THORAX

Review

Role of asbestos and other fibres in the development of diffuse malignant mesothelioma

Descriptions of diffuse malignant mesothelioma date from the nineteenth century[1] but it was not until 1960 that Wagner *et al*[2] described a series of cases of pleural mesothelioma from South Africa and linked them to crocidolite asbestos exposure. Malignant mesotheliomas may arise from the pleura, peritoneum, and pericardium and all may be associated with asbestos exposure. Malignant mesothelioma of the pleura should be distinguished from the so called localised pleural mesothelioma (pleural fibroma), which is rarely malignant[3] and which is not associated with asbestos exposure. Malignant mesothelioma is an uncommon tumour with an annual male incidence of 7–13/1 000 000 and a female incidence of 1–2/1 000 000 in the United States.[4] In Great Britain the death rate (equivalent to the incidence) in 1983 was 17·5/1 000 000 for men and 3·2/1 000 000 for women.[5] The average age at presentation is about 60 years but occasionally cases have occurred in children and young adults.[6 7] There is a long latent interval between first exposure to asbestos and the development of the tumour, usually over 20 years and averaging 30–40 years, which is unaffected by age at first exposure.[8]

Mesothelioma has a characteristic but not pathognomonic macroscopic appearance. It shows considerable histological diversity and its ability to mimic other tumours often makes diagnosis difficult. Good, well illustrated histopathological descriptions of these tumours are available[9–11] but are beyond the scope of this article. There is no satisfactory treatment at present and the prognosis is very poor; most patients die within 18 months of diagnosis.

Most cases of malignant mesothelioma are associated with asbestos exposure but other causes are recognised.[12] Since the paper by Wagner *et al* in 1960[2] there has been an explosion of research and scientific publications on the topic and controversy over the roles of the different fibre types and their capacity to cause disease. There are several reasons for this controversy: (1) the scarcity of populations exposed to only one fibre type; (2) the long latent periods between exposure and the development of the disease; (3) the problems of diagnosis; and (4) the lack of satisfactory data on the airborne fibre levels to which workers have been exposed.

This review is an attempt to synthesise and put into perspective the current information contributed by epidemiological, pathological, and mineralogical investigations to our understanding of the role of the various mineral fibre types in the development of malignant mesothelioma. The evidence from in vitro and in vivo experiments will also be considered and their relevance to the human disease discussed.

Mineralogy

In this paper I use the term fibre for any fibrous inorganic or organic substance possessing a length to diameter (aspect) ratio of more than 3:1. Fibres may be classified into two major groups—natural and synthetic. The natural group includes the asbestos family and other acicular (asbestiform) fibres such as attapulgite, sepiolite, and zeolite (including erionite). Erionite, one of the fibrous zeolites, is found naturally in volcanic rocks. In some areas of Turkey it is similar in its physical characteristics to crocidolite but appears to be even more dangerous. The synthetic group contains over 70 minerals, including glass fibres, rock wool, slag wool, and ceramic fibres. These man made mineral fibres are being used increasingly and substituted for asbestos but as yet there is little information about their health effects. There is concern that they may ultimately cause diseases similar to those resulting from asbestos exposure. Reports of an excess of lung cancers among slag wool workers, in both Europe and the United States, have appeared but whether this is due to the slag wool itself, to contaminants, or to other factors is not yet clear.[13] More long term studies, preferably including mineralogical examination of lung tissue, are needed to clarify this problem.

The term asbestos covers a group of naturally occurring inorganic, fibrous, crystalline, hydrous silicate minerals that possess high tensile strength, stability, and thermal properties. This group of minerals is widespread in nature and has been found in Arctic ice samples from 10 000 years ago.[14] There are two major groups—namely, serpentine and amphibole (fig 1). Serpentine includes the most commonly used asbestos mineral, chrysotile (white asbestos), whereas the amphibole group includes several fibre types, such as crocidolite (blue asbestos), amosite (brown asbestos), tremolite/actinolite, and anthophyllite. Chrysotile, crocidolite, and amosite have been the most commonly used industrially. Anthophyllite was exploited commercially in Finland up to 1974; it sometimes contaminates amosite and some chrysotile and talc deposits.[15] Tremolite has recently been recognised as an important contaminant of some chrysotile, talc, and vermiculite deposits.[16] These fibres have different chemical, physical, and biological properties and consequently different health effects. The physical dimensions and shape are particularly important in relation to their health effects.

The electron microscope shows that chrysotile is composed of very uniform fibrils that tend to form curly bundles, whereas the amphibole fibres are straight and rigid with parallel sides. The amphiboles vary in their aspect ratios and this influences their pathogenicity (fig 2).
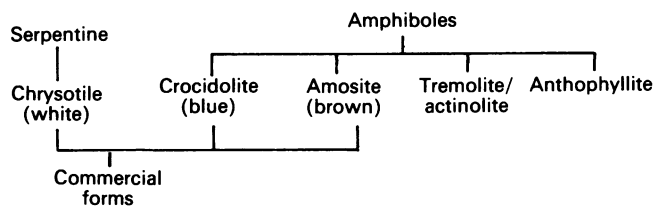

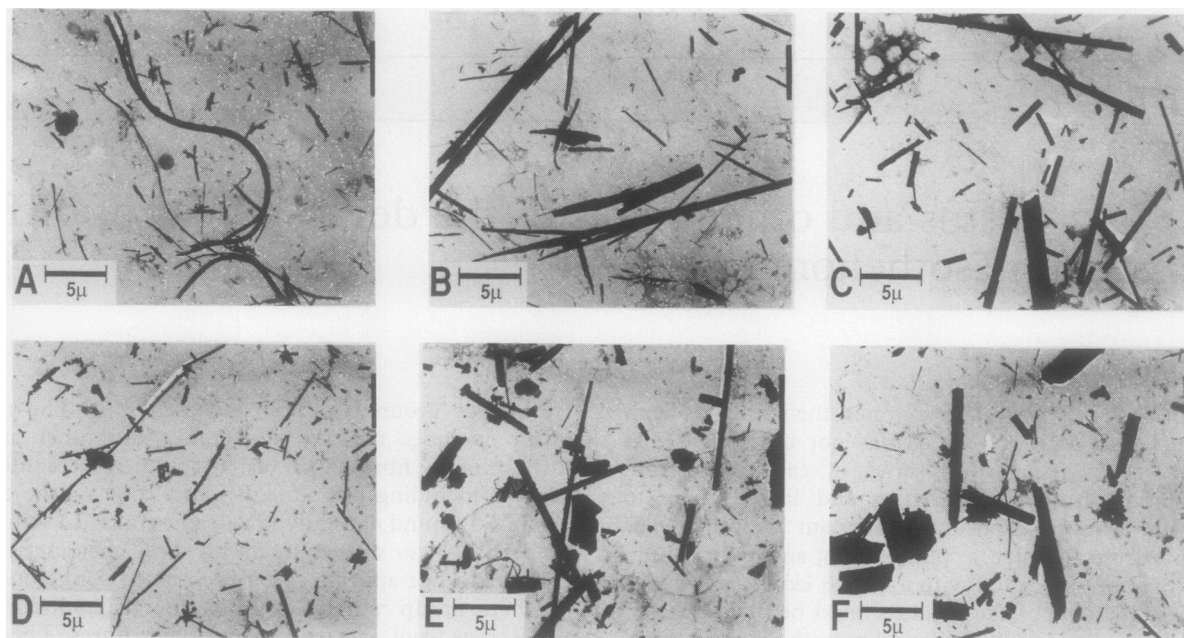*Figure 1 Classification of asbestos fibres.*

Figure 2   Transmission electron micrographs of mineral fibres: A—chrysotile; B—tremolite; C—amosite; D—crocidolite; E—anthophyllite; F—erionite. Reproduced by courtesy of D M Griffiths.

DEPOSITION, DISTRIBUTION AND CLEARANCE OF FIBRES

Information about the deposition of asbestos fibres within the lungs comes largely from animal studies. These have shown that the curly chrysotile fibres are more likely to be intercepted in the large airways, whereas thin, short amphibole fibres penetrate more deeply.[17] After several months these tend to become localised in subpleural foci.[18] Animal studies have suggested that interstitial fibrosis occurs in localised areas where the fibre concentration is greatest.[19] Some corroborative evidence has come from human studies but these have produced conflicting results. In cases with exposure to asbestos but without fibrosis Sebastien *et al*[20] found an accumulation of asbestos fibres, particularly chrysotile, in the peripheral areas of the lung; but in those heavily exposed to asbestos who had fibrosis, however, the periphery of the lower lobe differed from the other areas of the lung. The smallest concentrations of fibres were present in the periphery of the lower lobe but they were the larger fibres. Short chrysotile fibres were also found in parietal pleural plaques. Gibbs *et al*,[21] however, found that in cases of asbestos related diffuse pleural fibrosis the numbers of chrysotile fibres did not differ significantly between central, subpleural, and visceral pleural regions, but that the levels of amphiboles were much lower in the pleura than in the other sites. Nevertheless, occasional amphibole fibres were found within the visceral pleura.

There appear to be substantial variations in fibre accumulation within very small areas of the lungs. When examining different samples of subpleural tissue in nine cases with exposure to asbestos Churg and Wood[22] found mean within case ratios of maximum to minimum fibre concentrations of 7·5 for amosite and crocidolite, 7·0 for tremolite, 3·8 for chrysotile, and 4·0 for non-asbestos fibres. When Churg and DePaoli[23] examined fibre concentrations within the lungs of three groups of chrysotile miners and millers (11 who had died within two years of last exposure, seven who had died 12–15 years from last exposure, and five who had died more than 20 years after last exposure); they found no significant differences in length, width, aspect ratio, or concentration ratio of chrysotile to tremolite fibres between the three groups, suggesting that differences in fibre retention must reflect events occurring relatively early after inhalation. In rats exposed to asbestos by inhalation the amount of retained amphiboles increased linearly over time, whereas chrysotile after a relatively short time reached a steady state with equalisation between removal and deposition.[24] Preferential clearing of short fibres also appears to occur in experimental animals, so that retained fibre length increases with time.[25 26]

Animal studies

A critical review of experimental approaches to fibre induced lung diseases has been produced by Wagner.[27] Three main approaches have been used: (1) direct pleural implantation; (2) intratracheal injection; and (3) inhalation. Inhalation is the ideal method because it mimics most closely what happens in man, the material does not bypass the body's defence mechanisms, and the distribution of the fibres is more natural. The major disadvantages are that it is time consuming (tumours usually take two or three years to develop), complex, and prohibitively expensive. Moreover, except with erionite, there is a very low rate of malignant mesothelioma production. Implantation studies are cheaper and quicker, but they deliver very high doses of fibre to localised sites and bypass the normal defence mechanisms. They produce a relatively high rate of malignant mesothelioma. The results of these experiments may provide some useful information but should not be extrapolated to the human disease without corroborative evidence. Intratracheal experiments are also quicker and cheaper than the inhalation studies but again tend to deliver a large quantity of material to the trachea, which results in uneven pulmonary deposition, including large clumps that may block off airways. They also bypass the normal defence mechanisms. The classic implantation experiments by Stanton[28] have shown that fibres greater than 8 μm in length and less than 0·25 μm in width are the most potent in producing malignant mesothelioma, and this has been corroborated by Wagner *et al*.[29] When they

were given by inhalation Davies *et al* found that short fibres of amosite (almost all fibres less than 5 μm in length) were more likely to be retained in the lungs after 12 months than long fibres (more than 11% longer than 10 μm), but fibrosis developed only in the animals exposed to the long fibre preparation.[30] One third of the animals exposed to the long fibre preparation developed lung tumours or malignant mesothelioma but none of those exposed to the short fibred preparation. They also performed intraperitoneal injections and found that 95% of the animals given the long fibre preparation developed malignant mesothelioma, whereas only one animal exposed to short amosite fibres developed mesothelioma (4%). The mean tumour induction period 520 days. When Wagner *et al*[31] injected the pleural cavities of rats with three samples of tremolite of different physical configurations mesothelioma developed only in rats injected with the sample containing a high proportion of long, thin fibres. Although the experiments had some technical weaknesses, there appeared to be a good correlation between the physical characteristics of the dust, in vitro toxicity, and in vivo carcinogenicity.

Spontaneously occurring malignant mesothelioma has, however, been described in several animals, including rats.[32] Intraperitoneal injections of saline have produced malignant mesothelioma in animals of several species; a distinct background incidence appears to exist. Animal studies may provide useful information but care must be taken not to overinterpret them.

Human studies

CHRYSOTILE

Whether chrysotile contributes to the development of malignant mesothelioma has been controversial but the evidence that has come to light over recent years indicates that it is either very weakly carcinogenic or non-carcinogenic in man. Ninety five per cent of the world's production of asbestos is of chrysotile and the main producers are Canada, the Soviet Union, and Southern Africa. Studies of workers employed in the Quebec chrysotile production industry have provided very useful information about the relation of chrysotile exposure to lung disease. As the workers producing the asbestos would have had high exposures to chrysotile, estimates of disease in these workers should give an indication of possible risks to workers in other industries using chrysotile products. Asbestosis, excess lung cancers, and a few malignant mesotheliomas (a total of 10 up to 1980) have been found in the Quebec chrysotile miners and millers, and the risks appeared to increase with increasing dust exposure.[33] It was later realised that the chrysotile ore contained a small proportion of tremolite (less than 1%) and analyses of the fibre burden of. the lungs in some of the cases showed a substantial number of tremolite fibres.[34-36] Furthermore, the risk of malignant mesothelioma appeared to increase directly with the increasing ratio of tremolite to chrysotile fibres in the lung tissues.[34] In a report by Peto *et al*[37] 17 malignant mesotheliomas occurred in 850 men dying more than 20 years after exposure to asbestos at a Rochdale textile plant. These were initially attributed to chrysotile exposure because it was the predominant form of asbestos used,[38] but it became apparent that appreciable quantities of crocidolite had been used at the factory.[39] Further analysis of the lungs of workers who had been employed at the factory showed significantly raised levels of crocidolite.[40] A study comparing the mortality of two groups of women, one exposed to chrysotile and the other to crocidolite when producing two different types of gas mask during the second world war, showed that malignant mesotheliomas developed in the latter but not the former.[41]

A study by Thomas *et al*[42] of an asbestos cement plant that used chrysotile exclusively except during 1932–5, when crocidolite was used, found only two cases of mesothelioma and both occurred in workers exposed to crocidolite. Gylseth *et al*[43] examined lung tissues from four cases of malignant mesothelioma and four cases of lung cancer that had occurred in workers at a Norwegian asbestos cement plant. Although the asbestos used from 1942 to 1980 had been 91·7% chrysotile, 3·1% amosite, 4·1% crocidolite, and 1·1% anthophyllite, scanning electron microscopy and x ray microanalysis of lung tissue showed that 0–9% of the fibres were chrysotile whereas amphiboles ranged from 76% to 99%. The study by Berry and Newhouse[44] of the Ferodo friction products factory, where chrysotile was used apart from the occasional use of small quantities of crocidolite, found 10 patients in whom mesothelioma had occurred more than 10 years after first exposure. At least eight of these had been exposed to crocidolite whereas only three of the 40 workers chosen as controls had been exposed to crocidolite.

CROCIDOLITE

Crocidolite accounts for about 3% of the world's production of asbestos. Nowadays it nearly all comes from South Africa but in the past it was mined in Australia and Bolivia. Crocidolite is generally recognised as the most dangerous form of asbestos. Its use in several countries, including the United Kingdom, has been banned apart from very special applications. Its production continues, however, though it is not clear where the material is being used. The original discovery of an association between malignant mesothelioma and exposure to asbestos by Wagner *et al*[2] was in subjects exposed to crocidolite in the North West Cape region of South Africa. An appreciable number of malignant mesotheliomas have developed in women who produced military gas masks containing crocidolite.[41 45] In some cases exposure was very short—only four months. There is little reliable information, however, about the levels of fibres to which crocidolite workers have been exposed apart from some preliminary data from 6506 men employed in crocidolite mining and milling in Wittenoom, Western Australia, during 1943–66. These men were followed to the end of 1980, when 31 had developed mesothelioma;[46] no deaths from malignant mesothelioma occurred in workers who were employed for 90 days or less but men employed for longer periods showed about a 10 fold increase in mortality, with little indication of a gradient of increasing mortality with increasing duration of employment. There was a strong relation between death from malignant mesothelioma and the year of first employment but only weak evidence of an effect from intensity of exposure.

Interestingly, the incidence of malignant mesothelioma is strikingly lower in those exposed to crocidolite obtained from the Transvaal than in those exposed to the Northern Cape asbestos,[47] with hardly any reported cases following exposure to Transvaal crocidolite but hundreds following exposure to asbestos from the Northern Cape. This may be because the Transvaal crocidolite has a greater diameter than that from the Northern Cape.[48] In the United Kingdom most cases of malignant mesothelioma appear to be associated with crocidolite exposure.[49 50]

AMOSITE

Amosite accounts for about 1% of the world's production of asbestos and comes from South Africa. Less is known about its disease potential than that of crocidolite and chrysotile because populations exclusively exposed to it and to no other types of asbestos are rare. Webster[47] reported 232 cases of malignant mesothelioma from South

Africa, of which 78 developed in miners and millers of asbestos; of these, 75 were associated with the mining of Cape Blue (crocidolite) and two had exposure to amosite asbestos only. Factory workers from Patterson, New Jersey, where it was claimed that exposure was only to amosite and not to other forms of amphibole, have developed a large number of malignant mesotheliomas, with a particularly large number of peritoneal forms.[51-54] These studies, however, were criticised by McCullagh,[55] who suggested that insufficient attention was given to other possible sources of asbestos exposure before entry into the cohort under study. In the absence of any published studies of lung fibre analyses in these cases we cannot be certain that they were not exposed also to crocidolite. Mineral analyses of lung tissues have been performed on a few North American insulation workers and crocidolite as well as amosite has been found in some (F D Pooley and A R Gibbs, unpublished observations). Acheson *et al*[56] studied 5969 men employed at a factory (Cape Boards, Uxbridge) that manufactured insulation board from 1947 to 1979. Amosite was used predominantly, with small amounts of chrysotile but not crocidolite. Conditions were known to be very dusty in the plant before 1970. They found five mesotheliomas, a doubling of lung cancer risk, and nine deaths from asbestosis up to 1980. A study of the mineral content of the lungs from some of the workers who have died is under way but the results are not yet available. Amosite is generally agreed to be less carcinogenic than crocidolite but how much less is not certain.

TREMOLITE/ACTINOLITE
These minerals exist in nature in several physical forms and this appears to be important in determining what type of disease, if any, they cause. A considerable amount of evidence links the development of malignant mesothelioma with both occupational and environmental exposure to tremolite/actinolite fibres. Mineral ores from several industrial sources are contaminated by tremolite. The Quebec workers who mine and mill asbestos that is predominantly chrysotile are also exposed to tremolite, which is less than 1% of the ore. In the workers who show an excess risk of malignant mesothelioma, lung cancer, and fibrosis,[33] however, examination of the lung tissue has shown a high tremolite content,[57 58] whereas chrysotile had accumulated to a much smaller extent. At Libby, Montana, vermiculite, a micaceous mineral used in insulation, construction, and agricultural products, is mined and milled. The ore is contaminated by about 2% tremolite/actinolite fibres and it is of high aspect ratio.[59] These workers have an excess of malignant mesotheliomas and lung cancers, believed to be caused by exposure to tremolite.[60 61] Seven cases of mesothelioma were found in a Swedish cement plant where the workers were exposed mainly to chrysotile asbestos but also to smaller amounts of commercial amphiboles. The geometric mean concentrations of total amphiboles (tremolite and crocidolite) in lung tissue from the patients with mesothelioma were significantly higher than in exposed workers who had not developed mesothelioma.[62]

There are now several reports of non-occupational malignant mesothelioma occurring in different geographical locations where inhalation of tremolite fibres has been implicated. Baris *et al*[63] reported four patients with pleural malignant mesothelioma from a small Anatolian village, Caparkayi, in central Turkey. Tremolite was found in the lung tissue of one patient. It was suggested that the tremolite was inhaled from the walls of houses plastered with white stucco. Malignant mesotheliomas have also been reported in other Turkish districts where there are tremolite deposits that are quarried for use in

whitewash.[64] Boutin *et al*[65] have recorded five pleural malignant mesotheliomas in people living in north east Corsica, where there are numerous asbestos outcrops. Airborne samples have shown high tremolite concentrations; heavy asbestos burdens have been present in the lungs of the mesothelioma patients. Tremolite has also been implicated as the cause of malignant mesothelioma in Cyprus[66] and in Metsovo, Greece.[67] There is strong evidence that the potential for disease is associated with the physical configuration of the tremolite, and this is supported by the behaviour of the fibres in in vitro test systems.[31]

ANTHOPHYLLITE
Anthophyllite has been exploited in Finland and has been used as a cheap filler and as an insulation material. Pleural plaques have been found not only in anthophyllite miners but also in several hundred people living near but not working in the mines.[68] A study of asbestos disease in Finland found no cases of mesothelioma in workers exposed to anthophyllite only.[69] A recent study of 19 cases of mesothelioma from Finland showed a predominance of anthophyllite in the lungs in six cases.[70] Anthophyllite was the most common amphibole found in the reference groups, however. Moreover, the analyses were carried out by scanning electron microscopy, which may have failed to detect very fine crocidolite fibres. The study is therefore inconclusive. Anthophyllite has a much greater diameter before milling than other commercially important amphiboles. Transmission electron microscopy of anthophyllite fibres in the lungs of workers from the Finnish anthophyllite mines showed a median diameter of 0·6 μm.[71] This may account for the low mesothelioma potential of anthophyllite.

NON-ASBESTOS RELATED MESOTHELIOMAS
In the United Kingdom some 10–20% of cases of malignant mesothelioma are unrelated to asbestos exposure. These patients with no history of asbestos exposure have a lung mineral content similar to that of normal control subjects.[72] In nearly all of these no cause can be found. Other causes of malignant mesothelioma have been proposed,[12] including radiation, other minerals (such as silica, beryllium, and nickel), organic chemicals, viruses, and chronic inflammation. Spontaneous malignant mesothelioma has been described in various animal species, including the hamster and the rainbow trout.[73] The evidence linking radiation with mesothelioma appears to be reasonably strong. Mesotheliomas have developed, in the absence of known exposure to asbestos, in areas of the body that had been irradiated many years previously[74] but these are rare. The other possible causes listed above are very speculative, with few data to support them.

There is clear evidence that exposure to fibres other than asbestos may cause malignant mesothelioma in some areas of the world. There are certain villages in Turkey (Karain) where the houses are made out of volcanic material containing a fibrous zeolite called erionite. Inhabitants of these villages have a very high incidence of malignant mesothelioma.[75] In experimental studies erionite has produced the highest rate of malignant mesothelioma.[76]

Conclusions
It is unfortunate that asbestos is often thought of as one mineral and that equal weight is sometimes given to all types for disease potential. Animal experiments provide useful information but should not be extrapolated too readily to man. Animal studies indicate that the physical characteristics of the fibre are important in disease causation. Recent human studies show that chrysotile has a

much lower potential for causing disease than the amphibole minerals. There appears to be no good reason to ban the use of chrysotile asbestos and the policy of removing intact white asbestos from public buildings seems misplaced and wasteful of resources. It is better to use, with sensible precautions, materials that have been well studied than to rush into replacement with non-asbestos materials that have not been around for long enough for us to understand their disease producing potential.

A R GIBBS

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