SCIENTIFIC PAPERS

BIOLOGICAL EFFECTS OF SHORT FIBERS

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Evidence implicating fibre diameter in the development of mesotheliomas and pulmonary fibrosis is now generally accepted but the contribution that the length of mineral fibres makes is not so well established. As the difference in length of fibres found in the urban situation, and that in the occupational and para-occupational environments is revealed, so the importance of length may increase. Our investigations, reported here, confirm the concept that fibre length is a significant factor in the development of these asbestos related diseases.

Timbrell[1] illustrated that the maximum diameter of a fibre that could be inhaled into the parenchyma of the lung was 3.0 μm. This has subsequently been confirmed in both man and experimental animal, although fibres above 2.0 μm diameter are uncommon. The length/diameter characteristics were clearly defined by the experimental studies of Stanton,[2] Pott,[3] and Wagner[4] et al. These investigations confirmed that fibres of 0.25 μm in diameter and about 8 μm in length were associated with mesotheliomas, whereas the coarser fibres of between 1.0–3.0 μm in diameter and of 8 μm in length were probably responsible for pulmonary fibrosis.

Our investigations on tremolite exposure in both men and experimental animals[5] have contributed to clarification of the different fibre diameter associated with these different lesions. However, our statement that the shorter fibres physical forms are relatively innocuous was challenged with the request to define "relative." It was hoped that our experiments with Oregon erionite would satisfy the critics.[6] In these studies we showed that the relatively long erionite fibre produced a 100% incidence of mesotheliomas following exposures, both by intrapleural and inhalation exposures compared with no tumours being produced when a non-fibrous synthetic erionite was used. This established that the mineral fibres and not the chemical constituents were responsible for the lesions. The critics pointed out that the control material was non-fibrous and that we had not proved that short fibres within the experimental material were relatively innocuous. Therefore, to answer their queries we would have to produce dust samples of long and short fibre in sufficient quantities for both implantation and inhalation studies. In our investigations in order to produce both tumours and fibrosis by inhalation, the exposure must last twelve months and needs 2 kilograms of dust. Hitherto production of asbestos fibre of specific length has not been successful and milling crocidolite has usually resulted in the short fibre being reduced to non-fibrous particles. Alternatively, in an attempt to produce crocidolite <5.0 in length, for an intrapleural study, it was found that there were no long fibres seen in the pre-inoculation dust, but there were long fibres retained in the granulomas[7] (thus illustrating our theory about the selective retention of fibre).

We decided to use Oregon erionite[6] because of its friable nature and Mr. J.W. Skidmore was successful in producing sufficient quantities by precise milling over a very short time. A similar preparation was made with UICC crocidolite. Final assessments of the success of milling could only be made on fibre measurements at the end of the experiment, on the lungs from the inhalation study, and pleural granuloma from the implantation investigation. The other two samples used were the longer erionite as prepared for the original experiment, and standard UICC crocidolite for long crocidolite. It was accepted that these were mixed length samples, with sufficient long fibre to produce lesions. The dust for the short fibre was prepared by disc milling. By making empirical decisions, only fibres <5 microns in length were found using the following strategy of 10 sessions each of 10 seconds duration, the mill being opened after each session and the dust redistributed. The inhalation[8] and intrapleural[9] methods have previously been described, as have the characterisation of the dust clouds and the respirable inoculated materials. The animals used were SPF Fischer F344 rats (caesarian derived, barrier maintained, and free from disease as shown by random culling). Eighty rats of each sex for the inhalation study and 64 of each sex for intrapleural inoculation, were randomly allocated, in equal numbers, to the 4 treatment groups. Post mortem and histological examination were carried out.[10] The fibrosis grading[11] is standardised on an internationally accepted scale: Grade 1 normal; 2 dust in macrophages; 3 early interstitial reaction; 4 first signs of fibrosis; 5, 6, 7 increasing degrees of fibrosis; 8 severe fibrosis. The only other lesions noted were 1 Bronchiolar hyperplasia; 2 mesothelioma. Finally, characterisation of the fibres was carried out; recovery methods were used on a known weight of lung tissue from the inhalation; and tissue from the granuloma from the intrapleural experiment.

RESULT

Dust Studies

Measurements were carried out on the four dusts recovered after 24 months, i.e. exposure period of 12 months and a further survival time of 12 months. Our findings substantiated the previous experimental results on the retention of the longer fibres after inhalation. It also demonstrated our success in the production of fibres in the size ranges required. Figure 1 and

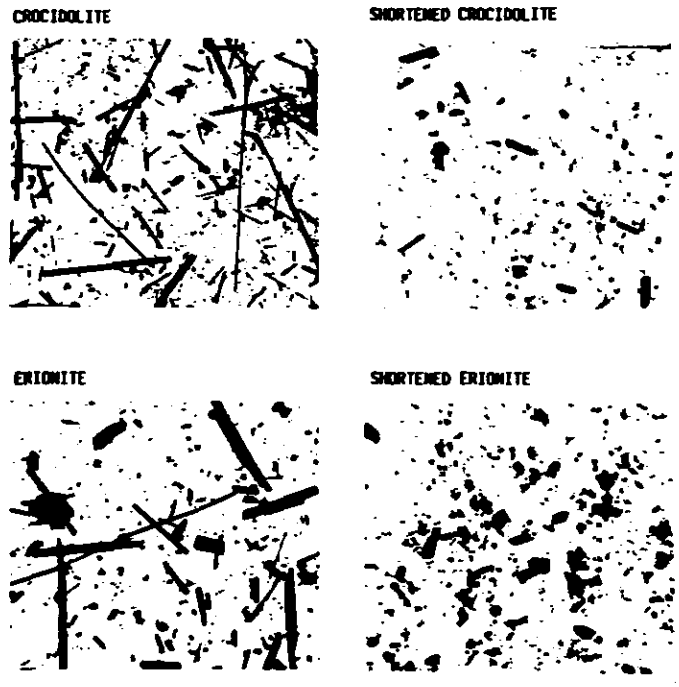

Figure 1. Fibre recovered from rat lung after 24 months.

Tables I and II show the fibre recovered from the lungs of animals after a period of 24 months. It can be seen from the electron micrographs taken of the shortened material the complete absence of any fibres with lengths greater than 5 microns.

DISCUSSION

We were endeavouring to answer two questions:—

1. Is it possible to show by animal experimentation that below a minimum length, fibre of standard diameter does not produce mesotheliomata of significant pulmonary fibrosis, whereas longer fibre of similar type are capable of their production?
2. What is the critical length of fibre?

Minimum Length (1)

We have succeeded in answering the first point, but have not been able to define the critical length of fibre as required in (2).

In the intrapleural inoculation study we were able to produce over 90% of tumours in the animals exposed to either of the long fibre dusts. Using the short fibre a single mesothelioma was produced with the crocidolite sample, no tumours occurred in the animals exposed to the erionite.

The inhalation experiment produced the expected tumour incidence of over 90% of the animals, exposed to the erionite, which had survived for a sufficient time period to develop mesotheliomas. It must be remembered that there had been a serial killing of animals at an earlier stage for the inhalation study which substantially reduced the number surviving for more than one year. The long crocidolite only produced a single tumour. This confirmed the importance of using the Oregon erionite material, as the crocidolite produced too few tumours for comparison with the short fibre results. No tumours occurred in the animals exposed to either of the short fibres.

The inhalation studies demonstrate that in the animals exposed to the long fibres minimal fibrosis occurs, whereas the short fibres only produce a tissue reaction.

Critical Length (2)

Production of fibre below 5 microns and to include a sufficient number of fibres in the 3–5 micron range proved to be extremely difficult. This is because a decrease in the milling time led to the appearance of fibres greater than 5 microns in length. The result of this difficulty was that the majority of the fibre used in the short samples was below 3 microns whilst still retaining the fibrous nature of the material. This was also apparent in the material recovered from the lungs of the animals. Very occasional longer fibre was found in the short crocidolite. This could account for the single mesothelioma seen in an animal exposed to this dust. These results proved that the milling was successful. In a previous experiment with milled dusts a large number of mesotheliomas were induced.[7] This was thought to be due to a long fibre component

Pathology

Intrapleural Inoculation

Dust	Mesothelioma	Non-mesothelioma
UICC Crocidolite	24	8
Shortened Crocidolite	1	31
Erionite	30	2
Shortened Erionite	0	32

Inhalation

	Fibrosis Gradings 4 rats/sacrifice				Tumours		Total Excl. Sacrif.
	3 mths.	6 mths.	12 mths.	24 mths.	Meso.	BAH	
UICC Crocidolite	2.9	3.0	4.1	3.9	1	2	24
Shortened Crocidolite	2.0	2.0	3.3	2.8	0	0	24
Erionite	2.4	3.0	4.0	4.0*	24	2*	27
Shortened Erionite	2.9	3.0	3.0	3.1	0	1	24

* 1 animal only remained for sacrifice

* 2 bronchiolar alveolar hyperplasia with mesotheliomas

remaining in the dust.

As in previous investigations, the animals treated with the long fibre dusts tended to selectively retain the longer fibres. In the inhalation study, it was of importance to see how little long erionite was retained in the lungs of the animals, as others with this exposure developed the tumours.

Attempts should be made to produce a more satisfactory short erionite sample closer to 5.0 microns in length. All investigations have failed to produce a satisfactory sample from amphibole asbestos. It is possible that by using more complex methods a small sample sufficient for the implantation study could be produced. When this was done using glass-micro fibre the cost of production was extremely high, and no attempt was made to produce a larger sample of inhalation experiments.

Table I

Inhalation Experiment

Percentage and Number of Fibres in Defined Categories per Gram of Dried Lung Tissue ($\times 10^6$)

	Fibre Size (μm) L.	Fibre Size (μm) D.	3 months	6 months	12 months	24 months
SHORT CROCIDOLITE	3 - 5	< 0.5	0.3 %	1.2 %	0.6 %	1.0 %
			7.0 *	42.6 *	47.9 *	63.0 *
	> 1	< 0.5	10.3 %	29.1 %	15.3 %	15.1 %
			231.3 *	1033.1 *	1221.6 *	948.6 *
LONG CROCIDOLITE	> 6	< 0.5	1.6 %	2.8 %	3.2 %	5.8 %
			425.5 *	991.7 *	1427.1 *	2529.3 *
	3 - 6	< 0.5	3.0 %	4.8 %	5.2 %	8.4 %
			797.9 *	1712.9 *	2319.0 *	3663.1 *

* No. of fibres

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Table II

Inhalation Experiment

Percentage and Number of Fibres in Defined Categories per Gram of Dried Lung Tissue ($\times 10^6$)

	Fibre Size (μm) L.	D.	3 months	6 months	12 months	24 months
SHORT ERIONITE	3 - 5	< 0.5	1.0 %	1.7 %	0.3 %	0.6 %
			2.4 *	8.5 *	9.1 *	6.3 *
	> 1	< 0.5	32.0 %	37.2 %	37.9 %	39.7 %
			77.1 *	186.0 *	1154.4 *	449.3 *
LONG ERIONITE	> 6	< 0.5	7.0 %	5.8 %	5.0 %	7.0 %
			130.0 *	350.9 *	419.1 *	350.8 *
	3 - 6	< 0.5	15.5 %	16.3 %	17.0 %	15.3 %
			287.9 *	991.6 *	1424.8 *	764.3 *

* No. of fibres

EXPERIMENTAL STUDY OF FIBROSIS EFFECT OF POLYPROPYLENE AND POLYETHYLENE DUST ON RAT LUNGS

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Polypropylene and polyethylene are all high molecular compounds and typical synthetic organic substances. To research the fibrosis effect of the dust of these two organic substances, experiments have been respectively carried out on animal—the rat. 500 mg of dust was respectively injected intratracheally into each of 134 rats (half male and half female), and observations were carried out for 18 months. The results of the experiment showed that the main change of pathological histology in the early period was the granulomatosis foci caused by the dust (the polyethylene dust group showed foreign body multinuclear giant cell granuloma) and the hyperplasia of recticular fibres. 18 months after dust injection both experimental groups were found to show pronounced hyperplasia of reticular fibres inside the foci and around the bronchi and presence of collagen fibres. The content of collagen protein in the whole lungs is higher than the physiological saline control group. Therefore, the authors consider that the dust of polypropylene and polyethylene has a light fibrosis effect on the rat lungs.

INTRODUCTION

Polypropylene and polyethylene are petroleum chemical products which are high molecular compounds obtained by polymerization of propylene and ethylene. They are solid powder in milky colour without poison and odor, insoluble in water at normal temperature, acid and corrosion resistant and good in insulation. Along with their wide use and rapid increase of output, more and more workers have the chance to be in contact with the two kinds of dust in production. The report has not yet been witnessed as to whether the dust of polypropylene and that of polyethylene can cause fibrosis. In order to study the fibrosis effect of polypropylene and polyethylene dust, experiments have been made on the animal and the results are as follows.

METHOD OF EXPERIMENT

1. Preparation of dust: The fresh dust is obtained from the workshop producing polypropylene and polyethylene from a chemical fibre company. In the dust no quartz was detected by an X-ray diffractometer, and the dust was classified by a Barkhausen-Kurtz type centrifugal classifier so that 80% of the dust was of the grain size under 5 microns. The dust was then sterilized by ultraviolet rays for 2 hours. Quartz dust for control was provided by the Labour Hygiene and Occupational Disease Research Institute under the Chinese Academy of Preventive medicine.
2. Animal selection and grouping: 134 wister rats were selected and divided at random into 4 groups (polyethylene group, polypropylene group, quartz control group and physiological saline control group).
3. Dust injection into the animal: 50 mg of physiological saline suspension solution, with a small amount of tween added, was injected at a time intratracheally. Then observations were carried out in turn respectively 1, 6, 12 and 18 months after dust injection. The animal was killed with the head cut off after slight anesthesia. The right lung was kept for collagen quantitative analysis. The left lung and hilus lymphonodi, after fixation, paraffin embedding, sectioning and staining with HE, Foot and VG, was subject to observation for histopathology.

RESULTS OF EXPERIMENT

Visible by the Naked Eye

1. Quartz group: 1 month after dust injection the hilus lymphonodi were as big as a soya bean or a broad bean. The surface of the lungs were found smooth. On partial lungs of most cases were found to have milk-white sections of different area, of which the surface was full of bumps and holes and felt hard as to have sand grains. 6, 12 and 18 months after dust injection, the above changes gradually became greater.
2. Physiological saline group: During the experiment, the hilus lymphonodi were all as big as a rice grain. The surface of the lung tissues were found smooth, soft and elastic.
3. Polypropylene and polyethylene groups: 1 and 6 months after the injection of dust, the hilus lymphonodi of both groups were of rice size. The lung tissues were soft and elastic. 12 and 18 months after dust injection, the lung tissues were still soft and elastic. Some cases showed local ecchymoma and emphysema.

Visible Under Microscope

1. Quartz group: 1 month after dust injection, the hilus lymphonodi and lung tissues were found to have 4th grade fibrous tubercula around which there were slight emphysema. 6, 12 and 18 months after dust injection, all cases showed fibrous tubercula.
2. Physiological saline group: Throughout the experiment

no dust reaction was found.

3. Polypropylene and polyethylene groups: 1 month after dust injection, the hilus lymphonodi of neither group showed coniosis cell foci. Inside the lung tissues there were cell foci of different shape and size which consists of macrophages, epithelioid cells, coniosis cells and a great amount of dust particles. The polyethylene group showed that there were divergent Langhams' or foreign body giant cells in the cell foci. In the foci slight hyperplasia of reticular fibres were found. On some of the air sacs the epithelioid cells got swollen. Some of the bronchi showed hyperplasia or disappearance of epithelioid cells. 6 months after dust injection, all hilus lymphonodi were found to have a small amount of coniosis cell foci and translucent dust particles, on the surface of which there was a brown coloured layer. Inside the lung tissues there were still visible cell foci of different sizes and in the foci there are still macrophages, coniosis cells and dust particles with a brown coloured layer on the surface of the particles. Hyperplasia of reticular fibres were visible in the foci. 12 months after dust injection both groups showed foci consisting of cells as those 6 months after dust injection. But the number of foci decreased whereas the foci became bigger with clear boundaries. The polyethylene group was still found to have foreign body multinuclear giant cells. Inside the foci and in between the foci there were hyperplasia of reticular fibres. In some of them fine collagen fibres were visible. In some of the foci, pronounced hyperplasia of reticular fibres were found in between the air sacs as well as around the bronchi and around blood vessels, and collagen fibres were also visible. Bronchi of various sections got seriously harmed.

The analytical results of the collagen protein content in the whole lungs are given in Table I and Figure 1.

DISCUSSION

Polypropylene and polyethylene are all synthetic organic substances without free silicon dioxide. Different views exist as to the research of fibrosis effect of synthetic organic dust. The present experiment on the dust injected animal, through observation 1 to 18 months intervals, showed that polyethylene and polypropylene dust may cause slight hyperplasia of fibre tissues of lungs. The hyperplasia of fibre tissues is more obvious in the lung mesenchyme and around the bronchi. The tissular structure of the lungs were obviously damaged but no typical experimental nodular change was found.

The two experimental groups, polyethylene and polypropylene, showed similar pathological features and course of affection. At the early period of dust injection (1~6 months), a considerable number of granuloma changes were irregular in shape and different in size. The granulomas were rich in cells and were generally found around terminal or respiratory bronchioles. Some of the granulomas leaned against the bronchi walls. The harmed bronchi showed epitheliosis. There were secretions in the cavities and inflammatory infiltration around them. 12 to 18 months after dust injection, granuloma foci decreased. Pronounced hyperplasia of reticular fibres inside the foci and around the bronchi. Some leaned against the bronchi walls with collagen fibres inside. Normal structure of air sacs around the foci disappeared.

There were, however, slight differences between the two groups. In the granuloma foci of the polyethylene group there were divergent Langhans' or foreign body multinuclear giant cells. But in the polypropylene group such cells could hardly be seen. The cause remains to be studied.

The analysis of collagen protein content in the whole lungs tallied with the features of pathological changes.

Table I
Analytical Results of Collage Protein Content
in Whole Lungs (mg)

Period of observation (month)	1		6		12		18	
	N	$\bar{X}$ + SD	N	$\bar{X}$ + SD	N	$\bar{X}$ + SD	N	$\bar{X}$ + SD
Polyethylene group	9	41.1±5.8	9	37.5±7.9	24	68.5±17.5	8	91.6±21.5
Polypropylene group	8	48.9±18.2	8	44.9±8.0	21	101.6±28.0	4	62.2±8.3
Quartz group	5	57.9±15.0	8	97.8±63.0	10	110.5±64.6	6	94.8±51.8
Physiological saline group	7	33.4±4.5	9	24.3±6.5	23	46.4±11.0	11	46.4±10.6

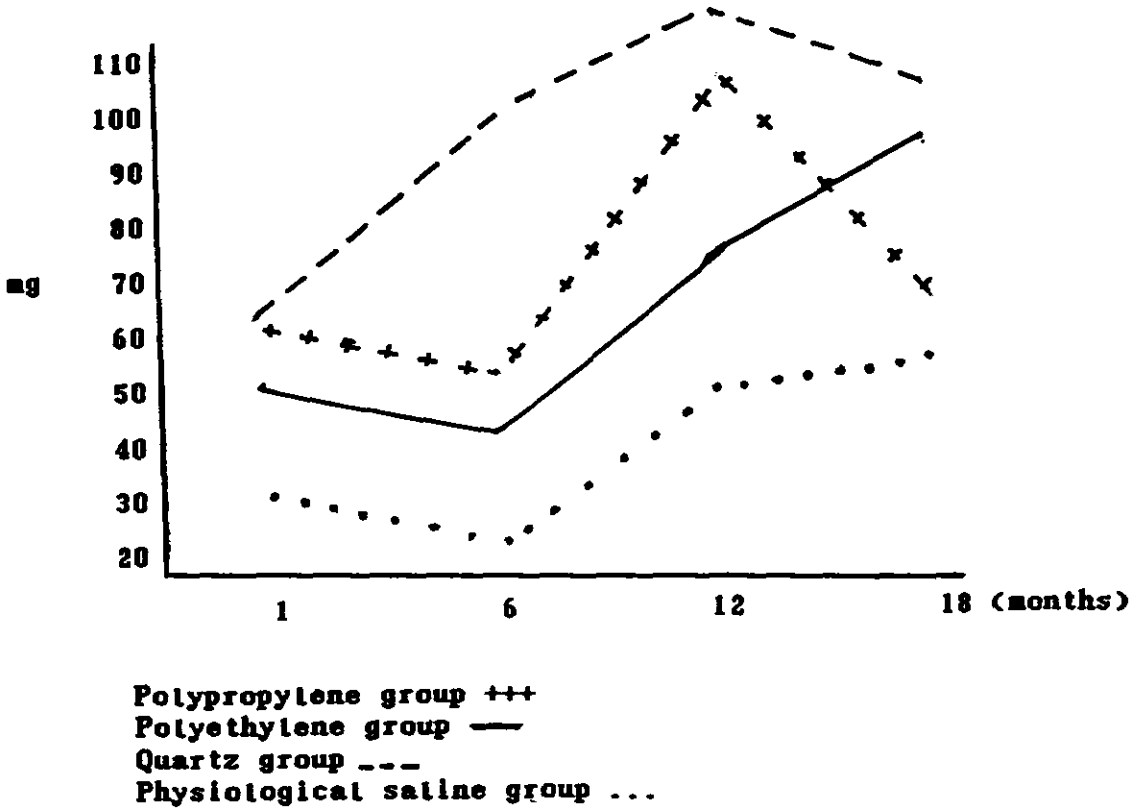

Figure 1. Variation curve of collagen protein content in the whole lungs.

SUMMARY

By unexposed injection intratracheally of 50 mg of dust at a time and through 1∼18 months histopathological observation and analysis for collagen protein content of whole lungs, we consider according to the experimental results that the dust of polyethylene and polypropylene dust has a slight fibrosis effect on rats. In the earlier period (1∼6 months) after dust injection the effect is mainly manifested in the form of granuloma changes, whereas in the later period (12∼18 months) after dust injection the lung tissues mainly show granuloma changes and hyperplasia of interstitial fibre tissues of the lungs.

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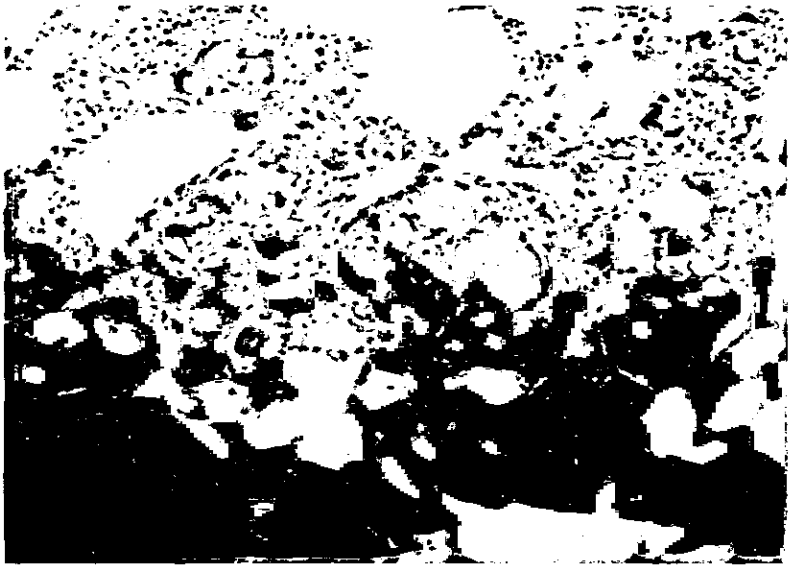
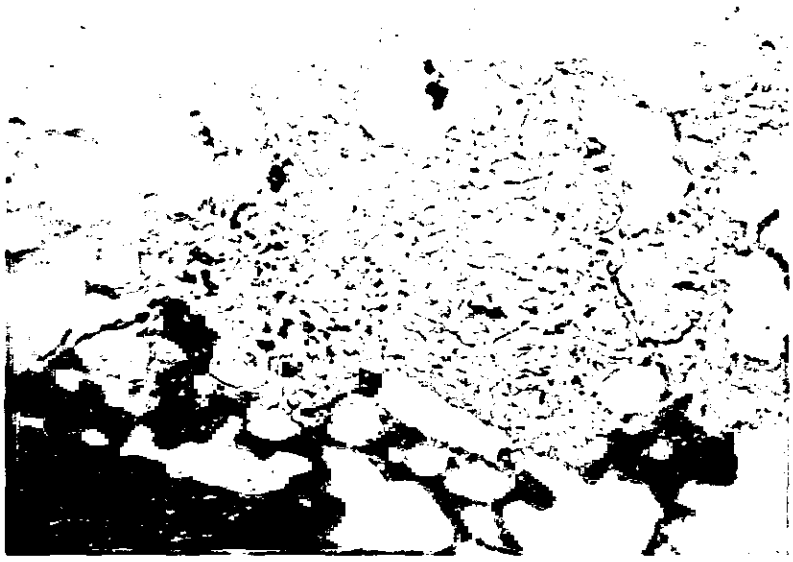
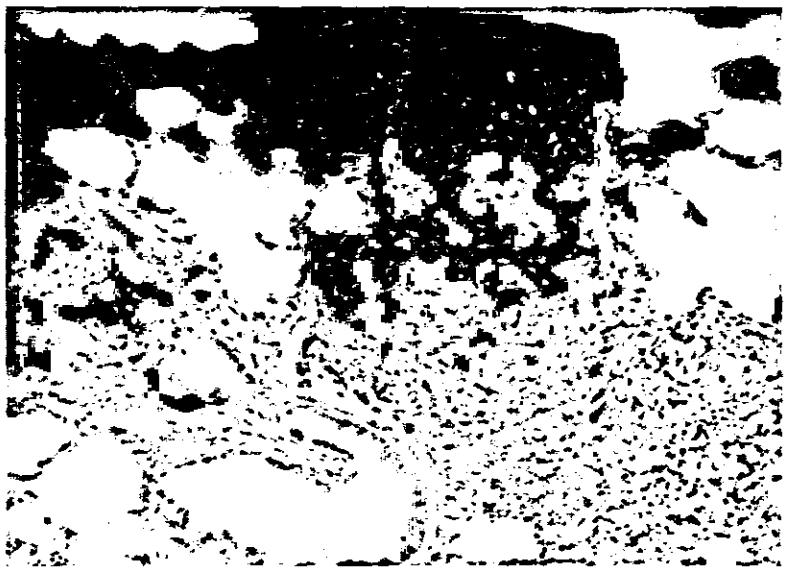


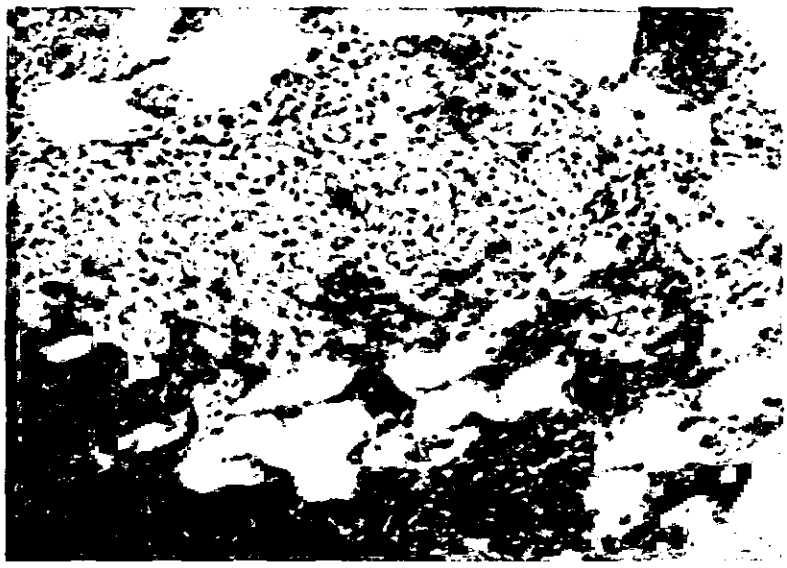
Polyethylene (One month) 34578 HE 6,7*10



Polyethylene (Six months) 35678 Foot 6,7*10



Polyethylene (One month) 34679 HE 6,7*10



Polyethylene (Twelve months) 3467 HE 6,7*10

APICAL PLEUROPULMONARY CHANGES IN PERSONS EXPOSED TO ASBESTOS—EXPERIENCE FROM 40 PATIENTS

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INTRODUCTION

Parenchymal changes due to asbestos exposure are classically situated in the lower lobes. Pleural plaques and diffuse pleural thickening are also found mainly in the lower or the mid zones of the lungs. However, there have also been reports on asbestos exposure leading to upper lobe changes.[1-3]

MATERIAL AND METHODS

Inclusion criteria and patients. Up to the end of 1986, about 1.600 patients with bilateral pleural and/or parenchymal changes due to exposure to asbestos on chest roentgenogram had been collected at the Department of Lung Medicine of Uppsala University. Among these 1.600 patients, there were 40 who showed an apical pleural thickening at least 5 mm thick on one side or both.

All patients have been followed until the end of 1987.

The mean age at the first sign of apical affection was 60 years; the youngest was 31 years old and the oldest 78 years. The mean latency time from the first exposure to the development of apical changes was 32 years, with a minimum of 5 years and a maximum of 51 years. Twenty-one patients showed apical changes only on the right side, four on the left side only and 15 on both sides. In all patients observed for more than five years there was an obvious progression of the apical lesions.

In five patients, CT was performed. In those patients it was seen that the lesions were mainly pleural but were causing compression of the lung parenchyma, and that some fibrous strands were reaching into the lung from the thickened pleura.

All patients had other asbestos-related pleural changes in the lungs on both sides, bilateral changes being a prerequisite for inclusion to the group in the first place. There was usually thickening around the whole lung, with a marked increase apically. In five patients a benign asbestos pleural effusion had been diagnosed before the apical lesions became evident.

In eight patients bronchoscopy was performed and culture for tuberculosis was negative. Five patients had a course of tuberculosis treatment because of a positive tuberculin test and suspicion of tuberculosis based on the radiological findings. This treatment did not affect the progression of the disease. A tuberculin test was performed in 25 patients and was negative in 12 of them, but in the rest it was positive, sometimes strongly so, the strongest reactor being 30 mm (2 tuberculin units).

Complete lung function test results were available in 21 patients. The vital capacity was affected in all cases. On an average it was reduced to 62 percent of the predicted. The total lung capacity was also decreased in all patients and in the mean 68 percent remained of the predicted value.

Upper lobe changes are a fairly rare manifestation of exposure to asbestos as judged from the paucity of reports in the literature.[1-3] There are a number of diseases which manifest themselves at the pulmonary apices. An unspecific fibrotic reaction is common in elderly persons but never reaches the sizes observed in the patients presented here. Many of these patients would previously have been diagnosed as suffering from tuberculosis. It is important to be aware of this manifestation of asbestos, mainly for clinical reasons, to avoid confusion with tuberculosis, but also for compensation purposes.

How specific is this type of lesion for exposure to asbestos? Our experience indicates that similar reactions are very rare in persons who are not exposed to asbestos. As mentioned, there are other diseases which can cause lesions of the upper lobe, but the typical primary thickening of the pleura with compression secondarily of the lung parenchyma is not seen with other diseases or is at least very rare. The lung department is the only one in the county and any lung changes of this type would very likely be referred to us for evaluation. They would also have been discovered at the general health survey, which was in practice in the county until fairly recently. Thus, the lesion seems to be as pathognomonic to asbestos as are pleural plaques.

Why does this lesion occur in some patients and not in others? It does not seem to be due to the degree of exposure. This seems to depend on individual factors, and my personal belief is that some disturbance of the immune system caused by asbestos is responsible for it.

Apical pleural thickening due to exposure to asbestos is usually only a part of a general reaction, and other parts of the same lung and usually also the other lung are also involved. The tendency to progression will, with time, in many patients cause a serious deterioration of lung function. The patients should be followed with chest roentgenogram and lung function regularly.

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RADIOGRAPHICAL APPEARANCE OF TALCOSIS AND COMPOSITION OF TALC

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The workers exposed to talc dust are increasing in number in textile, paper-making, glass-processing, ceramics, cosmetics, rubber and pharmaceutical industries, as well as paint, milling and carving of talc and so on. We investigated the concentration of the dust in the workshops in a mine and mill, and made a mineralogical examination. The chest X-ray films of the workers exposed to talc dust have been observed. The data are summerized and reported as follows.

INDUSTRIAL HYGIENE

This talc mine is a company of the mine and mill with an exploiting history of over 60 years. In the 50s and 60s, the dust concentration in the workplace of the mine ranged 68-582 mg/m^3 and the dust concentration in the mill ranged 208-5561 mg/m^3, and in talc carving factory, the dust concentration was several hundred mg/m^3.

The dust concentration in the workshop was reduced in the 70s, but it still ranged 50-395 mg/m^3. Over fifty percent of the particles were less than 5 μ in diameter; free silica dust ranged 0.75-2.87%.

MINERALOGICAL EXAMINATION OF THE TALC

The talc is pure, mineralogically, the ore is pure talc, the impurities are a little serpentine ($H_4Mg_3SiO_2O_9$) and phosphorite, little quartz, without tremolite $Ca_2Mg_5(Si_4O_{11})_2(OH)_2$ or other fibrous silicates (Figures 1-3).

In the talc mine, 80 cases of talcosis have been diagnosed under the medical supervision of Institute for Occupational Diseases since 1958 (male 70 cases, female 10 cases), exposure-onset duration ranging 5-22 years with an average duration of 13.6 years, grinder 57, excavator 19, worker for mineral separation 4. In talc-carving factory, 17 cases of talcosis were diagnosed, all of them are male, exposure-onset duration ranging 13-35 years with an average duration of 25.2 years. Of 97 cases of talcosis, 24 cases were complicated with tuberculosis (about 25%). In 73 cases of stage I talcosis, 12 cases (16.4%) complicated with tuberculosis, of 19 cases of the stage II talcosis, 9 cases (47.3%) were complicated ones. In 5 cases of stage III talcosis, complicated ones were 3 (60%). (Table I).

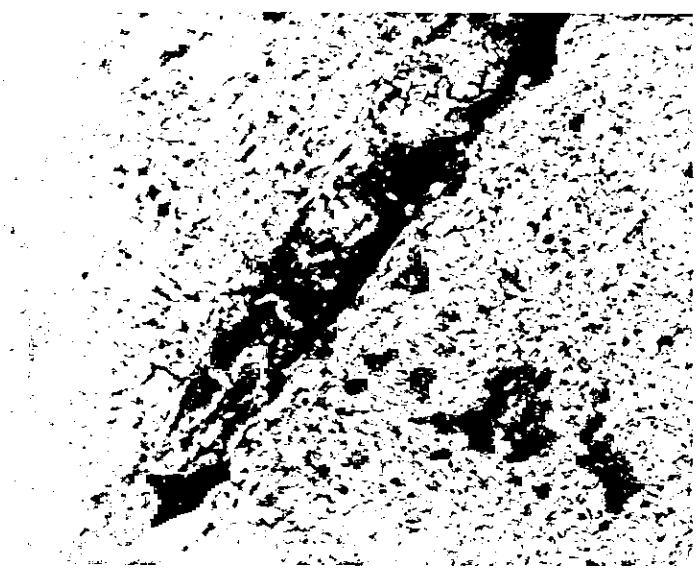

Figure 1. A fine streak of serpentine in talc in polarizing microscopy.

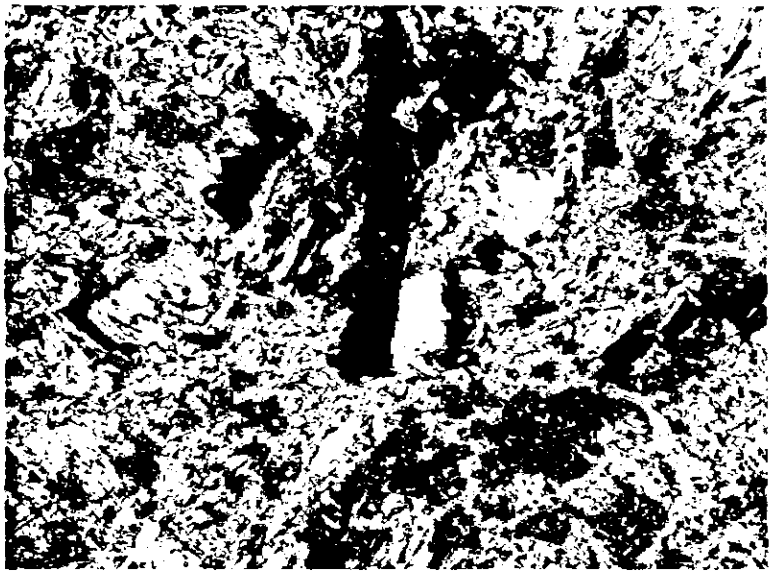

Figure 2. A bright silica particle in talc in polarizing microscopy.

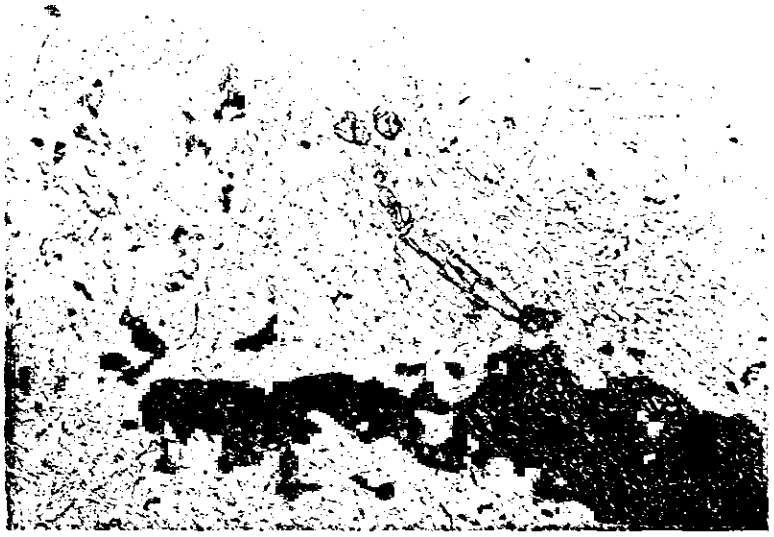

Figure 3. A few phosphorite particles in talc in polarizing microscopy.

X-RAY APPEARANCE

Unlike the radiographic appearance of silicosis, the enlarged hilar lymphnodes usually could not be found. The main characteristic findings of the talcosis were irregular small opacities; these abnormal findings must distribute beyond 2 zones for diagnosis. In some patients, the rounded small opacities were mainly observed. In most of them, the rounded opacities were 2-3 mm in diameter; occasionally, the rounded opacities were about 1 mm in diameter (Table II).

Nodular (Type) (15 cases): Of the 15 cases, 14 were grinders, exposure-onset duration was shorter than 10 years in 3 cases; 11-15 years in 11 cases; 16-20 years in 1 case. There were 3 cases of patients with 2nd stage talcosis, 2 cases with 3rd stage talcosis.

Reticulate-nodular Type: Of 56 cases, 40 were grinders, 16 excavators. The exposure-onset duration shorter than 10 years in 8 cases, 11-15 years in 22 cases, 16-20 years in 22 cases, more than 21 years in 4 cases. There was only one patient with 2nd stage talcosis.

Of 97 cases of talcosis, 5 cases with large shadow in the lung field, 3 of the cases were complicated with tuberculosis (Figures 4-8).

Pleural thickening, especially 'talc plaque' were not found in all of the patients. The relationship between the exposure-onset duration and the types of talcosis in 71 cases was noted (Table III).

COMMENTS

The relationship between silicates such as talc and pulmonary diseases was noticed at the end of 19th century, but the pulmonary damage and its X-ray changes in talc mine and talc processing workers had not been proved until the 30s of this century.[1,2] Serial survey reports began to appear in China since 1958. It has long been noticed that some impurities in talc (tremolite etc.) can cause pulmonary fibrosis, although this has not been confirmed yet.[3-10] In recent twenty years, the possibility of carcinogenesis by talc and impurities in talc was also a focus of much attention.[11-13]

Some authors held that the main causation factors in talcosis is the fibrous tremolite $Ca_2Mg_5(Si_4O_{11})_2(OH)_2$. Talc has cytotoxic effect, while tremolite has fibrogenic, besides the cytotoxic effects. They also held that the detrimental effect was related to the length of these fibers. The longer the fibers, the larger the effect.

Table I

97 Cases of Talcosis (X-ray Classification)

	I Grade		II Grade		III Grade	
	Simple	Complicated	Simple	Complicated	Simple	Complicated
No. Cases	61	12	10	9	2	3

Table II

X-ray Appearance of 97 Cases of Talcosis

	Hilus			Marking		Emphysema		Ret. and Nod.	Nod.	Pin Poi.	Larg Shad.
	Disturb. of Constr.	Dens.	Enl.	Incr.	Def.	Loc.	Dif.				
No.	80	57	23	89	75	10	6	75	14	6	6

Notes: Ret.Reticulat, Nod.Nodular, Nod.Nodular, Poi.Point, Larg.Large, Shad. Shadow, Dist.Disturbance, Constr.Constructure, Dens.Density, Enl.Enlargement, Incr.Increasing, Def.Deformity, Loc.Localized, Dif.Diffuse,

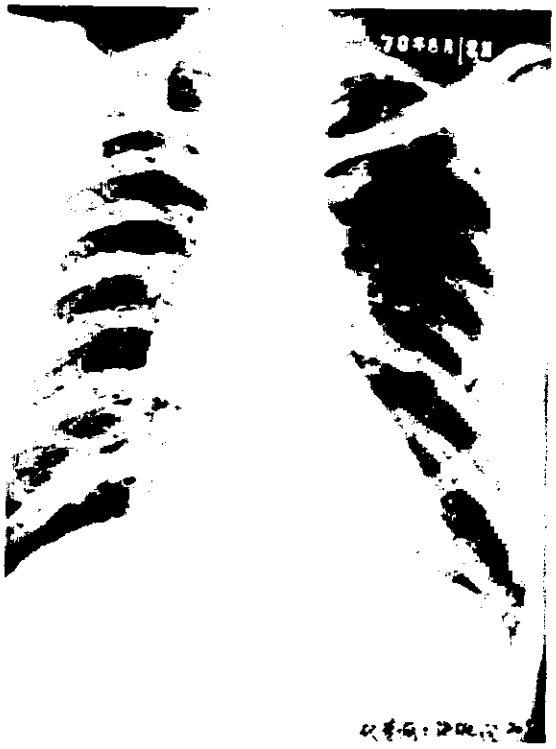

Figure 4. A male, 54 years of age, talc-cutter exposure-onset duration—23 years, 2nd stage talcosis with tuberculosis (nodular type).

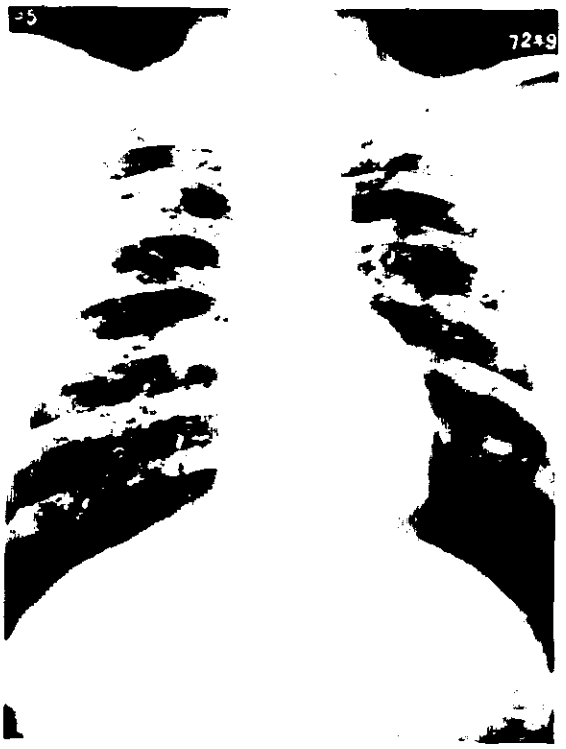

Figure 6. A male, 34 years of age, talc-cutter exposure-onset duration, 3rd stage talcosis.

Figure 5. A male, 29 years of age, talc grinder, exposure-onset duration—9 years, 2nd stage talcosis (reticulate—nodular type).

Figure 7. A male, 27 years of age, talc grinder, exposure-onset duration—6 years, 3rd stage talcosis.

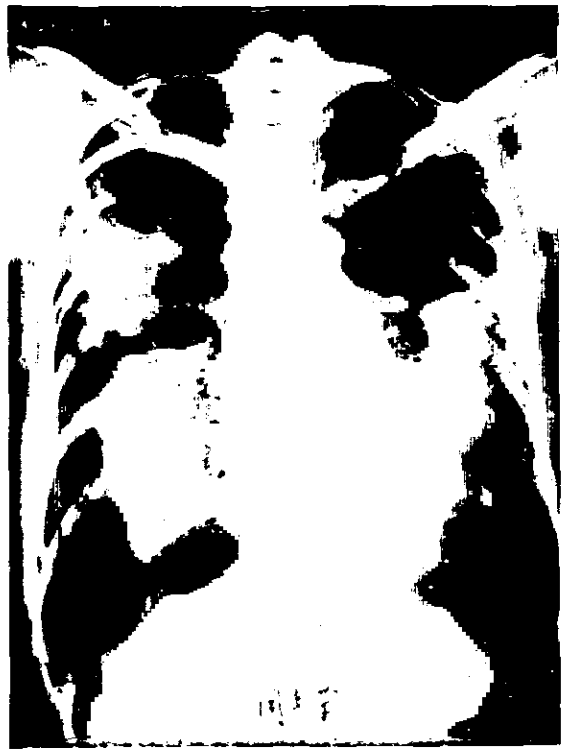

Figure 8. A female, 29 years of age, talc powder packager, exposure-onset duration—5 years, 3rd stage talcosis with tuberculosis.

Table III

Relationship between the Exposure-onset Duration and the Types of Talcosis

		Nodular type					Reticulate-Nodular Type				
Exposure-Onset Duration(yrs)		-5	6-10	11-15	16-20	21-	-5	6-10	11-15	16-20	21
Grinder	I		2	7*			1	7	16	15	1
	II		1	2							
	III			1	1						
Miner	I			1'					6	6	3
	II									1	
	III										

*Including 3 cases of pinpoint type. 'One case of pinpoint type.

A dichotomy has been identified in the classification of 'talc': asbestiform 'talc', including anthophyllite, tremolite and chrysotile, and non-asbestiform talc. Early studies did not recognize this dichotomy and their different effects.

The pathological changes of talcosis are diffuse pulmonary fibrosis and collagenic nodules. There were reports that 'asbestosis-like body' was found in the pulmonary tissue and localized pleural thickening, granuloma was found at autopsy or biopsy and its small opacities in the chest film disappeared after corticosterone treatment.

As regards to the various descriptions of the X-ray appearance of the talcosis, that is apparently related to the purity of the 'talc'. In workers exposed to asbestiform 'talc', their X-ray appearances look like those of asbestosis, especially the talc plaques can be seen and the films of the workers exposed to non-asbestiform talc, look like those of silicosis.

The workers in this series exposed to pure talc in which we can not find any fibrous mineral (without tremolite, anthophyllite, amosite or chrysotile), the reticulate and nodular opacities in early stage talcosis and the large shadows in the advanced talcosis can be observed. These X-ray appearances look like that of silicosis.

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PULMONARY ALVEOLAR PROTEINOSIS AND CEMENT DUST: A CASE REPORT— A PRELIMINARY REPORT

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ABSTRACT

A twenty nine year old white male developed pulmonary alveolar proteinosis within two years of working as a cement truck driver. Pulmonary alveolar proteinosis (PAP), an uncommon respiratory disorder characterized by the accumulation of phospholipid material within the alveoli, has been described in association with exposure to silica, aluminum oxide and a variety of dusts and fumes. Although a link between exposure to Portland cement and PAP has not been previously noted, this type of cement contains upwards of 20% silica. Lung biopsy material, originally used to diagnose PAP, was reviewed under electron dispersive spectroscopy. Analysis indicated the presence of silica particles within the alveolar fluid and macrophages. A number of items support a causal relationship between exposure to cement dust and PAP: (1) the temporal sequence between assuming job duties and the development of the illness, (2) improvement following removal from further exposure, (3) dusty, unprotected working conditions, (4) the presence of silica within the cement and the alveolar fluid from periodic acid-Schiff positive lung tissue.

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) an uncommon respiratory disorder first reported in 1958,[1] consists of the accumulation of periodic acid-Schiff (PAS) positive phospholipid material in the alveoli; inflammation of the lung interstitium usually does not occur. PAP can be a primary disease process or secondary to opportunistic infections;[2-4] it has also been described in AIDS patients.[5] Although the etiology of the disorder is poorly understood, the disease process appears to involve a disruption of the pulmonary surfactant—type II epithelial cell system.[2-6] Animal studies have demonstrated that PAP develops after exposure to a variety of mineral dusts and fumes,[7-13] whereas other reports have associated PAP with exposure to various occupational substances.[14-19] The purpose of this report is to describe a truck driver, who appears to have developed (PAP) as a result of exposure to Portland cement dust, a relationship not previously noted.

CLINICAL HISTORY

A twenty nine year old white male was referred for an occupational medical consultation. He was concerned as to whether his recent diagnosis of pulmonary alveolar proteinosis may have resulted from exposure to cement dust and whether it would be harmful for him to return to his work.

Initial evaluation included a review of medical records, a medical history, a comprehensive physical examination and laboratory testing such as a chest film, pulmonary function testing, allergy evaluation and review of diagnostic material, including results of an open lung biopsy. The patient, who had twenty-two pack year smoking history (1½ packs per day for 15 years) originally became ill in February, 1982 when he experienced a cough, with purulent sputum production, fever, and chest pain.

A chest film revealed diffuse bilateral alveolar infiltrates, suggestive of an acute pneumonia; the right lung was more affected than the left (Figure 1). He was prescribed ten days of penicillin and tetracycline for a presumed lower respiratory infection and clinically improved thereafter. A subsequent chest film (March, 1982) however, demonstrated persistent bilateral infiltrates. A PPD was negative and psittacosis serology was unremarkable. Pulmonary function tests later (May, 1982) revealed normal lung function (Table I). Since a repeat chest film revealed a persistence of the pulmonary infiltrates (Figure 2) the patient was advised to undergo bronchoscopy with transbronchial biopsy. Pathology review demonstrated PAS positive proteinaceous material within the alveoli, consistent with PAP (Figure 3).

In December, 1982, the patient developed acute dyspnea on exertion. Repeat PFTs demonstrated a deterioration of lung function (FEV_1: 3.62L—3.15L FVC 4.28L—3.79L). A room air arterial blood gas revealed a PO_2 of 73mm Hg, PCO_2 of 37mm Hg and a pH of 7.39. Because of persistent dyspnea on exertion, therapeutic bilaterial whole lung bronchopulmonary lavage was performed in January 1983. Lavage resulted in marked clinical improvement as well as in pulmonary function. By May 1983, the patient was clinically well; pulmonary function also improved. Evaluation in August 1986, revealed the patient to be free of pulmonary symptoms although chest X-ray abnormalities persisted and PFTs suggested mild obstructive airways disease (Table I). The patient continued to smoke one and one-half packs of cigarettes per day. Clinical evaluation at that time also included allergy skin

Figure 1. Chest film (initial).

Table I
Lung Function Values

	FEV_1 (L)	FVC (L)	FEV_1/FVC	SINGLE BREATH DIFFUSION CAPACITY
May 1982	3.62 (89% pred)	4.28 (84% pred)	83%	81% pred
Sept 1982	3.64 (91% pred)	4.27 (92% pred)	85%	———
December 1982	3.15 (77% pred)	3.79 (74% pred)	85%	64% pred
May 1983	3.27 (81% pred)	4.33 (85% pred)	76%	———
**August 1986	3.00 (76% pred)	4.06 (81% pred)	73%	

** negligible improvement after bronchodilators
FEV_1 3%; FVC 1%

Figure 2. Chest film.

testing for common substances such as dusts, ragweed, trees and grass, all of which were negative.

Biopsy material was further reviewed for the presence of inorganic particles, which have been previously reported in association with PAP.[25] Through electron dispersive spectroscopy (EDS), silicon particles (Figure 4) were noted in the lung biopsy material. An increased number of small birefringent particles had been noted earlier within the same proteinaceous material.

OCCUPATIONAL HISTORY

For almost two years prior to becoming ill, the patient operated a cement truck in a railroad freight yard. He oversaw the transfer of portland cement from railroad tank cars into the cylindrical tank of the truck that he drove. Heavy exposure to cement dust occurred (Figures 5-7) during the one to one and one-half hours required per load; two to three loads were transferred daily. By the end of the day, the patient claimed his hair, nose and skin were covered with dust. No dust mask or respirators were used. Air monitoring to quantify cement dust exposure was not conducted.

Portland Cement, commonly called cement, is classified by OSHA and ACGIH as a nuisance dust; a Time Weighted Average (TWA) Threshold Limit Value (TLV) of 10 mg/m^3 is recommended. Portland Cement consists of hydrated calcium silicates with small amounts of aluminum oxide, magnesium oxide, iron oxide, calcium sulfate and other impurities.

The chemistry and manufacture of various Portland cements, blended cements, and other hydraulic cements are related to their specifications and uses in concrete and other products. Portland cements are ordinarily manufactured from raw mixes including components such as calcium carbonate, clay or shale, and sand. Table II shows the compositions of some typical raw materials.[20-21]

During the manufacture of Portland cement, as the temperature of the materials is increased, the following reactions occur: (1) evaporation of free water; (2) release of combined water; (3) decomposition of carbonates (calcination); and (4) combination of the lime, silica, alumina and other oxides. This produces a mixture of solid and molten phases in the $CaO+SiO_2+Al_2O_3$ system which crystallizes during cooling to form a mixture of solid calcium silicates and calcium aluminate containing small amounts of magnesium oxide, iron oxide, calcium sulfate and other impurities. Table III shows the composition of some typical cements. Table IV shows the crystalline phases present.[20,22] Table V shows the phases present after hydration at normal temperatures.[20,23]

Of the components of Portland cement, calcium silicate, magnesium oxide, aluminum oxide, iron oxide and calcium

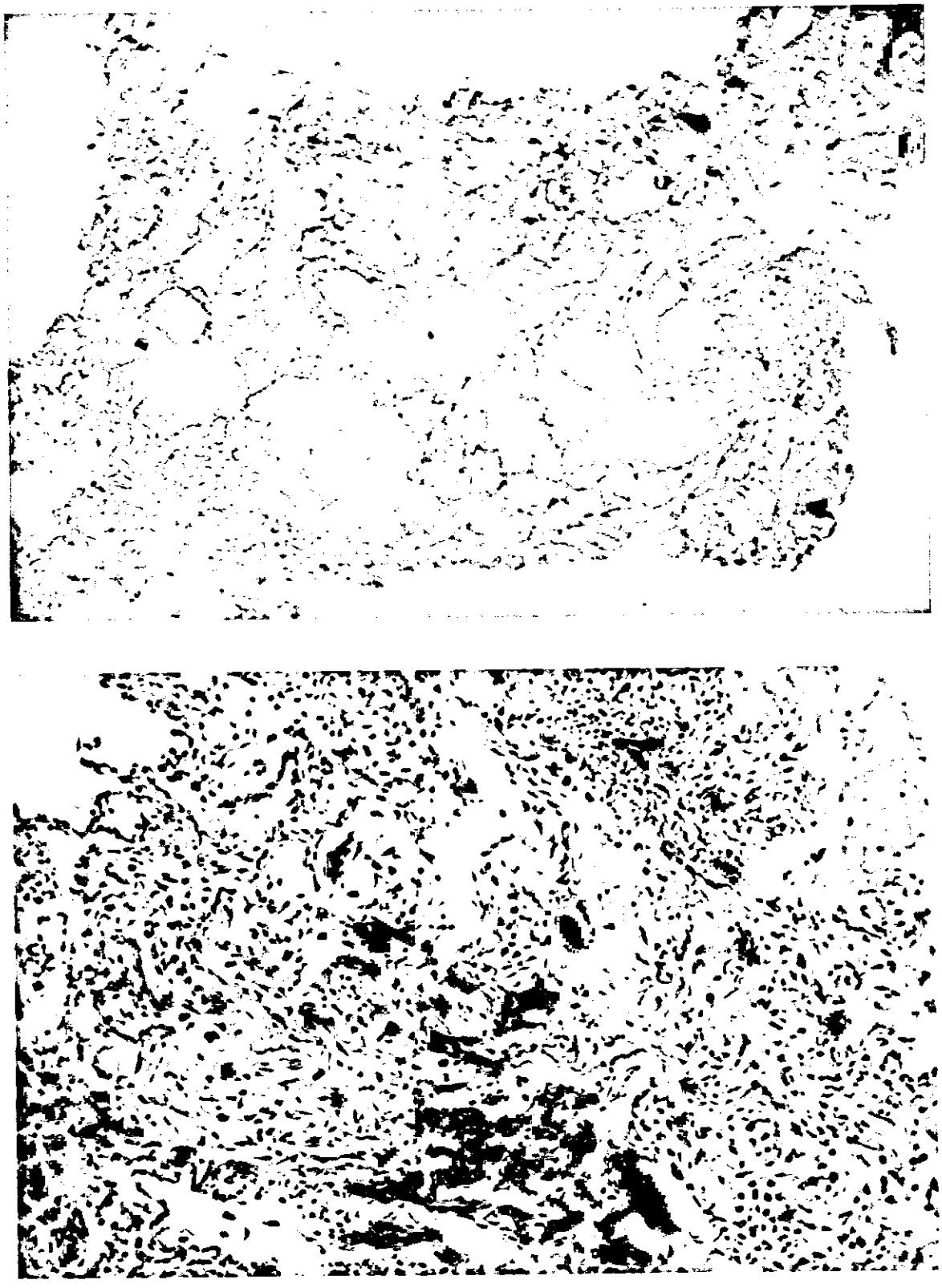

Figure 3A, 3B. Periodic acid-Schiff material (lung biopsy).

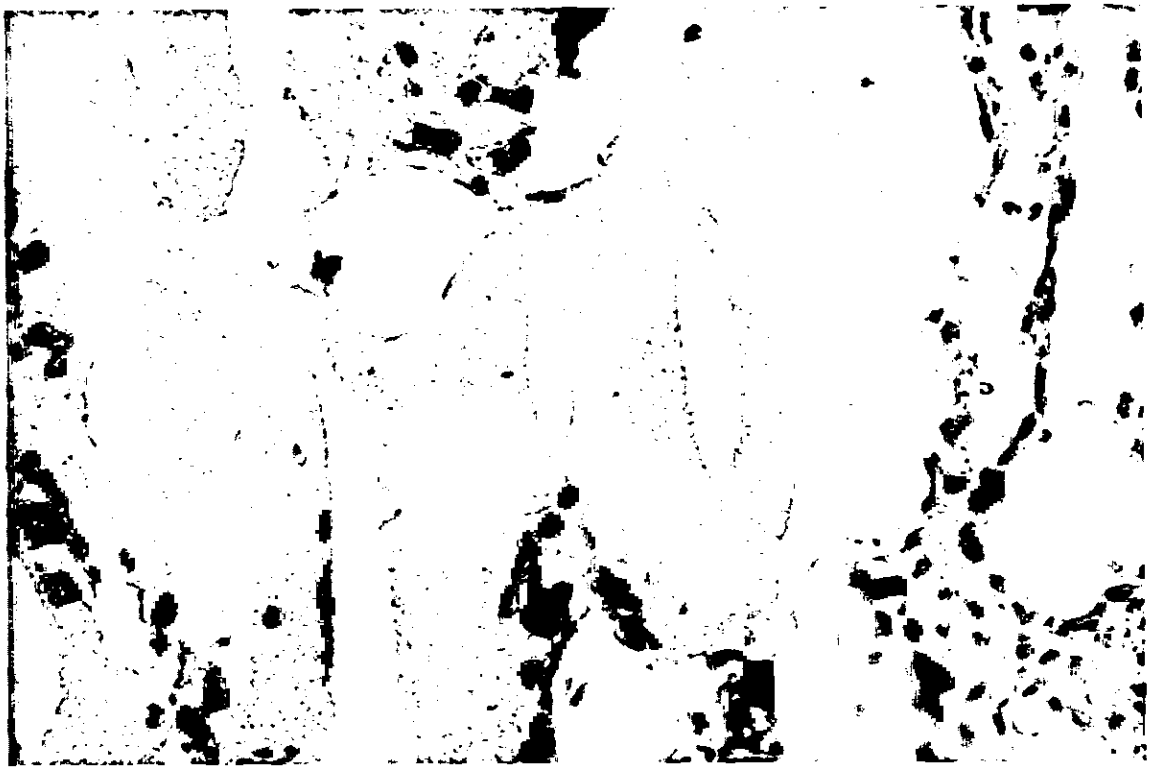

Figure 3C. Periodic acid-Schiff material (lung biopsy) (cont.).

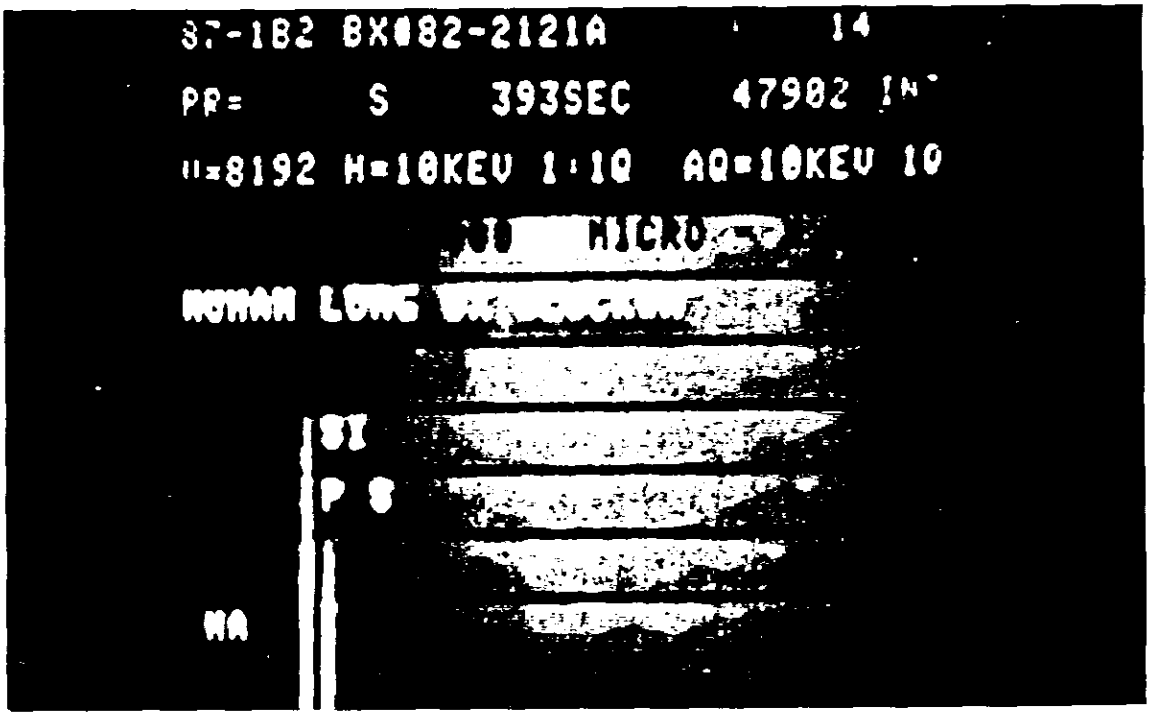

Figure 4A, 4B. Electron dispersive spectroscopy (A) Silica particle.

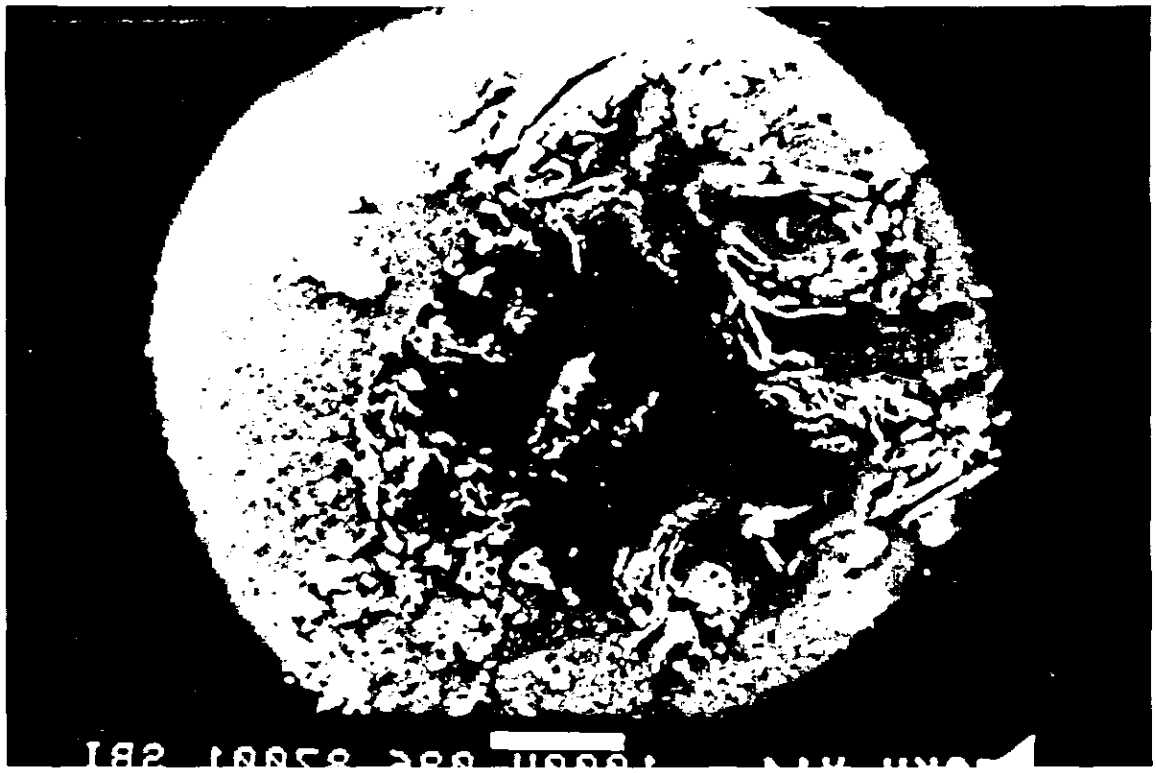

Figure 4A, 4B. Electron dispersive spectroscopy (A) Silica particle (cont'd).

Figures 5, 6. Working conditions.

Figure 7. Working conditions (cont.).

Table II
Chemical Composition of Raw Materials, %
(Courtesy of the American Concrete Institute)[20,21]

Type	SiO_2	Al_2O_3	Fe_2O_3	CaO	MgO
Cement Rock	13.4	3.5	1.7	42.9	1.0
Limestone	1.2	0.2	0.4	53.4	1.3
Limestone	4.5	0.5	1.6	35.0	14.9
Marl	6.0	0.6	2.3	49.1	0.4
Oyster Shells	1.5	0.4	1.2	52.3	0.7
Shale	53.8	18.9	7.7	3.2	2.2
Clay	67.8	14.3	4.5	0.9	1.2
Mill Scale			ca 100.0		
Sandstone	76.6	5.3	3.1	4.7	1.7
Bauxite	10.6	57.5	2.6		

sulfate are assigned TLV's of 10mg/m^3 by the ACGIH; calcium hydroxide and magnesium are assigned TLV's of 5mg/m^3.

DISCUSSION

The relationship of PAP to occupational exposures was first raised in 1969 by Davidson and MacLeod[16] who reviewed 139 cases of PAP that had been reported since 1958 and found that approximately half were associated with fume or dust exposures. Rosen et al,[1] however, in their classic paper, reported on the occupations of the 27 cases they described. It is ironic that the first patient they described was a cement truck driver. McEuen and Abraham later (1978)[24] evaluated 37 cases of PAP and found that 13 of their series had been exposed to various dusts and fumes. In their retrospective

Table III
Chemical Composition of Some Typical Cements, %

Type	SiO_2	Al_2O_3	Fe_2O_3	CaO	MgO	SO_3
Type I	20.9	5.2	2.3	64.0	2.8	2.9
Type II	21.7	4.7	3.6	63.6	2.9	2.4
Type III	21.3	5.1	2.3	64.9	3.0	3.1
Type IV	24.3	4.3	4.1	62.3	1.8	1.9
Type V	25.0	3.4	2.8	64.4	1.9	1.6
White	24.5	5.9	0.6	65.0	1.1	1.8
Alumina	5.3	39.8	14.6	33.5	1.3	0.4

Table IV
Compound Composition of Some Typical Cements, %
Calculated by the ASTM C150-76)

	Crystalline Form			
Cement	(2)	(3)	(4)	(5)
Type I	55	19	10	7
Type II	41	24	6	11
Type III	56	19	10	7
Type IV	28	49	4	12
Type V	38	43	4	9
White	33	46	14	2

Column Headings:

(2) Tricalcium Silicate
(3) Dicalcium Silicate
(4) Tricalcium Aluminate
(5) Tetracalcium Alumino-ferrite

Table V
Cement Phases Hydrated at Normal Temperatures

Name	CAS Registry No.
Calcium Sulfate Dihydrate (Gypsum)	10101-41-4 & 13397-24-5
Calcium Hydroxide (Portlandite)	1305-62-0
Magnesium Hydroxide (Brucite)	1309-42-8
Calcium Silicate Hydrate Gel (C-S-H gel)	12323-54-5
Tetracalcium aluminate 19-hydrate	12042-86-3
Tetracalcium aluminate 13-hydrate	12042-85-2
Tetracalcium aluminate 7-hydrate	12511-52-3
Tetracalcium aluminate monosulfate 16-hydrate	67523-83-5
Tetracalcium aluminate monosulfate 14-hydrate	12421-30-6
Tetracalcium aluminate monosulfate 12-hydrate	122522-10-7
4-Calcium aluminate sulfate 10,8,x-hydrate	12252-09-4 & 12445-38-4
Ettringite (6-calcium aluminate trisulfate, 32-hydrate	12252-15-2
6-Calcium aluminate trisulfate, 8-hydrate	11070-82-9
Garnet-hydrogarnet Solid Solution Series	12042-80-7

review, the same authors also found an increased number of small, inorganic particulates in the lung tissue as compared to controls. Crystalline silica is the most commonly implicated mineral associated with PAP.[15,18,19,24,25]

PAP has also been described secondary to exposure to Kaolin,[14] an aluminum silicate compound, and aluminum dust.[17] In these cases, minerologic analysis of lung tissue revealed high concentrations of aluminum silicate and aluminum particulates, respectively.

Although PAP has a variable prognosis, this patient's clinical improvement after a single pulmonary lavage is unusual. Kariman et al[26] for example, described complete remission or marked subjective and objective improvement in only two of eleven cases treated in this manner. Wilson et al[27] reported PAP in a welder who was successfully treated by a single bronchial lavage and removal from further occupational and environmental exposure to dusts and fumes. The improvement in our patient after a single pulmonary lavage and removal from further exposure to cement dust lends credence to the notion that PAP may be initiated by a nonspecific injury that results in a transient failure of alveolar clearance and the accumulation of surfactant materials.[18]

Documentation of an increased amount of inorganic particulates containing silicon within the biopsy material supports the notion that inhalation of cement dust precipitated the development of PAP in this patient. Abraham and McEuen[25] have also reported two individuals exposed to cement dust in whom an increased number of inorganic particulates (silicates found in cement dust) were noted in the proteinaceous lung tissue.

Further studies are necessary to elucidate the relationship between PAP and smoking. Abraham and McEuen[25] were not able to document smoking histories in their analysis of PAP cases. The role of smoking in the deposition of small particulates in the lung also needs further exploration.[28]

Workers involved in the manufacture of cement dust have also been evaluated. One study of 160 cement workers in Yugoslavia indicated a decline in pulmonary function (FEV_1, FVC, FEV_1/FVC) following four years of unspecified level of exposure; the authors controlled for cigarette smoking.[29] Similar analyses among cement workers have indicated obstructive defects[30] (decline in FEV_1/FVC), expiratory airflow obstruction[31] and a higher prevalence of respiratory symptoms,[32] even when controlled for cigarette smoking.

CONCLUSION

Pulmonary alveolar proteinosis is a rare disorder that in some cases "represents one mechanism by which the lung responds to a variety of insults."[33] Dust overload can provoke excessive discharge of surfactant and associated lipids from type II pneumocytes.[34] The mechanism for this reaction may be simply mechanical and not related to the presence of fibrogenic material. It is the destruction of the type II alveolar epithelial cells that leads to PAP. Although the amount of

cement dust to which this patient was exposed is unclear, verbal accounts ("it was so thick, that sometimes I couldn't see") and pictures (Figures 5-7) of the operations suggest that the working conditions were unarguably dusty and likely excessive at times. After a *single* intratracheal instillation of silica dust, laboratory animals developed PAP within three weeks.[35] The presence of silica particles within both alveolar macrophages and alveolar fluid and the temporal sequence of the patient developing PAP within 2 years of assuming his job responsibilities and improvement following removal from exposure lend further support to a causal relationship.

Whether this patient is at risk of recurrence of PAP upon further exposure to dusts is problematic. Prudence would dictate, however, that in light of PAP being a potentially life threatening illness, such exposure should be avoided.

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