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Physical factors as etiological mechanisms

V. TIMBRELL [1]

Prior to the 1964 New York meeting little attention had been given to the possible importance of physical factors in the etiology of lung diseases associated with exposure to asbestos dust. Animal experiments had indicated that the fibrogenicity of asbestos particles was probably related to fibre length (Vorwald *et al.*, 1951; Wagner, 1963; Holt *et al.*, 1964); but despite the fact that the relevant occupational exposures were by inhalation, a study described at the 1964 meeting (Timbrell, 1965) on the aerodynamic properties of fibres seems to have been the first attempt to investigate these aspects. Subsequent inoculation experiments (Burger & Engelbrecht, 1970) have re-emphasised the importance of fibre length in relation to fibrosis; while very recent intrapleural inoculation studies (Stanton & Wrench, 1972; Wagner *et al.*, 1972 [2]) have indicated a relationship between fibre size and the development of mesotheliomas. In the light of this evidence it is not surprising that studies of the physical characteristics of fibres in recent years have been profitable and now offer plausible explanations for some of the biological observations.

Studies of possible etiological factors are assisted by two features of asbestos minerals and of the associated lung diseases. First, asbestos minerals are crystals and as such exhibit certain constant physical properties: some of these features are illustrated in Figure 1. It is no small advantage in analysis that the particles are consistently of fibrous shape, thus effecting a major reduction in the number of possible particle shapes compared to, for instance, coal; and that a few samples from an asbestos geological entity appear to be sufficient to give a good indication of the particle characteristics of the whole deposit, probably back to the time it was first worked. Secondly, the epidemiological, pathological and experimental evidence presents a series of paradoxes which are useful in testing ideas concerning the etiology. As an example, the major difference in the incidence of mesotheliomas in north-western Cape Province compared with that in the Transvaal suggests a need to search for some factor (or factors) in the asbestos minerals that consistently have very different magnitudes in the two areas. In this instance it seems likely that such a factor is not chemical because, although there are variations in mineral content of the fibres, these differences do not appear sufficient to provide an explanation. In contrast, some of the physical properties differ so markedly that they impress as possible etiological factors.

FIBRE IN LUNGS

The aerodynamic study presented at the New York meeting provided explanations for some of the features of asbestos fibres detected in lung sections. The deposition of particles in lung airways is related to the aerodynamic diameter of the particles as measured by their free-falling speed. Most inhaled particles with falling speeds greater than that of a unit density sphere 10 μm in diameter are deposited in the upper bronchial tree by sedimentation or by impaction. So the demonstration that an asbestos fibre about 3 μm in diameter has the same falling speed as that of a 10 μm sphere of unit density indicates that fibres of this diameter are the thickest that are likely to penetrate to the alveolar regions and to be eventually seen in lung sections. This conclusion is in good agreement with measurements made on fibres in lungs of city dwellers (Gross *et al.*, 1971) and with measurements made on fibres in

[1] MRC Pneumoconiosis Unit, Llandough Hospital, Penarth, UK.
[2] Unpublished data.

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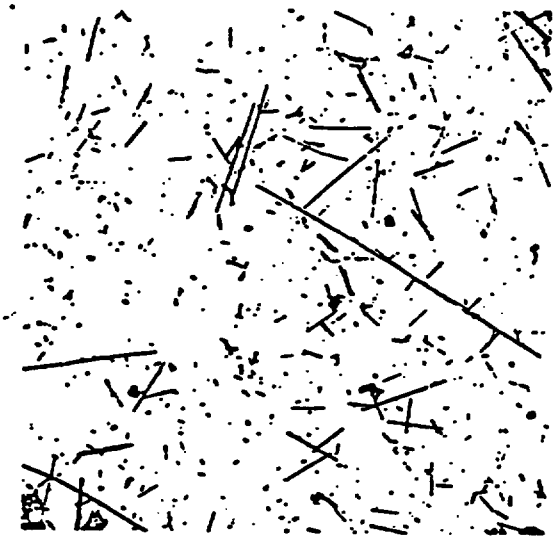
CROCIDOLITE



AMOSITE



ANTHOPHYLLITE



CHRYSOTILE



10μm

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lungs of rats exposed to airborne particles of amphibole asbestos (Timbrell *et al.*, 1970). It may be noted here that rat lungs have often provided data on particle deposition, retention and clearance which are comparable with those obtained from human lungs.

Calculations made in this aerodynamic study indicated that interception is likely to prevent fibres longer than 200 μm from penetrating the nasal passages. However, interception is not effective in depositing fibres, not even long ones, in the trachea and other wide airways of the upper bronchial tree. The conclusion that long fibres which are thin enough not to be deposited earlier by sedimentation and impaction can reach the alveolar regions explains satisfactorily the numerous long asbestos fibres detected in lung sections.

Further calculations indicated that long fibres which reach the respiratory bronchioles are efficiently deposited in these fine tubes, and that bifurcations are the preferred deposition sites. It has been suggested that long fibres are transported from these pulmonary regions less efficiently than are short fibres because they find anchorage in these complicated anatomical structures more readily than do short fibres (Timbrell & Skidmore, 1968), and that this may explain why fibrosis tends to be associated first with the respiratory bronchioles (Wagner, 1963) and with long fibres. These conclusions are in good agreement with the detection of accumulations of long fibres in small airways, especially at bifurcations; but the possibility of transportation of fibres to these regions from other deposition sites cannot be eliminated. Current studies on rats exposed by inhalation to radioactive crocidolite fibres (Morgan, 1972 [1]) are likely to produce much needed data on the pulmonary deposition pattern of fibres and their subsequent clearance.

Little information is available on the important question of the relative efficiency of pulmonary penetration of fibres of amphibole asbestos and chrysotile. In an experiment reported by Wagner (1972), in which rats were exposed to dust clouds of the UICC samples at equal concentrations, six times as much of each of the amphibole samples was still retained after several months compared to the amount of chrysotile. Timbrell (1970; 1972a) has suggested that this may be partly due to the characteristic rectilinear shape of amphibole fibres, compared to the curly morphology of chrysotile fibres, which could cause amphibole fibres to penetrate to the deeper parts of the lung more efficiently than do chrysotile fibres. The results of studies in lung casts and narrow tubes, which showed a relative penetration of amphibole and chrysotile fibres similar to that obtained in the animal experiment, are offered in support of this explanation. It is difficult to estimate what influence the tendency of chrysotile fibres to break down chemically and physically after prolonged residence in the lung (Langer *et al.*, 1971) may have had on the result of the animal experiment. The contribution may not be substantial since the asbestos content of the lungs was estimated from the silica present, and it appears that whereas magnesium is rapidly leached from a chrysotile fibre *in vivo* (Morgan & Holmes, 1970) a silicate skeleton remains.

There is a lack of information on whether asbestos fibres can reach the pleura during inhalation or whether they migrate to this region. This question is of particular interest in a consideration of the development of mesotheliomas. In an experiment to compare the effects of long (5–200 μm) fibres and small particles of the UICC crocidolite sample in monkeys and baboons, Rendall (1972 [2]) found that small particles are not fibrogenic but that they can reach the pleura in macrophages. Results available from a current electron microscope study on the lungs of rats exposed to dust clouds of the UICC samples at equal concentrations suggest that asbestos fibres can reach the alveoli near the pleura during

[1] Personal communication.

[2] Personal communication.

Fig. 1. Electron micrographs of crocidolite (north-western Cape Province), amosite (Transvaal), anthophyllite (Finland), chrysotile (Canada) at the same magnification (×1700). Features to note are:

(i) the rectilinear shape of the amphibole fibres compared with the curved and twisted morphology of chrysotile fibres;
(ii) the order of the diameters of the amphibole fibres.

crocidolite < amosite < anthophyllite,

which numerous e.m. examinations suggest is a characteristic of these fibres in the three geographical areas;
(iii) the longitudinal fragmentation of the chrysotile fibres and the small diameter (about 0.03 μm) of the ultimate fibrils.

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inhalation. In animals killed immediately after a short exposure to crocidolite, small numbers of these fibres have been detected near the visceral pleura: some fibres have been detected in the pleura itself, although this could be an artefact.

The numbers of amosite fibres observed near the pleura have been lower, as might be expected from the greater diameter and higher falling speed of this type of fibre.

The numbers of anthophyllite fibres detected near the pleura have been still lower, as might be expected from the still greater thickness of this fibre: the fact that anthophyllite fibres are capable at all of reaching the pleura during inhalation may be due to their lath-like shape (Timbrell *et al.*, 1970) which gives them lower falling speeds and thus greater penetration than they would have if they were of circular cross-section.

Chrysotile fibres have very seldom been observed near the pleura in this study. This suggests support for the conclusion, derived from considerations of the morphology and the aerodynamic behaviour of chrysotile fibres, that this type of asbestos does not penetrate efficiently to the deeper parts of the lung. But the fact that, in a current inhalation experiment, UICC Canadian chrysotile has produced mesotheliomas, suggests that the present examination techniques are not adequate to detect and quantify asbestos fibres in tissue, particularly very fine chrysotile fibres.

In a recent study Pooley (1972) used the electron microscope to examine chrysotile fibres in sections of 300 human lungs. The majority of the chrysotile particles were grouped together in large clusters of strands (bundles of single chrysotile fibres), which were often detected at the bifurcation of small airways. Very short individual fibres were also found scattered throughout the lung sections. This distribution of short chrysotile fibres resembles that of amosite fibres in the lungs of rats used in an inhalation experiment (Timbrell & Skidmore, 1968). Considerations of fibre morphology suggest an explanation for these results: short and long chrysotile fibres characteristically have the same radii of curvature, so that short chrysotile fibres, being short arcs, are virtually straight and behave aerodynamically like amphibole fibres. This indicates that chrysotile and amphibole fibres will exhibit different aerodynamic behaviour if they are long, but similar behaviour if they are short.

OCCUPATIONAL EXPOSURES

Although a substantial amount of dust sampling has been carried out to monitor occupational exposures to asbestos, very little sampling has been done to provide basic information on the nature of the airborne particles. In particular, there has been a lack of investigations designed to compare the nature of dust clouds in amphibole and in chrysotile exposures, and to compare these with experimental clouds. Major differences must be expected.

Whereas the animal experiment reported by Wagner (1972), using the UICC samples, indicated a 6:1 retention of amphiboles compared to chrysotile, substantially larger ratios may be expected to occur in occupational exposures. Both the amphibole and chrysotile UICC samples were specially prepared so as to be rich in fibres of respirable size. Measured by Hexhlet-type instruments, which take account of particle falling speed only, the proportions by weight of respirable particles are high (about 70%) and approximately equal in all the UICC samples. Furthermore, the samples contain only a small proportion by number of long fibres (up to 200 μm); and only these fibres, in conjunction with the difference in fibre morphology, could contribute to a difference in particle deposition patterns between amphibole and chrysotile in this animal experiment. In contrast, the industrial preparation of chrysotile is controlled to avoid excessive opening of the fibres (Sinclair, 1959) and the production of a high proportion of the fine fibrils; whereas milling experiments (Timbrell & Rendall, 1971/72) have shown that it is not possible to mill the amphibole asbestos types without producing extremely fine fibres: some crocidolites, for example that from north-western Cape Province, are particularly rich in fine fibre. The dense clouds of dust and the layers of settled dust often seen in chrysotile mining areas consist largely of relatively thick strands and big flocks which settle rapidly and are available for inhalation only for limited periods: some of these particles are of such large aerodynamic size that many types of dust sampling instruments do not even aspirate them. Rendall & Timbrell using Hexhlet-type instruments observed some low values (5%) for the proportion of respirable particles in air samples collected in some South African chrysotile mills, while Gibbs (1971) has reported low values (range 14–25%) in Canadian mills; but there is a great need for more data on chrysotile and amphibole

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milling and other processes, for comparison purposes. A study with this objective is in progress.

These considerations suggest that even in occupational exposures to chrysotile enough fibre may reach the bronchial regions of the lung to produce fibrosis and carcinoma, but that the amphibole asbestos types are more likely to produce these diseases because of higher effective exposures. Although the possibility of some chrysotile fibres reaching the pleura clearly cannot be dismissed, especially the short fibres detected by Pooley, this type of asbestos appears to be the least likely to be associated with pleural mesotheliomas from occupational exposures if penetration of fibre to the deeper alveoli adjacent to the pleura is an important factor in the production of these tumours.

There is also a need for information on the nature and concentration of airborne particles at various stages in the preparation of asbestos. It has been pointed out by Timbrell & Holmes (1970) that the application of fiberising processes must progressively increase the number of fibres and must make them more easily respirable because of the decrease in their diameters. This suggests that there may be major differences in exposures at different points in the industry, even when only one type of fibre is involved. That such differences do occur is supported by evidence that health risks have been high in the asbestos textile trade (Merewether & Price, 1930; Doll, 1955; Enterline & Kendrick, 1967; Mancuso & El-Attar, 1973; Newhouse, 1970), where the fibres are at their finest, shortest and cleanest.

PLEURAL MESOTHELIOMAS IN THE NORTH-WESTERN CAPE AND THE TRANSVAAL

Probably the greatest paradox presented by asbestos diseases is the clear association between the development of mesotheliomas and exposure to crocidolite dust in the north-western Cape (Wagner *et al.*, 1960; Oettlé, 1964), compared with the very rare occurrence of these tumours in the Transvaal where both crocidolite and the closely related amosite are mined (Oettlé, 1964; Harington *et al.*, 1971). This marked difference in mesothelioma risk is not satisfactorily explained by differences in the commercial production of fibre in the two areas (Keep, 1961; Harington *et al.*, 1971), nor by mineralogical factors, nor by the occurrence of asbestosis (Sluis-Cremer, 1965).

Cralley (1971) has suggested that the difference is due to the electromotive influence of the excess elemental manganese in the respirable dust of north-western crocidolite over that in the respirable dust of Transvaal crocidolite, whose parent rock is softer and requires less harsh milling treatment to free the fibre. The estimated three-fold excess of manganese does not, however, seem sufficient to explain the sharp disease pattern; but it is not possible to dismiss metals as the ultimate carcinogen, with the fibres acting as carriers. Suggestions that differences in oil content of the fibres in the two areas may be responsible are not supported by intrapleural inoculation experiments in which oil-extracted UICC crocidolite from a north-western Cape mine produced a very similar mesothelioma rate to that with untreated fibre (Wagner *et al.* 1972 [1]).

A recent suggestion is that differences in particle size may be important (Timbrell *et al.*, 1971). Electron microscope studies on fibres prepared by grinding rock specimens from the two areas showed a consistent difference in fibre size: Transvaal fibres, both crocidolite and amosite, were on average three times the diameter, three times the length, and hence 27 times the volume or mass of north-western Cape fibres. Very recent studies on air samples have confirmed these differences which, it has been suggested, indicate for the Transvaal compared to the north-western Cape less liberation of respirable fibres; higher fibre settling rates and shorter times available for inhalation; comparable deposition rates in the upper bronchial tree, but less efficient penetration to the deeper parts of the lung. The last comparison may explain the apparent lack of association between mesotheliomas and asbestosis in the two areas.

Electron microscope examinations of samples of Australian crocidolite have shown that the fibres are even smaller in diameter than those of north-western Cape crocidolite (Timbrell *et al.*, 1970). This may be related to reports from Australia (Wagner *et al.*, 1971) that mesotheliomas have occurred following exposure to crocidolite in the mining areas, and to the fact that mesotheliomas have been observed in workers who were exposed to Australian crocidolite when packing respirators during World War II (Jones, 1968 [2]).

[1] Unpublished data.
[2] Personal communication.

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INTRAPLEURAL INOCULATION EXPERIMENTS

The development of mesotheliomas in rats following intrapleural implantation or inoculation of fibrous materials has been studied in two recent experiments by Stanton & Wrench (1972) and by Wagner *et al.*, (1972 [1]). In these experiments chrysotile exposure, which in general presents a smaller mesothelioma hazard for man than does exposure to crocidolite (Wagner *et al.*, 1971), has produced mesotheliomas as readily as the latter. A probable explanation for this paradox is that such inoculation experiments do not take account of the natural factors which operate during inhalation or, consequently, of the important differences in the aerodynamic behaviour of fibres of the two main asbestos groups.

In such inoculation experiments, sizing of the particles by electron microscopy is necessary, since some of the materials may contain a high proportion of particles that are not visible in the light microscope. The data available on the physical and chemical characteristics of these materials are so complex that some indication of the important factors is essential for successful interpretation of biological results. Suggestions of which physical factors may be involved have been provided by recent studies on fibre-cell preparations. In investigations based on the working hypothesis that asbestos cancers may be related to the implantation of fibres in cells (which does not immediately kill the cells), the preferred orientations that fibres of amphibole asbestos types exhibit in a magnetic field (Timbrell, 1972b) have been used to apply the fibres end-on to the membranes to impale the cells. These studies have indicated that if fibres are thinner than a threshold diameter they may be thus implanted without destroying the morphology of the cells: the threshold diameter and its range remain to be determined, a tentative value being set at 0.5 μm. Similar experiments have emphasised that fibres are of an ideal shape to transmit force and motion over considerable distances in cell agglomerations, and that these features are functions of fibre length; also, that whereas fibres which are short compared with cell diameters are able to move comparatively freely, longer fibres readily find anchorage, giving rise to the possibility of relative motion between fibre ends and cells and of irritation and penetration of membranes. These observations suggest that if the carcinogenesis associated with asbestos is related to such mechanical action there may be a threshold length, of the order of the size of the cell diameters, that the fibres must exceed in order to produce this biological response.

A further factor that must be taken into account in examining the results of intrapleural inoculation experiments is the tendency of chrysotile fibres *in vivo* to fragment longitudinally into fine fibrils (Suzuki & Churg, 1969); thus the degree of fragmentation and hence the number of fibres produced can be expected to depend on variations in physical and physiological conditions (Timbrell, 1972a). Fibres of the amphibole types of asbestos, on the other hand, appear to retain their morphology and characteristic diameter distributions (Timbrell *et al.*, 1970).

Although a direct relationship between these physical factors and the development of mesotheliomas has not been demonstrated, they are the relevant factors in the Stanton & Wrench (1972) and the Wagner *et al.* (1972 [2]) experiments, if it can be considered that consistency in the interpretation of the biological observations made in these two studies is a satisfactory test. In examining the results, fibre diameter is once more found to be a central factor, largely because the number of fibres in a given quantity of material placed in the pleural cavity (in each study a standard weight of each material was inoculated or implanted) is determined more by fibre diameter (inversely proportional to diameter^2) than by fibre length.

When the non-chrysotile materials (samples of crocidolite, amosite, chrysotile, brucite, synthetic aluminium silicate fibre and aluminium oxide particles) used in the Wagner *et al.* (1972 [2]) experiment are classified according to fibre diameter, the order obtained is in good agreement with the order in terms of the number of mesotheliomas produced: the finer the fibre the greater its carcinogenicity. The *in vivo* dispersion of chrysotile materials and their fibre diameters are difficult to quantify, but their position in the classification by carcinogenicity is understandable from their fragmentation and agglomeration characteristics. In the Stanton & Wrench (1972) experiment a total of 17 samples, including samples of several types of asbestos as well as of fibrous glass and metallic nickel fragments, were used. When the results reported in that study are

[1] Unpublished data.

[2] Unpublished data.

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examined using the light microscope data provided by those authors for the size of the coarser materials and the electron microscope data collected by Timbrell for the size of the amphibole asbestos types, there is again good agreement between the order of the materials in terms of fibre diameter and their classification according to the number of mesotheliomas produced. The formation of mesotheliomas by fine glass fibres in this study, in contrast to the absence of these tumours in an earlier Wagner [1] experiment using coarser glass fibre, is consistent with the concept of a threshold fibre diameter. Furthermore, the observation made in the Stanton & Wrench experiment that the number of mesotheliomas produced decreased with degree of pulverisation of the materials is consistent with the concept of a threshold fibre length. Further experiments are needed using additional types of fibrous materials, and preferably employing fibres in narrow ranges of diameter and length.

POSSIBLE FACTORS IN CARCINOGENESIS

The fact that the fibrous form of a range of materials (including several types of asbestos, brucite, synthetic aluminium silicate and glass) produces mesotheliomas suggests that particle morphology may be an essential factor. The fact that fibrous materials differing greatly in chemical composition produce mesotheliomas suggests that the initiation of a tumour is unlikely to be due to special characteristics of the materials, for example, a certain type of molecular structure. It may be significant that fibres appear to be more carcinogenic the closer their diameters approach the thickness of cell membranes and the size of cell organelles.

CONCLUSIONS

Extracellular processes and the physical features of fibres thus appear to constitute a major part of the etiology of the lung diseases associated with exposure to asbestos dust, including the cancers. The biological responses which different types of asbestos fibres produce when inhaled seem to be governed largely by the aerodynamic properties of the fibres. This apparent deep involvement of physical factors suggests that enough basic information is already available to indicate the engineering measures needed to minimise the health risks, and that knowledge of the cellular processes may contribute little to the achievement of this objective. However, further investigations of asbestos cancers may provide valuable clues for the elucidation of mechanisms of carcinogenesis.

[1] Unpublished data.

SUMMARY

Studies in recent years have indicated that physical factors are deeply involved in the etiology of lung diseases associated with exposure to asbestos dust, and these studies now offer explanations for some of the biological observations. The physical characteristics of the fibres which form the basis of these suggested explanations are fibre diameter, fibre length and fibre morphology, the central parameter being fibre diameter. In this paper, physical factors are discussed as possible etiological mechanisms, and the apparent marked influence of fibre size in two very recent intrapleural inoculation experiments is described.

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