# Fiber Burden and Patterns of Asbestos-related Disease in Chrysotile Miners and Millers

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To examine how fiber type, fiber concentration, and fiber size correlate with the presence of asbestos-related disease in workers with heavy chrysotile exposure, we used analytic electron microscopy to determine the fiber content of the lungs of 94 long-term chrysotile miners and millers from the region of Thetford Mines, Quebec. Mesothelioma, airway fibrosis, and asbestosis were strongly associated with a high tremolite fiber concentration, whereas pleural plaques and carcinoma of the lung showed no relationship to tremolite burden. Similar patterns were seen for chrysotile concentration, but further analysis suggested that the apparent effect of chrysotile probably was due to the high correlation ($r = 0.70$) between chrysotile and tremolite concentration rather than to an independent effect of chrysotile. Increased tremolite-chrysotile ratio was marginally associated with the presence of pleural plaques but not with any other disease. Very high correlations ($r > 0.90$) between the concentrations of fibers longer or shorter than 8 μm prevented assessment of the effects of long compared with short fibers. Pleural plaques were very strongly associated with higher mean tremolite fiber aspect ratios, but no differences in mean fiber size (length, width, aspect ratio, surface area, and mass) were seen for any other disease. Total fiber size measures (total fiber length/g and others) showed differences similar to fiber concentration for mesothelioma, airways fibrosis, and asbestosis, but no one measure was clearly better than another or better than fiber concentration. We conclude that, in this population of heavily exposed chrysotile miners and millers, the presence of airways fibrosis and asbestosis and, probably, mesothelioma reflects high tremolite burden. Whether chrysotile fibers themselves play a role in disease induction remains uncertain. Mean fiber size appears to be of importance only in the genesis of pleural plaques. Carcinoma of the lung is not significantly associated with any mineralogic measure.

Despite extensive study, the exact relationship between fiber burden, taken in its broadest sense to include fiber type, concentration, and size measures, and disease patterns in workers with chrysotile asbestos exposure remains uncertain. This issue is complicated by contamination of most chrysotile ores with the amphibole, tremolite, and it has been suggested that tremolite is responsible for much of the apparent disease produced by chrysotile, especially in regard to mesothelioma (see reference 1 for a review). As well, there is disagreement about what size of fiber is important in the genesis of disease (2–12). Further, it was recently proposed that the most important predictor of toxicity is actually fiber surface area (6, 8), but some authors believe that better correlations with disease are to be found by examining total rather than mean fiber size measures (13). These problems are of considerable importance, since knowledge of the relationship between fiber burden and disease plays a role in determining allowable exposure limits, particularly for chrysotile, the only form of asbestos likely to be used in the future.

In this study we use analytic electron microscopy to measure the fiber burden in autopsy lungs from 94 chrysotile miners and millers, specifically to address the question, in a group of workers with heavy chrysotile exposure, what mineralogic measures are associated with the presence of specific asbestos-induced diseases?

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## METHODS

Cases for this study were selected from approximately 300 autopsy lungs from the Centre Hospitalier de la region de l'Amiante at Thetford Mines, Quebec. Cases, along with details of their occupational histories, were very kindly supplied by Dr. M. Poulin and Mr. C. Pratte. The 300 lung samples represented tissues from all workers in the Thetford Mines–Black Lake region autopsied at the Centre Hospitalier de la region de l'Amiante during 1981 through 1990.

The cases in the present study were selected to provide examples of mesotheliomas, asbestosis, asbestos-induced airways disease, pleural plaques, and lung cancers. In this study, airway fibrosis is defined as a morphologically distinctive pattern of fibrosis confined to the walls of respiratory bronchioles and alveolar ducts (see reference 14 for illustrations), whereas asbestosis is defined as interstitial fibrosis affecting the parenchyma between small airways, regardless of the presence of airway fibrosis. Some of the cases were previously analyzed for a variety of other studies involving mesotheliomas, airway fibrosis, and asbestosis, but no attempt was made specifically to select cases of plaques or carcinomas.

For each case at least two separate 5-g samples of wet fixed lung were dissolved in bleach and mineral fibers collected and evaluated by analytic electron microscopy according to our usual protocol (11). A minimum of 50 fibers of chrysotile and tremolite were counted and sized per sample. Additional samples of tissue were dried to constant weight to allow expression of concentrations per gram dry lung.

Fiber characteristics included in the analysis included fiber type and concentration, mean fiber size values (length, width, aspect ratio, surface area, and mass), and total fiber size values (total fiber length/g dry lung, etc). Initial inspection showed that these variables were log-normally distributed; all statistical analysis was done on log-transformed values, and geometric means were calculated for presentation of the data. Pearson correlation coefficients were used to assess the association between two continuous variables and *t* tests to evaluate the differences between groups. Associations between the fiber characteristics and the asbestos-related diseases were analyzed using multiple linear regression techniques, regressing log fiber characteristics on indicator variables for the presence of each specific disease. Covariates were included when relevant. All analyses were performed using SYSTAT® (15).

## RESULTS

### Demographic Data

Data were available on 94 subjects. Mean age, pack-years of smoking, years of asbestos exposure, and latency are shown in table 1, along with the number of subjects with specific diseases. Many patients had more than one disease: all but four subjects with mesothelioma also had airway fibrosis, two subjects had asbestosis and mesothelioma, and six had asbestosis and lung cancer. Although subjects with asbestosis were defined as a group distinct from the patients with airway fibrosis alone, virtually all subjects with asbestosis also had airway fibrosis. Lung cancer was approximately equally distributed among those with and without airway fibrosis and among those with and without pleural plaques. Pleural plaques were approximately equally distributed among those with and without other asbestos-related diseases; six subjects had no asbestos-related disease.

### Fiber Concentrations

The correlation between log tremolite or log chrysotile concentration and various exposure variables is shown in table 2: significant correlations were seen between log tremolite concentration and exposure or latency. Age was weakly correlated with log tremolite concentration, but pack-years of smoking was not. No correlations were seen between log chrysotile concentration and any exposure variables. There were moderately strong correlations between age and exposure ($r = 0.41$, $p < 0.001$) and between latency and exposure ($r = 0.39$, $p < 0.002$).

Tremolite and chrysotile concentrations are compared in subjects with a given asbestos-related disease and subjects without asbestos-related disease in table 3. On initial evaluation, tremolite concentrations were significantly higher in subjects with all asbestos-related diseases, and chrysotile concentrations were significantly higher in subjects with mesothelioma, asbestosis, or airway fibrosis than in subjects without disease.

Since more than one asbestos-related disease was present in some subjects, however, multiple linear regression models, in which fiber concentration was regressed against all the different disease indicator variables, were generated to identify the *independent* associations between fiber concentrations and asbestos-related diseases. These models confirmed (based on the statistical significance of the relevant regression coefficients) that concentrations of tremolite and chrysotile were significantly higher in subjects with asbestosis or airway fibrosis. After accounting for the presence of the other asbestos-related diseases, however, tremolite concentrations were no longer significantly higher in subjects with lung cancer or pleural plaques (table 3). The association of mesothelioma with concentrations of either fiber type, independent of associations with airway fibrosis and asbestosis, was of borderline statistical significance.

There was a strong correlation ($r = 0.70$) between log tremolite and log chrysotile concentration. This observation raised the possibility that the apparent associations of *both* chrysotile and tremolite with disease could have been found if, in fact, only one fiber type was actually associated with disease and the second fiber type only appeared to be associated with disease because of its association with the first fiber type. The first approach to attempt to resolve this problem was to stratify the analysis of one fiber type by quartiles of the other (table 4). In the stratification analysis, tremolite concentration was consistently higher in mesothelioma, asbestosis, and airway fibrosis in each chrysotile concentration stratum, whereas chrysotile concentration was not consistently higher in each tremolite stratum except in subjects with airway fibrosis. This stratification analysis suggests that tremolite concentration was associated with asbestos-related diseases independently of chrysotile concentration whereas chrysotile concentration was not, apart from its association with tremolite.

The second approach to this problem was to generate a series of linear regression models in which the concentration of one type of fiber was regressed on the presence of disease, with the concentration of the other fiber type included as a covariate (Models III to VI, table 5). This procedure in essence assessed the association between one fiber type and disease while controlling for the association between the other fiber type and disease. After controlling for chrysotile concentration, mesothelioma, asbestosis, and airway fibrosis were not significantly associated with tremolite concentration, although the associations for the last two diseases were of borderline significance. After controlling for tremolite concentration, no disease was significantly associated with chrysotile concentration. In a model in which airway fibrosis

TABLE 1

DEMOGRAPHIC AND DISEASE DATA*

| | |
|---|---|
| Age, yr | 65 ± 8† |
| Smoking pack-years | 37 ± 22 |
| Exposure, yr | 34 ± 10 |
| Latency, yr | 44 ± 11 |
| Mesothelioma | N = 15 |
| Asbestosis | N = 23 |
| Airway fibrosis | N = 35 |
| Pleural plaques | N = 63 |
| Carcinoma of lung | N = 35 |
| No asbestos-related disease | N = 6 |

* Some cases have more than one disease.

† Data on age were available for 94 cases, on smoking for 84 cases, on exposure for 91 cases, and for latency and time since last exposure for 64 cases.

TABLE 2

CORRELATIONS OF DEMOGRAPHIC VARIABLES AND FIBER CONCENTRATION*

| Variable | Log Tremolite Concentration | Log Chrysotile Concentration |
|---|---|---|
| Age | $r = 0.18$, $p < 0.10$ | $r = 0.04$, p NS |
| Smoking, pack-years | $r = 0.08$, p NS† | $r = 0.01$, p NS |
| Exposure, yr | $r = 0.26$, $p < 0.01$ | $r = 0.06$, p NS |
| Latency, yr | $r = 0.29$, $p < 0.05$ | $r = 0.12$, p NS |
| Time since last exposure, yr | $r = 0.06$, p NS | $r = 0.08$, p NS |

* Data on age were available for 94 cases, on smoking for 84 cases, on exposure for 91 cases, and for latency and time since last exposure for 64 cases.

† No significant difference.

TABLE 5

LINEAR REGRESSION MODELS OF TREMOLITE CONCENTRATIONS ON ASBESTOS-RELATED DISEASES WITH AND WITHOUT CONTROL FOR CHRYSOTILE CONCENTRATIONS*

| Model | Chrysotile | Mesothelioma | Asbestosis | Airway Fibrosis | Fibrosis† |
|---|---|---|---|---|---|
| I | | 0.81 (0.46)§ | 1.84 (0.41)‡ | 1.52 (0.39)‡ | |
| II | | 0.45 (0.46) | | | 1.76 (0.35)‡ |
| III | 0.69 (0.07)‡ | 0.39 (0.33) | 0.60 (0.32)§ | 0.45 (0.30) | |
| IV | 0.68 (0.07)‡ | 0.26 (0.32) | | | 0.57 (0.27)‖ |
| V | 0.70 (0.07)‡ | | 0.60 (0.32)§ | 0.54 (0.29)§ | |
| VI | 0.69 (0.07)‡ | | | | 0.64 (0.26)‖ |

LINEAR REGRESSION MODELS OF CHRYSOTILE CONCENTRATIONS ON ASBESTOS-RELATED DISEASES WITH AND WITHOUT CONTROL FOR TREMOLITE CONCENTRATIONS*

| | Tremolite | Mesothelioma | Asbestosis | Airway Fibrosis | Fibrosis† |
|---|---|---|---|---|---|
| I | | 0.60 (0.48) | 1.80 (0.42)‡ | 1.56 (0.40)‡ | |
| II | | 0.29 (0.48) | | | 1.73 (0.36)‡ |
| III | 0.74 (0.08)‡ | 0.01 (0.35) | 0.44 (0.33) | 0.44 (0.31) | |
| IV | 0.74 (0.08)‡ | 0.05 (0.34) | | | 0.42 (0.29) |
| V | 0.74 (0.08)‡ | | 0.44 (0.33) | 0.44 (0.30) | |
| VI | 0.74 (0.08)‡ | | | | 0.41 (0.28) |

* Entries are regression coefficients with standard error of the mean in parentheses, of the independent variables included in each model.
† Airway fibrosis or asbestosis.
‡ $p < 0.01$.
§ $p < 0.10$.
‖ $p < 0.05$.

ing aspect ratio on the plaque indicator variable, with length as a covariate. Aspect ratio remained significantly associated with pleural plaques after controlling for the association between plaques and fiber length, whereas length was not associated with pleural plaques after controlling for aspect ratio.

TABLE 6

PEARSON CORRELATION COEFFICIENTS (p-VALUE) BETWEEN LOG TREMOLITE CONCENTRATION AND LOG MEAN FIBER SIZE CHARACTERISTICS

| | Concentration | Length | Width | Aspect Ratio | Surface Area | Mass |
|---|---|---|---|---|---|---|
| Length | −0.10 (0.33) | 1.00 | | | | |
| Width | −0.05 (0.65) | 0.35 (0.000) | 1.00 | | | |
| Aspect ratio | −0.10 (0.34) | 0.77 (< 0.000) | −0.20 (0.05) | 1.00 | | |
| Surface area | 0.02 (0.84) | 0.79 (< 0.000) | 0.67 (< 0.000) | 0.31 (0.003) | 1.00 | |
| Mass | 0.03 (0.81) | 0.69 (< 0.000) | 0.65 (< 0.000) | 0.23 (0.02) | 0.96 (< 0.000) | 1.00 |

TABLE 7

GEOMETRIC MEAN TREMOLITE FIBER SIZES IN SUBJECTS WITH AND WITHOUT PLEURAL PLAQUES*

| | Plaque Present | Plaque Absent |
|---|---|---|
| Length, μm | 3.0† | 2.5 |
| Width, μm | 0.23 | 0.25 |
| Aspect ratio | 19.4‡ | 14.5 |
| Surface area, $\mu m^2$ | 3.08 | 2.71 |
| Mass × $10^{-13}$ g | 1.04 | 0.88 |

* Indicated values are significantly different between subjects with and without pleural plaques both by *t* test and in the multiple-regression model after controlling for the presence of the other asbestos-related diseases.
† $p < 0.05$.
‡ $p < 0.001$.

Models in which length or aspect ratio for one fiber type was regressed on disease indicators plus length or aspect ratio of the other fiber type as a covariate (models analogous to those constructed in table 5) showed that tremolite fiber sizes continued to be associated with pleural plaques after controlling for chrysotile fiber sizes, but the reverse was not true (data not shown).

### Total Fiber Sizes

Total tremolite fiber length in subjects with disease is compared in table 8 with that in subjects with no asbestos-related disease. The pattern of significant differences is similar to that seen with fiber concentration (table 3). Essentially identical results were obtained for total tremolite fiber width, aspect ratio, surface area, and mass and for the same chrysotile size measures (data not shown).

## DISCUSSION

The issue of fiber burden and disease patterns has been the subject of a fairly large number of studies with not entirely consistent

TABLE 8

GEOMETRIC MEAN TOTAL TREMOLITE FIBER LENGTH/g TISSUE IN SUBJECTS WITH AND WITHOUT ASBESTOS-RELATED DISEASES*

| Disease | Disease Present | No Asbestos-Related Disease |
|---|---|---|
| Mesothelioma | 430 ± 3.9 (15)†,‡ | 30 ± 7.7 (6) |
| Asbestosis | 320 ± 6.3 (23)†,§ | 30 ± 7.7 (6) |
| Airway fibrosis | 300 ± 3.2 (33)†,§ | 30 ± 7.7 (6) |
| Pleural plaques | 190 ± 5.5 (63)† | 30 ± 7.7 (6) |
| Lung cancer | 110 ± 5.7 (36)† | 30 ± 7.7 (6) |

* Geometric mean ± SD; values × $10^6$ μm. Number of subjects in parentheses.
† $p < 0.05$ for the difference from the no asbestos-related disease group by *t* test.
‡ $p < 0.10$ for the difference from the no asbestos-related disease group by multiple-regression analysis, controlling for the presence of the other asbestos-related diseases.
§ $p < 0.001$ for the difference from the no asbestos-related disease group by multiple-regression analysis, controlling for the presence of the other asbestos-related diseases.

results. Roggli and colleagues (16, 17), who recently reviewed the topic, concluded that in terms of fiber concentration, by far the highest mean levels were seen in patients with asbestosis; patients with mesothelioma had considerably lower levels, and patients with pleural plaques levels at or lower than those seen in mesotheliomas; all these values were higher than those found in the general population. A similar pattern can be discerned in the work of Wagner and coworkers (18) and in our own studies (19).

However, detailed evaluation indicates that these observations actually apply only to levels of the commercial amphibole fibers, amosite and crocidolite (19), and are often based on comparisons with nonexposed control groups. Relationships between disease pattern and fiber burden for chrysotile have been harder to discern and are complicated by contamination of most chrysotile ores with tremolite (1, 20), by the rapid disappearance of chrysotile from lung tissue (19), and by the failure of some studies to separate chrysotile with its contaminant from amosite and crocidolite. We previously suggested, based on analysis of a small number of cases, that the pattern of disease seen with chrysotile-induced mesotheliomas is quite different from that seen with amosite or crocidolite-induced mesotheliomas (1, 19); one of the purposes of this study was to confirm these impressions.

Fiber burden in its broadest context includes not only concentration of fibers but sizes of fibers and distribution of fibers within the lung, and for these measures very few human data are available. Some experimental data suggest that long fibers are much more dangerous than short fibers with regard to their propensity to induce both mesothelioma and asbestosis (2–5). However, we found that in humans local degrees of fibrosis (asbestosis) actually correlated better with short-fiber than with long-fiber burden (11, 12), and Goodglick and Kane (6) and Adamson and Bowden (7) have presented experimental results that support the proposition that under certain circumstances short fibers may have considerable fibrogenic and carcinogenic potential, at least in terms of mesothelioma induction.

Two recent studies attempted to address some of these issues by using case-control analyses of mesothelioma cases, evaluating relative risks for mesothelioma in terms of fiber type, fiber number, and fiber size. McDonald and colleagues (9) examined 78 autopsy cases of mesothelioma and matched controls and concluded that the risk of mesothelioma could be attributed entirely to the concentration of long (> 8 μm) fibers of crocidolite, amosite, or tremolite, with no contribution by shorter fibers and little effect from chrysotile. Rogers and colleagues (10) performed a similar study and concluded that, although long fibers were more important than short fibers, short fibers increased risk, and the concentration of chrysotile shorter than 10 μm was an important predictor of mesothelioma. The reasons for the contradictions between these reports are unclear, but these studies are likely complicated by the tendency of chrysotile to disappear from lung tissue and possibly by differences in analytic techniques as well.

In this paper we attempted a somewhat different approach, namely, evaluating the associations of disease and asbestos type, concentration, and size measures using a population with heavy exposure to chrysotile ore. This approach seeks to identify the mineralogic factors that determine the appearance of disease in a group of exposed workers, rather than in persons with exposure compared with control subjects generally exposed only to ambient (atmospheric contamination) levels of asbestos. Also, because of the relatively heavy tremolite exposure (and hence marked tremolite retention) to which all these workers were subjected, we hoped to obtain more accurate estimates of the risks with chrysotile compared with tremolite.

This approach proved to have a number of serious problems, and these must be stressed. First, the study population consisted of 94 subjects with one or more of five diseases, some subjects having more than one disease. Only six subjects had no disease. Although the small number of subjects in this reference gr( could potentially have limited the power of this study to det.. the differences of interest, the effect of increased power would most likely have been to distinguish more clearly the asbestos concentrations in subjects with mesothelioma from those with no asbestos-related disease after accounted for the effects due to asbestosis and airway fibrosis. It is also possible that improved power would have resulted in the ability to detect increased asbestos concentrations in subjects with lung cancer or pleural plaques.

A second peculiarity of this particular population turned out to be the fairly constant distribution of fiber sizes from subject to subject and the very high correlation between the concentration of fibers longer and shorter than 8 μm ($r > 0.90$). This problem confounded attempts to evaluate disease risk in terms of concentration of long or short fibers as was done by the McDonald (9) and Rogers (10) groups.

The most serious problem, however, relates to the question of exposure and disease patterns versus residual fiber burden and disease patterns. Somewhat different information is obtained from each approach: the use of residual fiber burden, as analyzed here, potentially indicates the role of persisting fibers in disease induction but cannot determine the role of fibers only briefly present in the lung and then cleared. This is a particular problem with chrysotile exposures, since most chrysotile is rapidly removed from lung (19).

It is probably impossible to rule out a significant role for rapidly cleared fibers, but the data in the present study suggest that the chrysotile burden data provide reasonable estimates of both ' posure and fiber-disease potential. In this regard it is impo to note that there is very strong correlation between tremolite and chrysotile concentrations ($r > 0.70$) and that both tremolite and chrysotile concentrations produce a similar and statistically significant pattern of correlations with specific diseases on initial analysis (table 3). Were there significant exposure misclassification, that is, were chrysotile fiber burdens essentially random residua of initial inhaled dose, then no such correlations would be expected. It may be true that the tremolite serves as a better measure of past chrysotile exposure than the chrysotile itself, which has largely disappeared, but the implication of the correlations we find is that, in such a case, there is a fairly consistent loss of chrysotile from the lung from case to case, or, again, there would not be any correlation between chrysotile burden and disease. At best, one can say that disease could have been caused by the initially much higher chrysotile burden, most of which has now disappeared. There are not data really to support this position, however, and the limited experimental data that exist (for example, reference 21) suggest that only retained fibers are important in disease induction.

Last, in formulating our models, we considered whether years of exposure and years since last exposure should have been included as covariates. The data available to us included only years of exposure without details of levels of exposure, and, given the known heterogeneity of jobs and levels of exposures in this population (22), crude years of exposure almost certainly provides a worse estimate of exposure than fiber burden; this can be appreciated from the significant but not particularly strong association between tremolite burden and crude years of exposure (r 2). As well, since fiber burden serves as an estimate of expo to include crude years of exposure in the regression essentially includes two different estimates of "exposure" in the same model.

a procedure that is not analytically sound. The same argument could be made about including years since last exposure. In practice, when we created such models, including years of exposure and/or years since last exposure did not change our results, suggesting that fiber burden indeed provides more useful information in this context.

These problems notwithstanding, a number of conclusions can be drawn from our data. The data strongly suggest that fiber concentration per se plays a basic role in the genesis of "chrysotile"-induced mesothelioma, airway fibrosis, and asbestosis. All three conditions appear at fairly high, and similar, mean fiber concentrations (table 3), although given the small number of subjects with mesothelioma who did not also have either airway fibrosis or asbestosis, conclusions regarding the fiber concentrations associated with mesothelioma alone are somewhat tentative. Nonetheless, these observations reemphasize in a more formal fashion our previous suggestion that induction of mesothelioma with chrysotile ore components requires roughly as great a fiber burden as induction of fibrosis (19).

As noted, several studies have suggested that the tremolite contaminant rather than the chrysotile itself might be the actual agent of mesothelioma in those exposed to chrysotile ore (1, 19, 20). The results of the stratification analysis (table 4), which controls for the presence of the other fiber type but not for the presence of other asbestos-related diseases, and the multiple-regression models (table 5), which control for both the other fiber type and the other asbestos-related diseases, are consistent in suggesting a role for tremolite in airway fibrosis and parenchymal fibrosis (asbestosis). Analysis of the mean fiber size data and its relationship to pleural plaques also leads to the conclusion that the presence of tremolite is important in the development of disease. The role of tremolite concentration in mesothelioma, although probable, is less clear because of the small number of subjects with mesothelioma who did not also have either airway fibrosis or asbestosis.

The problems of evaluating the role of chrysotile have been noted. The regression models suggest that tremolite is associated with fibrosis independently of chrysotile concentration, whereas chrysotile is not, independently of tremolite concentration. This conclusion is based on the observed changes in the respective regression coefficients following inclusion of the other fiber type as an independent variable in the model. Because of the relatively small number of subjects on whom these regression models were based, such changes in regression coefficients must be interpreted carefully and conservatively. Nonetheless, it is fair to state that the question of whether chrysotile in fact really plays any role in the genesis of these diseases remains to be answered.

Although pleural plaques are common in most populations with significant asbestos exposure, the factors that determine their genesis are essentially unknown. Gibbs (23) suggested a number of years ago that plaques were more frequent in workers from the Thetford Mines region than the Asbestos region of Quebec and that some contaminant of the chrysotile ore rather than the chrysotile itself was producing the plaques. Recent data indicate that there is much greater contamination of the chrysotile ore by tremolite in the Thetford mines region than in the Asbestos region (24). In the present study, subjects with pleural plaques had marginally higher tremolite-chrysotile ratio but not higher tremolite or chrysotile concentrations than those without pleural plaques. However, significant effects were found when mean fiber size characteristics were considered. Initial analysis suggested that both mean fiber length and mean fiber aspect ratio were associated with pleural plaques, but in models that controlled for the presence of both length and aspect ratio, only fiber aspect ratio proved to be of significance. This conclusion, however, must be understood to apply within the range of fiber lengths that produces disease.

Thus, although our data provide little support for the importance of tremolite fiber concentration in plaque induction, they do provide good evidence that the genesis of plaques is related to mean fiber size. These findings support the proposal made by Gibbs (23) that some substance other than chrysotile is responsible for pleural plaques, with the proviso that tremolite fiber size rather than concentration is the fiber characteristic of importance.

Goodglick and Kane (6) and Lippmann (8) suggested that fiber surface area is the most important determinant of asbestos-related disease; Timbrell and coworkers (13) proposed that it is total, rather than mean, fiber surface that provides the best correlation with disease. In this study, however, mean fiber size measures were associated only with the presence of pleural plaques, as noted, and mean fiber surface area was not associated with any condition. It is somewhat surprising that we were unable to detect an association between mean fiber size characteristics and the presence of mesothelioma, particularly in light of the animal studies mentioned earlier and the data of the McDonald (9) and Rogers (10) groups, but the latter, as noted, compare largely occupationally exposed mesothelioma cases to nonexposed controls. These observations indicate that, although fiber length may be an important factor distinguishing occupationally exposed cases with mesothelioma from nonexposed controls without mesothelioma, among heavily exposed chrysotile miners and millers other factors, primarily fiber load, are more important in mesothelioma induction.

All total fiber size measures were associated with mesothelioma, asbestosis, and airway disease, but no total fiber size measure was better than another, and the use of total fiber size measures did not lead to conclusions any different from those obtained with fiber concentrations alone. At this point we cannot prove or disprove the notion that fiber surface area (or total fiber surface area) is particularly important in the genesis of asbestos-related disease.

Perhaps most surprising was the absence of any relationship between fiber concentration or size and the presence of carcinoma of the lung after controlling for the association between lung cancer and the other asbestos-related diseases. It should be appreciated that the autopsy population from which is study is drawn is highly biased because the presence of lung cancer entitles the families of workers in the mining and milling industry to apply for compensation, and hence the number of carcinomas in the underlying autopsy population is artificially high (about one-third of all cases have lung cancer). This form of self selection might have the effect of diluting the lung cancer subjects whose tumors were actually associated with high fiber load with those whose tumors were due to cigarette smoking and thus abolishing any association between fiber concentration and lung cancer. It should also be noted that, in a study of a large number of deaths in chrysotile miners (an earlier cohort of the same work force from which the present study is drawn), McDonald and colleagues (22) were able to show an increased risk of lung cancer only for the highest exposure groups, suggesting that selected subgroups of these workers should be evaluated to demonstrate a relationship between fiber burden and carcinoma. When we examined a multiple-regression model using only the 29 subjects with 40 yr or more of exposure (presumably all high exposures), however, there was still no association between lung cancer and tremolite or chrysotile fiber concentration (data not shown). Thus the present data argue against an association between lung cancer and fiber burden.

In summary, our data suggest that, within this heavily exposed

work force, asbestosis, airway fibrosis, and probably mesothelioma are primarily generated by high fiber loads, and that, although the role of tremolite in all three diseases is established, the role of chrysotile is unclear; however, our data cannot rule out the possibility that chrysotile fibers, which are inhaled and rapidly cleared, are important in disease induction. The data also suggest that mean fiber size measures are important in the genesis of pleural plaques but that mean fiber size measures do not discriminate between subjects with and without the other asbestos-related diseases. Specifically, there is no demonstrable effect of fiber surface area. Last, we could not show any association between fiber burden and the presence of lung cancer.

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