A PATHOLOGICAL AND MINERALOGICAL STUDY OF ASBESTOS-RELATED DEATHS IN THE UNITED KINGDOM IN 1977


* MRC Pneumoconiosis Unit, Llandough Hospital, Penarth, Wales
† Department of Mineral Exploitation, University College, Cardiff, Wales
‡ Pathology Department, Llandough Hospital, Penarth, Wales

Abstract—Lung tissue samples from Pneumoconiosis Panel cases comprising workers whose deaths were considered to be asbestos-related and from controls exposed to different levels of urban pollution were examined histologically and analysed for mineral fibre content. The Panel cases had on average about 100 times more amphibole fibres in their lungs than the controls, but the amounts of chrysotile were similar. Considering the much greater industrial usage of chrysotile, this points to lower deposition and/or more rapid elimination of chrysotile from the lungs. There was a clear association between asbestos grade and amphibole, but not chrysotile, content in the Panel cases; the amount of amphibole was similar for those with mesothelioma, those with lung cancer and those with neither of these tumours.

INTRODUCTION

Detailed mineral analysis of the fibrous dusts in the lungs of cases of mesothelioma and controls was undertaken on material from Britain in 1976 (Jones et al., 1980). In 1977 the investigation was extended to include all deaths reported to the United Kingdom Pneumoconiosis Medical Panels, in which asbestos exposure was suspected of contributing to death. In the 1976 study there was some difficulty in obtaining lung tissue from matching control cases. On this occasion we endeavoured to obtain a contrasting population from areas of high, medium and low industrial pollution. This, we considered, would provide a useful control for asbestos exposure as well as providing evidence of other types of mineral fibre in the lungs of populations in 1977. The information obtained could then be used as a basis to establish whether there was a significant increase of the 'newer' fibres in the lungs of the populations in the future. Later, it is hoped that the lungs will be analysed for mineral particulates.

Information obtained from this study, and other similar investigations, will contribute to the relationship between mineral fibre inhalation and the pathological sequelae of exposure to fibrous and other mineral dusts, eventually covering type, size and amounts of dust retained in the lungs.

In this paper we present the preliminary information that has been obtained on the first 235 cases examined.

MATERIAL

(a) Lung tissue from Pneumoconiosis Medical Panels

As it was considered that this study would produce valuable information for diagnostic purposes, it was agreed that suitable material would be obtained from the
Pneumoconiosis Medical Panels. The Senior Medical Officers of these Panels were invited to submit lung tissue from workers who had been referred to them because exposure to asbestos dust had been considered to be a factor in the cause of death.

(b) Control population

Pathologists in six hospitals were requested to submit lung tissue from a series of consecutive necropsies on adults. The hospitals chosen were in two large industrial cities with a record of serious environmental pollution, two smaller cities with moderate pollution and two towns in which there was little industry.

(c) Mesotheliomas from other sources

During 1977 a number of suspected mesotheliomas were submitted to Dr. J. S. P. Jones (Nottingham) and he has kindly made them available.

METHODS

Specimens

All pathologists were requested to submit three blocks of lung tissue. These were to be labelled: (A) apex of the upper lobe, (B) apex of lower lobe, (C) base of lower lobe. An accompanying diagram indicated that each block should have a visceral pleural margin. It was recommended that the blocks should, if possible, be from the left lung which had been inflated with formal saline. If a tumour was present then the tissue should be taken from the less affected lung. In addition, tissue from any tumour was requested. It was suggested that the blocks should be $2 \times 2 \times 1$ cm. On receipt, the central slice of each block was taken for histology and the remaining outer slices were then sent to Dr. Pooley for maceration and subsequent analysis.

Paraffin sections were then prepared from the central block, stained with haematoxylin and eosin, or Van Gieson's method for fibrous tissue.

Examination of the histological preparations

(a) For asbestos bodies. The 6 \( \mu \)m H&E sections were used for this study. The three sections from the specific site were examined using a 25X objective, and were viewed by two observers for 10 min each before being recorded as negative (grade 0); grade 1 indicated that occasional bodies were observed after prolonged examination, usually more than one asbestos body being seen; grade 2 was recorded when asbestos bodies were found with relative ease—that is one body in at least every 10 fields; grade 3 represented numerous asbestos bodies, easily detected.

(b) Fibrosis. The extent of fibrosis was estimated from the histological sections. Grade 1 (minimal) fibrosis was recorded when minimal collagen was seen in interalveolar septa or around the respiratory bronchioles and alveolar ducts. In grade 2, more extensive thickening of the interalveolar septa extended beyond the centrilobular area but without disturbance of parenchymal architecture. The fibrosis was more extensive in grade 3, with preservation of recognizable alveolar sacs in some parts of the sections. In grade 4, there was complete distortion of the normal architecture, with either large diffuse areas of fibrosis, in which the remaining air spaces...
were distorted, or else diffuse thick-walled cystic spaces, some of which were lined with respiratory or hyperplastic squamous epithelium, no normal air spaces being present. These were the features of a fully developed ‘honeycomb’ lung.

In examining the sections from the apical segments of the upper lobes, the presence of apical sclerotic scar tissue was not included in the assessment.

Each section was assessed individually and the arithmetic mean of the three sections used.

(c) Asbestosis. For assessing the presence and severity of asbestosis, only the histological sections were available. Therefore, there were no means of observing the overall extent of the fibrous involvement in the more severe grades of the disease. This could only be calculated by considering the degree of involvement in all three sections.

The description of the grading of fibrosis covers that of asbestosis, except that more importance was placed on the centrilobular involvement. The presence of asbestos bodies was taken into account.

Thus, minimal asbestosis (grade 1) was essentially the same as that in grade 1 fibrosis, except for the presence of occasional asbestos bodies in the foci of interstitial thickening. Grade 2, which was the accepted pattern of slight asbestosis, showed definite fibrous thickening in the walls of respiratory bronchioles extending into the alveolar ducts in at least two of the three sections with the presence of asbestos bodies in air spaces and the interstitial tissues. Moderate asbestosis (grade 3) was when the lesions were more profuse in all three sections, the foci fusing with peribroncholar septa with strands of fibrous tissue linking some of the lesions. The final stage of marked asbestosis (grade 4) was seldom seen in these cases and was identical to the most severe grade of fibrosis except for the presence of asbestos bodies in the interstitial tissues and distorted air spaces. The possibility that these lesions were mainly due to factors other than exposure to asbestos dust was considered.

(d) The presence of other diseases. This category was confined to mention of any obvious pathology which could be responsible for pulmonary fibrosis. The presence of terminal pneumonia was ignored.

(e) Mesothelioma. The presence of a mesothelioma was confirmed on the opinion of two pathologists. If necessary, further material was obtained from the pathologist making the initial diagnosis. A significant group of these tumours were submitted independently to Dr. J. S. P. Jones, who kindly made them available for this investigation.

(f) Carcinoma of the lung. These tumours were classified on the basis of the current WHO classification.

Mineral fibre determination

Determinations of the fibrous particulate content of lung parenchyma samples were performed upon dust samples extracted from tissue using an analytical transmission electron microscope. Tissue samples were first dried to a constant weight at a temperature of 80°C and placed in clean centrifuge tubes. Approximately 50–100 mg of dried tissue was used in each case. The dried samples were then digested in 10 cm³ of 5N
sodium hydroxide at a temperature of 90°C on a water bath to digest the majority of the biological material, the residue obtained being centrifuged and washed twice with distilled water to remove the caustic solution. The washed residues were then dried and ashed in an oxygen atmosphere to destroy any remaining organic material and the final extract was suspended using a mild ultrasonic treatment in 10 ml of distilled water adjusted to a pH of approximately 1.0 with HCl and filtered immediately onto 25 mm diameter 0.2 pore size Nuclepore filters. If the mineral residue extracted from the tissue samples was excessive, only measured aliquots of the final suspension were taken for filtration. In each preparation an attempt was made to prepare a filter specimen with a distribution of particles adequately spaced to allow the unhindered examination of individual dust particles in the electron microscope.

The filter preparations laden with a dust extract from a known weight of dried tissue were then coated with a layer of carbon to form a carbon film in which the dust particles were trapped. Portions of the filter were then taken and the filter substrate removed with chloroform leaving a carbon film in which the dust extract was embedded. These carbon films were mounted on gold electron microscope support grids with a 117 µm aperture size for examination in the electron microscope. The electron microscope preparations were scanned for fibrous particles and their number concentration per unit area of the filter determined either directly from the microscope or from electron micrographs taken of random areas of the preparations. Number concentrations were thus established which could be related back to the initial dry weight of tissue used to prepare the specimen. As the specimens were scanned and fibres encountered they were analysed using an energy dispersive X-ray analysis system to establish their chemical composition which was used to identify the fibres. The counting techniques and identification procedure adopted have been described in detail elsewhere (Pooley, 1975, 1977; Pooley and Clark, 1979; and Gaudichet et al., 1980). Fibres of all sizes that were resolved by the electron microscope were included in the counts, provided that they had an aspect ratio greater than 3:1 as judged by eye.

RESULTS

Table 1 gives the sources and sexes of the 1272 cases submitted to the study. This presentation is confined to men from the Pneumoconiosis Medical Panels, the control series, and the mesotheliomas from other sources. Of these 309 have been examined histologically and the mineral fibre analysis carried out for 235. The distributions of

<table>
<thead>
<tr>
<th>Source</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumoconiosis Medical Panels</td>
<td>324</td>
<td>30</td>
</tr>
<tr>
<td>Control series:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>low pollution</td>
<td>59</td>
<td>50</td>
</tr>
<tr>
<td>moderate pollution</td>
<td>88</td>
<td>58</td>
</tr>
<tr>
<td>heavy pollution</td>
<td>206</td>
<td>136</td>
</tr>
<tr>
<td>Mesotheliomas from other sources</td>
<td>36</td>
<td>9</td>
</tr>
<tr>
<td>Other material</td>
<td>241</td>
<td>35</td>
</tr>
<tr>
<td>Total</td>
<td>954</td>
<td>318</td>
</tr>
</tbody>
</table>
asbestos bodies and fibrosis are given in Table 2 and of asbestosis grade and the presence of lung cancer and mesotheliomas in Table 3.

Asbestos bodies were frequently found in the Panel cases but infrequently in the control series, except for a few cases from one of the heavily polluted cities. The mesotheliomas from other sources were intermediate. Fibrosis of grades 3 or 4 occurred only in the Panel cases, but grade 1, and to a lesser extent grade 2, was unexpectedly common in the control series. Moderate asbestosis (grade 3) occurred in more than 20% of the Panel cases but not at all in the control series. There were seven cases from one of the heavily polluted cities with minimal or slight asbestosis. Of the Panel cases 60%, had either mesothelioma or lung cancer. For most of the suspected mesotheliomas from other sources the diagnosis was confirmed. In the control series there was one mesothelioma (this case also had asbestosis) and only three cases of lung cancer.

Figure 1 shows the distributions of fibre numbers, in millions per gram of dry tissue, for the Panel cases and the control cases. The control cases with asbestosis have been excluded. Figure 1(a) is for crocidolite asbestos, Fig. 1(b) is foramosite asbestos and Fig. 1(c) is for amphibole asbestos, i.e. amosite and crocidolite, the two commercial varieties, but ignoring actinolite, anthophyllite and tremolite which sometimes occurred. Figure 1(d) is for chrysotile asbestos and Fig. 1(e) for all commercial types of asbestos, i.e. amosite, chrysotile and crocidolite. Finally, Fig. 1(f) is for non-asbestos, i.e. fibres other than the three commercial types of asbestos. The Panel cases contained...
Fig. 1. Distribution of fibre counts for Pneumoconiosis Medical Panel cases and control series for (a) crocidolite, (b) amosite, (c) amphibole (amosite and crocidolite), (d) chrysotile, (e) asbestos (amosite, chrysotile and crocidolite), (f) non-asbestos (fibres other than those in (e))

significantly \( p < 0.001 \) more amphibole, both crocidolite and amosite, than the controls, but there was no such difference for chrysotile. Also, the amounts of non-asbestos fibre were similar for Panel cases and controls. There were no clear differences between the control areas.

In Fig. 2 the distributions are given for the Panel cases according to the grade of asbestosis. For both amphiboles there were trends of increasing lung content with increasing grade of asbestosis. The minimal (grade 1) and slight (grade 2) grades of asbestosis were combined in the figure, but those with minimal asbestosis contained significantly more amphibole, both crocidolite and amosite, on average, than those with no evidence of asbestosis (grade 0). The amounts of chrysotile and non-asbestos were not associated with grade of asbestosis.

For Panel cases the amounts of amphibole were similar for those with mesothelioma, lung cancer and cases without these two types of tumour. The mesotheliomas from other sources had less amphibole than the Panel cases but more than the control series. In three of these mesotheliomas amphibole was not detected.
DISCUSSION

This is a preliminary report on less than a quarter of the material submitted to the study. Nevertheless, some things are clear: first, that cases submitted from the Pneumoconiosis Medical Panels had, on average, about 100 times more amphibole fibres in their lungs than cases from the control areas but the amount of chrysotile was similar. Since cases from Panels will have been occupationally exposed to asbestos, the former observation is not surprising but, in view of the fact that chrysotile has been used in much greater quantities than amphibole, the latter finding was unexpected. The deposition and clearance of chrysotile from the lung are different from those of amphibole and, in particular, the elimination of chrysotile from the lungs is more rapid. Thus, a low chrysotile count may indicate little exposure or high exposure which finished some years before death. Nevertheless, one would expect to find more chrysotile in the lungs of men who have been occupationally exposed than in lungs of men in the general population who have only experienced environmental exposure.

A second clear finding was the association between the grade of asbestosis and the amphibole content of Panel cases. To some extent there is a circular argument
involved, since the grading of asbestosis took account of the grading of asbestos bodies, i.e. asbestosis was defined partly in terms of asbestos content as observed under the light microscope. However, most asbestos fibres are visible only with an electron microscope so that the association between asbestosis and amphibole counts was not inevitable. Of particular interest was that the association was apparent even at the earliest grade of asbestosis considered, that is minimal asbestosis.

In view of the association between mesothelioma and amphibole asbestos (ACHESON and GARDNER, 1979) it was perhaps surprising that in the Panel cases the amount of amphibole was similar for those with mesothelioma, those with lung cancer and those with neither of these tumours. At this stage we have no clear explanation of this, but it is possible that the selective forces which lead to a man coming to the attention of a Panel may be involved.

Many of the mesotheliomas from other sources are known to have had occupational exposure to asbestos; some have since been accepted by Panels. There were three mesotheliomas out of 64, i.e. 5%, with analysis of lung content for whom no amphibole was detected which agrees with the 1976 study (JONES et al., 1980).

Acknowledgements—We wish to thank the Principal Medical Officer, Dr. R. G. B. Williamson, and the Senior Medical Officers of the Pneumoconiosis Medical Panels, and all the Pathologists who have contributed to this study. We are most grateful for support received from the Asbestos Research Council.

REFERENCES


Asbestos-related deaths in the UK in 1977

DISCUSSION

H. WELL: I am very interested in your data concerning the influence of fibre type on asbestosis. While I agree that such a differential effect has not previously been established definitively, we presented epidemiological data at the last BOHS International Symposium which strongly suggested that crocidolite exposure in a population of asbestos-cement-pipe manufacturing workers resulted in increased prevalence and severity of asbestosis when compared with a group in the same industry with a similar total fibre exposure to chrysotile only. I am delighted to see this confirmed by Dr Pooley's elegant mineralogical techniques.

J. BIGNON: You reported that there was no difference between the chrysotile content of the lungs of mesothelioma cases and controls. Did you compare the fibre lengths of the two groups? If one group has a mean fibre length longer than the other, it might be due to inhalation of longer fibres; it could also be explained by translocation of the shorter fibres to other sites such as the pleura. We have shown previously that in most cases where there is a low lung content of chrysotile fibres, small fibres can be found in the pleura samples.

Mr BERRY: Dr Pooley has given data on the fibre length distributions of asbestos in lungs (Pooley, Ann. N Y Acad. Sci. 1979, 330, 711-716) but we have no data on this aspect from the study described today.

K. ROBOCK: I congratulate you and your co-authors on this excellent and objective paper. In the last sentence of your presentation you said that amphiboles are more correlated with the occurrence of mesothelioma, but in the text you say that, in the Panel cases, the amount of amphibole was similar for those with mesothelioma, those with lung cancer and those with neither. Could you explain this discrepancy?

Mr BERRY: The association of mesotheliomas and amphibole asbestos was apparent in our previous study of 1976 cases, to which we referred, and this is also strongly supported by epidemiology. In the present study the Panel cases would all have been occupationally exposed to asbestos, which usually would include amphibole. As only a minority of exposed people develop a mesothelioma it follows that high amounts of amphibole will also be found in exposed groups with other conditions, such as lung cancer and asbestosis.

F. D. K. LINDSELL: My question relates to Table 3. What were the distributions, by asbestosis grade among the lung cancer and among the mesothelioma cases? This might cast light on the difficult problem of whether asbestosis-induced lung cancer is necessarily preceded by fibrosis.

Mr BERRY: For the Panel cases, out of 49 mesotheliomas there were 14 without asbestosis, 18 with grade 1, 14 with grade 2 and 3 with grade 3. Out of 47 lung cancers there were 16 without asbestosis, 7 with grade 1, 11 with grade 2 and 13 with grade 3. Thus lung cancers had more asbestosis than the mesotheliomas, but even so one third of the lung cancers had no detectable asbestosis. We do not know whether all of the lung cancers were induced by asbestos.

J. C. McDONALD: In the U.K. a high proportion of asbestos-exposed workers have had exposure to amphiboles and chrysotile. In such circumstances, the correlation between asbestosis grade and amphibole content may tend to obscure the role of the chrysotile. Have you any information on the relationship between chrysotile content and asbestosis in cases where amphiboles were absent?

Mr BERRY: Unfortunately there were so few cases where amphiboles were absent that we have no such information.

NANCY TAIT: The cases on which this study was based were all recognized as asbestos-related deaths by the Pneumoconiosis Medical Panels. The panels have, until recently, insisted that only fibrosis detectable by the naked eye should be diagnosed as asbestosis. Furthermore, they count only asbestos bodies, not fibres, in lung tissue, although it is generally recognized that bodies form more readily on amphibole than on chrysotile fibres. How will this affect studies, like our own, based on PMP cases?

Mr BERRY: You are quite right to point out the importance of the methods which the Panels use to accept cases. Although not all the cases in this study were necessarily accepted, they had been referred for consideration. We do not know the answer from this study alone, but we are doing other studies of cases of mesothelioma and other types of asbestos-related cases which are collected from non-panel sources. When this study and others are complete and we can integrate them, we hope to be able to, at least partly, answer your question. I am afraid at the moment this study and more importantly the other studies are not far enough advanced to give any definite answer.