Fiber Burden and Patterns of Asbestos-related Disease in Workers with Heavy Mixed Amosite and Chrysotile Exposure

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To attempt to determine the mineralogic factors that relate to the appearance of specific types of asbestos-related disease in workers with heavy mixed exposure to amphiboles and chrysotile, we analyzed the pulmonary asbestos fiber burden in a series of 144 shipyard workers and insulators from the Pacific Northwest. Amosite was found in all lungs, and tremolite and chrysotile in most lungs, but the vast majority of fibers were amosite. Tremolite and chrysotile concentrations were significantly correlated, indicating that the tremolite originated from chrysotile products, but no correlation was found between tremolite or chrysotile concentration and amosite concentration. Time since last exposure was correlated with decreasing amosite concentration and the calculated clearance half time was about 20 yr. In a multiple regression analysis that accounted for the presence of more than one disease in many subjects, a high concentration of amosite fibers was correlated with the presence of airway fibrosis and asbestosis, whereas subjects with mesothelioma, lung cancer, pleural plaques, or no asbestos-related disease had about the same, much lower, amosite concentration. No relationship was found between the concentration of chrysotile or tremolite and any disease. Analysis of fiber size measures (length, width, aspect ratio, surface, mass) showed that pleural plaques were strongly associated with high aspect ratio amosite fibers and suggested that mesotheliomas were associated with low aspect ratio amosite fibers. We conclude that, in this population, the major residual fiber is amosite, and only amosite concentrations correlate with the presence of specific diseases, raising questions about the role of chrysotile in disease induction. There are distinct differences in the relationship of fiber burden and disease comparing workers with heavy amosite exposure to chrysotile miners and millers; in particular, mesothelioma appears at much lower amosite burdens than does asbestosis, in contrast to the situation previously reported for chrysotile-induced mesothelioma. Amosite clearance from the lung is extremely slow, requiring decades. Except for pleural plaques, the association of fiber size and disease remains uncertain. **Churg A, Vedal S. Fiber burden and patterns of asbestos-related disease in workers with heavy mixed amosite and chrysotile exposure. Am J Respir Crit Care Med 1994;150:663–9.**

That heavy occupational exposure to asbestos produces a variety of pleuropulmonary diseases is well established, but much less information is available about the relationship of pulmonary asbestos fiber burden, taken in its broadest sense of fiber concentration, fiber type, and fiber size, and the appearance of specific diseases. A variety of studies have investigated this issue (1–6), but most have considered only the issue of fiber concentration, and chrysotile has not always been separated from amphibole. Furthermore, many such studies compare exposed workers with nonexposed controls, and this approach may yield misleading information, particularly in respect to fiber size differences (see DISCUSSION).

In this study we examine a large group of shipyard and insulation workers and workers in related trades with heavy mixed amphibole and chrysotile exposure to ask the question: Within a group of heavily exposed workers, what are the mineralogic measures that correlate with the appearance of specific diseases? We also compare our results with data from a previous, similarly designed, study of chrysotile miners and millers, and with various fiber size–related predictions from the experimental and human literature.

METHODS

Cases for this study were selected from a series of approximately 160 autopsy lungs referred to our laboratory for mineral analysis (and, in many cases, for pathologic diagnosis as well). These cases constituted all the cases received and analyzed by our laboratory from 1981 through 1991 for which the following criteria were met. All of the cases were from the Pacific Northwest (Oregon, Washington, British Columbia) and all of the patients had been at some time in their careers shipyard workers, asbestos insulators, or in related trades such as pipefitters. Approximately half the cases were medical-legal referrals and half were initially referred by pathologists, although after completion of diagnoses and mineral analysis, the majority of cases referred by pathologists became medical-legal cases. We were thus able to obtain detailed occupational and smoking

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TABLE 1

DEMOGRAPHIC AND DISEASE DATA

Variable	N	Mean	SD	Range
All subjects, N = 144				
Sex	134M, 10F			
Age	136	66	9.8	37–86
Smoking, pack-years	126	30	33	0–150
Exposure, yr	128	20	15	1–50
Latency, yr	114	43	7.8	20–64
Years since last exposure	113	25	15	1–47
Subjects without asbestos-induced disease, N = 8				
Sex	8M			
Age	8	72	8.8	60–84
Smoking, pack-years	6	37	10	20–50
Exposure, yr	6	33	8.7	19–43
Latency, yr	5	47	9.4	38–63
Years since last exposure	5	14	6.3	5–20

Disease	No. Subjects	No. Subjects Having Only This Disease
Asbestosis	23	3
Airway fibrosis	16	0
Mesothelioma	83	13
Lung cancer	32	12
Pleural plaques	103	9
No asbestos disease	8	

Subjects with multiple diseases

Plaques Plus	No.	Lung Cancer Plus	No.	Mesothelioma Plus	No.
Asbestosis	17	Asbestosis	8	Asbestosis	5
Airway fibrosis	14	Airway fibrosis	5	Airway fibrosis	9
Mesothelioma	69				
Lung cancer	16				

histories from legal records in about 75% of the cases. Historic data for the remaining cases were obtained from referring pathologists or clinicians. All of the patients were either known to have been exposed to mixtures of amphibole (amosite) and chrysotile, or presumed to be so exposed because of general historic information about the types and levels of asbestos exposure encountered in these specific occupations.

The lungs for each case were reviewed by standard gross and microscopic techniques to determine the presence of each of the asbestos-related diseases listed in Table 1. In most cases four standard histologic sections (two upper lobe, two lower lobe) were prepared. A number of cases were excluded because we could not determine whether pleural plaques were present from the pathologic material and neither autopsy nor radiologic data could be obtained to answer this question, leaving 144 cases for the study.

Asbestos-induced airway fibrosis as used here denotes a specific pattern of asbestos-induced fibrotic thickening of the walls of membranous and respiratory bronchioles (see ref. 7 for a complete description and illustrations of this lesion), and a case was considered to have airway fibrosis if any airways fitting this pattern were observed. Asbestosis is used to refer to diffuse interstitial fibrosis affecting alveolar walls along with the presence of at least one asbestos body in the tissue sections; airway disease by itself was not considered asbestosis. Only one case showed both of these lesions.

For each case at least one 5-g sample of formalin-fixed lung tissue was dissolved in bleach, and the mineral fibers collected for analytical electron microscopy. In general if only one sample was analyzed it was taken from the peripheral upper lobe, and if two were analyzed, then both peripheral and central upper lobe were used. An additional piece of lung was dried to constant weight to allow expression of results in terms of fibers per gram dry lung. For each sample, a minimum of 50 randomly selected grid squares were examined and all asbestos fibers longer than 0.5 μm found were counted, measured, and identified using a combination of fiber morphology, and fiber chemistry as determined by energy-dispersive x-ray spectroscopy. Fiber concentrations were calculated using an algorithm relating weight of lung tissue used and number of grid squares examined. Crocidolite fibers were found in only a very few cases, usually in quite small numbers, and have been excluded from all analyses.

The following fiber characteristics were included in the analyses: fiber type, fiber concentration, and mean fiber size (length, width, aspect ratio, surface area, mass). Initial inspection showed that fiber concentration was log-normally distributed, and statistical analyses were performed using log-transformed values. Geometric means were calculated for presentation of the data on concentration. The fiber size data were best normalized using a square root transformation and the data are presented using means derived from the square roots. Pearson correlation coefficients were used to assess the association between two continuous variables. For each fiber type, concentration or size values for subjects with each specific disease were initially compared with subjects without any disease using *t* tests. However, because most cases had more than one disease, multiple regression models in which the asbestos measure of interest was regressed on indicator variables for each of the diseases plus any relevant covariates were constructed. All statistical calculations were performed using SYSTAT (8).

RESULTS

Demographic data and the number of subjects in the sample with specific asbestos-related disease are shown in Table 1, along with data on the subjects with no asbestos-related disease. Exposure to asbestos was generally long (mean 20 yr, range less than 1 to 50 yr); no actual exposure measurements were available, but historic data indicate that exposure levels in many instances were high. Most subjects had more than one asbestos-related disease, as listed in Table 1.

Table 2 shows correlations of asbestos exposure with log fiber concentrations. Amosite concentration decreased with time since last exposure, but was not associated with length of exposure or exposure latency, or with age. The amosite tissue half-life, estimated from a regression of concentration on time since last exposure, was 20 yr. Neither tremolite nor chrysotile concentration was associated with any measure of asbestos exposure. Table 3 lists correlations between the concentrations of the various fiber types: A moderately strong correlation ($R = 0.37$, $p < 0.001$) was seen between tremolite and chrysotile concentrations, but there was no correlation between tremolite or chrysotile concentration and amosite concentration.

Amosite fibers were found in all 144 cases, chrysotile fibers in 102 cases, and tremolite fibers in 125 cases. Mean fiber concentrations in subjects with the various asbestos-related diseases were compared with those with no asbestos-related disease for amosite (Table 4), chrysotile (Table 5), and tremolite (Table 6). Where no chrysotile or tremolite was detected, a concentration

TABLE 2

CORRELATIONS (p VALUE) OF ASBESTOS EXPOSURE AND FIBER CONCENTRATION

	Age	Exposure	Latency	Time Since Last Exposure
Log amosite	−0.12 (0.15)	0.12 (0.18)	−0.15 (0.12)	−0.28 (0.002)
Log tremolite	0.02 (0.85)	0.09 (0.31)	0.14 (0.13)	−0.05 (0.59)
Log chrysotile	0.03 (0.71)	0.07 (0.47)	−0.02 (0.83)	−0.11 (0.24)

TABLE 3

CORRELATIONS OF CONCENTRATIONS OF DIFFERENT FIBERS

Tremolite*chrysotile	$R = 0.37$ $p < 0.001$
Amosite*chrysotile	$R = 0.10$ $p = 0.21$
Amosite*tremolite	$R = 0.02$ $p = 0.82$

of zero was assumed. Subjects with asbestosis had significantly higher amosite concentrations than subjects with no asbestos-related disease, and this also appeared to be true for subjects with airway fibrosis. Multiple linear regression models, in which fiber concentrations were regressed on indicator variables for each asbestos-related disease, were generated in an attempt to determine associations between concentration and disease that were independent of the presence of other asbestos-related diseases. These models confirmed the association of asbestosis and airway fibrosis with high amosite fiber burdens (Tables 4 and 7). No correlations were found between chrysotile or tremolite concentration and the presence of any disease; the few values which appear significant in Table 5 actually reflect higher concentrations in the subjects without disease compared with those with disease. Table 7 shows the regression coefficients and standard errors for these models.

We attempted to examine the effects of long versus short fibers of amosite using an arbitrary definition of "long" as greater than 8 μm (see DISCUSSION), and regressing the concentration of long or short fibers on the same disease indicator variables used above. Because of the very high correlation ($r = 0.99$) between concentrations of long and short fibers, this procedure produced results essentially identical to those found using total fiber concentrations.

The association of amosite fiber length and aspect ratio with the asbestos-related diseases is shown in Tables 8 and 9. Fiber

TABLE 4

GEOMETRIC MEAN AMOSITE CONCENTRATIONS IN SUBJECTS WITH ASBESTOS-RELATED DISEASE COMPARED WITH SUBJECTS WITHOUT ANY DISEASE*

	Cases With Disease			Cases Without Disease			t Test†	Multiple Regression Model‡
Disease	N	Geometric Mean	SD	N	Geometric Mean	SD	(p)	(p)
Asbestosis	23	10	6.6	8	0.67	5.1	< 0.001	< 0.001
Airway fibrosis	16	4.3	12	8	0.67	5.1	0.072	0.001
Mesothelioma	83	0.86	7.6	8	0.67	5.1	0.74	0.21
Lung cancer	32	1.1	8.3	8	0.67	5.1	0.53	0.20
Pleural plaques	103	1.4	7.8	8	0.67	5.1	0.31	0.08

* Concentration values in millions of fibers/g dry lung.
† Comparison of cases with specified disease to those with no disease by *t* test.
‡ Multiple regression model accounting for the presence of more than one disease in most subjects.

TABLE 5

GEOMETRIC MEAN CHRYSOTILE CONCENTRATIONS IN SUBJECTS WITH ASBESTOS-RELATED DISEASE COMPARED WITH SUBJECTS WITHOUT ANY DISEASE*

	Cases With Disease			Cases Without Disease			t Test†	Multiple Regression‡ Model
Disease	N	Geometric Mean	SD	N	Geometric Mean	SD	(p)	(p)
Asbestosis	23	0.005	300	8	0.035	81	0.38	0.38
Airway fibrosis	16	0	1000	8	0.035	81	0.006	0.06
Mesothelioma	83	0.004	250	8	0.035	81	0.29	0.67
Lung cancer	32	0.031	150	8	0.035	81	0.95	0.30
Pleural plaques	103	0.004	250	8	0.035	81	0.29	0.30

* Concentration values in millions of fibers/g dry lung.
† Comparison of cases with specified disease to those with no disease by *t* test.
‡ Multiple regression model accounting for the presence of more than one disease in most subjects.

TABLE 6

GEOMETRIC MEAN TREMOLITE CONCENTRATIONS IN SUBJECTS WITH ASBESTOS-RELATED DISEASE COMPARED WITH SUBJECTS WITHOUT ANY DISEASE*

	Cases With Disease			Cases Without Disease			t Test†	Multiple Regression Model‡
Disease	N	Geometric Mean	SD	N	Geometric Mean	SD	(p)	(p)
Asbestosis	23	0.034	125	8	0.079	85	0.67	0.27
Airway fibrosis	16	0.092	73	8	0.079	85	0.93	0.82
Mesothelioma	83	0.051	63	8	0.079	85	0.78	0.81
Lung cancer	32	0.21	13	8	0.079	85	0.43	0.31
Pleural plaques	103	0.049	65	8	0.079	85	0.76	0.20

* Concentration values in millions of fibers/g dry lung.
† Comparison of cases with specified disease to those with no disease by *t* test.
‡ Multiple regression model accounting for the presence of more than one disease in most subjects.

TABLE 7

LINEAR REGRESSION MODELS OF ASBESTOS FIBER CONCENTRATION ON ASBESTOS-RELATED DISEASES*

Fiber	Intercept	Asbestosis	Airway Fibrosis	Mesothelioma	Lung Cancer	Pleural Plaques	r^2
Amosite	13.33	2.59 (0.46)†	1.70 (0.51)†	−0.55 (0.44)	−0.63 (0.49)	0.66 (0.37)‡	0.29
Chrysotile	10.14	−1.15 (1.31)	−2.77 (1.45)‡	−0.54 (1.25)	1.47 (1.39)	−1.12 (1.07)	0.06
Tremolite	11.94	−1.07 (0.96)	0.25 (1.06)	−0.22 (0.91)	1.03 (1.02)	−1.00 (0.78)	0.04

* Concentration data as fibers/g dry lung. Entries are regression coefficients of log fiber counts, with standard errors of the coefficients in parenthesis, on each of the independent variables included in the model.
† $p < 0.01$.
‡ $p < 0.10$.

TABLE 8

MEAN AMOSITE FIBER LENGTH IN SUBJECTS WITH ASBESTOS-RELATED DISEASE

	Cases With Disease		Cases Without Disease			
Disease	N	Mean* (μm)	N	Mean* (μm)	t Test† (p)	Multiple Regression Model‡ (p)
Asbestosis	23	6.4	8	4.6	0.18	0.33
Airway fibrosis	16	6.0	8	4.6	0.29	0.64
Mesothelioma	83	5.5	8	4.6	0.48	0.32
Lung cancer	32	5.7	8	4.6	0.39	0.73
Pleural plaques	103	5.9	8	4.6	0.32	0.16

* Mean derived from square root transformed values.
† Comparison of cases with specified disease to those with no disease by t test using square root transformed values.
‡ Multiple regression model accounting for the presence of more than one disease in most subjects and using square root transformed values.

TABLE 9

MEAN AMOSITE ASPECT RATIO IN SUBJECTS WITH ASBESTOS-RELATED DISEASE COMPARED WITH SUBJECTS WITHOUT ANY DISEASE

	Cases With Disease		Cases Without Disease		t Test	Multiple Regression Model‡
Disease	N	Mean*	N	Mean*	(p)	(p)
Asbestos	23	45	8	36	0.48	0.46
Airway fibrosis	16	37	8	36	0.92	0.72
Mesothelioma	83	36	8	36	0.99	0.077
Lung cancer	32	39	8	36	0.80	0.50
Pleural plaques	103	40	8	36	0.73	0.004

* Mean derived from square root transformed values.
† Comparison of cases with specified disease to those with no disease by t test using square root transformed values.
‡ Multiple regression model accounting for the presence of more than one disease in most subjects and using square root transformed values.

length was not associated with disease. On initial comparison of the aspect ratio data (i.e., analyzed by simple *t* test), no differences were seen because of confounding due to the presence of multiple diseases. The multiple regression analysis, which reflects the associations of each disease with aspect ratio independent of associated diseases, indicated that the subjects with plaques had significantly higher aspect ratios than those without disease, and that the subjects with mesothelioma had near significantly lower ratios. This latter conclusion is not apparent in Table 8, but if one compares the mean aspect ratios in subjects with both mesothelioma and plaque (37, n = 69), subjects with plaque but not mesothelioma (47, n = 34), subjects with mesothelioma but not plaque (30, n = 14), and subjects without disease (36, n = 8), then it becomes clear that the aspect ratios associated with plaque alone are higher and the aspect ratios associated with mesothelioma alone are lower than the aspect ratios in subjects with no disease.

No associations between amosite fiber width, surface area, or mass and specific diseases were observed. Because of the low concentrations of chrysotile and tremolite fibers no attempt was made to evaluate associations between chrysotile or tremolite size measures and disease.

DISCUSSION

In this study we have examined the relationship of a variety of fiber-related measures and specific asbestos-related diseases to attempt to determine which of these measures are responsible for the appearance of given diseases within a heavily exposed workforce. As noted in the introduction, this question has been studied by several groups, with somewhat inconsistent results.

For both amphiboles and chrysotile there is general agreement that patients with asbestosis have the highest lung burdens (1–6), but no agreement about what size of fiber is related to asbestosis. Experimentally long fibers appear to be much more fibrogenic than short fibers (9–12), but in previous studies of both amosite-

and chrysotile-induced asbestosis in humans (13, 14), we found that the concentration of short fibers correlated better with fibrosis grade than did the concentration of long fibers. Whether these findings reflect local interference with clearance mechanisms (15, 16), an effect of modifying agents such as cigarette smoke which particularly appears to increase short fiber retention (17), or whether the experimental data simply do not apply to humans, remains unresolved.

There is also general agreement that, for amosite- or crocidolite-induced disease, mesotheliomas and plaques appear at much lower burdens than does asbestosis (2–5). How cases of amphibole-induced mesothelioma and amphibole-induced plaques relate to each other in terms of fiber burden has been less clear (2–4), as, indeed, has the question of what factors discriminate between these two pleural diseases.

The effect of fiber size on the induction of mesothelioma has been an area of considerable interest. Stanton and colleagues (18) originally proposed that, within a specific set of fiber lengths, relatively longer and thinner (i.e., higher-aspect-ratio) fibers have a greater propensity to induce mesothelioma than do shorter and thicker (lower-aspect-ratio) fibers; experimental studies by Davis and colleagues (11, 12) have suggested that fibers shorter than about 5 μm have little propensity to induce mesothelioma.

Again, the question of how well such predictions apply to humans is unresolved. In a general sense, the reported human data on the ability of tremolite to induce mesothelioma are consistent with the Stanton hypothesis, because populations exposed to long high-aspect-ratio tremolite fibers (for example, those at the Libby vermiculite mine [19] and those in the Metsovo area of Greece [20]) have much higher incidences of mesothelioma than do Quebec chrysotile miners and millers whose exposure is to shorter fibers with lower aspect ratios (23). McDonald and coworkers (21) and Rogers and coworkers (22) performed case control studies of patients with mesothelioma compared with control subjects; the former group found that the concentration of amphiboles (amosite, crocidolite, tremolite) longer than 8 μm was the best predictor of mesothelioma, with no contribution by shorter fibers, whereas the latter group found that shorter fibers, including fibers of chrysotile, also appeared to be important.

It should be noted that both these studies used a general population control group, and this may have influenced the results, because persons with occupational asbestos exposure generally have much longer fibers in their lungs than do persons in the general population inhaling asbestos from ambient air (23). This observation also raises a related issue which returns to the basic question raised in this study: namely, that while it is clear that persons with asbestos-induced pleuropulmonary disease have considerably higher fiber burdens than members of the general population, it is not clear whether fiber concentration differences, fiber dimension differences (24, 25), or some other factors explain the occurrence of disease among members of an exposed workforce.

In this report we have studied a workforce with heavy, but nonetheless quite variable, exposure to both amphiboles and chrysotile. The limitations of our approach must be stressed. The group is not ideal in many respects. No details of exposure levels are available for these workers, and we were unable to correlate exposure in years with measured fiber burdens. This is not surprising, because many members of the group had exposure for only a few years to the very high fiber levels that prevailed inside ships during construction and ripout during World War II.

A second potential problem is the selected nature of the subjects for whom we obtained lung tissue. In our previous study of chrysotile miners and millers (7) we used sequential autopsy cases, and in the present study, sequential cases referred for mineral analysis (and sometimes diagnosis). Both sets of cases tend to include those who have a disease which either is clearly compensable, or will be if a certain diagnosis or a certain mineral burden can be established. Thus neither group can be regarded as providing any useful data about the relative frequency of the various asbestos-related diseases. However, we are interested in examining the relationship of disease to fiber concentration and size measures, and the latter data could not be known by those referring the cases. Thus selection per se should not affect our results.

Selection does, however, limit the statistical power of the study. Most of the cases referred to our laboratory are referred because they have disease. Lungs from workers with this type of exposure and no disease are hard to obtain and thus the reference (no disease) group is quite small. Power calculations for amosite show that we would be unable to statistically detect anything less than a tenfold increase in fiber counts in the disease groups relative to the group with no disease. But the multiple linear regression analysis, by estimating differences in fiber counts between each disease and the no disease group independent of the associations of each disease with the other diseases, effectively enhanced the ability to detect differences due to airway fibrosis and to pleural plaque by removing the effect of the diseases (in this case mesothelioma and lung cancer) that did not have higher fiber counts than the no disease group. It is clear that many of the differences that are not statistically significant (for example, the amosite concentrations in subjects with mesotheliomas and lung cancers—see Table 4) are very small and are unlikely to be biologically important.

Moreover, we are dealing with a population in which each subject tends to have more than one asbestos-related disease. This problem can be accounted for to some extent by multiple regression analyses, but might in theory be better approached using groups of subjects having only one disease. However, since exposure sufficient to produce disease appears to produce multiple abnormalities in many patients, it is probably unrealistic to expect to find such a set of subjects. Indeed, although we and others have proposed a general schema which relates fiber concentration and disease pattern in amphibole-exposed workers (2–5), the failure to account for the effects of multiple diseases turns out to have created some subtle errors, as discussed subsequently.

Lastly, we have deliberately chosen not to include exposure in our models. In part we have made this choice because there is, for reasons mentioned previously, no correlation between exposure as measured in years and fiber concentration in this group of workers. More important, however, we have excluded years of exposure because we are specifically interested in the effects of fiber burden, irrespective of nominal exposure, and disease. In this sense fiber burden serves as our measure of exposure, and including both fiber concentration and years of exposure appears to us to be analytically incorrect. Similar comments apply to years since last exposure.

Our results show clearly that, despite known historic exposure to amosite and chrysotile, amosite is by far the predominant residual fiber, and there are correlations between amosite measures and disease. Chrysotile was present inconstantly and in relatively small amounts, and no correlations were found between chrysotile measures and disease. Similar observations have been made by others (5) and there is general agreement that chrysotile does not persist in lung tissue (1). For this reason analyses of this type by definition grossly underestimate chrysotile exposure, and therefore considerable caution must be exercised in drawing conclusions about the effects of chrysotile.

We have proposed elsewhere that tremolite, which is a natural

minor constituent of chrysotile ore, might serve as a substitute marker for chrysotile, and that tremolite rather than chrysotile may actually be the agent responsible for "chrysotile-induced" mesothelioma and perhaps other diseases as well (6). In a previous study of fiber burden in chrysotile miners and millers (6), tremolite concentrations and sizes correlated well with the presence of specific diseases, whereas chrysotile measures did not provide correlations after accounting for the presence of tremolite. The fact that there is a correlation between chrysotile and tremolite concentration in the present study confirms the idea that the tremolite seen in these lungs is derived from the chrysotile, but we were unable to show any correlations between tremolite measures and disease. It is possible that this failure simply reflects very low contamination of processed chrysotile products with tremolite, and hence very low lung burdens of tremolite. But the failure to find correlations of disease and either chrysotile or tremolite burden again raises questions about the role of chrysotile in workers with this type of mixed exposure.

Our results emphasize the importance of high fiber concentration in the induction of airway fibrosis and asbestosis by amosite; this conclusion is similar to that reached in our study of chrysotile miners and millers (6). However, there is a marked difference in the relationship of mesothelioma and fiber burden between these two studies. For amosite our data confirm in a formal fashion that mesothelioma typically appears at much lower burdens than are seen with asbestosis or airway fibrosis, whereas our previous study showed that chrysotile-induced mesothelioma appeared at very high fiber burdens of tremolite and chrysotile, burdens comparable to those that produce asbestosis or airway fibrosis. These findings support the idea that, even where a role for chrysotile ore (chrysotile plus tremolite) is unequivocal, there are major differences in the relationship of fiber concentration and disease between these fibers and amosite or crocidolite.

A new finding from the present work is that, in contrast to previous conclusions that we and others have reached that mesotheliomas appear at greater fiber burdens than do plaques (2–4), the current data suggest that fiber concentration does not discriminate among heavily exposed subjects with mesothelioma, lung cancer, or no asbestos-related disease, and the association of pleural plaques with increased amosite concentration is marginal. The differences between this study and previous ones most likely arise from the use of regression techniques that account for the presence of multiple diseases in some subjects. This observation also emphasizes the necessity to examine measures other than fiber concentration to attempt to determine which mineralogic measures are associated with different diseases.

Measures of fiber size do provide some information in this regard. In particular, there is an association of high aspect ratio with the presence of pleural plaques, perhaps implying that high-aspect-ratio fibers specifically play a role in the genesis of plaques. Exactly the same association of plaques and high-aspect-ratio fibers was found for tremolite in our study of chrysotile miners and millers (6), suggesting the importance of aspect ratio in the production of pleural plaques with all types of asbestos.

It is also clear that, in our study, mesotheliomas are not associated with long fibers and in fact are probably associated with lower-aspect-ratio fibers than are found in subjects without asbestos-related disease. This is a surprising finding that contradicts the experimental data cited previously and also the studies of McDonald and coworkers (21) and Rogers and coworkers (22) that concluded that mesotheliomas are associated with long fibers. The latter may possibly be explained by examining Tables 8 and 9, because, overall, subjects with asbestos-related disease tend, as a group, to have longer and higher-aspect-ratio fibers than those with no asbestos-related disease, and even our subjects with exposure but no disease have longer fibers in their lungs than members of the general population (23), the group used as control subjects by McDonald and coworkers (21) and Rogers and coworkers (22). Nonetheless, we cannot explain the anomalous finding of low-aspect-ratio fibers in subjects with mesothelioma compared with exposed subjects with no disease, and again must ask whether the experimental data really apply to humans, and what specific role long, high-aspect-ratio fibers play in the genesis of mesothelioma.

It has also been proposed from experimental studies (26) and reviews of human data (15, 24, 25) that fiber surface area might be the most important predictor of some diseases. This idea makes intuitive sense if available surface reactants (for example, iron to catalyze the generation of active oxygen species) are important in producing disease. However, in this study we were unable to find an association of fiber width, surface area, or mass with disease.

An additional point that emerges from our data is the slow clearance of amosite from the lung. In a recent review (1), we noted that, despite marked interlaboratory variations in fiber counting methods and despite quite discrepant interlaboratory results for any given specimen (27), the available data suggest that clearance half times for amosite and crocidolite are on the order of years to decades. The present calculation of a clearance half time of 20 yr for amosite fits into this pattern. In contrast, in most studies, including this one, there is no correlation between chrysotile concentration and time since last exposure when times are measured in years. This finding implies that the bulk of chrysotile clearance must be completed within weeks to months of exposure.

In one sense our results are disappointing because the models examining correlations with fiber concentration or with fiber size measures (and even models combining concentration and size measures) fail to provide fiber-related discriminating factors for some diseases. In particular, it remains unclear what factors favor the development of amphibole-induced mesothelioma, a question of considerable importance. This issue needs further examination.

References

1. Churg A, Wright J. Persistence of natural fibers in lung tissue. Environ Hlth Perspectives (In Press).
2. Churg A. Analysis of lung asbestos content. Br J Ind Medicine 1991;48:649–52.
3. Roggli VL. Human disease consequences of fiber exposures—a review of human lung pathology and fiber burden data. Environ Hlth Perspectives 1990;88:295–303.
4. Roggli VL, Pratt PC, Brody AR. Asbestos content of lung tissue in asbestos associated disease: a study of 110 cases. Br J Ind Medicine 1986;43:18–29.
5. Wagner JC, Newhouse ML, Corrin B, Rossiter CER, Griffiths DM. Correlation between fibre content of the lung and disease in East London asbestos factory workers. Br J Ind Medicine 1988;45:305–8.
6. Churg A, Wright J, Vedal S. Fiber burden and patterns of asbestos-related disease in chrysotile miners and millers. Am Rev Respir Dis 1993;148:25–31.
7. Wright JL, Cagle P, Churg A, Colby TV, Myers J. State of the art: disease of the small airways. Am Rev Respir Dis 1992;146:240–62.
8. Wilkinson L. SYSTAT: the System for Statistics. Evanston, IL: SYSTAT, Inc, 1991.
9. Adamson IYR, Bowden DH. Response of mouse lung to crocidolite asbestos. 1. Minimal fibrotic reaction to short fibers. J Pathol 1987;152:99–107.
10. Adamson IYR, Bowden DH. Response of mouse lung to crocidolite asbestos. 2. Pulmonary fibrosis after long fibers. J Pathol 1987;152:109–17.
11. Davis JMG, Addison J, Bolton RE, Donaldson K, Jones AD, Smith T. The pathogenicity of long vs short fibre samples of amosite asbestos administered to rats by inhalation and intraperitoneal injection. Br J Exp Path 1986;67: 415–30.

12. Davis JMG, Jones AD. Comparisons of the pathogenicity of long and short fibre chrysotile asbestos in rats. Br J Exp Path 1988;69:717–37.
13. Churg A, Wright JL, DePaoli L, Wiggs B. Mineralogic correlates of fibrosis in chrysotile miners and millers. Am Rev Respir Dis 1989;139:891–6.
14. Churg A, Wright J, Wiggs B, DePaoli L. Mineralogic parameters related to amosite asbestos induced fibrosis in man. Am Rev Respir Dis 1990;142:1331–6.
15. Timbrell V, Ashcroft T, Goldstein B, Heyworth F, Meurman L, Rendall REC, Reynolds JA, Shilkin KB, Whitaker D. Relationships between retained amphibole fibres and fibrosis in human lung tissue specimens. Ann Occup Hyg 1988;32(Suppl 1):323–40.
16. Coin PG, Roggli VL, Brody AR. Deposition, clearance, and translocation of chrysotile asbestos from peripheral and central regions of the lung. Environ Res 1992;58:97–116.
17. Churg A, Wright JL, Hobson J, Stevens B. Effects of cigarette smoke on the clearance of long and short asbestos fibers from the lung. Int J Exp Pathol 1992;73:287–97.
18. Stanton MF, Layard M, Tegeris A, Miller E, May M, Morgan E, Smith A. Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. JNCI 1981;67:965–75.
19. McDonald JC, McDonald AD, Armstrong B, Sesbastien P. Cohort study of mortality of vermiculite miners exposed to tremolite. Br J Ind Medicine 1986;43:436–44.
20. Langer AM, Nolan RP, Constantopoulos SH, Moutsopoulos HM, Association of Metsovo lung and pleural mesothelioma with exposure to tremolite-containing whitewash. Lancet 1987;1:965–7.
21. McDonald JC, Armstrong B, Case B, Doell D, McCaughey WTE, McDonald AD, Sebastien P. Mesothelioma and asbestos fiber type. Evidence from lung tissue analysis. Cancer 1989;63:1544–7.
22. Rogers AJ, Leigh J, Berry G, Ferugson DA, Mulder HB, Ackad M. Relationship between lung asbestos fiber type and concentration and relative risk of mesothelioma. Cancer 1991;67:1912–20.
23. Churg A, Wiggs B. Fiber size and number in users of processed chrysotile ore, chrysotile miners, and members of the general population. Am J Ind Med 1986;9:143–52.
24. Lippmann M. Effects of fiber characteristics on lung deposition, retention, and disease. Environ Hlth Perspectives 1990;88:311–7.
25. Lippmann M. Asbestos exposure indices. Environ Res 1988;46:86–106.
26. Goodglick LA, Kane AB. Cytotoxicity of long and short crocidolite asbestos fibers in vitro and in vivo. Cancer Res 1990;50:5153–63.
27. Gylseth B, Churg A, Davis JMG, Johnson N, Morgan A, Mowe G, Rogers A, Roggli V. Analysis of asbestos fibers and asbestos bodies in human lung tissue samples. An international interlaboratory trial. Scand J Work Environ Hlth 1985;11:107–10.