

Correlation Between the Tissue Response and Asbestos Fiber Content

by A. G. Heppleston*

Asbestos fiber concentration increases in proportion to the degree of pulmonary fibrosis as far as the moderate grade. No such correlation occurs with severe asbestosis, nor with the morphological form which the fibrosis assumes, and here secondary factors may be concerned. Electron microscopy suggests that optically visible fibers constitute a reasonably constant proportion of the total irrespective of the pathological reaction. Light microscopy may thus afford a guide to the total asbestos concentration. Finally, the development of mesothelioma, whether of the pleura or the peritoneum, appears to be unrelated to the concentration of coated or uncoated asbestos fibers residing in the lung.

Chemical analysis suggests that no relationship exists between pulmonary asbestos concentration and the degree of fibrosis. Enumeration of asbestos fibers affords another approach to this problem, and Dr. T. Ashcroft and I employed both light and electron microscopy. (1). The findings may have an indirect bearing on the genesis of mesothelioma.

Light Microscopy

Asbestos fibers were quantitated in lung tissue from 35 individuals by macerating samples in concentrated KOH, washing the residue in distilled water, counting coated and uncoated asbestos fibers in the resuspended sediment in a Fuchs-Rosenthal chamber, and expressing the concentration as the number of fibers per gram of dry tissue. To minimize errors several technical points should be stressed.

Phase contrast microscopy must be employed so as to reveal fine uncoated fibers which are easily overlooked when viewed by normal illumination.

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Repeated washing of the macerated suspension causes loss of fine uncoated fibers. Although counts of coated fibers varied little, uncoated fibers progressively declined in number with each centrifugation. We therefore limited the washings to one.

Drying the tissue before maceration, to obtain a dry weight, causes fracture of the longer coated and uncoated fibers and gives spuriously high counts. It is better to macerate tissue in the wet state and to calculate the equivalent dry weight of lung tissue from the alteration in weight on drying an adjacent piece of lung showing the same pathological reaction as the test sample.

All the samples of lung tissue were taken from individuals with asbestos bodies in histological sections of lung, and all but one of the cases had a definite or probable history of occupational asbestos exposure. Lung tissue was examined from five necropsy cases of severe asbestosis, the extent and form of the fibrosis varying within a given lung. This permitted a comparison of fiber counts from areas appearing macroscopically normal or showing patchy fibrosis, honeycomb change, or solid fibrosis.

Considered in relation to increasing severity

of asbestosis, there was on the whole a progressive rise in fiber concentration, in so far as the initial stages of the disease are concerned. Mean counts of coated, uncoated, and total fibers showed successive and statistically significant 6- to 10-fold increases between the groups of cases with nil-mild and mild-moderate asbestosis. The mean proportion of uncoated fibers also showed a small progressive rise with increasing fibrosis, but the differences between grades were not statistically significant. No relationship existed between grade of asbestosis and duration of asbestos exposure, time from first exposure to death or time from last exposure to death. Cases with nil, mild, or moderate degrees of asbestosis, that is, with widely varying pulmonary concentrations of asbestos fibers, were all associated with mesothelioma of the pleura or peritoneum.

Turning to severe asbestosis, the cases were not associated with mesothelioma and fell into two groups. One group of three cases, which we have called the "low" group, had fiber concentrations within the range associated with mild asbestosis, and the other two cases, which we have called the "high" group, showed concentrations within the range for moderate asbestosis. In neither group was there any correlation between the macroscopic form of the fibrosis and the fiber concentration or the proportion of uncoated fibers.

It is apparent that while progression of disease from "no asbestosis" through "mild asbestosis" to "moderate asbestosis" was associated with a progressive increase in the fiber content of the lung, further progression to "severe asbestosis" was not associated with any further increase in asbestos concentration. There was, in fact, a wide variation in asbestos concentration between areas in the same lung showing no fibrosis, fibrocystic change, or solid fibrosis. These considerations, coupled with the irregular distribution of the morphological changes, suggest that the changes of severe asbestosis are due to the intervention of one or more secondary pathological processes. There was no evidence of tuberculosis in any of the cases here considered, and we believe that the

presence of asbestos or the reaction to it predisposes to nonspecific inflammatory states which may leave residual solid fibrosis or progress to honeycombing in the manner previously described. (2).

Electron Microscopy

Much of the dust in human asbestotic lungs has a very small particle size and most fibers are less than $0.3 \mu\text{m}$ in diameter. Such fine fibers would not be visible with the light microscope, and penetration into the lung parenchyma is determined by fiber diameter. In an effort to estimate the proportions of finer fibers, additional samples of lung from six cases were macerated as before, and, after dialyzing out the residual KOH and ashing the residue, a drop of resuspended sediment was allowed to dry on a Formvar-coated grid, and the diameter distribution of the asbestos fibers was determined from electron micrographs.

Less than a third, and usually less than a fifth, of the fibers were optically visible, that is had a diameter of $0.4 \mu\text{m}$ or over. In this respect, there was no variation between the different grades of asbestosis. However, although the number of cases examined was small, the proportion of optically visible fibers was reasonably constant between 12% and 30% of the total, so that an optical count could be held to give a fair indication of the total asbestos concentration.

The micrographs from which the fiber distributions were obtained revealed a preponderance of amphibole asbestos, and although some chrysotile fibers were present, they were relatively few. It seems unlikely that all the patients could have been exposed almost exclusively to amphibole.

REFERENCES

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