Severe diffuse small airways abnormalities in long term chrysotile asbestos miners

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ABSTRACT To determine the nature and extent of pathological changes in the small airways induced by asbestos, the pathological lesions of fibrosis and pigmentation of the membranous and respiratory bronchioles and alveolar ducts in lungs obtained from necropy from a group of 36 non-asbestotic long term chrysotile miners and 36 age, sex, and smoking matched controls who had no history of exposure to dust were compared. The airways were graded using a standard visual grading system. Appreciably greater airway fibrosis was found for all types of airway in the whole group of miners compared with the controls. Differences for pigmentation were generally similar but less pronounced. It is concluded that long term exposure to mineral dust as an asbestos miner produces severe diffuse pathological changes in the small airways; these findings may relate to the physiological observation of unusual degrees of airflow obstruction in this group of workers.

It has been suggested that workers exposed to asbestos dust may develop airflow obstruction greater than can be accounted for by cigarette smoking.1–7 The exact pathological lesions with which such functional changes might be associated are disputed. Begin et al, on the basis of observations in a sheep model of asbestosis, suggested that the important mechanism is compression of the respiratory bronchioles by an asbestos induced inflammatory and fibrotic reaction.8 The same group has shown that in non-smoking asbestos workers those with asbestosis (diffuse interstitial fibrosis) have an appreciably increased upstream resistance, and even those without asbestosis have an increased isoflow volume as well as decreased flows at low lung volumes; they attribute this abnormality to the same type of respiratory bronchiolar lesion. Nevertheless, the importance of pathological changes at this site in the development of airflow limitation is disputed. Wright et al found an inverse relation between increasing fibrosis of the respiratory bronchioles and decreasing FEV1,9 but Thurlbeck and Wang believe that the cross-sectional area of the respiratory bronchioles is too great to produce such changes10 (WM Thurlbeck, personal communication).

We have previously described a lesion consisting of fibrosis and pigmentation of the respiratory bronchioles that appears in workers exposed to a wide variety of asbestos and non-asbestos dusts,12 13 and which is associated with small airways airflow obstruction.14 In a morphological study of asbestos workers with this lesion we suggested that not only are pathological lesions present in the walls of the respiratory bronchioles but that the membranous bronchioles are also affected, implying that asbestos produces pathological changes diffusely throughout the small airways.13 That study, however, was concerned with only a few cases and was prejudiced by the selection of a set of patients with obvious histological abnormalities of the respiratory bronchioles, a group that is clearly only a subset of asbestos workers. In the present report we have extended our observations on the reactions of the airways to mineral dusts by evaluating a large series of long term chrysotile miners and millers selected only because they had no histological evidence of interstitial fibrosis (asbestosis). We show that all such patients have diffuse abnormalities of their small airways, and propose that functional abnormalities in such workers may reflect this diffuse process.

Materials and methods

The lungs used for this study were obtained from a series of 64 sequential necropsies of long term chrysotile miners and millers performed at the Hôpital Général de le Région de l'Amiante at Thetford...
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Mines, Quebec, between 1981 and 1983. Tissues and smoking histories (obtained from relatives) and detailed occupational histories were kindly supplied by Dr M Poulin and Monsieur C Pratte of that institution. All the lungs were fixed in formalin; a midsagittal slice of left and right lung was available for almost all cases. Seven of these cases had been used in our initial study of airway changes in asbestos workers.13

For each case, two tissue blocks were randomly selected from the upper lobe and two from the lower lobe. Because the possible effects of diffuse interstitial fibrosis (asbestosis) on the appearance of small airways is not known, all cases with histological evidence of interstitial fibrosis were excluded from this analysis, leaving a study group of 36 cases.

The control population was obtained from the necropsy service of local hospitals in Vancouver, BC, and was selected on the basis of age (within 10 years), and smoking (within 10 pack years) matching with the test cases, and of a lack of occupational exposure to dust. Smoking and occupational histories were obtained by a standard questionnaire administered to the relatives. For all the control lungs two upper and two lower lobe random sections were obtained from a midsagittal slice. Tissue for test and control cases was processed in a usual fashion, embedded in paraffin, and sectioned at 5 microns; slides used for pathological grading were stained with Masson’s trichrome.

Using our previously described modification12 of the visual histological grading scheme of Cosio et al.,15 we graded membranous bronchioles (MB), respiratory bronchioles (RB), and alveolar ducts (AD) for fibrosis and pigmentation on a scale of 0 (normal) to 3 (most abnormal). Alveolar ducts were graded only if they could be determined to arise from a respiratory bronchiole. A mean result of all the values for each airway type and each pathological variable was calculated in each case. Differences between the test and control groups were calculated using a paired t test.

The cases were graded by both observers using a double headed microscope. We tested interobserver variation by separately grading 120 airways of all three types, and we tested the reproducibility of the grading system by regrading another 120 airways. Scores were compared using the concordance analysis for non-parametric data. For both interobserver and intraobserver variation, the concordance coefficient was 0.94 (p < 0.001).

Since not all the lungs used in this study were fixed by inflation, we checked that differing degrees of inflation did not affect the grading system. For six control cases, one lung was fixed in inflation, whereas the other was sliced and sectioned in the non-inflated state. Random sections were obtained and the tissue was processed, stained, and graded as described above. The number of airways scored as 0, 1, 2, or 3 in the inflated and non-inflated lungs was compared using an odds ratio analysis.16 There was no significant difference in the scoring characteristics of any parameter between the inflated and non-inflated lung sections.

Results

Table 1 shows the age and smoking data; the test group was well matched with the controls. Table 2 shows the pathology scores for the test and control groups. These data indicate a highly significant (p < 0.001) increase for fibrosis in all three types of airway. The respiratory bronchioles and alveolar ducts were also significantly more pigmented in the miners than the controls (p < 0.001) but there was no difference in the pigmentation in the membranous bronchioles. When the test population was divided into two groups on the basis of smoking history (less than or more than 35 pack-years) no differences were found for the amount of airway disease. Although this may suggest that smoking does not have a synergistic effect with mineral dust, the val-

Table 1 Age, smoking, and work characteristics of the test groups. (All values mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>Smoking</th>
<th>Dust exposure (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 Chrysotile miners</td>
<td>62 ± 7</td>
<td>36 ± 19</td>
<td>31 ± 11</td>
</tr>
<tr>
<td>Controls</td>
<td>65 ± 8</td>
<td>38 ± 22</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Comparison of pathological scores for miners versus controls

<table>
<thead>
<tr>
<th></th>
<th>Miners</th>
<th>Controls</th>
<th>p less than</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membranous bronchioles</td>
<td>1.2 ± 0.6</td>
<td>0.3 ± 0.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Respiratory bronchioles</td>
<td>1.1 ± 0.6</td>
<td>0.2 ± 0.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Alveolar ducts</td>
<td>0.6 ± 0.5</td>
<td>0 ± 0</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean fibrosis grades ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Membranous bronchioles</td>
<td>0.7 ± 0.5</td>
<td>0.65 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Respiratory bronchioles</td>
<td>0.9 ± 0.7</td>
<td>0.5 ± 0.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Alveolar ducts</td>
<td>0.4 ± 0.4</td>
<td>0.1 ± 0.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean pigmentation grades ± SD</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
ues may reflect only the rather heavy smoking habits of the test miners.

**Discussion**

Studies from several laboratories have shown that individuals who smoke cigarettes develop fibrosis and pigmentation of the membranous and respiratory bronchioles. In ordinary cigarette smokers the major pathological changes are seen in the membranous bronchioles and involvement of the respiratory bronchioles tends to be minimal; the alveolar ducts are generally unaffected. Typically these changes are, as in this study, reflected in mean fibrosis scores of less than 0.5 for membranous bronchioles, and less than 0.3 for respiratory bronchioles and alveolar ducts. The correlation between pathological scores of this type and abnormal pulmonary function tests has been found to be significant in cigarette smokers.

By contrast, in workers exposed to dust, we have frequently observed respiratory bronchioles with fibrosis of grades 2 and 3, an observation which leads to the formal description of the fibrotic lesion that we consider to be highly suggestive if not pathognomonic of exposure to mineral dust. The mean fibrosis scores for the respiratory bronchioles in such workers are frequently greater than 1.0. This type of observation is not merely a pathological curiosity, because workers exposed to dust with this lesion appear to have greater abnormalities in pulmonary function than those without.

The cases in our previous small studies of workers exposed to mineral dust were selected because of microscopic evidence of fibrotic respiratory bronchioles. A surprising finding in those studies was that the mean fibrosis scores for the membranous bronchioles were also appreciably raised, although the changes were not discernible on casual observation. This finding lead us to wonder if all such workers, and not just those with visible lesions of the respiratory bronchioles, might have diffuse pathological changes in their small airways.

In the present report we have confirmed this hypothesis by showing that, when a group of long term asbestos workers selected solely on the basis of a microscopic absence of asbestosis—that is, the small airways were ignored in the selection process—is compared with control population matched on smoking habits, the pathological changes in the small airways differ appreciably in the two groups. It could be argued that these changes result from comparing a population from Quebec with a population from British Columbia; however, in the study of Cosio et al, which is derived from the population of Montreal, values for pathological abnormalities in the small airways (when converted to our method of calculating results) were similar to those observed in our control population from British Columbia. We have also examined lungs from the few non-miners necropsied at Thetford during the period in which the miners' lungs were collected and have found that these lungs resembled those of our control population.

Our results indicate that exposure to mineral dust produces a generalised fibrosis of the small airways greater than that which may be accounted for by cigarette smoking; these changes are present even when, on casual examination, the lungs appear no different from those of ordinary cigarette smokers. Whether the changes in this population result only from exposure to asbestos is uncertain, because asbestos miners, like other miners, are exposed to large amounts of other dusts, and various dusts appear to produce similar airway abnormalities.

Additionally, these results confirm our previous suggestion that the pathological changes in the small airways in these workers are not confined to the respiratory bronchioles, but also affect the membranous bronchioles. This observation is important, since most pathologicofunctional studies have suggested that it is the abnormalities of the membranous bronchioles that correlate best with airflow obstruction; the role of the respiratory bronchioles in this regard is less certain, as noted at the beginning of the paper.

We assessed pigmentation in this group of workers both because abnormalities of pigmentation have been one of the variables contributing to the overall correlation of pathological and physiological changes in other studies, and because we were curious to know if optically visible pigment might serve as a good dust marker. Pigmentation, however, appears to be a relatively poor marker of exposure to dust and of pathological changes, since the mean grades for pigmentation of the membranous bronchioles in the miners did not differ significantly from those of the controls, despite the miners' exposure to dust and despite the much more severe fibrosis in their membranous bronchioles.

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