ASBESTOS RETENTION IN HUMAN RESPIRATORY TISSUES: COMPARATIVE MEASUREMENTS IN LUNG PARENCHYMA AND IN PARIETAL PLEURA

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INTRODUCTION

As has been extensively documented, the pleura is often the target organ for asbestos exposure (Zielhuis, 1977). A possible explanation could be that very active asbestos fibres are accumulated within the pleural tissues after their translocation from the lung. In order to verify this idea, asbestos fibres were assessed in pleural and parenchymal tissues from several autopsy cases.

MATERIAL AND METHODS

Asbestos fibre content was analysed in 112 samples from 29 cases, which had been sent to the laboratory by pathologists requesting confirmation of diagnosis. Lung parenchymal samples from different locations and parietal pleural samples were available for each case reported. In a few cases, mediastinal lymph nodes were also available.

The cases are listed in Table 1. Information concerning age, sex, history of asbestos exposure, pathological features and location of the collected samples was obtained from the pathologists.

Table 1. History of asbestos exposure and pathological features in 29 cases available for study

Case number	Age	Sex	Asbestos exposure		Relevant occupation	Pathological features[a]
			Duration (yrs)	Latent period (yrs)		
1	45	F	1	26	Asbestos textile worker	LF, PF, PMD
2	61	M	29	47	Shipyard insulator	PMS
3	54	M	Undiscovered		Unskilled labourer	PE
4	71	M	Undiscovered		Unknown	PF, PE, PMD
5	50	M	17	25	Shipyard worker	PF
6	56	M	1	31	Asbestos mill worker	LF, BC, PF
7	75	M	4	59	Asbestos sheet cutter	PF, PMS
8	63	M	27	27	Asbestos cement worker	LF, PF, PMS
9	42	M	17	17	Dock labourer	PF, PMS
10	52	F	2	25	Asbestos insulator	PE
11	68	M	Occasional		Plumber	BC, PF
12	58	M	Probable		Glass maker	PF, PMS
13	63	F	9	19	Asbestos textile worker	LF, BC, PF
14	78	F	Undiscovered		Unskilled worker	PF, PMS
15	48	M	Specified		Unknown	PF, PE
16	53	M	Specified		Mason	PF, PE
17	39	F	3	23	Asbestos textile worker	LF, PF, PMD
18	43	M	5	17	Brake maintenance and repair worker	PF
19	58	M	7	45	Boiler cleaner	LF, PF, PE
20	72	M	1	45	Boiler maker	PE
21	57	M	8	36	Insulator	PF
22	70	M	Specified		Unskilled worker	BC
23	58	M	2	38	Boiler maker	BC, PE
24	64	M	12	12	Asbestos plant worker	PE
25	63	M	2	27	Asbestos sheet cutter	PF, PMS
26	64	M	37	40	Asbestos textile worker	LF, BC, PF
27	67	M	25	37	Shipyard worker	PF
28	50	M	35	35	Boiler maker	PF, PE
29	64	M	10	20	Dock labourer	PF, PMD

[a] LF = lung fibrosis; BC = bronchogenic carcinoma; PF = pleural fibrosis; PE = pleural effusion; PMD = pleural mesothelioma (definite by the mesothelioma panel within the register); PMS = suspected pleural mesothelioma (in discussion within the panel)

Fibres were individually characterized, counted and sized using a transmission electron analytical microscope (Sébastien et al., 1978).

Measurement data were computerized in order to assess the following parameters:

(1) Numerical concentration of fibres (10^5/cc of fixed tissue)
(2) Proportion attributable to amphibole type fibres (%)
(3) Mean diameter
(4) Mean length
(5) Proportion of fibres longer than 4 µm
(6) Proportion of fibres longer than 8 µm

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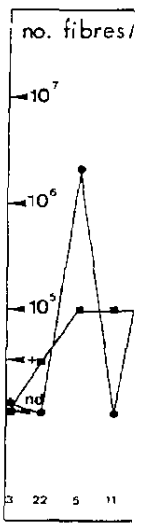

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RESULTS

Most of the fibres isolated from the tissue samples appeared as individual particles without overlapping or clumping. It was therefore possible to characterize fibres as objects with a length:diameter ratio greater than 3:1 and to size them individually (length and diameter).

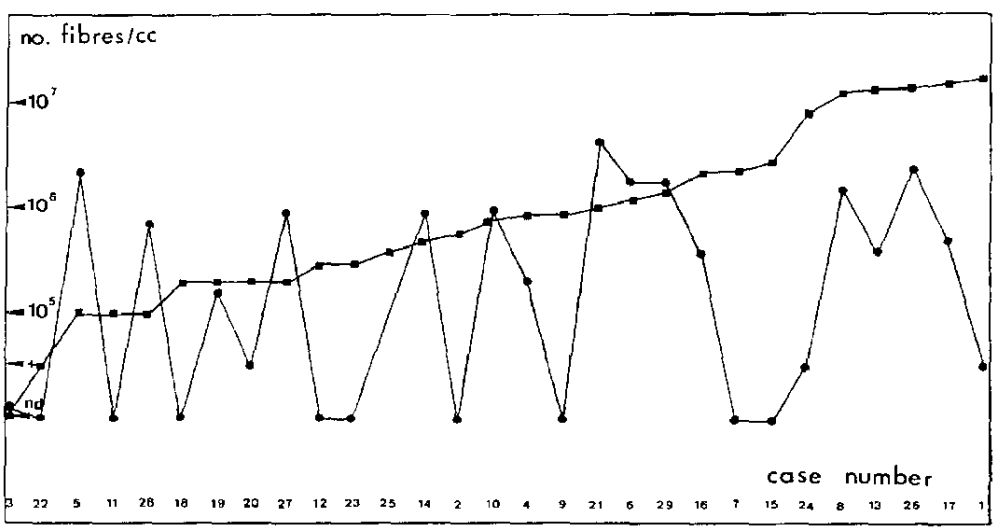
Numerical concentrations of asbestos fibres in tissue

In 27/29 cases, results were significantly positive for fibres in lung parenchymal samples. Concentrations were in the range 'not detected' to 420 × 10^5/cc. On the other hand, in only 16/29 cases were results significantly positive for fibres in parietal pleural samples. Concentrations were in the range 'not detected' to 51 × 10^5/cc.

In Figure 1, a comparison is made of the maximal parenchymal and pleural concentrations when cases are ordered according to increasing parenchymal concentrations. This graph shows no evident relationship between parenchymal and pleural concentrations.

FIG. 1. NUMERICAL CONCENTRATIONS (no./cc) OF ASBESTOS FIBRES IN LUNG PARENCHYMA (■) AND PARIETAL PLEURA (●)

From Sébastien et al. (1979)



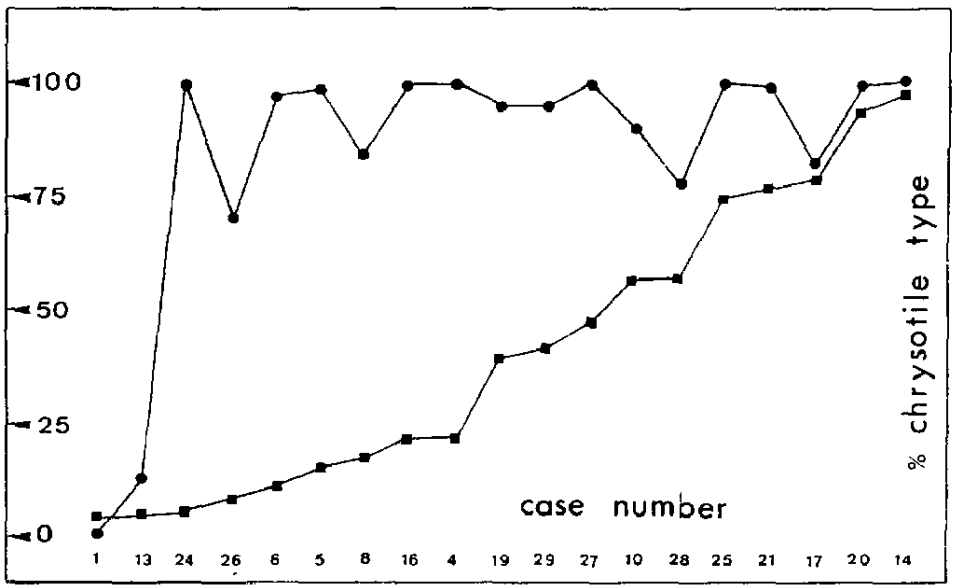
Three types of samples were available from the parietal pleura: normal tissue from a costal location (NT), costal plaques (CP) and diaphragmatic plaques (DP); the frequencies of significantly positive samples for each type of sample were 5/15 (27%), 7/11 (64%) and 5/7 (71%), respectively.

Mineralogical type of asbestos fibres

In the cases studied, the proportion of amphibole-type fibres within the lung ranged from 0 to 100% (mean, 56; standard deviation, 32). On the other hand, when a pleural sample was positive for asbestos, almost all of the fibres encountered were of the chrysotile type, as shown in Figure 2.

FIG. 2. MINERALOGICAL TYPE OF ASBESTOS FIBRES IN LUNG PARENCHYMA (■) AND PARIETAL PLEURA (●)

From Sébastien et al. (1979)



Size of asbestos fibres

Table 2 shows the mean parameters with regard to the size distribution of asbestos fibres in lung parenchyma and parietal pleura in the 29 cases. More detailed information concerning the size distribution of chrysotile in lung parenchyma and parietal pleura is contained in Table 3; for the thinnest fibres (diameter less than 0.25 µm), the

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Table 2. Parameters of size distribution of asbestos fibres in lung parenchyma and parietal pleura

	Lung parenchyma	Parietal pleura
Mean length (μm)	4.9	2.3
Mean diameter (μm)	0.13	0.06
Longer than 4 μm (%)	42	16
Longer than 8 μm (%)	15	2

Table 3. Size distribution (in percent) of chrysotile-type fibres in lung parenchyma (LP) and parietal pleura (PP)

Length (μm) \ Diameter (μm)	From 0.03 to 0.25		From 0.25 to 1	
	LP	PP	LP	PP
From 0.4 to 4	60	84	1	0
> 4	38	14	0	0

data clearly show the increased frequency of short fibres and the decreased frequency of long fibres from lung to pleura. It can also be seen that only a few thick chrysotile fibres, more than 0.25 μm in diameter, were observed in those lungs.

In only one case was a significant amount of amphibole-type fibre found in the pleura. The size distributions of amphibole-type fibres are given in Table 4. It is clear that, as in Table 3, with thin fibres there is an increase of short fibre and a decrease of long fibre frequencies from lung to pleura, while for fibres thicker than 0.25 μm the frequencies of short and long fibres are not significantly different.

Table 4. Size distribution (in percent) of amphibole-type fibres in lung parenchyma (LP) and parietal pleura (PP) in one case (number 26)

Length (μm) \ Diameter (μm)	From 0.03 to 0.25		From 0.25 to 1	
	LP	PP	LP	PP
From 0.4 to 4	44	61	14	15
> 4	26	10	15	14

DISCUSSION

It is interesting to compare the retention of asbestos fibres in parenchymal and pleural tissues.

(1) Our study has clearly demonstrated that *lung parenchymal retention is not a good indicator of pleural retention*: indeed, there was no relationship between parenchymal and pleural concentrations, many pleural samples being free of asbestos fibres.

The finding of many negative samples may be due to a heterogeneous distribution of fibres in the pleural tissue: if fibres are concentrated in certain areas, they can be overlooked by the transmission electron microscope, which examines a very small sample. However, fibres were found more readily in plaques than in normal tissue and more readily in diaphragmatic than in costal locations.

With regard to the topographic distribution of numerical concentrations of fibres in lung parenchyma, it has been shown previously that, for a given case, variations from one sampling site to another never exceed one order of magnitude (Sébastien et al., 1977).

(2) This study has demonstrated that the retention of asbestos dusts in parietal pleura was related to type and size: most of the fibres were *short chrysotile fibres*.

The finding of only chrysotile-type fibres within the parietal pleural tissue suggests two possible explanations: fibres of all types are transported to the pleural area, but only chrysotile fibres are retained in pleural tissue; or only chrysotile fibres can migrate to the pleura. At least three mechanisms may be involved in the translocation of small chrysotile fibres towards the parietal pleura:

(a) It has been suggested that the lymphatic circulation is the route used for the transport of fibres from the lung to the pleura (Brown, 1974; Hourihane, 1965; Taskinen et al., 1973). The exact route must be assessed, but the finding of amphiboles fibres preferentially to chrysotile fibres in mediastinal lymph nodes suggests that asbestos fibres are cleared from lung parenchyma and/or bronchi to the mediastinal lymph nodes, which can retain only the largest fibres of the amphibole type (Bignon et al., 1979). The route followed by chrysotile fibres from the lymph nodes to the parietal pleura still remains unclear, however; it might be retrograde (Taskinen et al., 1973).

(b) A second hypothesis is that the fibres migrate from the lung through the visceral pleura and the pleural cavity and are resorbed into the parietal pleura. In this respect, it has been suggested that

stiff amphibole fibres might pass more readily through the lung tissue from a mechanical point of view (Zielhuis, 1977). If pulmonary macrophages are also involved in this translocation (Webster, 1977), the effect of different mineral dusts (chrysotile and amphiboles) on the mechanism of phagocytosis must be considered (Miller et al., 1978).

(c) Thirdly, the presence of asbestos in non-lymphoid organs suggests that some fibres may enter the blood stream, which may be involved in their translocation. If such transportation mechanisms are type and size selective, this could be an explanation for the preferential accumulation of short chrysotile fibres in pleura.

Autopsy studies are of limited value for elucidating the history of the translocation of fibres in the respiratory tract. The retention of fibres in tissue as assessed by transmission electron microscope measurements is the result of dust retention, translocation and clearance which occurred in the past. Moreover, these biological events took place within tissues which were greatly modified by pathological changes. Thus, experimental data are required for a better understanding of the migration of fibres in the respiratory system.

(3) There seems to be general agreement that the risk of mesothelioma is related to fibre type in the following descending order: crocidolite, amosite, chrysotile, anthophyllite (Zielhuis, 1977). Moreover, some animal experiments have shown that the risk is related to fibre size, since fibres thinner than 0.25 μm and longer than 8 μm have the greatest ability to induce tumours when implanted into the pleural cavity of rats (Stanton et al., 1977). The present study shows that although such carcinogenic fibres (amphibole-type fibres longer than 8 μm) are present in lung parenchyma, in parietal pleural tissues short chrysotile fibres greatly outnumber long fibres of the amphibole type. These findings stress our poor understanding of mesothelioma induction in humans.

SUMMARY

Asbestos fibres in respiratory tissues from 29 cases diversely exposed to asbestos dusts have been characterized, sized and counted using a transmission electron microscope.

Comparison of data obtained by measurement of fibres in lung parenchyma and in parietal pleura samples showed the following:

- In each case, the proportion of chrysotile fibres (as opposed to amphiboles) was higher in parietal pleura than in lung parenchyma. (The proportion of chrysotile in pleura was greater than 90% in 30 of the 40 samples.)

- Fibres encountered in parietal pleura were shorter than those in the parenchyma.

- There was no evident correlation between numerical concentrations of fibres in lung parenchyma and those in parietal pleura.

This study has shown that characteristics of asbestos retention in parietal pleura cannot be derived from measurements in lung parenchyma. On the basis of the cases analysed here, who were exposed to mixed types of asbestos dust, chrysotile seems to be the asbestos type retained almost exclusively in parietal pleural tissues. These findings might be taken into account when assessing the risk of pleural diseases (especially mesothelioma) attributable to each type of asbestos fibre.

RESUME

Au moyen d'un microscope électronique à transmission les auteurs ont caractérisé, calibré et compté les fibres d'amiante dans les tissus de l'appareil respiratoire de 29 sujets différemment exposés aux poussières d'amiante.

La comparaison des données obtenues en mesurant les fibres dans des échantillons de parenchyme pulmonaire et de plèvre pariétale a révélé ce qui suit:

- Dans chaque cas, la proportion des fibres de chrysotile (par opposition aux amphiboles) était plus forte dans la plèvre pariétale que dans le parenchyme pulmonaire (dans 30 des 40 échantillons la proportion de chrysotile dans la plèvre était supérieure à 90%).

- Les fibres rencontrées étaient plus courtes dans la plèvre pariétale que dans le parenchyme.

- Il n'y avait pas de corrélation évidente entre les concentrations numériques de fibres dans le parenchyme pulmonaire et dans la plèvre pariétale.

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Cette étude montre qu'on ne peut déduire les caractéristiques de rétention de l'amiante dans la plèvre pariétale des mesures effectuées dans le parenchyme pulmonaire. Si l'on se fonde sur les cas ici analysés, qui ont été exposés à des mélanges de poussières d'amiante, le chrysotile semble être la variété presque exclusivement retenue dans les tissus de la plèvre pariétale; observation dont on pourrait tenir compte pour évaluer le risque de maladies pleurales (mésothéliome notamment) imputable à chaque variété de fibre d'amiante.

ACKNOWLEDGEMENTS

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QUANTIFICATION AND PARTICLE SIZE DISTRIBUTION OF INHALED FIBRES IN THE LUNG

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Quantification and estimation of distribution of fibre size in the lung are important in the evaluation of the fibrogenic and carcinogenic effects of inhaled asbestos (Bossard, 1979; Whitwell et al., 1977). The present investigation involved a comparison of fibre counts in the lungs of asbestos-exposed *versus* nonexposed individuals.

MATERIALS AND METHODS

A total of 21 lungs were examined, from two groups of necropsies:

Group NL: 10 lungs from persons with no known occupational or paraoccupational exposure to asbestos. Three were from males 46-74 years of age, and seven were from women 28-83 years of age.

Group AL: 11 lungs from persons with known occupational exposure to asbestos, all males. Asbestosis was confirmed histologically in eight cases only. Among the 11 cases, three were mesotheliomas, two were lung carcinomas and one was a carcinoma of the renal pelvis.

For isolation of fibres, entire formalin-fixed lungs or randomized samples of lung tissue were dehydrated with acetone, and the fat was removed with ether. After drying, the tissue was homogenized; and 1-5 g of dried tissue were incinerated in a low-temperature asher (Tracer Lab ICN) until the weight of the probe remained constant. The ash was then suspended in double-distilled water, containing a few drops of Triton X, and sonicated for 30 minutes. In the AL group, which was

presumed to have a high fibre content, approximately 0.05 mg from each case was processed. In the NL group, with a presumably low fibre content, the samples were between 0.3-0.5 mg. The distilled water sample was filtered slowly through a cellulose-acetate filter (pore diameter, 0.22 µm); and the filter was then put on a cover-slip, with the dusty surface upwards, and was allowed to dry in a dust-free environment. It was then placed on immersion oil for clearing and, subsequently, with the dusty surface facing downwards, was again put on a cover-slip and covered with a photographic grid comprising 4425 numbered 0.2 mm squares. Finally, the 'sandwich' was mounted on a slide and embedded in Eukitt.

Fibre counting was performed using a phase-contrast microscope, at a magnification of × 400, combined with a system for quantitative evaluation of images (MOP/AM - 03). Counting was continued until the mean number of fibres per square had stabilized. Both coated and uncoated fibres were counted. A fibre was defined as a solid body with a length: width ratio of at least 3:1 and a maximum width of 2 µm. In the system used, only fibres with a minimal length of 2 µm could be distinguished clearly.

RESULTS

The numbers of fibres counted per gram of dry lung weight are shown in Table 1 (NL) and Table 2 (AL). For lungs exposed to asbestos, the values vary over almost three powers of 10; for normal lungs, they range over only one.

Table 1. Asbestos fibre counts in lungs from nonexposed persons (NL)

Case no.	Age (yrs)	Sex	Cause of death	No. of fibres per g dried lung ± SD (millions)	Mineral content of dried lung weight (%)
NL 8	68	F	Traumatic rupture of the aorta	4.8 ± 1.2	1.25
NL 6	49	M	Leukaemia	3.16 ± 0.95	0.76
NL 7	50	F	Carcinoma of the ovaries	1.6 ± 0.6	0.85
NL 9	80	F	Gastrointestinal haemorrhage	1.36 ± 0.56	0.81
NL 10	56	M	Myocardial infarction	0.94 ± 0.54	0.75
NL 5	83	F	Myocardial infarction	0.84 ± 0.35	0.55
NL 4	28	F	Hypothermia	0.7 ± 0.43	0.74
NL 2	72	F	Pulmonary embolism	0.66 ± 0.36	0.20
NL 3	74	M	Myocardial infarction	0.54 ± 0.22	0.99
NL 1	64	F	Carcinoma of the stomach	0.36 ± 0.24	1.08

Table 2.

Case no.	Age (yrs)
AL 11	59
AL 1	70
AL 8	51
AL 3	64
AL 9	61
AL 7	52
AL 5	62
AL 10	62
AL 4	56
AL 2	65
AL 6	81

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Table 2. Asbestos fibre counts in lungs from exposed persons (AL)

Case no.	Age (yrs)	Profession	Asbestosis	Other diseases of the lung/pleura	No. of fibres per g cried lung ± SD (millions)	Mineral content of dried lung weight (%)	Asbestos type and concentration
AL 11	59	Asbestos insulator	+	-	720 ± 180	1.0	Crocidolite (10%)
AL 1	70	Foundry worker	+	Silicosis	720 ± 93	1.3	Amphibole (7-10%)
AL 8	51	Mechanic	-	Mesothelioma	57 ± 23.5	1.35	Chrysotile (2%) Amosite (2%)
AL 3	64	Asbestos insulator, sand blaster	+	Silicosis	18.3 ± 4.5	2.12	Amphibole (2%)
AL 9	61	Potter	+	Silicosis, peripheral carcinoma	13.8 ± 3.4	5.41	Chrysotile (2-10%)
AL 7	62	Asbestos-cement worker	-	Mesothelioma	10.2 ± 2.4	0.42	Chrysotile (2%) Amosite (2%) Amphibole (2%)
AL 5	62	Asbestos-cement worker	+	-	9.4 ± 2.7	1.1	-
AL 10	62	Asbestos-cement worker, miner	+	Tuberculosis	6.3 ± 2.4	2.88	Chrysotile (2%)
AL 4	56	Asbestos insulator	+	-	4 ± 1.4	0.32	Amosite (2%) Crocidolite (2%) Anthophyllite (2%)
AL 2	65	Worker in brake-lining plant	+	Bronchial	1.6 ± 0.5	0.11	-
AL 6	81	Mechanic (steel pipes)	-	Mesothelioma	0.7 ± 0.5	0.5	Chrysotile (2%) Amosite (2%)

The mean fibre counts were as follows:

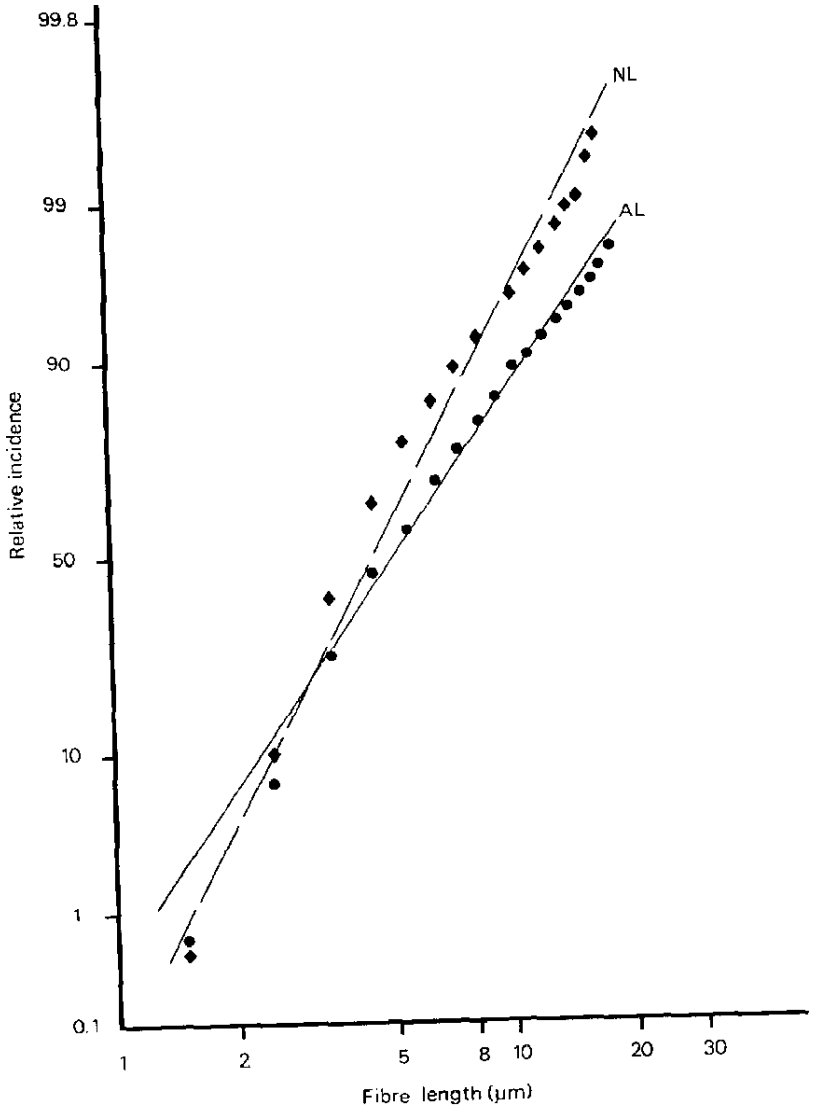
NL, 1.5×10^6/g of dry lung weight (range, $0.36 - 4.8 \times 10^6$);
AL, 141.9×10^6/g of dry lung weight (range, $0.7 - 720 \times 10^6$).

If the two groups are compared, using the ranking test of Wilcoxon (1945) for two random samples, the result $P = 0.05$ demonstrates that there is a higher value for the fibre concentration in asbestos-exposed lungs than in normal lungs.

The mineral contents, expressed in percentage of dry lung weight, are also given in Tables 1 and 2. The values are comparable for NL and AL. The two cases with high values, listed in Table 2, were also exposed to dusts other than asbestos; the asbestos concentration in 10 of the 11 asbestos lungs was very low, amounting to a total mineral content of less than 10%.

The relative frequency of fibre lengths closely approaches a standard logarithmic distribution (Fig. 1). The fibre lengths encountered most frequently in both NL and AL ranged between 3-5 μm; this finding corresponds to those of other authors (Le Bouffant, 1974; Sébastien et al., 1975). These length categories represent 40-60% of all fibres in normal lungs and 30-60% in asbestos-exposed lungs. According to the Wilcoxon test, the mean values for the fibre lengths are lower in the NL group than in the AL group.

FIG. 1. DISTRIBUTION OF FIBRE LENGTHS IN LUNGS FROM PERSONS NOT EXPOSED TO ASBESTOS (NL) AND IN PERSONS KNOWN TO HAVE BEEN EXPOSED TO ASBESTOS (AL), EXPRESSED AS MEAN VALUES OF THE RELATIVE INCIDENCES



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DISCUSSION

Isolation of mineral particles by incineration at low temperature proved to be a useful method for quantifying inhaled fibres in the lungs and for studying their size distribution. Plasma incineration of tissue is practical and does not lead to the substantial losses that occur with chemical degradation. The following results were obtained:

1. Lungs of individuals with known occupational exposure to asbestos exhibit, in general, a remarkably higher content of mineral fibres than lungs of individuals with no known exposure. This is in agreement with the findings of Ashcroft & Heppleston (1973) and of Friedrichs & Einbrodt (1976).

2. The distribution of fibre lengths is similar in the two groups. The most frequent fibre length measured by light microscopy ranges between 3-5 μm. In a preliminary electron microscopic analysis of lung dust, it was found - as expected - that only about 10% of all mineral fibres deposited in the lungs can be seen in the light microscope. About 90% of the fibres have lengths of less than 2 μm, with a peak at 0.2-0.3 μm. The submicroscopic study revealed furthermore that not all fibres in asbestos-exposed lungs are asbestos.

3. Mineralogical and chemical analyses demonstrated the presence of asbestos, either chrysotile or amphibole, exclusively in the lungs of asbestos-exposed persons. The mineral content of the lung does not correlate with the fibre count. In addition, the total quantity of minerals deposited in the lungs of asbestos-exposed persons did not differ significantly from that in nonexposed individuals.

4. No correlation between fibre counts and pathological changes in the lungs could be made in the present study. For instance, in the three mesothelioma cases (Table 2), although a marked difference in number of fibres was seen, ranging between $0.7\text{-}57 \times 10^6$ fibres per gram of dry tissue, the mesotheliomas were not accompanied by asbestosis, although the fibre count was sometimes higher than in some cases of histologically verified asbestosis. Our results differ from the observations of Ashcroft & Heppleston (1973), who demonstrated a correlation between grade of asbestosis and fibre count. This may be due to variations in the exposure time, the nature of the asbestos involved, as well as the method used for sampling and isolation. It has been our experience, especially in cases of asbestosis following exposure to chrysotile asbestos, that this mineral cannot always be identified. This may be attributed to the solubility of chrysotile in the lung.

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