

Epidemiological and quantitative relationships between mesothelioma and asbestos on Tyneside

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SYNOPSIS Thirty-five necropsied cases of diffuse malignant mesothelioma of pleura and six cases of mesothelioma of peritoneum are reported. Occupational histories from 40 cases showed that 32 cases (80%) were definitely exposed to asbestos; six cases (15%) were probably exposed and two (5%) had no known exposure. The mean latent interval was 34 years. Occupational histories of 56 control patients matched in pairs for age and sex with 28 of the mesothelioma cases revealed definite exposure to asbestos in 12 controls (21%), probable exposure in 11 (20%), and no evidence of exposure in 33 (59%). The difference in incidence of exposure between mesotheliomas and controls is statistically highly significant. Six-micron histological sections of lung, available in 39 mesothelioma cases, contained coated asbestos fibres in 36 cases (92%). Sixteen cases of mesothelioma showing fibres were free of asbestosis; asbestosis was slight in 14 cases, moderately severe in five cases, and severe in one case. The incidence of asbestos bodies in sections from mesothelioma cases was significantly higher than in a previously reported series of routine necropsies examined by lung smear.

Counts of coated and uncoated asbestos fibres were performed on samples of lung tissue from 33 mesothelioma cases. No fibres were identified in one case and only occasional coated fibres in a second case. The remainder gave counts ranging from 154 thousand to 684 million fibres per gram dry weight. Uncoated fibres were invariably present and usually comprised 50 to 80% of the count. No relationship was found between total fibre count and the latent period of the mesothelioma. Fibre counts were also performed on lung samples from 18 smear-positive and 30 smear-negative routine necropsies. Cases with numerous coated fibres in the smear gave total fibre counts similar to those of mesothelioma cases without asbestosis. Routine cases with only one fibre in the smear usually yielded only occasional fibres on analysis. Coated and uncoated fibres were found in 13 out of 30 smear-negative cases, indicating a true incidence of 56% of exposure to asbestos in the whole necropsy series. When compared with the mesothelioma series the difference in incidence of fibres remains statistically significant.

The data suggest that, on Tyneside, exposure to asbestos sufficient to cause an appreciable risk of developing mesothelioma has usually occurred through occupational exposure rather than by general environmental pollution by asbestos.

Although noted independently by Weiss (1953), van der Schoot (1958), and König (1960), the association between exposure to asbestos and diffuse malignant mesothelioma first attracted wide attention through the publication of a series of South African cases by Wagner, Sleggs, and Marchand (1960). Subsequent comparisons between cases of this pathologically controversial condition and control patients have, with one exception (Hägerstrand,

Meurman, and Ödlund, 1968), confirmed a statistically significant association with asbestos (Hourihane, 1964; Elmes, McCaughey, and Wade, 1965; Selikoff, Churg, and Hammond, 1965; Newhouse and Thompson, 1956; McEwen, Finlayson, Mair, and Gibson, 1970; Whitwell and Rawcliffe, 1971). But although several writers have remarked on the absence of asbestosis and the mildness of asbestos exposure in many cases of mesothelioma, no estimates of pulmonary asbestos concentration appear to have been made.

The present study explores the relationship

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between mesothelioma and asbestos on Tyneside, with emphasis on quantitative aspects of the association. Preliminary reports of part of the present material have already been published (Ashcroft and Heppleston, 1970; Ashcroft, 1973).

The largest local asbestos consumer is the ship-building and repair industry, which has been active on a large scale since before the beginning of the century. Other Tyneside industries use asbestos in the manufacture of products such as floor tiles, brake linings, and insulating mattresses, and a large asbestos factory produces other insulation materials. Asbestos is also imported through Newcastle docks.

Materials and Methods

MESOTHELIOMA CASES

Sources of material

Necropsy records in the principal Tyneside hospitals were examined for cases of pleural or peritoneal tumour with no primary growth in the viscera. The histological sections of all likely cases were reviewed and in those not immediately excluded on morphological grounds, further histochemical investigations were carried out in the Pathology Department at the Royal Victoria Infirmary. Necropsy records from 1948 onwards were generally included but in some departments records before 1958 were not available.

A provisional diagnosis of diffuse mesothelioma was made in 13 cases in surgical histopathological material in the Royal Victoria Infirmary and was later confirmed at necropsy. Postmortem specimens from 13 further cases were received from the Newcastle Pneumoconiosis Medical Panel and six cases were contributed by local pathologists. Biopsies from six additional patients showed microscopic features highly suggestive of mesothelioma, but as necropsy had not been performed they have been excluded from this study. Collection of cases ceased in September 1969.

Asbestos exposure

After a case had been accepted on pathological grounds as a mesothelioma, evidence of exposure to asbestos was sought by investigating the occupational history. When a provisional diagnosis was made during life, a full occupational history was obtained by personal interview. Otherwise, the patient's relatives were interviewed. During all interviews, enquiries were also made about non-occupational exposure to asbestos. Occupational information for some patients was obtained from the Pneumoconiosis Medical Panel.

Evidence of asbestos exposure was also sought by systematic microscopic examination of 6-micrometre (μm) paraffin sections of lung tissue for coated asbestos fibres (asbestos bodies). Coated fibres were counted as 'scanty' when they were found only infrequently on traversing a slide and as 'numerous' when they could be found without difficulty in many fields. The degree of asbestosis was also noted and this aspect is more fully described elsewhere (Ashcroft and Heppleston, 1973). When sufficient lung tissue was available counts of coated and uncoated asbestos fibres were carried out using an alkali digestion technique resembling that of Gold (1968) but differing in several important respects (Ashcroft and Heppleston, 1973).

MATCHED CONTROL PATIENTS

The occupational histories of the mesothelioma patients were compared with those of matched control patients who were free of malignant disease. For each of the 28 mesothelioma patients identified up to mid-1967, two controls of the same sex and within five years of the same age were selected from the records of the hospital in which the propositus had died or received treatment. A more detailed occupational history can generally be obtained from a patient in person than from the relatives of a deceased patient, and to avoid possible bias arising from this fact controls for 11 mesothelioma patients who had been interviewed in life were chosen from admission records and were also interviewed in person. Occupational histories for 17 necropsy cases of mesothelioma had been secured from relatives, and histories were obtained in the same way for their controls, chosen from necropsy records. No account was taken of the diseases from which control patients suffered, apart from excluding malignancy. As before, non-occupational asbestos exposure was also considered.

ROUTINE NECROPSIES

The incidence of coated fibres in 6 μm lung sections of mesothelioma was compared with that in basal lung smears prepared at 310 routine necropsies in the Royal Victoria Infirmary (Ashcroft, 1968a). Asbestos fibre counts were performed on samples of lung tissue from nine routine cases with numerous coated fibres in the smear, from nine cases with one coated fibre in the smear, and 30 smear-negative cases.

Results

MESOTHELIOMA CASES

Thirty-five cases were accepted as mesothelioma of pleura and six cases as mesothelioma of peritoneum.

Thirty-six patients were male and five patients, all with pleural tumours, were female. The average age was 57 years, with a range of 42 to 76 years. The tumour arose in the left pleura in 14 patients and the right pleura in 21 patients. Twenty-five tumours were of mixed epithelial and mesenchymal variety, 12 were purely epithelial, and four were purely mesenchymal.

Occupational histories

The evidence for exposure to asbestos derived from occupational histories and lung sections is summarized in table I.

A history was not obtained for case 3, since no living relative could be traced, but some information was obtained for each of the remaining cases and

in most instances a reasonably full history was available. The patients fall into three groups: those with (1) definite exposure to asbestos; (2) probable exposure; (3) no known exposure.

Group 1 consists of 32 persons definitely exposed to asbestos (table I). All received their exposure at work except case 25, the widow of an asbestos worker who for a period of three years returned from work with asbestos dust on his hair and shoes. The duration of exposure varied widely, the majority being exposed for many years but seven patients only for five years or less. The concentration of asbestos dust experienced by the patients was generally low. Most had either been users of asbestos insulation materials or had worked at other jobs beside insulation workers who were using asbestos.

Case Number	Age (yr)	Sex	Histological Type	Fibre Counts (millions/g dry weight)	Percentage Uncoated Fibres	Asbestos Exposure		Relevant Occupation	
						Duration (yr)	Latent Interval (yr)		
<i>Pleural tumours</i>									
1	44	M	Mixed			P ¹	20	30	Welder Ships engineer
2	58	M	Epithelial						
3	59	M	Epithelial						
4	60	M	Epithelial			P	30		Shipyards plater
5	60	M	Mixed			P	32	39	Shipyards fitter
6	62	M	Mixed	0.789	49	P	17	44	Shipyards plater
7	42	F	Mixed	44.746	77		4	24	Asbestos factory worker
8	57	M	Mixed	0.434	63		12	20	Shipyards labourer
9	47	M	Mixed	54.228	71		30	33	Pipe lagger
10	52	M	Mesenchymal	0.166	63		31	35	Gas cooker renovator
11	60	M	Mesenchymal			P	34	45	Shipyards plumber
12	76	M	Epithelial			P	50	58	Shipyards plumber
13	62	M	Epithelial	1.710	50		2	37	Shipyards insulator
14	67	F	Epithelial	0.438	84		5	39	Asbestos factory worker
15	71	M	Mixed	0.494	75		30	30	Engine fitter
16	46	F	Mixed	20.686	79		1	32	Asbestos factory worker
17	62	M	Mixed	43.760	71		47	47	Shipyards electrician
18	55	M	Mixed	4.039	54		25	25	Shipyards insulator
19	67	M	Mixed	0.000			0		
20	63	M	Epithelial	0.892	79		6 months	30	Shipyards electrician
21	48	M	Epithelial	4.975	65		27	32	Asbestos factory electrician
22	60	F	Epithelial	Occasional			0		
23	52	M	Mixed	7.705	83		Few months	27	Carpenter
24	44	M	Mixed	101.130	68		25	30	Shipyards plater
25	54	F	Mixed	1.749	72		3	33	Wife of asbestos worker
26	66	M	Mixed	25.747	60		24	25	Boiler cleaner
27	62	M	Epithelial	8.018	37		Not known		Not known
28	58	M	Mixed	337.009	79		37	40	Pipe lagger
29	56	M	Mixed	64.865	72		34	41	Shipyards engineer
30	45	M	Mixed	6.508	55		25	25	Shipyards plater
31	68	M	Mixed	12.276	73		40	43	Pipe lagger
32	54	M	Mixed	2.291	75		23	23	Refrigeration engineer
33	65	M	Epithelial	8.189	51		25	25	Shipyards joiner
34	55	M	Mesenchymal	0.154	83				Marine fitter
35	55	M	Mixed						Pipe lagger
<i>Peritoneal tumours</i>									
36	64	M	Mixed	26.370	76		30	47	Asbestos factory worker
37	50	M	Mixed	53.865	76		22	22	Pipe lagger
38	43	M	Mixed	166.296	80		29	29	Pipe lagger
39	49	M	Epithelial	684.314	72		18	18	Asbestos sprayer
40	59	M	Mesenchymal	82.839	68		31	40	Pipe lagger
41	73	M	Mixed	6.975	69		40	40	Dock labourer

Table I Pathological type, asbestos fibre counts, and exposure to asbestos in cases of mesothelioma

¹P = probable

Only four patients had worked in an asbestos factory.

Group 2 contains six patients who were probably exposed to asbestos. Cases 5, 6, 11, and 12 had occupations in which incidental exposure to asbestos dust must almost certainly have occurred, but the relatives could not definitely confirm this. Case 4 spent 30 years as a shipyard plater. Case 2 was a retired ship's engineer—an occupation with a high probability of intermittent exposure during repair of insulation. Asbestos exposure in cases 6, 11, and 12 was confirmed by the presence of asbestos bodies in lung sections, but adequate lung tissue was not available for cases 2, 4, and 5.

Group 3 contains two individuals. Case 22, for whom a full history was available, had never worked with asbestos or held any job where incidental exposure seemed likely. Case 19 had a vague history of brief exposure some 10 years before death but this could not be confirmed and he has been counted as 'not exposed'.

Thus, out of the 40 patients for whom occupational data are available, 32 (80%) had definite exposure to asbestos, six (15%) had probable exposure, and two (5%) had no known exposure. The mean latent interval (time elapsing between first exposure to asbestos and development of mesothelioma), combining 'definite' and 'probable' exposure, was 34 years (range 18 to 58 years). No patient had pure exposure to any one mineral variety of asbestos.

Coated fibres were found histologically in 36 (92%) of the 39 cases for which sections of lung were available. Fibres were scanty in 24 cases and numerous in 12. Fibres were numerous in a higher proportion of peritoneal mesotheliomas (five out of six) than of pleural mesotheliomas (seven out of 30). Asbestosis was absent in 16 of the cases showing coated fibres in lung sections. Slight asbestosis (as defined by Beattie and Knox, 1961) was present in 14 cases, moderate asbestosis in five cases, and severe fibrosis in only one case. Asbestosis was moderate or severe in a higher proportion of peritoneal mesotheliomas (four out of six) than of pleural mesotheliomas (two out of 30). In contrast to the findings of Thomson (1962), mild asbestosis showed no predilection for the basal subpleural regions of the lungs.

When histological and occupational findings are combined for all 41 cases of mesothelioma, 39 (95%) had definite or probable asbestos exposure.

Asbestos fibre counts

Total fibre counts and proportions of uncoated fibres are shown in table I. No fibres were identified in case 19 and only occasional fibres, including coated fibres of typical appearance, were detected

in case 22. Neither of these patients had a history of asbestos exposure or showed any coated fibres in lung sections.

There was a very wide range of fibre counts in the remaining cases, extending from 154 thousand to 684 million total fibres per gram dry weight. Uncoated fibres usually outnumbered the coated fibres and comprised 50 to 80% of the count. No relationship was found between the latent period of the mesothelioma and the total fibre count (table II).

Total Fibre Count (millions/g dry weight)	No. of Cases	Mean Latent Period (yr)
Less than 1	6	34.7 ± 5.9
1-9.9	9	30.6 ± 8.0
10-99	10	35.3 ± 9.1
100 and over	4	29.3 ± 9.0

Table II Total asbestos fibre count related to the length of the latent period in mesothelioma cases

MATCHED CONTROL PATIENTS

A definite history of asbestos exposure was obtained in 12 of the 56 control patients (table III). Exposure was usually brief or intermittent and was often incidental to the patient's work, eg, a shipyard plater working beside pipe ladders. In half of the affected patients, the exposure was mild or even trivial, eg, a farmer roofed his chicken coops with asbestos.

Asbestos Exposure	Control Patients	Mesothelioma Patients
	No.	No.
None known	33 (59%)	2 (8%)
Definite	12 (21%)	19 (70%)
Probable	11 (20%)	6 (22%)
Definite + probable	23 (41%)	25 (92%)

Table III History of asbestos exposure in 27 mesothelioma patients and in 56 age- and sex-matched control patients¹

¹No history available in one mesothelioma patient for whom controls were selected.

Eleven further patients had a history of work with a strong possibility of exposure to asbestos, often incidental, although the relatives could not say for certain that exposure had occurred, and these patients have been counted as having had 'probable' exposure. Some such individuals had worked for a few years in a shipyard, in trades known to involve incidental asbestos exposure.

The remaining 33 control patients had no history of asbestos exposure or of any occupation in which incidental exposure seemed likely.

Thus there was definite asbestos exposure in 12 out of 56 controls (21%) and definite or probable exposure in 23 out of 56 controls (41%). When these figures are compared (table III) with corresponding figures for mesothelioma propositi (27 in number since no history was available for case 3) there is a statistically highly significant difference whether the 'definite exposure' groups ($\chi^2 = 16.6$, $P < 0.001$) or 'definite' plus 'probable' exposure groups ($\chi^2 = 17.8$, $P < 0.001$) are compared.

ROUTINE NECROPSIES

A full account of the incidence of asbestos bodies in lung smears at routine necropsy has been published (Ashcroft, 1968a). A total of 311 smear cases was then described but one of these, a case of mesothelioma with positive smear, has been transferred from the smear group to the mesothelioma series (case 6). Coated fibres were found in basal lung smears in 62 (20%) out of 310 necropsies in patients aged over 15 years (25.1% of 195 males and 11.3% of 115 females). They were scanty (up to 34 per smear) in 45 cases, and numerous (over 170 per smear) in 17 cases. Information about occupation was obtained for 53 of the smear-positive patients and 30 (57%) were definitely or probably exposed to asbestos. Among those with numerous coated fibres in the smear, 13 out of 15 (87%) received definite or probable exposure to asbestos at work. (Owing to confusion of two cases with similar serial numbers, the previously reported proportion of 12 out of 14 was incorrect.) Comparison of smears and 6 μ histological sections in smear-positive cases indicated that the smears were a more reliable means of detecting scanty coated fibres than the sections.

Comparison with mesothelioma cases

The sex ratio of the routine necropsy cases differs widely from that of the mesothelioma cases, the mesothelioma group being predominantly male (M:F = 7.2:1) whereas the control group is more evenly balanced (M:F = 1.7:1). Since female mesothelioma cases are few, however, the difficulty can be overcome by omitting all female cases and comparing male mesothelioma and male control cases only. There was no significant difference in age distribution of males between controls and mesotheliomas. The incidence of coated fibres in lung sections of male mesothelioma cases (94%) was much greater than that in lung smears of male routine necropsies (25%) and statistically the difference is highly significant ($\chi^2 = 47.8$; $P < 0.001$).

Fibre counts in routine necropsies

Fibre counts obtained in nine cases showing numerous coated fibres in lung smears (N-fibre cases) and in nine cases with one coated fibre per lung smear (1-fibre cases) are given in table IV. The N-fibre cases showed total, uncoated, and coated fibre counts comparable with those of most mesothelioma cases showing scanty coated fibres in lung sections.

Only two of the 1-fibre cases possessed fibres sufficiently numerous for practicable counting, one of these giving the remarkably high total count of 7.76 million fibres. Five other cases produced occasional coated and uncoated fibres, while no fibres at all were detected in the last two cases.

No fibres were detected in 17 of the 30 samples from smear-negative cases. Occasional fibres were found in 10 cases and the remaining three cases gave total counts of 0.298, 0.104, and 0.061 millions

Coated Fibres in Lung Smear	Smear Case No.	Fibre Count (millions/g dried tissue)			Percentage Uncoated Fibres
		Total	Uncoated	Coated	
428	1	0.435	0.094	0.341	22
912	2	0.489	0.112	0.377	23
513	3	1.322	0.762	0.560	58
855	4	2.667	1.146	1.521	43
855	5	3.227	2.100	1.127	65
3363	6	3.536	1.196	2.340	34
912	7	4.136	1.707	2.429	41
855	8	5.645	3.035	2.610	54
570	9	7.171	2.859	4.312	40
1	10	7.760	3.851	3.909	50
1	11	0.995	0.492	0.503	49
1	12	Occasional	Occasional	Occasional	
1	13	Occasional	Occasional	Occasional	
1	14	Occasional	Occasional	Occasional	
1	15	Occasional	Occasional	Occasional	
1	16	Occasional	Occasional	Occasional	
1	17	None			
1	18	None			

Table IV Fibre content of lung specimens from routine necropsy cases with lung smears positive for coated fibres

per gram respectively, with, on average, 68% of uncoated fibres. Coated fibres were found in eight out of 15 males and five out of 15 females.

Discussion

DIAGNOSIS

The principal difficulty in the pathological diagnosis of diffuse malignant mesothelioma of pleura or peritoneum lies in distinguishing the condition from metastatic carcinoma, spreading from a primary tumour in lung or elsewhere. The diagnostic criteria used in this study were based initially on the work of Campbell (1950), Godwin (1957), and McCaughey (1958). Further valuable descriptions of the pathological features of mesothelioma have been given by Hourihane (1964), McCaughey (1965), Churg, Rosen, and Moolten (1965), Webster (1965), Whitwell and Rawcliffe (1971), and the UICC Working Group on Asbestos and Cancer (1965).

The most important criteria were: (1) Necropsy should fail to demonstrate any other primary malignant tumour from which the serosal growth could have metastasized. (2) The tumour should show microscopic appearances in keeping with those described for mesothelioma.

Necropsy examination was carried out in all cases in this series, and none showed a primary tumour of the viscera.

Gross appearance

Previous writers have emphasized the diagnostic importance of diffuse involvement of the affected pleurae and all but three of the present series of pleural mesothelioma showed diffuse thickening, usually with involvement of the interlobular fissures and often obliterating the pleural cavity (fig 1). However, the gross appearance of neoplastic pleural thickening is an unreliable guide to the nature of the tumour. Figure 2 shows a pneumonectomy

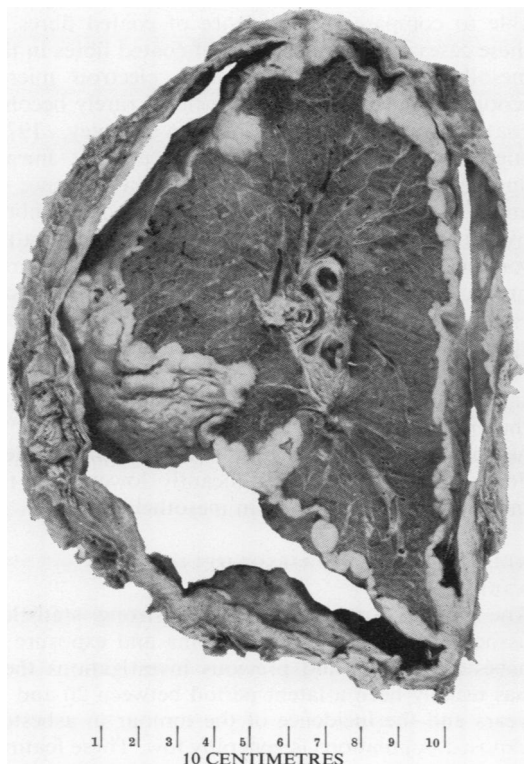


Fig 1

Fig 1 *Sagittal slice of a pleuropneumectomy specimen (case 16). Mesothelioma involves the visceral and parietal pleural surfaces, which have fused at the apex and the base of the lung.*

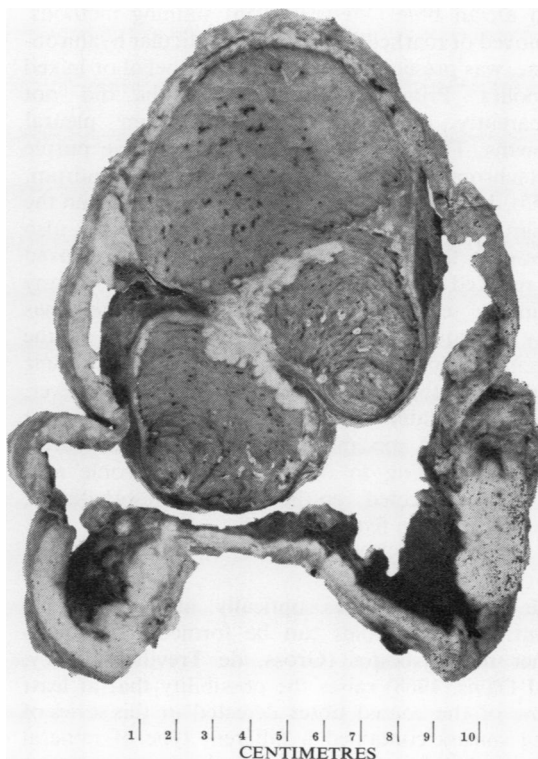


Fig 2

Fig 2 *Slice of a pleuropneumectomy specimen in which metastatic carcinoma diffusely involves the pleural surfaces and closely mimics a mesothelioma.*

specimen with diffuse pleural tumour closely resembling a malignant mesothelioma. Histologically this tumour was a metastatic mucin-secreting adenocarcinoma. By contrast, the tumours of three histologically characteristic mesotheliomas took the form of scattered and confluent plaques on the visceral and parietal pleurae.

Microscopic appearance

The diagnostic importance of a mixed epithelial and mesenchymatous structure has been repeatedly stressed by previous writers. Twenty-five cases in this series showed such a structure. In addition there was usually much variability in the architecture of purely epithelial or mesenchymal tumours.

Considerable importance was attached to the histochemical demonstration of hyaluronidase-labile mucopolysaccharide within the lumens of tumour tubules or spaces (Wagner, Munday, and Harington, 1962). Secretion negative to the periodic acid Schiff (PAS) reaction but giving positive reactions with the colloidal iron (Mowry, 1958) and alcian blue (Mowry, 1956) staining methods, removed or markedly reduced by testicular hyaluronidase, was present in 29 out of 37 epithelial or mixed tumours. Primary peritoneal growths did not apparently differ histochemically from pleural growths. The secretion in many cases gave purple metachromasia with Azur A (Kramer and Windrum, 1955), but this reaction was less consistent than the alcian blue or colloidal iron. Many cases also showed a faint reaction with mucicarmine, removed or reduced by hyaluronidase. The absence of any stainable secretion in eight mixed mesotheliomas may be attributable to primary fixation of the specimens in formol saline, in which hyaluronic acid is soluble (Wagner *et al*, 1962). However, residual stainable material was found in many other formalin-fixed specimens, and it is always worthwhile attempting to demonstrate hyaluronic acid in any suspected epithelial-type mesothelioma, despite formalin fixation.

ROUTINE NECROPSIES

The fact that bodies optically indistinguishable from asbestos bodies can be formed from fibres other than asbestos (Gross, de Treville, Cralley, and Davis, 1968) raises the possibility that at least some of the coated fibres detected in this series of lung smears contained a different type of mineral fibre and did not necessarily indicate exposure to asbestos. 'Pseudo-asbestos bodies', with a black central fibre, were specifically ignored when examining smears, but bodies derived from substances such as glass fibre, silicon carbide, filamentous aluminium silicate, and talc could be confused

with coated asbestos fibres. However, bodies derived from glass, talc, or diatomaceous earth are most unlikely to have produced false-positive smears in this series (Ashcroft, 1968b). Filamentous aluminium silicate is used as a thermal insulation material for specialized purposes but it only began to be used in Great Britain towards the end of the period when this series of lung smears was being collected. On Tyneside fibrous silicon carbide is used only in tiny experimental quantities.

On the other hand, the coated and uncoated fibres extracted from lung tissue in routine necropsies were indistinguishable from fibres recovered from the lungs of patients with known exposure to asbestos. In some specimens thicker uncoated fibres were birefringent in polarized light—a feature of asbestos fibres. More than half of the patients for whom an occupational history is available had either worked with asbestos or had worked where incidental exposure to asbestos is virtually certain. It is thus likely that the vast majority of smear-positive cases had been exposed to asbestos and it is justifiable to compare the incidence of coated fibres in these cases with the incidence of coated fibres in the mesothelioma cases. Moreover, electron microscopic evidence that chrysotile fibres rarely become coated after inhalation in man (Pooley, 1972) suggests that asbestos bodies detected in smears and sections are likely to indicate the presence of amphibole fibres. The detection of coated fibres by tissue digestion in 13 out of 30 smear-negative routine necropsy cases indicates that the true proportion of fibre-containing routine necropsies is higher than that initially estimated. Fifteen specimens came from male patients and 15 from female patients and are assumed to represent random samples of the necropsies surveyed. On this basis the true incidence of coated fibres in the routine necropsy population of both sexes is approximately 56%, but this is still significantly lower than the incidence of coated fibres in mesotheliomas.

RELATIONSHIP OF MESOTHELIOMA TO ASBESTOS

The present studies indicate a strong statistical association between mesothelioma and exposure to asbestos. In this and previous investigations there has usually been a latent period between 20 and 60 years and the incidence of the tumour in asbestos-exposed populations is generally low. These features are compatible with the hypothesis that asbestos acts as a carcinogen of low potency for the mesothelial cells, tumours appearing only in the most susceptible individuals after a long latent period.

A possible objection lies in the lack of relationship between the dose of asbestos, as judged by fibre

counts in lung tissue, and the latent period of the mesothelioma (table II) since, in experimental carcinogenesis, increasing the dose of a carcinogen causes tumours to appear earlier (Bryan and Shimkin, 1943). A similar objection has been made with regard to the effects of tobacco smoke in lung cancer (Passey, 1962). Kreyberg (1965), however, has shown, with reference to tobacco smoking, that an apparent lack of relationship between dose and latent period can occur with a weak carcinogen, because of the intervention of deaths from other causes. Similar considerations may well apply to asbestos and mesothelioma, particularly as exposure sufficiently severe to cause clinical asbestosis may lead to death of the patient from cor pulmonale or bronchogenic carcinoma within the latent period required for mesothelioma.

ASBESTOS IN THE GENERAL POPULATION

There is ample evidence from surveys of routine necropsies that a substantial number of modern city dwellers have coated fibres in their lungs and in Newcastle these are probably asbestos fibres. The question therefore arises whether people so affected are at risk of developing malignant mesothelioma (Thomson, Kaschula, and MacDonald, 1963).

The Newcastle routine necropsies showing coated fibres fell into two groups: (a) those with numerous coated fibres in lung smears and (b) those in whom fibres were detected only by tissue maceration or appeared in small numbers in lung smears. Patients of group b out-numbered those of group a by approximately 9 to 1. Pulmonary fibre counts in patients of group a gave results similar to those obtained in many mesothelioma patients. Lung tissue from patients in group b usually yielded on analysis only 'occasional' fibres or numbers of fibres considerably lower than patients in group a. By contrast, 29 out of 31 mesothelioma cases had fibre concentrations equal to or greater than those of group a patients, while only one mesothelioma case had 'occasional' fibres on analysis. A further mesothelioma case yielded no pulmonary fibres at all and presumably had a spontaneous tumour unrelated to exposure to asbestos. Thus, as judged by numbers of pulmonary asbestos fibres, persons with group b levels of exposure have a very small chance of developing pleural mesothelioma compared with people having group a exposure.

If it is assumed that the incidence of pulmonary asbestos bodies throughout Tyneside is the same as that in routine necropsies in Newcastle, ie, approximately 5% group a exposure and 50% group b exposure, then the population of Tyneside aged over 15 years, which numbers approximately a million (calculated from the Sample Census, 1966),

will include about 50 000 persons with group a exposure and 500 000 with group b exposure. Only 38 cases of mesothelioma, however, are known to have come to necropsy between 1968 and mid-1969 (the other three cases in the series came from beyond the Tyneside area). Even if six probable cases excluded from the present investigation through lack of necropsy, and two further cases dying in the relevant period, which have recently come to my notice, are included, Tyneside has produced fewer than 50 cases of mesothelioma of pleura or peritoneum over a period of 12 years. These cases represent less than 0.1% of persons apparently at risk as a result of the asbestos content of their lungs (group a exposure), suggesting that some other factor in addition to the presence of asbestos may be concerned in the genesis of mesothelioma. Tobacco smoking seems unlikely to be involved (McEwen *et al*, 1970). The occupational data for routine necropsies indicate that a large majority of group a patients had definite or probable exposure to asbestos at work, while those with no known source of exposure generally fell into group b. This suggests that, on Tyneside at least, exposure to asbestos comparable to that of most cases of mesothelioma has usually occurred through occupational exposure rather than through general asbestos contamination of the urban environment. If urban air is to remain safe, however, present and future pollution by asbestos must be rigorously controlled.

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