestos fibers to these extrapulmonary sites results in deposition of a typically shorter uncoated fiber. For example (table 4), no uncoated chrysotile fibers > 5 µm were found in the nodes, and only 3.1% of the chrysotile found in the plaques was > 5 µm in length, whereas 14% of the chrysotile in the lung was > 5 µm in length. Ten percent of the amphibole fibers in the plaques and 6% in the nodes were > 5 µm in length compared with 41% in the lung > 5 µm in length. The lengths of both types of asbestos were significantly shorter ($p < 0.00005$) in both plaques and nodes compared with those found in the lung parenchyma. Node amphibole fibers were significantly longer ($p < 0.00005$) than plaque amphibole fibers. Some longer amphibole fibers (> 10 µm in length) were found in both the nodes (2.5%) and the plaques (8%).

The accumulation of uncoated asbestos fibers in nodes and plaques resulted in the highest concentrations occurring outside the lung in all of the subjects (table 2). In six subjects, this occurred in the nodes, whereas in two, the plaques contained the highest number of uncoated asbestos fibers among the sites.

The chrysotile fibers in the lung tissue were significantly thinner than those in the plaques or the nodes ($p < 0.00005$), whereas the node amphibole fibers were significantly wider than those in the lungs or the plaques ($p < 0.00005$). When the amphibole and chrysotile dimensions were compared at each site, the amphibole fibers were significantly longer and thinner ($p < 0.00005$). Assessing the dimensions of width in another perspective, 97% of all chrysotile and 80% of all amphibole fibers from all sites were less than 0.3 µm in diameter.

Discussion

The lungs of humans are protected by various defense mechanisms that are activated by foreign particles from the environment. The deposition of dusts (including asbestos) is met with an efficient clearance system that eliminates inhaled particles (26) via the "escalator" concept of an upward shifting of particulates (27) until they are eventually removed in spu-

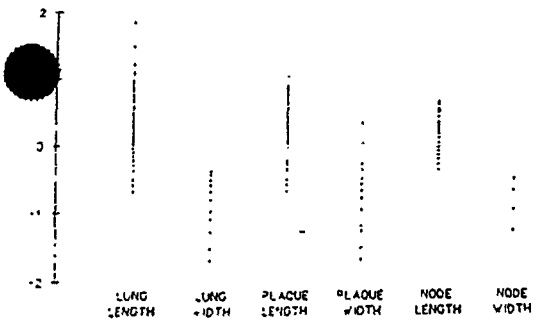

Fig 2. Log of chrysotile asbestos dimensions by site (micrometers).

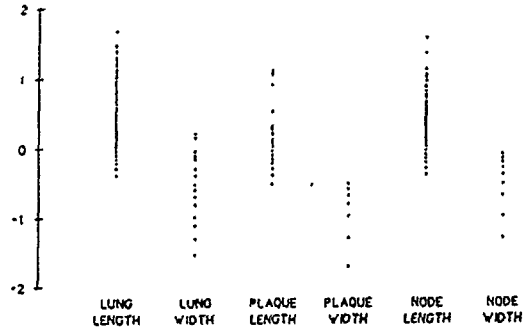

Fig 3. Log of amosite asbestos dimensions by site (micrometers).

tum (28). When the combined protective systems are overwhelmed (26), potentially irreversible damage and/or a relocation of inhaled dusts to more permanent deposition sites in subpleural areas (29, 30) can occur.

In the specific case of inhaled fibers, selective clearance rates occur according to fiber length. The short fibers can be relocated more easily and/or cleared by the mucociliary pathway or other routes more efficiently over time than are the longer fibers (31–33).

A slower pathway for clearance of fibers from lung parenchyma is through the interstitium, the lymphatics (27, 34, 35), or the lung vasculature. These routes are the least rapid but, as shown in our present study, result in an appreciable number of asbestos fibers being deposited over time within lymph nodes and pleural tissues. Although most of the fibers in both nodes and plaques are short (≤ 5 μm), their numbers are often higher per gram than those in lung tissue from the same person. It is assumed that the higher burden in nodes and plaques can be explained by the less efficient clearance of these areas as contrasted with the impact of the more efficient clearance mechanisms operating in the lung parenchymal areas. Although the route from the original site of fiber deposition in the lung to relocation into lymph nodes and plaques is speculative, the deposited fibers are characterized by significantly shorter lengths, supporting some type of selection process.

Chrysotile has been noted as the predominant asbestiform in parietal pleura (36). This observation is of particular interest since the lower limit of fiber length used in that study would have preferentially excluded many of the shorter chrysotile fibers included in the ≥ 0.5 μm limit set in the present study. The data of both studies indicate that chrysotile can accumulate in the pleural regions. Several other studies have indicated that chrysotile makes up a majority of these short, uncoated fibers (8, 16, 37). An explanation of this stems from length being a determinant of which fibers were relocated to the pleural regions.

A greater number of longer amphibole fibers reached the nodes than the plaques as is reflected by the observation of FBs (on amphibole cores) in the former and not in the latter. Although most uncoated amphibole fibers in both extrapulmonary sites are short, amphibole fibers that fit the dimensions of the "Stanton hypothesis" (38, 39) do reach both of these extrapulmonary sites. Thus, although relatively few of these longer amphiboles are present in the overall burden, these fibers, which are potentially more carcinogenic (because of their dimensions), do reach the plaques. No chrysotile fibers fitting Stanton's dimensions were found in the nodes, but a small percentage found in the pleural plaques did conform to these aspect ratios.

It must further be recognized that the data from this study require a resolution best attained by the transmission electron microscope and counting criteria that include short, thin fibers. Furthermore, processing must include fiber collection on filters with optimally sized pores since the diameter of many of these uncoated fibers are such that they could pass through filters with larger pore sizes (40).

Although this study was not intended to address issues of long versus short fibers and their potential toxicity, it nevertheless has shown that some longer fibers (> 5 μm) and large numbers of short (≤ 5 μm) fibers reach lymph nodes and plaques.

Stringent standards of technique, preparation, and resolution are required to include these short, uncoated fibers in a quantitative analysis of tissue burden, but their presence and numbers justify this type of study. This is particularly important since recent data suggest that short fibers may be important in lung fibrosis (41), and nothing is known about their impact in extrapulmonary areas.

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