MINERAL FIBRE IN THE LUNGS OF WORKERS FROM A BRITISH ASBESTOS TEXTILE PLANT

FREDERICK DAVID POOLEY, Ph.D., MIMM, MAIME, CEng • Ravi Mitha, BSc.

School of Engineering, Newport Road, University of Wales College of Cardiff
P.O. Box 917, Cardiff CF2 1XH, United Kingdom

INTRODUCTION

The material examined in this study consisted of random specimens of lung parenchyma which had originally been collected at autopsy for histopathological examination. The specimens of fixed tissue were embedded in paraffin wax blocks and represented samples obtained from individuals previously employed at a British asbestos textile plant who died between the years 1964 and 1975.

The asbestos textile plant where the various individuals had been employed had used chrysotile as its principal raw material, this being imported from Canada and Africa. Crocidolite was used between 1932 and 1969 and over this period represented approximately 5% of the total amount of asbestos processed.[1] No amosite was apparently used at any time for production purposes.

When these tissue samples were originally collected the assay of the specimens for their fibrous mineral content had not been considered. They represented a unique collection of biological material from individuals who for various lengths of time were employed in a plant which has been extensively studied for more than 30 years.

The plant has been the focus of several publications concerned with relating the effects of exposure to asbestos on health.[1-7] However, these studies have not been able to assess the effects of exposure to the various asbestos minerals processed. The British Occupational Hygiene Society used data from this factory in determining its hygiene standard[10] for chrysotile and the mesotheliomas occurring in this factory have been attributed to chrysotile exposure.[11] Information on the mortality of the workers at this plant has been shown to be very different from that of an American textile plant where crocidolite was not extensively used.[8,9] Mesothelioma, lung cancer and asbestosis have been causes of death of the workers in the British plant but not in the American operation where lung cancer and asbestosis cases have been more prevalent.

An examination of the limited working histories of the cases revealed that three had originally been employed in an asbestos fibre store some distance from the textile plant and for a further six, no information regarding period of employment was available. Results from these eight cases are therefore not reported here. The available information regarding the causes of death of the remaining 98 individuals showed that 20 were due to a mesothelioma, 24 to asbestosis and/or lung cancer and 54 were due to other causes.

The specimens have been examined to estimate fibre loadings, the relative concentrations of the various fibre types retained in the tissue and their physical characteristics. These results are reported here and compared with similar data obtained from 46 cases of exposure from an American asbestos plant.

A fibrosis category for the 98 British textile plant cases was also estimated from histopathological sections which had been previously cut from the paraffin wax blocks examined in this study. This information was used to compare fibrous grading with asbestos fibre lung burdens.

METHODS

In each case the tissue specimen was first extracted from its wax block in warm Xylene solution. When separated from the Xylene each specimen was immediately washed in ethanol to remove the wax-rich Xylene solution and dried at 80°C to evaporate the ethanol. The weight of the dry tissue specimen was then recorded. Tests with wet lung tissue specimens which had been prepared in wax and then subsequently extracted in the manner outlined have shown that the dry weight of the tissue recovered was on average 15% of the wet tissue weight. This value of dry tissue weight as a percentage of wet weight corresponds closely to figures obtained from wet lung tissue specimens dried to a constant weight at 80°C.[18]

The tissue specimens were placed in glass centrifuge tubes and digested with 5 mls of 5N KOH solution at a temperature of 80°C in a heated block. The KOH digests were then diluted with distilled water and centrifuged to the bottom of their respective tubes and the diluted KOH solution decanted. The residue was resuspended in distilled water and centrifuged again to remove residual KOH. The washed pellet was then dried in the centrifuge tube and the remaining organic material removed by oxidation at 300°C in an oxygen atmosphere. The ashed pellet was finally resuspended in distilled water whose pH had previously been adjusted to a value of 1.5 and filtered almost immediately onto 0.2 μm pore size polycarbonate (Nuclepore) filters to produce an even deposit. If the suspension was judged to be too concentrated aliquots of 50%–20% were taken. In this particular study this problem was only encountered in a few instances

because of the small quantity of dried tissue available from each wax block which varied from 1.3 mg to 85.7 mg.

The filtered tissue extract was prepared for examination in a Philips EM 400T analytical electron microscope by the direct transference technique.[19] A layer of carbon was deposited onto the dust deposit on the filter and portions cut to the approximate size of gold specimen support grids. The carbon-coated filter portions were deposited carbon upon the grids and the filter material removed using a bath of chloroform.

The mineral fibres in the preparations were examined at a magnification of 20,000X, random areas being scanned to determine their concentration per unit area of the filter preparation. Each fibre when encountered was identified using an energy dispersive X-ray analysis sytem attached to the microscope. The quantity, length, diameter and identity of all fibres (i.e., particles observed in random areas of the grid with a 3:1 axial ratio) in the preparations were therefore recorded. The preparation, counting techniques and identification procedure adopted have been described in detail elsewhere.[12,13,14,15,16] The extent of fibrosis in the various cases was estimated from microscopic examination of histological sections and were graded on a scale of 0–4, 0 being normal, 1 minimal, 2 slight, 3 moderate and 4 severe. This grading has been described in more detail in a similar study of asbestos-related deaths in the United Kingdom in 1977.[16]

RESULTS

The average results for the concentrations of asbestos and other fibre types observed in the 98 cases examined are given in Table I from which it can be seen that all the asbestos mineral types were detected. The geometric mean values for the cases are presented together with arithmetic means because of the very wide range of fibre concentrations determined. Geometric mean values have also been employed as a means of presentation of other data in this paper. Chrysotile fibres were the most numerous of the asbestos particles observed but appreciable quantities of both crocidolite and tremolite were present together with minor concentrations of amosite and anthophyillite.

The combined size distributions of the major asbestos fibre types extracted from the samples are given in Table II. It can be seen from this table that the majority of the chrysotile fibres observed were less than 5 microns in length and finer than 0.25 microns in diameter. More crocidolite and tremolite fibres were longer than 5 microns when compared with chrysotile and a larger proportion of these fibres were greater than 0.25 microns in diameter with tremolite on average the larger of the fibre types. Some consideration must be given to the size of fibres detected in tissue specimens when the quantities of the various asbestos minerals are being assessed as the number of concentrations of the individual fibrous minerals do not equate directly to their mass concentrations because of size distribution differences. It is likely

Table I

Mean Concentrations of Number and Mass of Various Fibre Types Determined in 98 Cases from a British Asbestos Textile Plant

Mineral Fibre Type	Fibre Concentrations 10^6 gram dry lung tissue			
	10^6 fibres/ gram A.M.	10^6 fibres/ gram G.M.	Range of concs.detected 10^6 fibres/gram	Fibre Mass ug/gram A.M.
Chrysotile	175.4	89.4	1.5 - 1389.6	6.0
Crocidolite	79.8	10.1	ND - 2056.9	8.4
Amosite	4.9	0.2	ND - 153.3	4.2
Tremolite	21.8	2.4	ND - 203.7	8.5
Anthophyllite	0.5	0.02	ND - 15.2	0.2
Mullite	31.8	11.3	ND - 246.8	-
Rutile	6.2	0.2	ND - 411.3	-
Iron	4.1	0.7	ND - 25.2	-
Others	3.8	-	ND - 29.7	-
Total	328.3	190.0	11.1 - 2508.4	-

ND - Not Detected
A.M. - Arithmetic Mean
G.M. - Geometric Mean

that the techniques used in the preparation of lung tissue specimens do enhance the number concentration of chrysotile fibres to a greater extent than amphibole fibres. This can be related directly to the fibrilar structure of chrysotile and is supported by the scarcity of fibre bundles observed in lung preparations.

In Table III the fibre concentration data collected has been presented on the basis of cause of death. This shows that on average larger concentrations of amphibole asbestos were detected in lung tissue where the cause of death was due to asbestosis and/or lung cancer than either mesothelioma or other causes of death. Crocidolite levels can be seen to be similar for mesothelioma cases, asbestosis and lung cancer cases, these levels being higher than the average for other causes of death. Table IV presents the average lung fibre burdens of chrysotile, amphibole and total asbestos on the basis of fibrosis grading together with average years of service for cases falling within each category. The chrysotile levels were found to increase in step with the fibrosis grading but the amphibole levels did not. It was also observed that the fibrosis grading did not increase directly with the average years of service. The average lung fibre burdens for the significant asbestos minerals are compared on the basis of years of service in Table V which show that the amphibole mineral fibres tend to accumulate with years of service but chrysotile levels are relatively static.

The average results for the concentration of fibres detected in the lung tissue of 46 cases from an America textile plant are presented in Table VI. When compared with the British results in Table I, it can be seen that chrysotile and amphibole levels are lower. The marked reduction in the amount of amphibole fibre in the American cases is due mainly to the difference in the higher concentration of crocidolite observed in the tissues from the British cases. The tremolite levels in both groups of cases are similar. A greater range of all fibre concentrations were also detected in the British cases when compared with the American group.

The results from the British and American cases are compared further in Table VII where size distribution data has been used to calculate the average concentration of fibres longer than 5 microns for each asbestos type. In Table VIII this analysis has been extended further to compare the averages of fibres longer than 5 microns and finer than 0.25 microns. From both tables the most significant difference between the fibre concentrations is the greater proportion of long and thin amphibole fibres in the British cases. The major contributor to this difference being the significant amount of crocidolite occurring in the British cases.

DISCUSSION

In this study the asbestos mineral fibre detected in the lungs from 98 individuals previously employed in a British asbestos

Table II

Combined Size Distributions of Major Asbestos Fibre Types Observed in the Lungs of British Textile Plant Cases (%)

Length Ranges Microns	Diameter Ranges Microns						
	Chrysotile	Crocidolite			Tremolite/Actinolite		
	0-0.25	0-0.25	0.25-0.5	> 0.5	0-0.25	0.25-0.5	> 0.5
< 5	91.8	88.0	1.5	-	73.6	12.0	3.1
5-10	4.9	8.3	0.7	0.2	5.5	1.8	1.1
10-20	2.3	0.9	0.3	-	1.0	0.5	0.6
> 20	1.0	0.1	-	-	0.6	-	-

Table III

Geometric Mean Concentrations of Asbestos Fibres Detected in Lung Tissue and Expressed on the Basis of Cause of Death

Number of Cases	Cause of Death	Fibre Concentrations 10^6/gram of Dry Tissue				
		Chrysotile	Crocidolite	Amosite	Tremolite	Total Amphibole
20	Mesothelioma	64.5	13.0	0.4	2.0	24.8
24	Asbestosis & Lung Cancer	100.4	14.3	0.1	8.9	47.5
54	Other Causes	99.1	8.4	0.2	1.5	19.4

Table IV

Geometric Mean Asbestos Lung Fibre Burdens of Chrysotile, Amphibole and Total Asbestos Fibre Counts with Years of Service Compared on the Basis of Fibrosis Grading

Number of Cases	Years of Service	Fibrosis Grading	Mean Fibre Levels 10^6/gram of Dried Lung Tissue		
			Chrysotile	Total Amphibole	Total Asbestos
16	20.6	0	59.7	12.5	83.7
12	7.1	1	84.4	9.6	130.3
54	16.6	2	95.1	24.4	153.2
16	20	3	103.9	107.2	240.4

Table V

Geometric Mean Lung Fibre Burdens of the Significant Asbestos Minerals Compared on the Basis of Years of Service

Number of Cases	Years of Service Range	Mean Fibre Levels 10^6/gram of Dried Lung Tissue				
		Chrysotile	Crocidolite	Amosite	Tremolite	Total Amphibole
23	0-10	67.3	2.5	0.2	0.5	7.3
29	10-20	102.0	7.3	0.2	2.9	21.6
23	20.30	115.6	26.7	0.2	2.5	37.9
23	30-50	78.6	29.5	1.0	13.6	64.4

Table VI

Mean Concentrations of Number and Mass of Various Fibre Types Determined in 46 Cases from an American Asbestos Textile Plant

Mineral Fibre Type	Fibre Concentrations 10^6/gram Dried Lung Tissue			
	10^6 fibres/ gram A.M.	10^6 fibres/ gram G.M.	Range of concs. detected 10^6 fibres/gram	Fibre Mass ug/gram A.M.
Chrysotile	58.1	29.3	1.6 - 319.7	1.9
Crocidolite	2.3	0.1	ND - 67.2	2.7
Amosite	1.8	0.1	ND - 16.8	3.8
Tremolite	15.8	2.2	ND - 95.8	17.1
Anthophyllite	0.2	0.03	ND - 2.7	0.01
Mullite	5.6	1.3	ND 43.6	-
Rutile	1.0	0.2	ND - 8.1	-
Iron	1.6	0.2	ND - 5.3	-
Others	0.3	0.02	-	-
Total	86.7	47.4	2.1 - 319.7	-

ND - Not Detected
A.M. - Arithmetic Mean
G.M. - Geometric Mean

textile plant who died between the years 1964–75 was found to consist of chrysotile in association with appreciable quantities of amphibole fibre. On average the most prominent amphibole mineral detected was crocidolite with a lower concentration of tremolite and only minor quantities of other amphibole fibre types. The quantity of asbestos was found to accumulate an average with years of service, this accumulation being more pronounced for the amphibole minerals than chrysotile. This provides further proof of the selective retention of amphibole fibre which has been demonstrated in many investigations of mixed fibre occupational exposures. There was no clear relationship between years of exposure and fibrosis grading indicating that exposures within a particular industrial operation have varied significantly for various individuals. An increase of amphibole asbestos mineral concentrations in tissue with fibrosis grading is more pronounced than corresponding chrysotile fibre levels. This would lend further support to the hypothesis that the major cause of asbestosis in Great Britain has been the result of the inhalation and retention of amphibole asbestos mineral.[16] The average levels of amphibole fibre in tissue were found to be larger in those cases where the cause of death was due to asbestosis and/or lung cancer when compared with either mesothelioma cases or other causes of death. Chrysotile levels did not, however, vary significantly with cause of death; these observations are similar to those reported elsewhere.[20]

Comparing fibre lung burdens of British textile plant workers with those of an American plant have revealed that there are some similiarities in the mineralogy of the asbestos dust retained. Tremolite levels are similar although chrysotile contents are on average higher in the British cases. The most significant difference between the two groups is the high level of crocidolite fibre in the British cases. If these mineralogical

Table VII

Comparison of the Geometric Mean Concentration of Asbestos Fiber Types and Proportion Greater Than 5 Microns in Length Detected in the Lungs of Cases from British and American Textile Plants

Fibre Type	Number Concentrations 10^6/gram of Dry Tissue			
	British Cases		American Cases	
	Total	> 5um in length	Total	> 5um in length
Chrysotile	89.4	7.5	29.3	3.2
Crocidolite	10.1	1.1	0.1	0.058
Amosite	0.2	0.05	0.1	0.049
Tremolite/Actinolite	2.4	0.3	2.2	0.34
Total Amphibole	24.7	2.8	3.5	0.6

Table VIII

Comparison of the Geometric Mean Concentration of Asbestos Fibre Types and Proportion Greater Than 5 Microns in Length and Less Than 0.25 Microns in Diameter Detected in the Lungs of Cases from British and American Textile Plants

Fibre Type	Number Concetnrations 10^6/gram of Dry Tissue			
	British Cases		American Cases	
	Total	> 5um in length < 0.25um diameter	Total	> 5um in length < 0.25um diameter
Chrysotile	89.4	7.5	29.3	3.2
Crocidolite	10.1	0.97	0.1	0.048
Amosite	0.2	0.02	0.1	0.023
Tremolite/Actinolite	2.4	0.2	2.2	0.1
Total Amphibole	24.7	2.1	3.5	0.2

differences are compared with the information on mortality of workers from both plants, it would appear that the mesothelioma cases occurring in the British factory can only be related to the more extensive use of crocidolite in their manufacturing operations. This conclusion could only have been obtained by a comparison of the mineralogy of the lung contents of workers from the two textile plants.

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PATHOLOGICAL STUDIES OF ASBESTOTIC PLEURAL PLAQUES —PRELIMINARY EXPLORATIONS OF HISTOGENESIS

WANG MINGGUI • Zhao Jinduo • Zhang Lanying • Liu Jingde

Shenyang Research Institute of Industrial Hygiene and Occupational Diseases
Wang Bingsen Shanghai Research Institute of Industrial Hygiene and Occupational Diseases
Cheng Decheng, Chungqing Medical University P.R. China

Pleural plaques were present in 33 of 55 autopsy cases of asbestos workers. Their exposure periods to asbestos were 5–23 years (mean 18.1 years). Twelve of them employed as miners, 21 millers. They were mainly exposed to chrysotile.

Pleural plaque is local patchy thickening with sharp borders from the surrounding normal pleura, yellow-white, harder texture. The surface may be smooth, nodular or navel. No adhesion between visceral and parietal pleura is a conspicuous feature. Pleural plaques are often found on the parietal pleura, particularly on bilateral, posterior and diaphragm pleura. In a few cases they can be seen on visceral pleura or parietal pericardium. Pleural plaques are not encountered at the apex or the costophrenic angles. Plaques are wide variety of shapes and sizes. In order to grade severity of plaques, the total area of pleural plaques is surveyed and expressed as cm^2. The total area has been graded into 3 degrees according to less than 100 cm^2; and 100–300 cm^2; and more than 300 cm^2. The degree 1, 2, and 3 were recognized in 11, 10, and 12 cases, respectively. To determine whether degrees of plaques related to exposure periods to asbestos we divided 33 cases into groups according to the interval of 10 years. There appears to be no significance to correlation between the degrees of plaques and exposure periods to asbestos. A man with degree 1 or less had been exposed to asbestos for more than 20 years. Conversely, degree 3 plaques can be seen in a case of less than 10 year standing. The maximum area of plaques was 916 cm^2 in the present reported cases. Degrees of pleural plaques were not related to standings; it could be conceivable that individual differences, especially, the differences in the sensitivity to asbestos stimulation on pleura play a role in the occurrence of the plaque.

We analyzed previously 15 lung tissues with plaques by the bleach digestion technique and carried out asbestos body counts, SEM-EDXA for core fibre elemental component of the fibre. The results of asbestos body counts are given in Table I. These results showed that the extent of the degree of plaque was not also related to asbestos body counts in the lung tissues.

Typical pleural plaques are made up of bundles of collagen fibres. They are arranged in basket-weave, or concentric circle, avascular and having few cellular elements. Sometimes, a mesothelial cell lining can be seen on the plaque surface (Figure 1). Fibrocytic nuclei were found in collagenous fibre bundle. The structure of thinner plaques was different from this. They consist of the mesothelial lining on surface and beneath loose connective tissue, fibroblasts and monocytes; these changes can be also found on some portions of typical plaques. We refer to the changes as an earlier stage of plaques. On the other hand, a massive chronic inflammation cellular infiltration of lymphocytes and plasma cells and vascularity were often found in deeper portions or periphery of plaque (Figures 2,3). There are many polarizing particles

Table I
Results of Asbestos Body Counts in 15 Cases with Various Degrees of Pleural Plaques

Grades of plaque	Case number	No. of Bodies per gram of dried tissie	G	SD_{lg}	SE_{lg}	T test Compare with grade0–I	T test Compare with grade I
I	5	3.3×10^3–95×10^3	21.253	0.568	0.254	T=1.602 P>0.05	
II	7	0–218×10^3	1.626	2.270	0.858	T=0.411 P>0.05	T=0.961 P>0.05
III	3	6.7×10^3–114×10^3	3.228	0.674	0.389		

in intercollagenous fibres, the deepest and beneath mesothelial lining in polarized light microscopy. Most of them are needle-like, free, a few in dust-cells. A few fibres can be found in deposits digested plaques and on sections of plaques *in situ* in SEM. Their elemental compositions are mainly Si, Mg and a few Fe, similar to that of chrysotile, while other fibre compositions are mainly Si and Ca. To classify these fibres is difficult only according to EDXA. On the basis of above-mentioned results, we regard initial formation portion of plaque was beneath the mesothelial lin-

Figure 1. Mesothelial lining on the surface, lower earlier plaque changes. H.E. x 200.

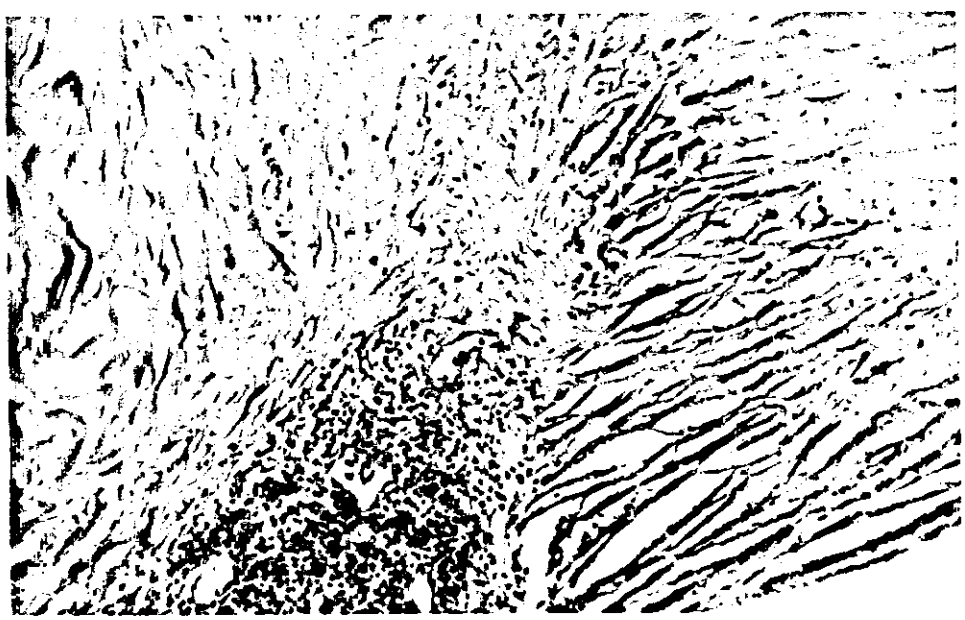

Figure 2. A massive infiltration of chronic inflammation cells on periphery of the plaque. H.E. x 100.

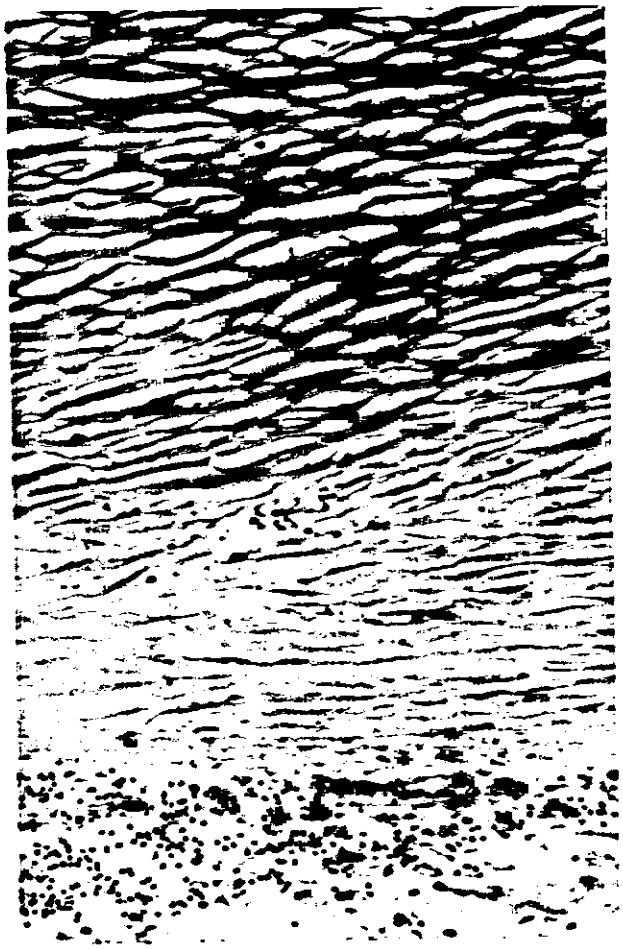

Figure 3. The plaque was clearly divided into 3 zones from base to top: lymph-like cells and vascularity, fresher connective tissue, and hyalinized collagen fibres. The picture showed that development of the plaque was from base of it. H.E. x 100.

ing. Earlier stage changes were dust-fibrous reaction then typical plaque pictures occurred owing to increasing and hyalinization of collagenous fibres. An important point to note is similarity in histopathological pictures of pleural plaques and chronic pleurisy (suppulative or tuberculous). It is not easy to distinguish among them even in light microscopy. But, there is a mesothelial cell lining on surface of plaque; only for this reason, pleural plaques surface was smooth. On the contrary, initial changes of chronic pleurisy occurred in pleural cavity, mesothelial cells desqamate firstly, then adhesion of parietal and visceral pleura

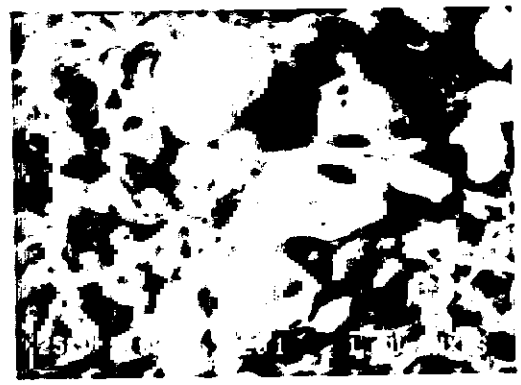

Figure 4. Asbestos fibre and its energy dispersive X-ray spectra, elemental composition. The fibre seems to be chrysotile.

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SI  K  0.440  1.022  0.460  1.002
P   K  0.014  0.988  0.304  1.002
S   K  0.014  1.014  0.405  1.002
K   K  0.021  0.974  0.704  1.009
CA  K  0.037  0.997  0.767  1.009
TI  K  0.020  0.913  0.861  1.019
FE  K  0.264  0.914  0.966  1.000
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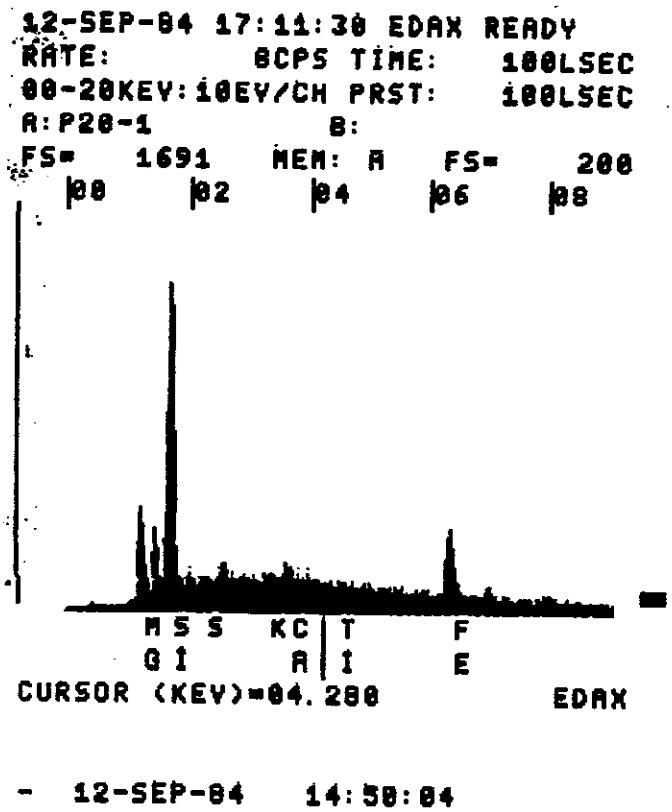
ELEM	CPS	WT % ELEM
MG K	39.790	25.315
SI K	147.999	44.455
P K	4.800	2.964
S K	4.730	2.187
K K	6.470	1.953
CA K	10.420	2.989
TI K	4.680	1.572
FE K	43.020	18.565



developed, and resulted in the cavity disappearing. It is true, for Thomson noted the mesothelial cells play no part in plaque formation,[1] but, because the mesothelial cell lining had still remained it is possible to explain the peculiarity of plaques; i.e., no adhesion, smooth. In addition, infiltration of chronic inflammation cells in basic or peripheral portions of plaques might play a role in development of plaques, because there are general changes seen in chronic inflammation fibrosis. Yet fibrocytic nuclei were most in base of the plaque, and the fewer, the more surface. Therefore, portion of plaque formation is beneath mesothelial cell lining, origin of growth is the base of plaques. Of course, reformation of plaque can also occur beneath mesothelial lining of typical plaque. We have found that infiltration of chronic inflammation cell was sandwiched between collagenous fibres, and earlier changes were beneath mesothelial lining of typical plaque.

The exact route by which the inhaled fibres reach the parietal pleura is yet unknown. Three possible routes have been drawn by Bignon.[2] 1) Asbestos fibres penetrated directly into pleural cavity, 2) by lymph vessels, 3) by blood system. Our cases have mainly been exposed to chrysotile, but the fibres extracted from lung tissues belong to amphibole according to EDXA results. These fibres were long and straight. The penetration of amphibole is stronger than chrysotile because the latter is curved. It is suggested the first hypothesis seems impossible. It seems possible that inhaled chrysotile fibres broke into thinner and shorter fibres in lung tissue, then they were transported to pleura by lymph vessels, and induced formation of pleural plaque. In view of these reasons, we may understand the presence of chrysotile fibres in pleural plaques (le Bouffan).[3] That is the reason, why chrysotile was hardly found, and amphibole easier seen in our deposits of digested lung tissues.

SUMMARY

In order to assess the severity of pleural plaques the degree of the plaques has been reported. It is adaptable for asbestos workers that pleural plaques were graded into 3 degrees by the area interval of 100 cm^2 and 300 cm^2. Because the degree of plaques have no relation with asbestos standing, individual differences might play a role in occurrence of plaque. It has been observed that initial portion was beneath mesothelial cell, and origin of growth was the base of plaques. Some aspects, such as absence adhesion, smooth surface, asbestos body counts in lung tissues were not concerned with degrees of plaques and can be explained by the findings. Studies seem to suggest that inhaled asbestos fibres can be transferred from lung tissue to parietal pleura, but exact routes have yet to be demonstrated.

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SIMILARITIES IN THE FIBROGENICITY OF ASBESTOS FIBRES AND OTHER MINERAL PARTICLES RETAINED IN HUMAN LUNGS

VERNON TIMBRELL,* MRC • P. Paakko† • T. Ashcroft‡ • L.O. Meurman§ • K.B. Shilkin°

*MRC Epidemiology Unit Cardiff, Wales
†University of Oulu, Oulu, Finland
‡Freeman Hospital, Newcastle Upon Tyne, England
§University of Turku, Turku, Finland
°The Queen Elizabeth II Medical Centre, Nedlands, Nedlands, Australia

INTRODUCTION

Many new types of fibrous materials are being developed for application in advanced technology and industry. A mathematical model constructed for predicting the fibrosis-inducing potential of airborne particles of such materials has two parts. Data on fibre inhalation required by the first part, which computes from the size distribution of the particles the fraction that would achieve long-term pulmonary retention, were obtained from a uniquely suitable environment in the asbestos mining industry.[1] The asbestos mining industry has also been the source of an index of fibrogenicity for use in the second part of the model which estimates the severity of fibrosis produced by the retained particles.[2]

Asbestosis, the interstitial pulmonary fibrosis induced by inhaled asbestos dust, has long been recognized as a dose-related disease. Epidemiologists and industrial hygienists have mainly used fibre counting methods for estimating exposures. Fibre counting has also been the method used in inhalation studies. In inoculation and 'in vitro' experiments with materials such as the UICC standard reference samples, doses have been measured by gravimetric means. Many authors have suggested that fibrosis is a particle surface effect but no study appears to have been based on the measurement of exposure in terms of particle surface area. Since results of animal experiments are often at variance with epidemiological findings, mainly because the methods for dose evaluation differ, any data that are obtained require epidemiological verification. Three recent studies have therefore been based on human pulmonary material.

FIRST STUDY

Identification of the fibrosis-related fibre parameter proved particularly elusive until use was made of a South African report[3] that in the period 1959 to 1964 prevalence of 'slight asbestosis' and 'total asbestosis' in asbestos miners had been the same in North Western Cape Province, which produces a small-diameter crocidolite, and in the Transvaal which mines crocidolite and a closely related amosite, both of large diameter. The first part of the mathematical model was applied to data on the size and concentration of airborne fibres in South African asbestos mines[4] in order to determine which concentration parameter of retained fibres (number, surface area or volume) would show equal asbestos dose in the two regions with equality in asbestosis response. The relevant parameter turned out to be the total surface area of retained fibres per unit weight of tissue and fibrogenicity was independent of amphibole type. Analogous evidence on the Finnish anthophyllite mine at Paakkila supported these findings.

SECOND STUDY

For this study to determine relationships between retained amphibole fibres and fibrosis, tissue specimens were obtained from post-mortem lungs of workers who had been employed at one of four mining locations: Paakkila, NW Cape, Transvaal and the Australian crocidolite mine at Wittenoom. A sample, about 1.5 ml in volume, taken from each lung specimen was sliced into three portions. The middle portion was used to prepare a paraffin section, stained either by haematoxylin and eosin or by a trichrome method. Figure 1 shows the continuous numerical scale of fibrosis[5] one of us (TA) employed in a blind assessment of the severity of interstital fibrosis by scanning the paraffin section in a microscope fitted with a x10 objective. Each successive field was allotted a score between 0 and 8. The mean score for about 50 fields examined was taken as the fibrosis for the sample.

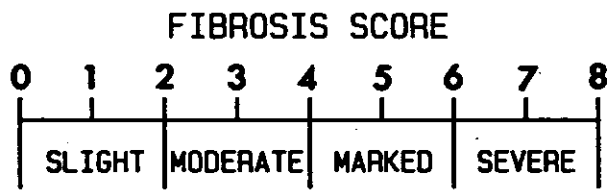

Figure 1. Fibrosis Scale.

The other two portions of the sample were treated together with potassium hydroxide for the extraction of mineral dust. Evaluation of the dust by a method combining magnetic alignment of fibres with subsequent examination by light scattering[6] gave fibre concentration in terms of fibre volume

per microgramme of dry tissue; data on fibre diameters and lengths were used to calculate the concentration in terms of fibre number and fibre surface area.

When surface area was used as the parameter of fibre quantity, the fibre concentrations in specimens showing a given degree of fibrosis were approximately equal:

Wittenoom = NW Cape = Transvaal = Paakkila.

This relationship confirmed the findings of the first study that the severity of fibrosis was related to aggregated fibre surface area and was independent of amphibole type.

When volume was used as the parameter, the fibre concentration in specimens showing a given degree of fibrosis increased progressively:

Wittenoom NW Cape Transvaal Paakkila.

Table I shows the large differences in fibre size in the four mining areas that account for this relationship. For instance, the average ratio of surface area to volume (which is inversely proportional to fibre diameter) for Wittenoom fibres is about 20 times that for Paakkila fibres; consequently, a given degree of fibrosis was induced by a smaller volume of Wittenoom fibres than Paakkila fibres. When number was used as the parameter, the fibre concentrations in specimens showing a given degree of fibrosis decreased progressively:

Wittenoom NW Cape Transvaal Paakkila.

Differences in fibre size also account for this relationship. The surface area of the average Paakkila fibre is about 25 times that of the average Wittenoom fibre; consequently, a given degree of fibrosis was induced by far fewer Paakkila fibres than Wittenoom fibres.

THIRD STUDY

The second study gave an intimation that chrysotile and quartz had fibrogenicity similar to that of amphiboles. The third study was designed to pursue this interesting lead and attempt to quantify the fibrogenicity of asbestos and other minerals. As tissue specimens with preponderance of a specified mineral are difficult to find, the study examined the feasibility of a method that would treat specimens as sources of relationships somewhat akin to simultaneous equations and make multiple-mineral specimens an advantage. Far more specimens were required than the number of equations needed in the algebraic analogy, to compensate for the expected wide intra- and inter-subject variations in severity of fibrosis such as had been observed in the second study. Specimens ranging widely in particle concentration and mineral type were obtained from asbestos mines and factories, gold mines, a platinum mine, shipyards and other workplaces. The compositional data presented in Figure 2 show that often the predominant mineral type in a specimen was not the nominal work material.

Dust was extracted from specimens by removal of tissue by either the potassium hydroxide method or low temperature ashing. Scanning transmission electron microscopy was used for identification and size analysis of individual mineral particles. Fibres were modelled as cylinders, the width of the image seen in the electronmicrograph being taken as the fibre diameter. Talc, kaolinite, chlorite, mica, clay and other flaky particles were modelled as elliptical discs lying flat, 0.2 times the length of the minor axis of a disc being recorded as its thickness. Quartz particles were modelled as spheres, the observed projected area diameter of a particle being taken

Table I
Fibre Size Characteristics

	PAAKKILA anthophyllite	TRANSVAAL amosite crocidolite	NW CAPE crocidolite	WITTENOOM crocidolite
MEDIAN DIAMETER (μm)	0.6	0.2	0.06	0.04
RELATIVE VOLUME	500	50	4	1
RELATIVE SURFACE AREA	25	10	2	1
RELATIVE SURFACE AREA / VOLUME	1	4	10	20

as the diameter of the sphere. Because no measurement could be made on the vertical projected area of particles, which for assessing the surface area of quartz particles is as important as the horizontal projected area, the size data for quartz are less accurate than for most other minerals.

The results obtained from the third study provided further confirmation of the findings regarding amphibole fibres, and discussion will therefore be directed to ascertaining what they say about the fibrogenicity of mineral particles in general.

Figure 3a shows the results of plotting the fibrosis score for each tissue sample against the corresponding concentration for all particles expressed in terms of surface area. In this Figure, and more so in Figures 4 and 5, some of the data points lie on or are close to an axis, and in order to avoid

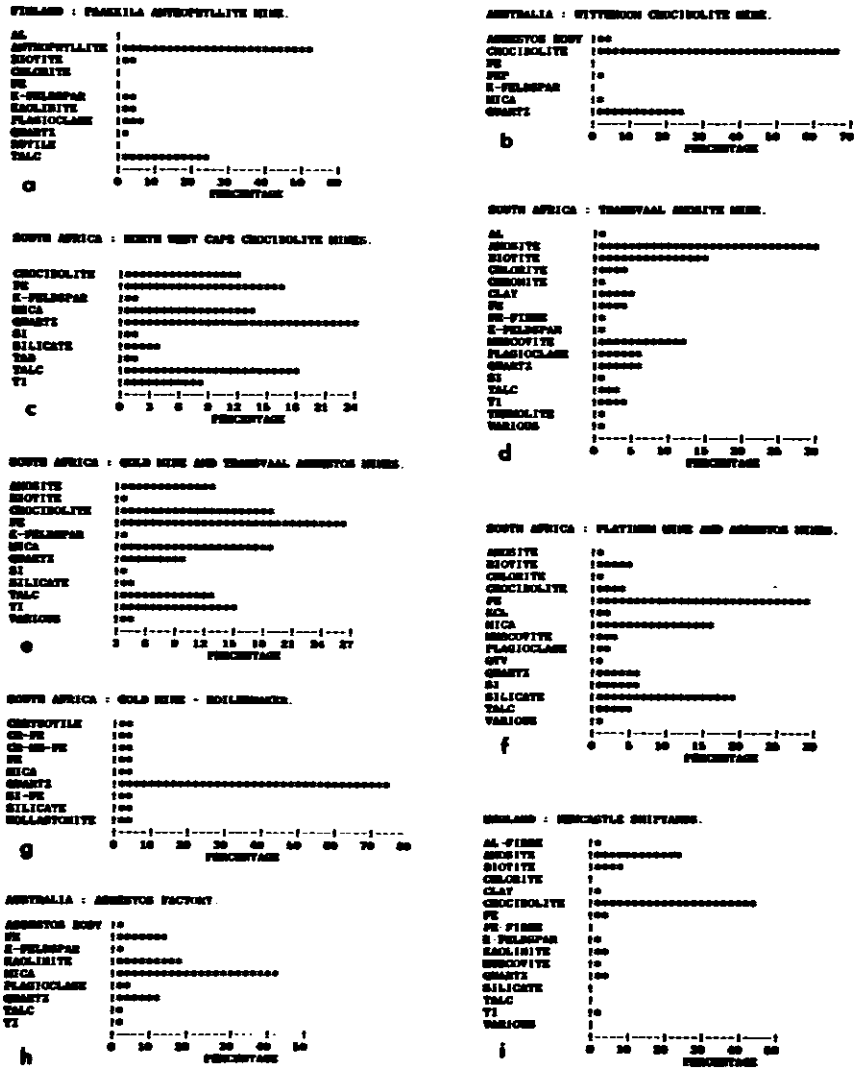

Figure 1. Country of origin of lung tissue specimen; industry; percentage frequency of retained mineral particles.

their obscuration by the scales each scale has been displaced transversely. The regression line is also omitted as it too would otherwise obscure some interesting data points, but may be visualized using the open circles K and E that mark the ends. The point K gives the value of the constant in the regression equation that represents the degree of fibrosis at zero particle concentration. The value of the constant is shown above the graph, together with the correlation and the coefficient (the slope of the regression line) that represents the fibrogenicity for 'all particles.'

Figures 3b-e show the results of plotting the fibrosis score against concentration of various particle fractions ('asbestos + quartz', 'asbestos', 'quartz', 'all-asbestos-quartz'), again with the concentration expressed in terms of aggregated particle surface area. Figures 4 and 5 show data of the type given in Figure 3, and refer to concentrations now expressed in terms of aggregated particle volume and particle number respectively. The statistical data given in the Figures 3-5, are collated in Tables II–IV. Comparison in rows is invalid in Table IV since the fibrogenicity units differ.

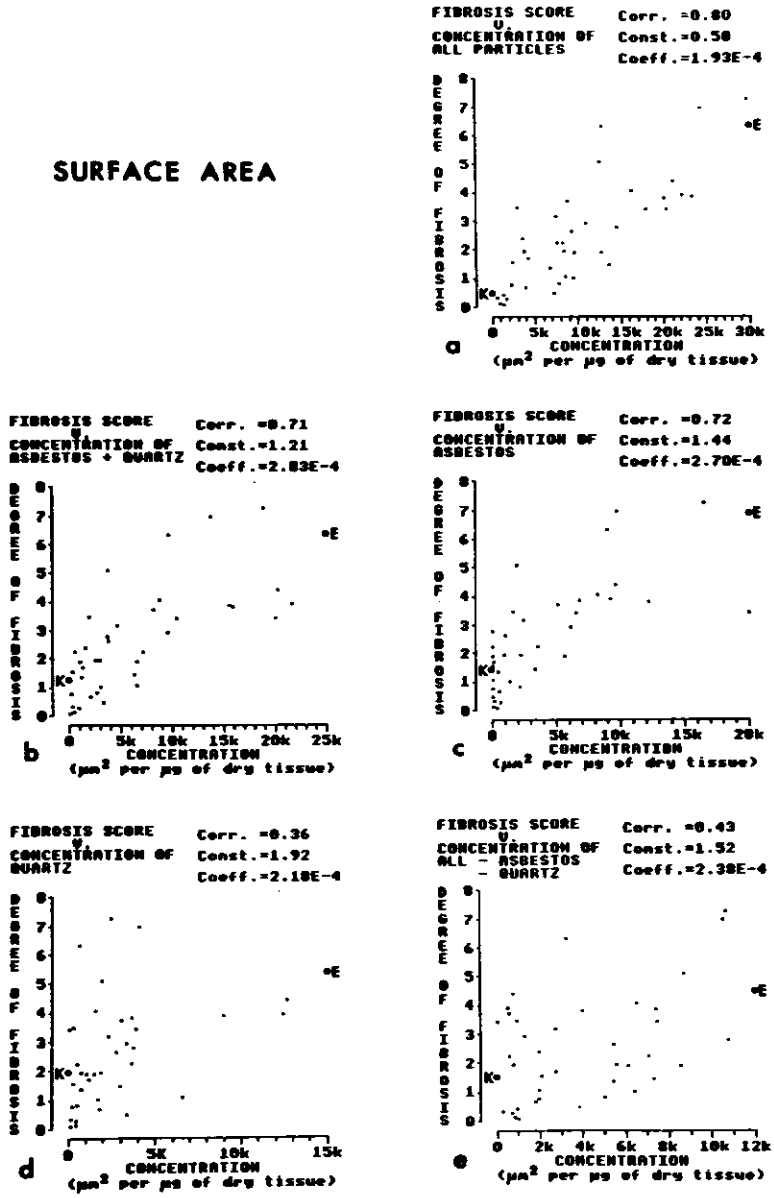

Figure 3. Relationship between severity of fibrosis and particle surface area (μm^2) per unit weight (μg) of dry tissue for various fractions of the retained dust.

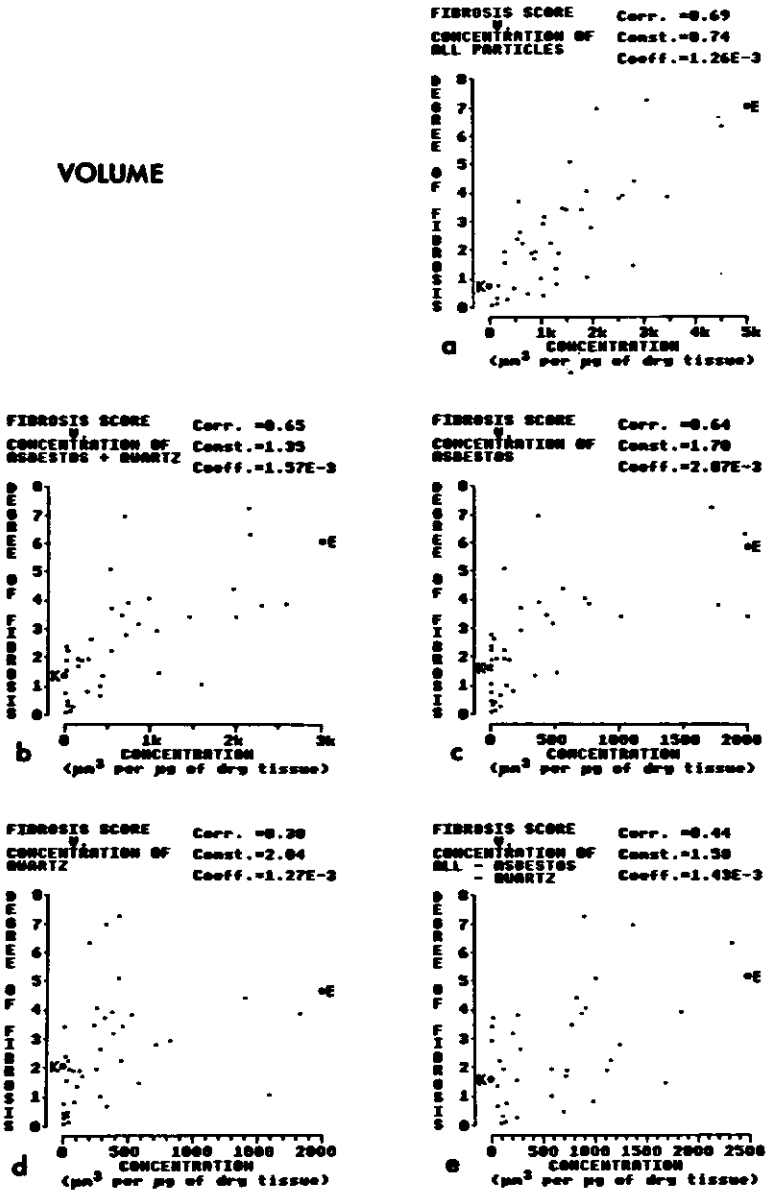

Figure 4. Relationship between severity of fibrosis and particle volume (μm^3) per unit weight (μg) of dry tissue for various fractions of the retained dust.

The substantial scatter of the data points in Figure 3a reflects the wide inter- and intra- subject variations in the degree of fibrosis which are associated with a given particle concentration and stem from differences in the cellular composition of samples taken from different parts of the lung. These are random variations however, and the correlation of 0.80 is the highest seen in Figures 3–5. The data points near the origin suggest that the value of 0.5 for the constant overestimates the fibrosis that is associated with zero particle exposure. The fibrogenicity is 1.93E-4 units (significance level 0.0001); or rounding the reciprocal, 5000 million μm of particle surface area per gramme of dry tissue induce one degree of fibrosis.

The greater scatter of the data points in Figure 3b for 'asbestos + quartz' than that in Figure 3a for 'all particles', the decrease of correlation from 0.80 to 0.71, and the increase in the constant from 0.50 to 1.21, all testify to the presence in the tissue specimens of fibrogenic particles that are not asbestos or quartz. The fibrogenicity of 2.38E-4 units shown in Figure 3e for these other particles which constitute the'all-asbestos-quartz' fraction is, in the present biological context, equal to that for 'all particles'. This fraction, as may be seen in Figure 2, contains a wide assortment of minerals including talc, kaolinite and iron particles. The suggestion that these data indicate similar fibrogenicity of most of the

Table II
Correlation of Fibrosis Score with Particle Concentration

	SURFACE AREA	VOLUME	NUMBER
ALL PARTICLES	0.80	0.69	0.50
ASBESTOS + QUARTZ	0.71	0.65	0.49
ASBESTOS	0.72	0.64	0.49
QUARTZ	0.36	0.30	0.37
ALL - ASBESTOS - QUARTZ	0.43	0.44	0.33

Table III
Constant in Regression Equation

	SURFACE AREA	VOLUME	NUMBER
ALL PARTICLES	0.50	0.74	1.55
ASBESTOS + QUARTZ	1.21	1.35	1.82
ASBESTOS	1.44	1.70	1.90
QUARTZ	1.92	2.04	1.83
ALL - ASBESTOS - QUARTZ	1.52	1.58	1.78

of the minerals is more acceptable than that some are not fibrogenic while others are more fibrogenic than asbestos and quartz.

The relatively low correlation of 0.36 shown in Figure 2d for the 'quartz' fraction may be attributed to the inaccuracy, mentioned earlier, in the measurement of the surface area of quartz particles compared with other particles. However, the value of 2.18E-4 units for the fibrogenicity is comparable to those for the other fractions and for 'all particles'.

Examination of Table II shows that evaluating 'all particles' and expressing their concentration in terms of aggregated surface area provides the best correlation between particle concentration and fibrosis. This indicates that an index of fibrogenicity needs to be closely related to surface area, which is dependent on both particle size and shape and may be a major factor in the disease mechanism. The lower correlation values which occur when concentration is expressed in terms of volume instead of surface area are not unexpected; while volume is a function of particle size it is not a function of shape and cannot therefore be a complete substitute for surface area in the quantification of concentration, or in turn, of fibrogenicity. Table IV shows that, for similar reasons, if the index of fibrogenicity is based on particle volume instead of surface area then this changes the ranking of the fractions in order of increasing fibrogenicity. Tables II and IV also show that when concentration is expressed in terms of particle number, the correlation values fall even lower, the fractions differ more in fibrogenicity and the ranking order alters yet again. These marked changes stem from the fact that particle number is not a function of either particle size or shape and consequently, even more than volume, cannot be a complete substitute for surface area. Quartz illustrates the marked influence particle shape and size have on the value obtained for a mineral's fibrogenicity when assessment of concentration is based on particle number. Figure 5d for quartz shows the most complicated of all the relationships represented in Figures 3–5. Notable is the marked difference in Table IV between the fibrogenicity of 6.09E-4 units for quartz and the more equal values for the other fractions. The sources of this difference are the

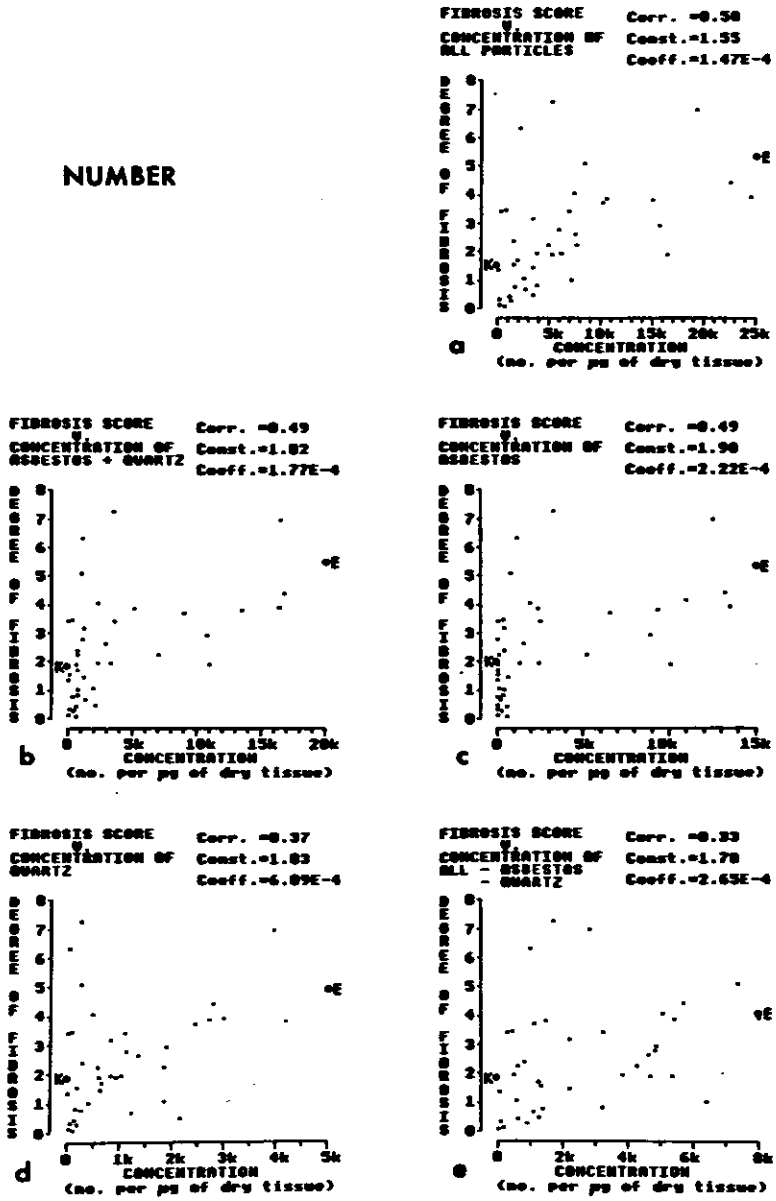

Figure 5. Relationship between severity of fibrosis and particle number per unit weight (µg) of dry tissue for various fractions of the retained dust.

dissimilarities between quartz and the majority of the other minerals in particle shape and size, factors that particle number cannot represent.

Thus the third study showed that evaluating the aggregated surface area of a retained dust provided the best index of its fibrogenicity. Evaluation of aggregated particle volume provided a reasonable index. The index based on particle number was unrealistic, especially when evaluation did not include all particles.

IMPLICATIONS

Many tissue specimens used in the third study showed mineral contents markedly different from those implied by the type of industry from which they came. Figure 2h shows the recorded contents, which include an asbestos body but no asbestos particle, of a specimen from the lungs of a man who had worked in an asbestos factory. The specimen gave a fibrosis score of 6.96, the penultimate score obtained in the second and third studies. Results of the third study indicate that, at a concentration of 5000 particles per micro-

Table IV
Fibrogenicity by Particle Surface Area, Volume or Number

	SURFACE AREA (degree of fibrosis /μm^2 /µg dry tissue)	VOLUME (degree of fibrosis /μm^3 /µg dry tissue)	NUMBER (degree of fibrosis /no. /µg dry tissue)
ALL PARTICLES	1.93E-4	1.26E-3	1.47E-4
ASBESTOS + QUARTZ	2.03E-4	1.57E-3	1.77E-4
ASBESTOS	2.70E-4	2.07E-3	2.22E-4
QUARTZ	2.18E-4	1.27E-3	6.09E-4
ALL - ASBESTOS - QUARTZ	2.38E-4	1.43E-3	2.65E-4

gramme of dry tissue, the contents, which are typical of asbestos-associated minerals, could have made a substantial contribution to the fibrosis observed. This specimen, together with others which show similar features, suggests that even in the asbestos industry evaluation of air samples should include all mineral types and, preferably, should assess the aggregated surface area of the particles which would achieve long-term pulmonary retention.

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PATHOLOGY OF MALIGNANT MESOTHELIOMA AMONG ASBESTOS INSULATION WORKERS

YASUNOSUKE SUZUKI, M.D. • I.J. Selikoff, M.D.
Mount Sinai School of Medicine
New York, NY, USA

ABSTRACT

An epidemiological investigation of a cohort of 17,800 asbestos workers has revealed a high incidence of malignant mesothelioma among these workers during the period covered by this study (1975–1986). 278 consecutive cases of definite (234) and probable (44) mesothelioma in the cohort group were pathologically characterized. Data was derived from; 113 (40.7%) autopsies, 153 (55.0%) biopsies, and in 12 (4.3%) cases, there was a combination of autopsy and biopsy. The site of the tumor was 160 (57.5%) peritoneal, 97 (34.9%) pleural, 18 (6.5%) pleural and peritoneal, 1 (0.4%) pleural and pericardial and 2 (0.7%) pleural, peritoneal and pericardial. Cell type was 178 (64.0%) epithelial, 25 (9.0%) fibrous and 75 (27.0%) biphasic. The presence or absence of both diffuse interstitial fibrosis and asbestos bodies in the lung sections were ascertained in 137 of the 278 cases. Fibrosis was seen in all but 6 (95.6%). All but 6 cases were positive for the presence of asbestos bodies (95.6%). There were no deaths at age 39 or younger; between 40 and 49, 28 (10.1%); between 50 and 59, 99 (35.6%); between 60 and 69, 89 (32.0%); between 70 and 79, 50 (18.0%) and $\geq$ 80 years, 12 (4.3%). It was possible to calculate years from first exposure to death in 273 of the 278: none among 9 years or shorter; 1 between 10 and 19 (0.4%); 50 (18.3%) cases between 20 and 29; 129 (47.3%) between 30 and 39; 58 (21.2%) between 40 and 49, and 35 (12.8%) were 50 years and longer.

INTRODUCTION

Since January 1, 1967, we have been conducting an extensive prospective mortality study of a cohort of 17,800 asbestos insulation workers in the U.S.A. and Canada. The study continues; however, significant initial important data have been obtained, and have been published.[1] Data 1967-1976 revealed that in 2,221 consecutive deaths, approximately 20% of the insulation workers died from lung cancer, approximately 7% died from malignant mesothelioma: other cancers such as esophagus, colon, rectum, larynx, kidney and stomach were also higher in incidence among these workers in comparison with the general population.[1] Further experience (1967-1984) has shown that malignant mesothelioma in approximately 10% of the insulators (356/3,500) have died from malignant mesothelioma and the incidence of the tumor has increased with extension of years after first exposure to asbestos.[2]

Since 1975, one of us (YS) has evaluated all pathological materials of the study. 278 cases of the malignant mesothelioma were reviewed. It was found that these could be categorized as definite (234) and probable (44) (1975-1986). Here, our objective is to clarify the pathological characteristics of these 278 cases of malignant mesothelioma, and to study relationships of the tumor to other factors, such as the severity of pulmonary fibrosis (revealed by histopathological study), age at death, years after first asbestos exposure to death, and to cigarette smoking.

MATERIALS AND METHODS

278 consecutive cases of malignant mesothelioma in which pathological diagnosis was established (YS) between 1975 and 1986, were used as materials.

Pathology slides (histopathology) from various hospitals, additional slides systematically stained at our laboratory, autopsy and surgical pathology reports, and operative reports were thoroughly reviewed: type of specimens, primary site, cell type and the presence of pulmonary asbestosis were investigated.

Levels of diagnostic certainty of malignant mesothelioma has been classified into 5 categories, definite, probable, possible, unlikely and definitely not.[3] Classification of diagnostic certainty was decided by comprehensive pathological analysis of the tumor[4] consisting of gross appearance (from atuopsy or surgical pathology reports or the operative report), histology, histochemistry, immunocytochemistry and electron microscopy. Gross appearance and histology were used as the essential components in the comprehensive analysis in all cases, and both histochemistry (PAS with and without diastase, colloidal iron with and without hyaluronidase) and immunoperoxidase for CEA and cytokeratin were used in the large majority of the cases. Electron microscopy of the tumor was also available for the diagnosis in a small number cases.

Pulmonary asbestos was evaluated by histopathology of non-

neoplastic lung parenchymal sections. The presence of diffuse interstitial fibrosis has been accepted as the histopathological criterion of pulmonary asbestosis, particularly if associated with ferruginous bodies, when adequate material is available for study of the latter. The severity of asbestosis was classified as none/minimal, mild, moderate and severe, as reported previously.[5]

Age at death, years after first exposure to death, and smoking history were investigated in each of the cases.

RESULTS

Based on the foregoing diagnostic criteria, the 278 cases were classified as 234 definite mesothelioma (84.2%) and 44 probable (15.8%). Although 30 additional cases were "possible" mesothelioma, these 30 cases were excluded for the present study. Derivation of the pathology specimens consisted of 153 (55.0%) surgical, 113 (40.7%) autopsy and 12 (4.3%) both autopsy and surgical. The primary site of the tumor was 160 (57.5%) peritoneal, 97 (34.9%) pleural and 21 (7.6%) other (Table I). The primary site of the 21 "other" cases could not be ascertained since the tumor was spread along two or three body cavities (pleura and peritoneal or pleura and pericardium or pleura, peritoneal and percardium) at autopsy. The ratio of the incidence between the pleural and peritoneal mesotheliomas was 4 to 6. Cell types were classified as 178 epithelial (64%), 75 biphasic (27%) and 25 (9%) fibrous (Table II). The ratio of the 3 cell types was quite similar between the pleural and peritoneal mesotheliomas. Age at death was; none in 39 years and younger, 28 between 40 and 49 years old (10.1%), 99 between 50 and 59 (35.6%) and 151 in 60 years old and older group (54.3%). Years from first exposure to death was; none in 9 years or shorter, 1 between 10 and 19 years (0.4%), 50 between 20 and 29 years (18.3%), 129 between 30 and 39 (47.3%), 58 between 40 and 49 (21.2%) and 35 in 50 years and longer (12.8%). Such long latency is similar to lung cancer among insulators.[5]

Histological evaluation of pulmonary asbestosis was done in 137 of the 278 cases (in which pulmonary parenchyma slides or paraffin blocks were submitted). Diffuse interstitial fibrosis and ferruginous bodies were seen in 131 of the 137. The degree of diffuse interstitial fibrosis was 6 (4.4%) none, 31 (22.6%) mild, 39 (28.5%) moderate and 61 (44.5%) severe. Ferruginous bodies were 6 none (4.4%), 41 small in number (29.9%), 36 moderate (26.3%) and 54 large (39.4%). It is to be noted that, in general, it may be difficult or impossible to detect ferruginous bodies in standard 5 μ sections. Indeed, we were rather surprised to see them as frequently as we did. Pulmonary asbestosis (diffuse inter-

Table I

Malignant Mesothelioma Insulation Workers—Primary Site

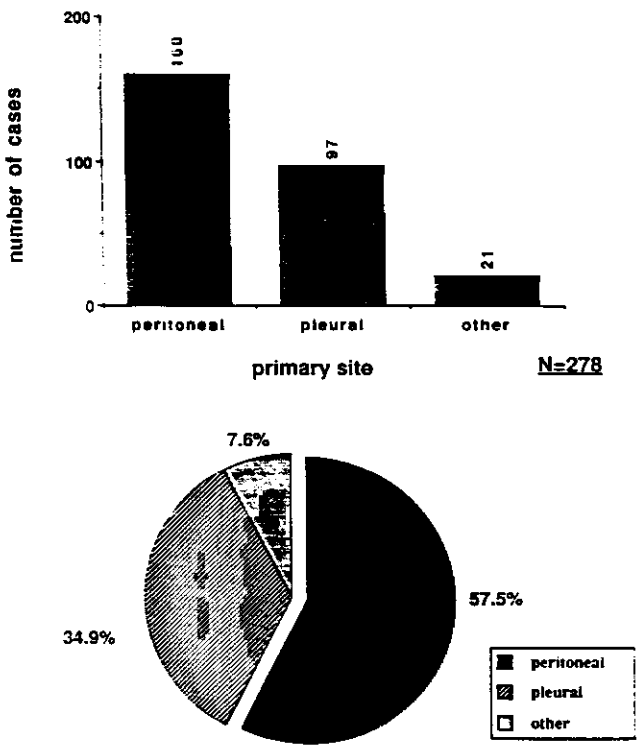
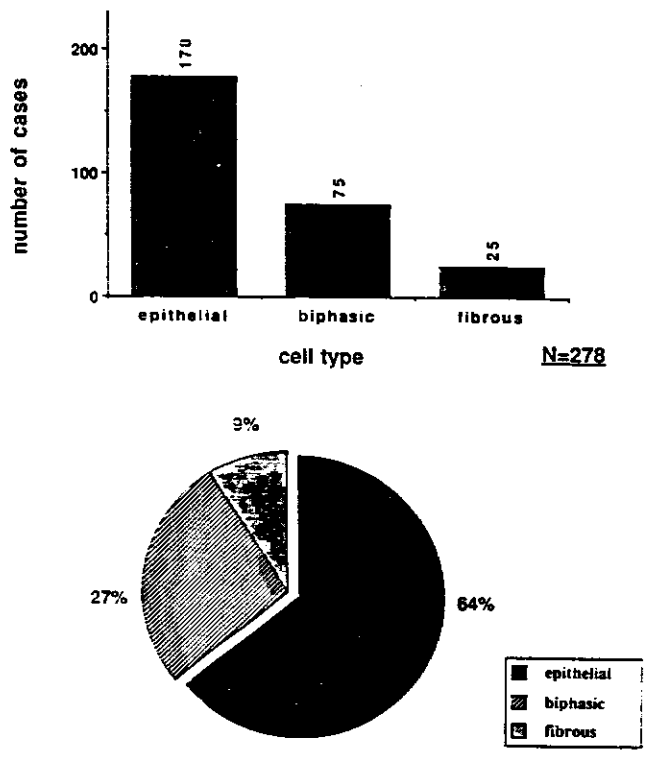


Table II

Malignant Mesothelioma Insulation Workers—Cell Type



stitial fribrosis with ferruginous bodies) was present in 95.6% of the 137 mesothelioma cases. The severity of asbestosis (represented by the degree of diffuse interstitial fibrosis) was compared between the pleural and peritoneal mesotheliomas; proportionally, severe interstitial fibrosis was higher in incidence in pleural mesothelioma (48.2% to 36.5%). The degree of asbestosis was compared between the 137 malignant mesothelioma and the insulators' lung cancer (415 consecutive cases; unpublished data). The severity of asbestosis was proportionally milder in the mesothelioma cases (44.5% vs. 56.0% in severe, 28.5% vs. 36.3% in moderate, 22.6% vs. 6.5% in mild, and 4.4% vs. 1.2% in none/minimal. (Table III).

Smoking history was available in 185 of the 278 mesothelioma cases. There were 144 present and ex-cigarette smokers (77.8%), 17 pipe and/or cigar smokers and tobacco chewers (9.2%) and 24 who had never smoked (13%). This smoking history data were compared with that of the insulators' lung cancer cases (532 in which smoking history was known): present or ex-cigarette smokers were smaller in proportion (77.8% vs. 91.6%) in the mesothelioma group, and the non-smokers were larger in proportion in the mesothelioma group (13% vs. 1.3%). (Table IV).

COMMENTS

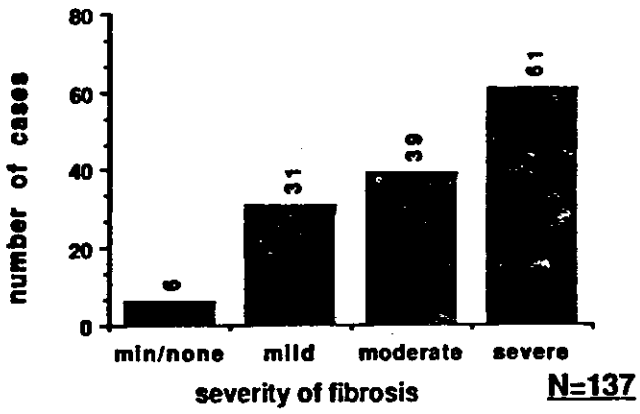
To the present, no specific single method has been available to establish a definitive diagnosis of malignant mesothelioma. Consequently, comprehensive pathological analysis of the tumor is still the best approach to establish such a definite diagnosis.[4]

It has been reported that the incidence of peritoneal mesothelioma was higher than that of pleural mesothelioma among insulation workers.[1,2] The present study has confirmed these initial reports. Presently, no clear explanation has been available as to why the incidence of the malignant peritoneal mesothelioma is so high among insulators.

The comparative proportion of cell types (epithelial, biphasic and fibrous) of the insulators' mesothelioma is similar to that of mesothelioma in general. Pulmonary asabestosis was almost always present (95.6%) in the insulators mesothelioma cases. It is known however, that pulmonary asbestosis is occasionally absent in the lung sections of malignant mesothelioma patients who had been mildly exposed to asbestos by environmental asbestos exposure or family contact to asbestos. It was interesting, when the severity of pulmonary asbestosis between malignant mesothelioma and

Table III

Malignant Mesothelioma Insulation Workers
—Interstitial Fibrosis



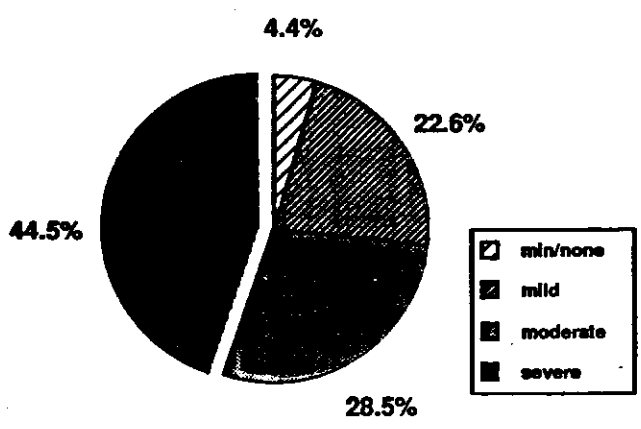
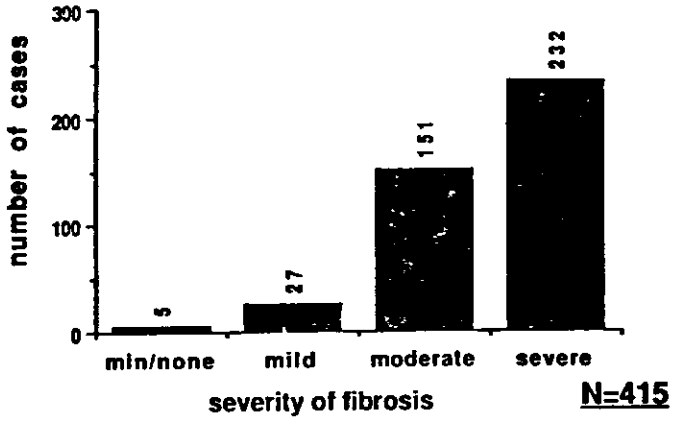


Table III

Lung Cancer-Insulation Workers
Interstitial Fibrosis



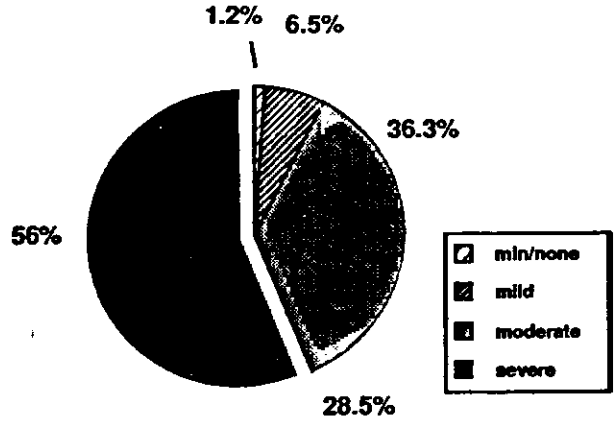
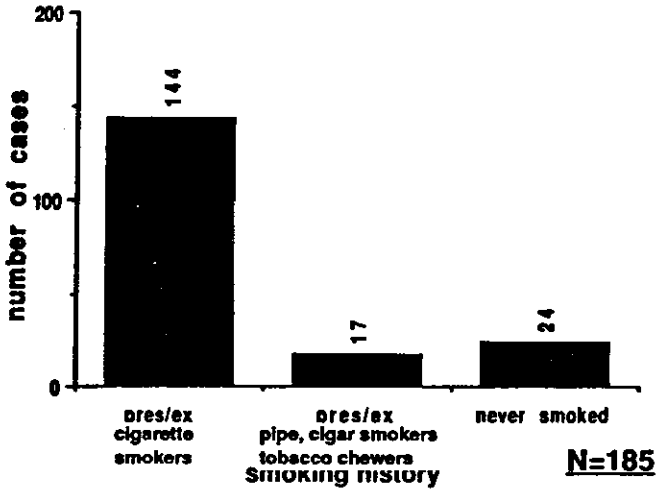


Table IV
Malignant Mesothelioma-Insulation Workers
Smoking History



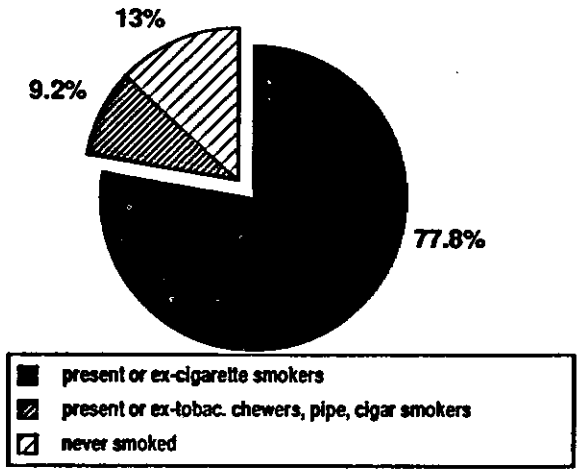
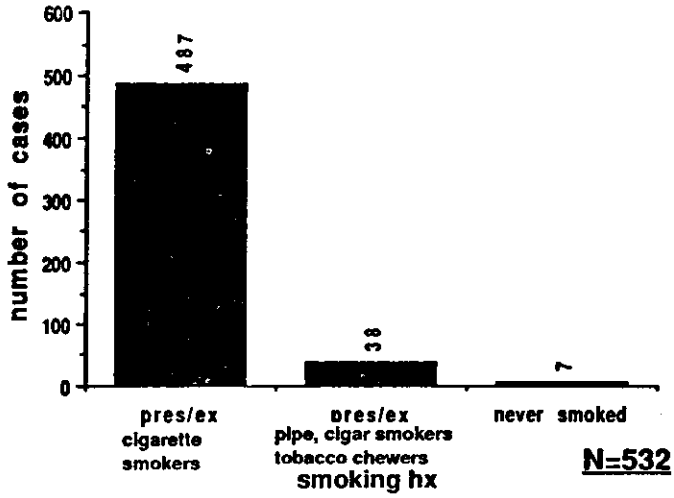
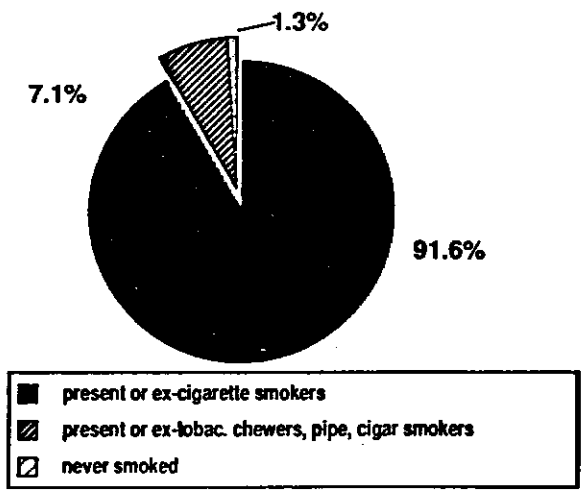


Table IV
Lung Cancer-Insulation Workers
Smoking History





lung cancer among asbestos insulation workers was compared, the former was comparatively milder in the severity.

It has been suggested that malignant mesothelioma may be induced with smaller doses of asbestos, in comparison to asbestos related lung cancer.

Age at death and years from first exposure to death were similar to that seen in other studies, including our preliminary ones of the same cohort.[1,2]

It has been reported that, unlike lung cancer, cigarette smoking does not exert a causal influence in malignant mesothelioma.[6,7] The present study has revealed that the current and ex-cigarette smokers were smaller in proportion in the mesothelioma cases, compared with those in the lung cancer cases among the asbestos insulation workers and that non-smokers were proportionally much higher in the mesothelioma cases (13% vs. 1.3%).

SUMMARY

The pathology and epidemiological features of 278 cases of malignant mesothelioma (234 definite and 44 probable) among asbestos insulators were investigated. These cases were those personally studied since 1975.

1. The primary site was 160 (57.5%) peritoneal, 97 (34.9%) pleural and 21 other (7.6%; 18 pleural and peritoneal, 2 pleural, peritoneal and pericardial, and 1 pleural and pericardial).

2. Cell types were 178 (64.0%) epithelial, 75 (27.0%) biphasic and 25 (9.0%) fibrous. These proportions were quite similar in pleural and peritoneal mesothelioma.

3. Histopathologically, pulmonary asbestosis was found in 95.6% (131/137) of the mesothelioma cases; 44.5% were severe, 28.5% moderate, 22.6% mild, and 4.4% were minimal or none.

4. 89.9% (250/278) were 50 and older at death. None were 39 or younger. Years after 1st exposure to death were 20 years and longer in 99.6% (272/273). None were found in less than 9 years. A single case was seen between 10 and 19 years.

5. There were present and ex-cigarette smokers in 144/185 (77.8%), 9.2% cigar, pipe and chewing tobacco, and 13% (24/185) were non-smokers. Non-smokers were proportionally much higher in comparison with the insulators' lung cancer cases.

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PLEURAL PLAQUES IN A U.S. NAVY ASBESTOS SURVEILLANCE POPULATION: PREDOMINANT LEFT-SIDED LOCATION OF UNILATERAL PLAQUES

A. M. DUCATMAN • B. F. Withers • W. N. Yang

Environmental Medical Service, M.I.T. Room 20B–238
77 Massachusetts Avenue, Cambridge MA 02139, USA

ABSTRACT

The radiographic distribution of pleural plaque was studied in a U.S. Navy Asbestos Medical Surveillance population of 105,064 workers. Chest radiographs were interpreted to show "possible" (1.8%), probable (2.5%), or "definite" (1.8%) plaque. Plaques were more likely to be bilateral as interpreter certainty increased, but 19% of "certain" pleural plaques were still unilateral. Of these unilateral plaques there was a marked left-sided predominance, which increased with increasing certainty of interpretation. Further research is needed to determine whether this consistent left sided predominance of unilateral plaque represents: lateralizing interpreter bias, greater visability of plaques when they are on the left, or some physiologically greater susceptibility of the left side.

No paper provided.