Asbestos-related mesothelioma: factors discriminating between pleural and peritoneal sites

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ABSTRACT Up to the end of 1980, 144 confirmed cases of mesothelioma were identified among employees of an organisation using asbestos in manufacturing and insulation. The primary site was peritoneal in 74 cases, pleural in 66, and undetermined in four. All employees had been exposed to amphibole asbestos, and evidence from different factories confirmed the predominant role of crocidolite in the production of mesothelioma. The ratio of pleural to peritoneal sites showed a continuous change when related to the year of first exposure, varying from 5:1 pleural to peritoneal before 1921 to 1:3 after 1950. The strong temporal relationship appeared to reflect progressive dust suppression, including the non-fibrous dusts present in insulation materials and perhaps also the degree to which the fibres had been opened. Other predisposing factors were related to the degree of individual exposure, the peritoneal site being associated preferentially with longer and heavier exposures.

One of the curiosities of the epidemiology of mesothelioma has been the wide difference in the pleural:peritoneal incidence ratio in the many published series. Some of these are listed by McDonald and McDonald.¹ The four largest series collected either by pathologists or through mesothelioma (and therefore unrelated to aetiology) registration show pleural:peritoneal percentage ratios of 94:6 (700 cases S Africa),² 88:12 (413 cases Britain),^{3*} 88:12 (304 cases Britain),^{4*} and 94:6 (251 cases W Germany).⁵ Some smaller series show greater variation: 91:9 (32 cases Australia),⁶ 94:6 (64 cases Switzerland),⁷ 52:48 (52 cases Israel),⁸ 62:38 (52 cases Japan),⁹ and 74:26 (47 cases Quebec).¹⁰ Other series—for example, from Finland¹¹—have omitted peritoneal cases as being too rare to provide useful information. In unselected series, therefore, the evidence is that the proportion of peritoneal cases will be small by comparison with pleural.

Series restricted to asbestos related mesothelioma cases have also shown widely differing proportions. In mining the proportion of peritoneal cases reported has always been low. The original series of South African crocidolite miners of Wagner *et al*¹² consisted wholly of pleural cases, and although this may partly reflect the direction of their pioneer

work, subsequent investigation has confirmed that the peritoneal variety appears to be rare in South African miners.²

In Australia 26 mesotheliomas arising in crocidolite miners were all pleural, and in Canada, while mesothelioma in chrysotile miners and millers was relatively rare, 10 of the 11 cases identified by McDonald and Liddell¹³ were pleural. The experience of the inhabitants of Karain in Turkey may also be mentioned, since exposure is to unprocessed erionite fibre. Deaths here were not confirmed by postmortem examination but in just over three years there probably occurred 17 cases of mesothelioma, of which only one was peritoneal.¹⁴

In manufacturing, however, higher proportions of peritoneal tumours have been reported in several series. Newhouse and Berry¹⁵ traced 35 cases of peritoneal mesothelioma and 32 of pleural in their mortality study of a London asbestos factory, while Seidman *et al*¹⁶ identified seven cases of each type among ex-employees of a New Jersey factory. Among ladders also a high peritoneal:pleural ratio has been observed. Selikoff *et al*¹⁷ found 112 peritoneal cases in their total of 175 United States and Canadian ladders, while Elmes and Simpson¹⁸ reported five peritoneal in a total 13 cases among Belfast ladders.

To elucidate factors that influence the tumour site, we have examined the cases of mesothelioma among employees of a large industrial group using asbestos in manufacturing and insulation.

*These two series overlap to the extent of 110 cases included in both.

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Methods

The manufacture of asbestos products within the group began in 1913 at a factory in the East End of London (factory A), where production was maintained without interruption until its closure in 1967. Manufacturing began at factory B in Yorkshire in 1939, where it continued until 1968. Further subsidiary factories have been set up or acquired by the group since the second world war. Finally, from the early years the group has had an insulating division undertaking lagging work on outside sites under contract.

The histories of all employees who were known to have died in the past 30 years were scrutinised and only those who satisfied the following criteria were included in the series:

(1) A postmortem examination had been carried out. The diagnosis of mesothelioma must be morphological as well as histological in view of the uncertainty attached to the latter. A few cases have therefore been excluded where the diagnosis had been made on clinical grounds but without post-mortem examination.

(2) The diagnosis had been confirmed histologically by members of the pneumoconiosis medical panel.

(3) An adequate work history was obtained. This is available for almost all past employees.

The company medical files are the main source of information about deaths among employees. When mesothelioma became a prescribed disease in 1966, case identification became more complete, since all notifications to the pneumoconiosis medical panel were automatically followed up by requests to the company from the Department of Health and Social Security for details of past employment, thereby notifying the company of a possible case. All such cases were subjected to necropsy followed by a subsequent report by the pneumoconiosis medical panel. The series was then compared with the cohort study of employees of factory A, which was set up in 1965 by Newhouse¹⁹ and which is still continuing. By checking death certificates Newhouse and Wagner²⁰ were able to obtain postmortem information and histological material that resulted in certain deaths being reclassified as due to mesothelioma. A further small number of cases fulfilling the study criteria were obtained in this way.

Personnel records showed for all employees the date of birth, the date of starting employment, the duration of employment, and the department in which they had worked. In those first employed since 1945 there was additional detail on previous employment, including possible exposure to asbestos. Since this was not available before 1939 there

may have been earlier exposure in a very small number of cases. The effect of this would be to add slightly to the average latency time. Exposure rank was calculated for employees of factory A by using the rating scale prepared for Newhouse.¹⁹ This scale provides a crude index of the severity of exposure to asbestos dust, since no dust counts were available for the years covered by the study.

Results

A total of 144 cases fulfilled the study criteria. Of these, 74 were peritoneal, 66 pleural, and in the remaining four both pleura and peritoneum were affected and the site of origin could not be determined.

DISTRIBUTION BY FACTORY AND SEX

The 144 cases in the series are classified by work and by site of mesothelioma (table 1). At factory A, from which most of the cases have arisen, peritoneal cases exceed pleural in a ratio of nearly 3:2. For ladders the numbers of the two types are equal, while for the remaining factories, in which exposure has been chiefly since 1945, pleural easily outnumber peritoneal. Table 1 also shows the ratio of male to female cases at factory A. Only two female cases (both pleural) occurred in the other groups. The ratio of pleural to peritoneal was similar for both sexes.

LATENT PERIOD

The latent period is defined as the duration from first known exposure to asbestos to death. The mean for the whole series is 32.3 years with a standard deviation of nine and a range of 14–57 years. Since factory B opened only in 1939, there has not yet been time for employees with long latencies to make a contribution to the mean. Moreover, since 1945 the number of men (but not women) employed in factory A has increased as has the number of ladders employed. Men employed since 1945 will again, as with factory B, not yet have contributed cases with long latencies. Possibly this accounts for some if not all of the difference in age at death between men and women. Certainly the mean latency for women,

Table 1 *Number of cases of mesothelioma classified by site, sex, and employment*

Date of operation	Factory A 1913–67		Factory B 1939–68	Ladders 1913–80	Other 1902–80	Total
	Men	Women				
Peritoneal	35	22	2	13	2	74
Pleural	27	14	9	13	3	66
Both	2	2				4
Total	64	38	11	26	5	144

36.3 years, is likely to be a better estimate of the true mean than the overall mean for the present series of 32.3. A longer latent period for peritoneal tumours appears consistently for all places of work (table 2).

The frequency distribution of latencies (figure) shows that only two cases had a latent period of under 18 years. One was a logger first employed at the age of 15, and previous exposure was improbable unless he was a household contact of relations working with asbestos. The other was a woman whose first employment recorded at factory A was in wartime at the age of 34 and previous occupational contact with asbestos was possible but could not be substantiated.

One problem in estimating the latent period is that the exposure to asbestos that triggered off the malignant change may in theory have occurred at any time during the period of employment. The mean latency of those whose employment was of short duration (thereby pinpointing the relevant exposure) was compared with those who worked for the company for longer periods. The results (table 3) show surprisingly little difference.

DURATION OF EXPOSURE

The mean duration of exposure was 10.5 years but exposures varied widely, from one month to 50 years, the standard deviation being 11 years. The frequency distribution (table 4) shows the high proportion of cases with very brief exposures; no

Frequency distribution of latency times.

Table 2 Mean latent period in years classified by site, sex, and employment

	Factory A	Factory B	Laggers	Other	Total Men	Total Women	Total
Pleural	33.5	24.6	28.8	29.4	30.0	34.8	31.2
Peritoneal	34.1	27.9	32.3	35.0	31.9	37.7	33.6

Table 3 Mean latent period classified by duration of exposure

		Exposure (months)	No	Mean latent period (years)
Factory A	Women	1-24*	18	37.3
		≥25	20	36.5
	Men	1-24†	23	34.0
		≥25	41	30.3
Total all workplaces		1-12	36	35.9
		13-24	13	28.1
		≥25	95	31.5

*Only one started after 1944.

†Only four started after 1944.

Table 4 Distribution of exposure durations

Months worked	No of cases				Cumulative total
	Pleural	Peritoneal	Both	Total	
1	2	1		3	2
2	3	2		5	6
3	1	—		1	6
4	3	—		3	8
5	2	3		5	12
6	2	2		4	15
7-9	4	4	1	9	21
10-12	5	2		7	26
13-24	8	4		12	34
25-36	2	6		8	40
37-48	1	3		4	43
49-96	7	13	1	21	57
97-192	6	10		16	69
193-	20	23	2	45	100
Total	66	73	4	143	

fewer than 32 (22%) were exposed for under one year, of whom 21 (15%) had no more than six months' exposure and nine (6%) no more than three months.

The mean exposure of pleural cases was 113 months and peritoneal 138 months, but this difference does not reach the level of statistical significance. In table 5 the duration is divided into three categories, short (under one year), medium (one to three years) and long (over three years). The proportion of peritoneal cases tends to increase as the duration of exposure lengthens.

RELATIONSHIP WITH CERTIFIED ASBESTOSIS

Thirty-six employees (26%) had been certified while still alive as suffering from asbestosis and in a further 85 (60%) asbestosis was found at postmor-

Table 5 Tumour sites classified by duration of exposure

Months	Pleural		Peritoneal		Total	
	No	%	No	%	No	%
≤ 12	21	32	14	19	35	25
13-36	10	15	11	15	21	15
≥ 36	35	53	48	66	83	69
Total	66	100	73	100	139	100

$\chi^2 = 3.14$, 2 df $0.1 < p < 0.2$.

Test for trend: (increasing proportion of peritoneal cases with increasing duration of exposure).

$\chi^2_1 = 3.06$, 1 df, $0.1 < p < 0.05$.

χ^2 for departure from linear trend = 0.08 (not significant).

tem examination; it was absent in the remaining 20 (14%). A slightly higher proportion of cases of peritoneal (28%) than pleural (22%) mesothelioma was associated with antemortem asbestosis. This is in accordance with the findings of Elmes and Simpson⁴ but does not reach statistical significance.

CHANGES OVER TIME

Although developments in dust suppression have taken place with changes in engineering practice throughout the past 50 years, two major changes occurred during this period—firstly, with the introduction during 1933 of the 1931 Regulations and, secondly, with the postwar changes that may be dated from 1946.

Table 6 shows that the ratio of pleural to peritoneal cases changed continuously and significantly over the period. The mean year of first exposure for peritoneal cases was 1936 and for pleural cases 1942 ($p = 0.001$), while the median years of death were 1969 and 1974 respectively.

Table 6 Changes over time in pleural: peritoneal ratios

	No of cases		
	Pleural	Peritoneal	Pleural:peritoneal ratio
≤ 1920	1	5	0.2
1921-1930	3	12	0.25
1931-1940	22	29	0.76
1941-1950	12	10	1.20
≥ 1951	3	1	3.00

Table 7 Severity of exposure. Rating scale for Factory A

Exposure (years)	Pleural		Peritoneal		Both		Total	
	No	Mean score	No	Mean score	No	Mean score	No	Mean score
≤ 1	17	5.29	11	5.45	1	6.0	29	5.38
1-3	8	4.75	10	5.30			18	5.06
≥ 3	16	4.19	35	5.31	3	5.67	54	5.00
Total, all cases	41	4.76	56	5.34	4	5.75	101	5.12

Comparison of mean scores for total cases, pleural v peritoneal: $\chi^2 = 2.34$, df 95, $p = 0.02$.

SEVERITY OF EXPOSURE

Unfortunately, relevant exposures took place before the days of effective dust counting, and to assess the exposure experienced by employees anecdotal evidence must be used, combined with a knowledge, based on recent counting, of the levels of respirable fibre arising from different processes.

Newhouse¹⁹ in her original paper on factory A published a rating scale for jobs based on evidence of this type. Her scale classifies all jobs with a rank score from 1 to 6. Personnel records have information on all jobs worked by individual employees, who have therefore been classified according to the department worked in with the heaviest rating score.

Application of this rating scale to factory A shows that employees subsequently developing a mesothelioma worked predominantly in departments where exposure was heavy. The average figure on the rating scale of mesothelioma cases was 5.1. Within this group peritoneal cases had a mean score of 5.3, compared with 4.8 for pleural cases, a difference that was significant at the 5% level (table 7).

When these figures were broken down by duration of exposure, peritoneal cases had a consistently higher exposure rating at each duration. Pleural cases showed a small trend for shorter exposures to be associated with higher ratings, but the coefficient of determination for correlation between exposure duration and severity (R^2) was only 0.14, showing a virtual absence of relationship.

FIBRE TYPE

In view of the evidence already accumulating that crocidolite is the most potent among asbestos fibres in causing mesothelioma in man as distinct from animals, the type of fibre used in the factories under review is important. Table 8 summarises the experience of some of the factories within the group.

Crocidolite was used extensively at factories A and B. Factory A began operations in 1913 with crocidolite only; amosite and chrysotile began to be used in the late 1920s and early 1930s, their proportional share of total fibre use increasing until, in the 1950s, their use in terms of weight exceeded that of crocidolite. Factory B opened in 1939 with

Table 8 Type of fibre used in the factories

Output	Years of operation	Approx total No of employees	Type of fibre used	Mesotheliomas recorded up to end 1981
Factory A Textiles Insulation materials Friction materials	1913-67	10 000	Crocidolite initially. Amosite and chrysotile also from 1930	120*†
Factory B Textiles Insulation materials	1939-68*	2 000	Crocidolite, amosite, chrysotile	13
Factory C Insulation boards	1948-80	6 000	Amosite. Chrysotile and crocidolite for brief periods only	4‡
Factory D Insulation boards	1954-80	1 500	Amosite only	None
Factory E Textiles Friction materials	1902-	15 000	Chrysotile only	None

*Estimate based on data from the present series and from Newhouse.¹⁹

†Before 1948 the average payroll was under 50.

‡Attributable deaths from mesothelioma.²¹

crocidolite as a substantial proportion of its fibre use and continued to use it until it closed in 1968. Unfortunately, it is not possible to relate exposure in these two factories to any single type.

Amosite was the basic fibre at factories C and D. The experience of C has been summarised by Acheson *et al.*²¹ Amosite was used almost exclusively since production began in 1948; a small quantity of chrysotile was also used and crocidolite for a few days during 1962-4 on an experimental basis only. During these years, roughly 6000 employees worked at the factory for varying periods, in conditions of fairly heavy dust exposure in the early years, and four deaths from mesothelioma attributable to exposure at the factory have occurred. Factory D opened in 1954 and carried an average payroll of 200. Amosite has been used exclusively, and no cases of mesothelioma have so far been recorded.

Chrysotile is the only asbestos fibre ever used at factory E, which has been operating since 1902 producing textiles and friction materials for the motor industry. It has averaged 800 to 900 employees in recent years, but no case of mesothelioma has been recorded from this factory.

HISTOLOGY

Although all cases in the present series were confirmed histologically, the histological report was available for only 50 cases. The proportions of the three types, epithelial, spindle cell, and mixed, within each sex are almost identical, but there are obvious differences between pleural and peritoneal sites. If those with mixed histology are ignored seven out of 16 pleural cases (44%) were of spindle cell type compared with only three of the 15 (20%)

peritoneal cases ($\chi^2 = 5.5$ $p < 0.05$). These findings agree with those of Kannerstein and Churg²² and Elmes and Simpson,⁴ who have found a higher proportion of epithelial cases in peritoneal mesothelioma and more spindle cell cases in pleural. There was no significant difference between the means of the two sites for latency, age at death, or age at first exposure.

Pleural v peritoneal

Differences found in the present series are:

Mean year of first exposure	Peritoneal earlier than pleural	$p = 0.001$
Mean year of death	Peritoneal earlier than pleural	$p < 0.01$
Mean exposure severity rank	Peritoneal greater than pleural	$p < 0.05$
Mean latent interval	Peritoneal longer than pleural	$p < 0.1$
Trend of proportions associated with increasing exposure	Peritoneal longer than pleural	$p < 0.2$
Mean duration of exposure	Peritoneal longer than pleural	$p = 0.26$
Asbestosis diagnosed before death	Peritoneal more than pleural	$p = 0.5$

A linear discriminant analysis was carried out with five of the variables listed above (omitting year of death). On this basis 63% of known cases were correctly classified ($p = 0.01$). Of the four cases classified at postmortem examination as both peritoneal and pleural, three fell into the peritoneal and one into the pleural group.

Discussion

It has long been believed that peritoneal mesotheliomas are associated more often with heavy exposure and the presence of asbestosis than pleural tumours,^{4,23} and it has been suggested that interstitial pulmonary fibrosis at the lung bases results in retrograde lymph drainage from the pleural to the peritoneal cavity.²⁴ If the trend over the years has been for a reduction in exposure all the differences shown above between pleural and peritoneal cases are consistent with the possibility that heavier exposure to asbestos dust tends to produce peritoneal rather than pleural mesotheliomas. Although the differences are small, their direction is consistent and the results as a group are coherent.

Nevertheless, it must be questioned whether this is the whole explanation, since conditions are reported to have been extremely dusty in the Quebec,¹³ Western Australian,²⁵ and Cape¹² mines in their early years, yet cases of peritoneal mesothelioma have been recorded infrequently or not at all. The difference between occupations has been attributed to the fact that the more the asbestos is handled, the more the fibre bundles are opened and the higher the proportion of fine fibres among those of respirable diameter. This would not, however, account for the changing proportions over the years in the present series. An alternative explanation is a qualitative difference in the inhaled dust. Possibly other dusts inhaled with asbestos may tend to produce peritoneal mesotheliomas, perhaps by a blocking effect on the normal lymphatic drainage mentioned above. Sodium and calcium silicate were commonly used as fillers with asbestos in insulating materials. These and other materials have, in the past, made their own contribution to the dustiness of the manufacturing and especially the application and removal of insulating materials, in contrast with textile processes that are relatively free of extraneous dust. In this connection it is worth repeating Selikoff's observation that all "environmental" family cases have been pleural.²⁶

Evidence for differing propensities for producing mesotheliomas among the different types of asbestos has been reviewed by Acheson and Gardner.²⁷ Animal inhalation experiments have suggested that chrysotile in rats is both more fibrogenic and carcinogenic than other types of asbestos and that it produces the highest proportion of mesotheliomas. Human epidemiology, on the other hand, has consistently incriminated crocidolite as the fibre type most likely to produce mesotheliomas, with chrysotile, in mining and manufacturing at least, as relatively innocuous. Reasons for this discrepancy have been reviewed by Davis²⁸; the most probable is the inap-

propriateness of the short-lived rat as a model from which to draw conclusions applicable to man, because chrysotile is chemically the least stable and the most likely to dissolve in tissue fluids.

The experience within this industrial group is in agreement with other human evidence regarding the three fibres, crocidolite, amosite, and chrysotile, and is summarised in table 8. The complete absence of any recorded case of mesothelioma from the exclusively chrysotile-using factory is particularly important. Similarly, the small number of cases from amosite-using factories C and D contrasts with the experience of factories A and B.

There is no good evidence that one fibre type has a greater propensity to produce peritoneal rather than pleural mesotheliomas. Despite the statement by Peto *et al*²⁹ that peritoneal mesothelioma probably does not occur with chrysotile, cases of either site attributable with any confidence to pure chrysotile exposure are too rare to permit the exclusion of confounding factors. For exposure to amosite alone, there is only the experience of the New Jersey factory described by Seidman *et al*¹⁶ where seven cases each of pleural and peritoneal mesothelioma have so far occurred and the two factories in the present series, from which Acheson *et al*²¹ have identified four cases attributable to amosite exposure—one peritoneal and three pleural. It has been suggested by J Gilson (personal communication) that a mixture of fibres may be more likely to produce tumours at the peritoneal site. (A comparable suggestion regarding the frequency of tumours was made and then subsequently withdrawn by Acheson and Gardner.³⁰) The evidence given above, however, is not in accord with this suggestion, since the trend over time for the proportion of peritoneal tumours to decrease is accompanied by a trend, after at least a decade during which crocidolite was the only fibre used, for increasing proportions of amosite and chrysotile to be used in factories A and B.

In considering crocidolite asbestos an added complication is that it is not a homogeneous product. Crocidolite has been mined in the past in three different areas, in the Cape region of South Africa, in the Transvaal where crocidolite and amosite are mined in proximity, and at Wittenoom Gorge in Western Australia. Morphologically the Transvaal crocidolite has a greater mean fibre diameter than the Cape product—that is, it is thicker and blunter and tending towards amosite in this respect. The Australian fibre, on the other hand, is finer and more needle-like than the Cape output, with an average diameter of under 1 μ m.

The main supply of crocidolite has always come from the Cape mines. Transvaal crocidolite, the mining of which was not carried out on any large scale

until the late 1920s, never amounted to more than 15% of total supplies of crocidolite to factories A and B. During and after the second world war Australian crocidolite was specified in contracts for the manufacture of filter pads for military gas masks, although probably very little arrived in Britain before 1950.

In their original work on the South African mines Wagner *et al*¹² drew attention to the lack of cases of mesothelioma associated with the mines of the Transvaal, in contrast with the numbers arising in the neighbourhood of the Cape mines, and this contrast was subsequently confirmed by Webster.³¹ Then Jones *et al*³² drew attention to the high incidence of mesothelioma in assemblers of service gas masks in Nottingham, a finding that was paralleled in comparable workers in Quebec by McDonald and McDonald.³³ Exposure in most of these cases was brief, suggesting that the production of the laps, and from them the filter pads, and their subsequent assembly into gas masks was a particularly hazardous operation. This may have been due to a finer mean diameter crocidolite being airborne during these operations, though whether this was wholly accounted for by the admixture of Australian crocidolite is doubtful. A more probable explanation is that a higher proportion of long fine fibres was produced by the extra carding done in producing the gas mask laps.

The filter pads that these workers assembled into gas masks were manufactured at factory A, and the experience of the employees from factory A whose main dust exposure was from gas mask pad manufacturing is interesting. Nine cases occurred in all, of which eight were peritoneal. Six of these eight cases had three years' exposure or under, and of these, five had under one year. This may be compared with the distribution in table 4. For the proportion exposed for under one year the probability is less than 0.005 that the difference in the exposure durations could have arisen by chance (Fisher's exact test). The conclusion is, therefore, that by comparison with the general distribution of mesothelioma cases, the experience of the workers on this particular task was significantly different.

But again it appears unlikely that the pleural:peritoneal ratio can be attributable to characteristics of the fibre. All the cases recorded in Australian miners have been pleural, and while with the Quebec gas mask workers six of the nine cases were peritoneal, as were eight of our nine cases, at Nottingham 13 of 17 cases were pleural. The Nottingham workers assembled their gas masks in a pharmaceutical factory, and conditions have been described as good, whereas the factories at Montreal and Quebec and factory A in the present series were

all engaged in the manufacture of other asbestos products and levels of both crocidolite and other dusts were probably higher. It is more likely that the explanation lies in the degree to which the fibres had been opened, the magnitude of the fibre count, or the amount of contaminating dust in the atmosphere, or a combination of all these factors.

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