THE PATHOLOGY AND MINERAL CONTENT OF LUNGS IN CASES OF MESOTHELIOMA IN THE UNITED KINGDOM IN 1976

J.S.P. JONES
Department of Pathology,
City Hospital,
Nottingham, UK

G.H. ROBERTS
Department of Pathology,
Southern General Hospital,
Glasgow, UK

F.D. POOLEY & N.J. CLARK
Department of Mineral Exploitation,
University College,
Cardiff, UK

P.G. SMITH
Department of Pathology,
General Hospital,
Nottingham, UK

W.G. OWEN
Department of Pathology,
Royal Infirmary,
Preston, Lancs., UK

J.C. WAGNER & G. BERRY
MRC Pneumoconiosis Unit,
Llandough Hospital,
Penarth, South Glamorgan, UK

D.J. POLLOCK
Institute of Pathology,
The London Hospital,
Whitechapel,
London, UK

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In 1976 a joint investigation was undertaken by the Medical Research Council Pneumoconiosis Unit, the IARC Mesothelioma Panel (United Kingdom) and the Department of Mineral Exploitation, University College, Cardiff. The objectives were:

(1) to identify patients who had died from pleural or peritoneal mesothelioma in 1976 in the United Kingdom;

(2) to obtain samples of tumour from each autopsy in order to classify histological features;

(3) to examine lung tissue from each autopsy in order to establish which types of asbestos and other mineral fibres were present and to estimate the amounts of those identified; and

(4) to obtain lung tissue from matched controls and to examine this material using the same methods as in (3).

MATERIALS AND METHODS

A letter was sent to each histopathologist in the United Kingdom and to each of Her Majesty's coroners in England and Wales, inviting them to notify the Mesothelioma Panel in Nottingham of any deaths due to mesothelioma in 1976. This survey was not to interfere with the usual procedures of diagnosis by the individual pathologists and it was not to impede the reference of material to the Pneumoconiosis Medical Panel for compensation purposes.

Those pathologists who wished to participate in the survey were requested to send to the Mesothelioma Panel the following:

(a) from each mesothelioma case:

(i) multiple samples of formalin-fixed wet tumour tissue taken from widely different sites; and

(ii) a sagittal slice of formalin-fixed lung, 2 cm thick, taken from the lesser diseased side;

(b) from control cases:

(i) bronchial carcinoma - two pieces of formalin-fixed wet tumour tissue;

(ii) a sagittal slice of formalin-fixed lung, 2 cm thick, taken from the lesser diseased side; and

(iii) cerebrovascular disease - a sagittal slice of formalin-fixed lung, 2 cm thick, taken from the lesser diseased side;
(c) information pertaining to the post-mortem samples: name, address, age, sex, date of death, autopsy report, hospital index number, names of hospital, clinician and general practitioner and - if known - any information about asbestos exposure during life. This information was retained on file in Nottingham and was not made available to the Panel pathologists or to the mineralogists.

The procedure for pathology was that histological sections of the tumour from the mesothelioma cases were stained with haematoxylin and eosin, with diastase periodic acid-Schiff and with alcian blue. Each case was sent to two of the five members of the Mesothelioma Panel on a strict rota system, so that the same two pathologists only examined the same case on a one-in-ten frequency, thus minimizing individual diagnostic bias. If there was agreement between the two pathologists on the diagnosis of mesothelioma, the case was accepted. If there was disagreement or particular difficulty or interest in the histological features of a case, the sections were then examined by all five members of the Panel, followed by a discussion and voting procedure (Plantey'dt1). The details of the histological analysis will be published elsewhere.

The lung tissue from the mesotheliomas and from the bronchial carcinoma and cerebrovascular disease control cases were sent to the MRC Pneumoconiosis Unit, Penarth, where standard blocks of tissue were taken from specific sites. The specimens were coded so that the control material was indistinguishable from the mesothelioma material. Mineral fibre analysis was then carried out at the Department of Mineral Exploitation by the method of Pooley & Clark2, using electron microscopy and X-ray diffraction microprobe techniques.

RESULTS

Post-mortem material was submitted to the Mesothelioma Panel from 117 cases, the majority of which had been diagnosed by the referring pathologists as being mesotheliomas. In a small number of cases, the pathologists had not made a definite diagnosis and sought the Panel's opinion on tumours that were macroscopically suspected of being mesotheliomas. Some cases were therefore finally diagnosed as carcinomas, and in a few the limited amount of tissue did not permit a reliable diagnosis. The sources of the various cases are shown in Figure 1.

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FIG. 1. CITIES AND TOWNS IN THE UNITED KINGDOM FROM WHICH CASES OF MESOTHELIOMA WERE REFERRED TO THE PANEL IN 1976

Note the clusters in the shipyard areas of Belfast, Glasgow, Newcastle/Gateshead, Barrow-in-Furness, Liverpool and Devonport.
The numbers of cases and controls submitted to the Mesothelioma Panel are shown in Table 1. Table 2 gives the age at death and sex distribution of confirmed mesothelioma cases and Table 3 the sites at which the mesotheliomas occurred. Table 4 shows the history of exposure to asbestos of the mesothelioma cases.

Table 1. Material submitted to the Mesothelioma Panel

<table>
<thead>
<tr>
<th>Description</th>
<th>No. with adequate lung tissue for mineralogy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases confirmed as mesothelioma</td>
<td>93 86</td>
</tr>
<tr>
<td>No. of cases not confirmed as mesothelioma</td>
<td>24 22</td>
</tr>
<tr>
<td>No. of control cases with bronchial carcinoma</td>
<td>28 27</td>
</tr>
<tr>
<td>No. of control cases with cerebrovascular disease</td>
<td>30 29</td>
</tr>
</tbody>
</table>

Table 2. Age at death and sex distribution in confirmed mesothelioma cases

<table>
<thead>
<tr>
<th>Sex</th>
<th>No. of cases</th>
<th>Age range (yrs)</th>
<th>Mean age at death (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>72</td>
<td>32 - 83</td>
<td>62.3</td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
<td>43 - 87</td>
<td>64.7</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Sites of mesothelioma

<table>
<thead>
<tr>
<th>Site</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural</td>
<td>43</td>
<td>11</td>
<td>54</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>33</td>
<td></td>
<td>33</td>
</tr>
</tbody>
</table>
Table 4. History of asbestos exposure in mesothelioma cases

<table>
<thead>
<tr>
<th>History</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive history of exposure</td>
<td>59</td>
</tr>
<tr>
<td>Assumed exposure (due to nature of occupation)</td>
<td>10</td>
</tr>
<tr>
<td>Negative history of exposure</td>
<td>3</td>
</tr>
<tr>
<td>Occupational history unknown</td>
<td>21</td>
</tr>
</tbody>
</table>

Table 5 shows the numbers of cases in each group of patients whose lungs contained fibres of different types of asbestos dust. Figure 2 shows the distribution of the numbers of fibres of chrysotile, amosite and crocidolite per mg of lung tissue for each of the four groups of patients. The numbers of fibres are divided into intervals, each - except for the lowest - covering a 10-fold range in count. In most of the cases in which the count is shown as less than 100, no fibres of that type were found.

Table 5. Numbers of cases with different types of asbestos dust in lung tissue (% in brackets): A - mesothelioma cases; N - non-mesothelioma cases; B - controls with bronchial carcinoma; C - controls with cerebrovascular disease

<table>
<thead>
<tr>
<th>Type of asbestos</th>
<th>A (%)</th>
<th>N (%)</th>
<th>B (%)</th>
<th>C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chrysotile</td>
<td>56 (65)</td>
<td>14 (64)</td>
<td>18 (67)</td>
<td>26 (90)</td>
</tr>
<tr>
<td>Amosite</td>
<td>71 (83)</td>
<td>18 (82)</td>
<td>12 (44)</td>
<td>13 (45)</td>
</tr>
<tr>
<td>Crocidolite</td>
<td>76 (88)</td>
<td>21 (95)</td>
<td>16 (59)</td>
<td>19 (66)</td>
</tr>
<tr>
<td>Anthophyllite</td>
<td>18 (21)</td>
<td>6 (27)</td>
<td>7 (26)</td>
<td>7 (24)</td>
</tr>
<tr>
<td>Tremolite</td>
<td>19 (22)</td>
<td>9 (41)</td>
<td>8 (30)</td>
<td>8 (28)</td>
</tr>
<tr>
<td>Actinolite</td>
<td>11 (13)</td>
<td>4 (18)</td>
<td>3 (11)</td>
<td>8 (28)</td>
</tr>
<tr>
<td>Amphibole (amosite &amp; crocidolite)</td>
<td>82 (95)</td>
<td>22 (100)</td>
<td>21 (78)</td>
<td>24 (83)</td>
</tr>
</tbody>
</table>

\(a\) In view of the rarity of anthophyllite, tremolite and actinolite, and since no marked differences in their occurrence were observed between the groups, these three fibres were not considered further. They occurred in only a minority of lungs, and when they did occur they did so usually in small numbers: only two lungs contained more than 10,000 fibres/mg of any of these three types.
FIG. 2. DIFFERENT TYPES OF ASBESTOS FIBRE IN THE LUNGS OF PATIENTS IN THE FOUR GROUPS, SHOWING THE NUMBER OF CASES WITHIN EACH ZONE OF FIBRE CONCENTRATION

A - mesothelioma patients; N - non-mesothelioma patients; B - controls with bronchial carcinoma; C - controls with cerebrovascular disease
The differences in distributions between the groups were assessed using $\chi^2$ tests for trend (Fig. 3). These tests showed that the mesothelioma cases contained more amosite and more crocidolite than did the two groups of controls combined ($P < 0.001$); the amount of chrysotile was similar for mesotheliomas and controls. Comparison of the confirmed mesotheliomas with the other index cases showed no evidence of any differences; however, when the two control groups were compared there was significantly more chrysotile in the controls with cerebrovascular disease than in those with lung cancer ($P < 0.05$). This difference was small and will not be considered further. For each of the two types of amphibole, there was about 10 times as much present - on average - in the mesothelioma cases than in the controls.

**FIG. 3. THE QUANTITIES OF DIFFERENT ASBESTOS FIBRES IN LUNG TISSUE OF MESOTHELIOMA CASES, COMPARED WITH THOSE IN CONTROLS**

--- Mesothelioma; ----- Controls (B and C)
Tables 6 and 7 give fibre counts in patients with no known history of exposure to asbestos dust and those in mesothelioma patients with a history of slight exposure to asbestos dust. Four of the mesothelioma patients had no amphibole fibres in their lungs; the counts of fibres that did occur are given in Table 8.

Table 6. Fibre counts in patients with no known history of asbestos dust exposure

<table>
<thead>
<tr>
<th>Fibres/mg lung tissue</th>
<th>Chrysotile</th>
<th>Amosite</th>
<th>Crocidolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesothelioma patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MP 12 No history of exposure</td>
<td>0</td>
<td>95</td>
<td>284</td>
</tr>
<tr>
<td>MP 45 Textile worker</td>
<td>0</td>
<td>0</td>
<td>4303</td>
</tr>
<tr>
<td>MP100 No history of exposure</td>
<td>2712</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-mesothelioma patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MP 3 Waiter</td>
<td>74</td>
<td>629</td>
<td>222</td>
</tr>
</tbody>
</table>

Table 7. Fibre counts in mesothelioma patients with a history of slight asbestos dust exposure

<table>
<thead>
<tr>
<th>Fibres/mg lung tissue</th>
<th>Chrysotile</th>
<th>Amosite</th>
<th>Crocidolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP 32 Worked for 3 weeks in an asbestos factory at age 15 years (died aged 59)</td>
<td>0</td>
<td>253</td>
<td>6745</td>
</tr>
<tr>
<td>MP 15 Lived 300 yards from the same asbestos factory at age 3-7 years (died aged 43)</td>
<td>34</td>
<td>575</td>
<td>508</td>
</tr>
</tbody>
</table>
Table 8. Counts of other fibres in mesothelioma patients with no amphibole (amosite or crocidolite) fibres in their lungs

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Fibres/mg lung tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP 25  Boiler maker in naval dockyard for a</td>
<td>2900 nonasbestos fibres</td>
</tr>
<tr>
<td>few years during early part of working life</td>
<td></td>
</tr>
<tr>
<td>MP 28  Naval dockyard worker</td>
<td>2900 nonasbestos fibres</td>
</tr>
<tr>
<td>MP 63  Naval dockyard worker and railway</td>
<td>83,600 fibres of which 543 were chrysotile</td>
</tr>
<tr>
<td>goods yard worker</td>
<td></td>
</tr>
<tr>
<td>MP100  No known asbestos exposure</td>
<td>24,000 fibres of which 2712 were chrysotile</td>
</tr>
</tbody>
</table>

DISCUSSION

Ninety-three cases of confirmed mesothelioma were referred to the Panel for the year; this was about two-thirds of the number expected when the survey was being planned. Considerable support was given to the project by pathologists and coroners: material was sent promptly and was mainly received in good condition. The Mesothelioma Panel was conscious of the additional work that was being imposed on their colleagues, many of whom had been asked to collect a variety of materials for numerous other national and local projects. Some cases were therefore lost to the survey due to pressure of work on the pathologists. In 1976, 209 deaths were certified as due to malignant neoplasm of the pleura (ICD 163.0; Registrar General), so that only about half of these were available to the survey. A disappointing aspect was that only 58 control samples were obtained for the 117 indexed cases. Here again, pressure on the pathologists' time was a factor; but, in addition, we have since realized that our design for control material was too restrictive. In many instances, pathologists who worked at chest hospitals did not have the opportunity of carrying out autopsies on patients with cerebrovascular disease; pathologists in general hospitals had difficulty in finding age- and sex-matched controls with bronchial carcinoma. In order to obtain the best response, it is important to be sensitive to the demands that are made on colleagues' time and to make requests as modest and as simple as possible.

As members of the Mesothelioma Panel gained experience in seeing the many variants of this comparatively rare tumour, so the diagnosis of mesothelioma was made with greater agreement over a period of time. In the early stages, when certain individual cases provided a divergence
of opinion, they were reviewed at later meetings, by which time
diagnostic criteria had become more firmly established, and much
better agreement was reached. Three cases were of particular interest:
they had originally been diagnosed as mesotheliomas, but after further
histological study it became apparent that these tumours showed differ­
entiation towards different types of mesenchymal tissue (muscle, bone
and cartilage). These particular variants are currently under dis­
cussion in the European Mesothelioma Panel, and A. Donna\(^1\) has suggested
that they be designated 'mesodermomas'. The three cases in the current
survey were not included in the mesothelioma group; however, their
occupational histories and the levels of asbestos dust in their lungs
are similar to those of well-established asbestos-induced mesotheliomas.
Further examples will need to be studied to evaluate whether these
tumours are asbestos-associated. Our cases would suggest that they
are.

**Mineralogy**

The results show that all of the three commercial types of asbestos
- chrysotile, amosite and crocidolite - occur frequently in the lungs
of both mesothelioma cases and controls. However, chrysotile was
present no more frequently, nor in greater amounts, in the mesothelioma
cases than in the controls: no chrysotile was found in 30 (35%) of
the 86 cases of mesothelioma that were analysed nor in 12 (21%) of
the 56 controls. This study therefore provides no evidence to indict
chrysotile in the etiology of mesothelioma. In contrast, both amosite
and crocidolite were present more frequently, and in larger amounts,
in the mesothelioma cases than in the controls. In only four cases of
mesotheliomas (5%) were neither of these types found, as opposed to
11 (20%) of controls. The study provides no evidence on the relative
hazards of amosite and crocidolite in producing mesotheliomas.

An overlap occurred between the concentrations of amphibole fibre
in the lungs of mesothelioma cases and those in controls with cerebro­
vascular disease. The majority of mesothelioma cases contained more
than 1000 amphibole fibres/mg, but 22% had less. Although nine (31%)
of the cerebrovascular controls had more than 1000 amphibole fibres/mg,
only one contained more than 2000 fibres/mg. Thus, although the
mesothelioma cases contained much more amphibole, amphibole was also
present in the lungs of controls with cerebrovascular disease. We
do not know the occupational histories of the controls in detail, but
some of the amphibole in control cases may be the result of environ­
mental exposure. The controls were matched with the mesothelioma
cases for area, so that they provide data only from those areas in
which mesotheliomas occur. Our study provides no information on the
fibre content of control lungs in those areas of the country where
mesotheliomas either did not occur or were not submitted to our survey.

\(^1\) Personal communication
Of the three mesothelioma patients with a negative asbestos exposure history (Table 8), all had some asbestos fibres in their lungs - possibly due to environmental dust, but two had no chrysotile and one had no amphibole fibres. The two cases of 'slight asbestos exposure' have been investigated in detail, and their lung fibre counts are a more accurate reflection of their exposure history.

**SUMMARY**

A study was made of 93 cases of mesothelioma who died in 1976 in the United Kingdom. Lung tissue was available for mineral fibre analysis from 86 of these cases, and also from 29 cases of cerebrovascular disease and 27 cases of bronchial carcinoma, matched for place of death, age and sex with the mesothelioma cases. It was observed that:

1. mesothelioma patients had more amphibole fibres in their lungs than did control cases;
2. chrysotile fibres were not present in greater numbers in the mesothelioma patients than in the control cases;
3. four of the mesothelioma cases had no amphibole fibres in their lungs; two of these had chrysotile fibres, and the other two had no asbestos fibres; and
4. 30 cases of mesothelioma had no chrysotile fibres in their lungs.

**RESUME**

Les auteurs ont étudié 93 cas de décès dû au mésothéliome en 1976 au Royaume-Uni. Pour l'analyse des fibres minérales, ils disposaient de tissu pulmonaire de 86 de ces sujets, ainsi que de 29 personnes atteintes de maladies cérébro-vasculaires et de 27 atteintes de cancer bronchique, appariées avec les cas de mésothéliome selon le lieu du décès, l'âge et le sexe. Ils ont observé ce qui suit:
(1) les fibres d'amphibole étaient plus nombreuses dans les poumons des sujets atteints de mésothéliome que dans ceux des témoins;

(2) les fibres de chrysotile ne se rencontraient pas plus fréquemment chez les sujets atteints de mésothéliome que chez les témoins;

(3) quatre sujets atteints de mésothéliome n'avaient pas de fibres d'amphibole dans leurs poumons; deux d'entre eux avaient des fibres de chrysotile et les deux autres étaient exempts de fibres d'amiante;

(4) 30 sujets atteints de mésothéliome n'avaient pas de fibres de chrysotile dans leurs poumons.

ACKNOWLEDGEMENTS

The authors would like to thank the many pathologists throughout the United Kingdom for their considerable help and the trouble they took in sending material for this survey, and they gratefully acknowledge the help given in notifying the Mesothelioma Panel of cases by Her Majesty's coroners. An especial debt of gratitude goes to Mr Keith Miller for the preparation of material and for technical assistance to the Panel and to Mrs Margaret Richardson and Mrs Valerie Bolton for documentation and secretarial assistance. Mr Dennis Mundy of the MRC Pneumoconiosis Unit kindly collated and coded the lung specimens.

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