CARCINOGENESIS AND MINERAL FIBRES

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In a previous issue of British Medical Bulletin we discussed the epidemiology of the asbestos cancers (Wagner et al. 1971). In the intervening years it has been realized that the problem may not be restricted to asbestos fibres, and we now feel justified in enlarging the field to include other mineral fibres, both man-made and naturally occurring. The number of other mineral fibres being exploited has burgeoned over the last few years. In addition, there are a large number of natural fibres that are released in mining and tunnelling. These have been known to geologists for many years, but only recently have they been considered as possible environmental and occupational hazards.

The industrial proliferation of mineral fibres has been partly due to attempts to find a substitute for asbestos and partly to an increasing need for a cheap and reliable source of insulating material to counter the ever-threatening fossil fuel crisis.

In 1971 we gave the available epidemiological evidence, based on co-ordinated international study, which clearly demonstrated that there was an association between exposure to asbestos dust and the development of carcinoma of the lung and diffuse mesotheliomas of the pleura and peritoneum. We further stated that there was evidence to show that cigarette smoking was a significant exacerbating factor in lung cancers but not in mesotheliomas. The reasons for implicating the blue asbestos (crocidolite) as the major industrial cause of the mesotheliomas were stated, but did not rule out the possibility that other types of asbestos were involved, though, if so, to a lesser extent.

A significant observation was that of Timbrell et al. (1970), who showed that the ultimate diameter of crocidolite fibres was less than that of amosite. Chrysotile, although the fibres have a diameter less than that of crocidolite, occurs in a woven coil formation, and the total coil diameter has to be considered from the aerodynamic standpoint. On this basis the chrysotile fibrils appear as coarse fibres and would find difficulty in reaching the pleural surfaces through the peripheral airways.

It has been shown that alveoli arising directly from the respiratory bronchiule are the sites at which interstitial fibrosis or asbestosis is initiated. Fibres up to 3 μm in diameter are theoretically capable of penetrating to these airways. In practice, however, it is most unusual to recover a fibre of more than 1 μm in diameter from the lung. The problem of significant length of fibre is still undecided. There is considerable evidence to support the hypothesis that a length of more than 5 μm is effective both in production of mesotheliomas and in pulmonary fibrosis. The upper limit of effective length is not known.

1 Types and Uses of Asbestos and Man-Made Mineral Fibres

Asbestos is at present considered to consist of six naturally occurring minerals (International Agency for Research on Cancer, 1977); these are crocidolite, amosite, anthophyllite, tremolite, actinolite and chrysotile (see Plate II). The first five minerals are members of one mineralogical group referred to as the amphiboles. They are very similar in crystal structure, being chain silicates, but they vary in their chemical composition. Crocidolite and amosite are iron-rich varieties, anthophyllite is a magnesium-rich mineral, while tremolite and actinolite contain a large amount of calcium together with magnesium. Chrysotile is a member of a completely different group of minerals referred to as the serpentine and is composed almost exclusively of magnesium in combination with silica. Basically, chrysotile has a sheet structure which curls to produce hollow tube-like fibres.

The annual world production of asbestos is still increasing and in 1976 reached 5 x 10^6 kg. Most of this was chrysotile and the remainder was amosite and crocidolite. Anthophyllite, tremolite and actinolite are not produced as individual minerals for industrial use, but they often occur as contaminants in other natural mineral products.

Asbestos has a large number of uses, well exceeding a thousand (Hendry, 1965), so that contact with the various minerals and possible exposure to asbestos dust by the general population is widespread. Chrysotile is the most widely distributed mineral and has been used extensively in construction, in insulation and in the production of frictional materials such as brake linings in automobiles, and is also employed exclusively in asbestos textiles. Amosite and crocidolite have been employed for reinforcement, insulation and fillers in a wide variety of products, crocidolite being preferred for use in situations where chemical resistance to acid attack was required. The introduction of legislation relating to the use and handling of crocidolite in 1969 has severely limited its use in Great Britain (Health and Safety Executive, 1970), and there has been a corresponding increase in the amounts of amosite and man-made mineral fibres employed in industry. In Europe one of the major consumers of crocidolite is the asbestos cement industry.

The concern surrounding the many uses of asbestos and its possible health effects upon the general population has stimulated efforts to replace these natural minerals with man-made fibre alternatives. These materials can be divided into three groups: namely the slag wools, rock wools, and glass wools and filaments. The materials of each group consist of glassy mineral fibres but with important differences in individual physical and chemical properties, which are dependent on their chemical composition. All man-made mineral fibres are made from a liquid melt at temperatures of 1000–1500 °C, but the methods of producing the fibres vary. Three basic methods of manufacture are employed (Klingholz, 1977). The first is performed by drawing; this consists of the production of a single
continuous fibre with a predetermined diameter. The other methods employ centrifugation or the dispersion of the liquid melt glass with a blast of hot gases, and both produce aggregates of fibres of different lengths and diameters mixed together with non-fibrous particles.

The chemical composition of man-made mineral fibre products varies considerably and can be controlled to ensure particular properties, especially resistance to chemical attack. The major chemical components of all fibre types are the oxides of silicon, aluminum and boron. Besides these major chemical components, all the various fibre groups contain combinations of other elements. Glass wools and filaments have sodium, potassium and barium in their structure together with small amounts of calcium, magnesium, iron and titanium, while the rock and slag wools have large amounts of the latter group of elements and smaller amounts of the former group.

All the man-made mineral fibres produced have glassy structures and are amorphous, while their physical sizes, i.e., length and diameter distribution, vary considerably and are dependent upon the method of production and the chemical composition. On average, commercially produced fibres of man-made minerals are considerably coarser than the fibres of the asbestos minerals, although specialized samples have been produced with average dimensions very similar to those of asbestos. They fall into three broad categories of fibre size, the first being the continuous filament glass fibres that are used in textiles and as a reinforcement for plastics and other materials; these products have fibre diameters of 9-25 μm. In the second category are insulation wools with fibres nominally 1-6 μm in diameter. The third category contains fibres below 1 μm in diameter; these are produced for specialized purposes such as scientific filter-paper. The methods of production and the size characteristics of man-made mineral fibre materials have changed over the years as manufacturers have sought to produce more-specialized materials for an increasingly diversified market. This has resulted in a reduction of the average fibre diameter.

Man-made mineral fibres are usually coated with bonding compounds to produce fabricated shapes and forms. In the past, insulation wool binders have included bitumen, urea and phenol-formaldehyde resin compounds. Today, innovations in binding agents based upon resin systems are continuously being made. Binders for continuous glass filaments are also becoming increasingly complex in composition.

There are other fibrous materials that are used industrially or occur naturally which are not classified either as asbestos or man-made mineral fibres. These include sepiolite, siliimanite, components of various clays such as fuller's earth, certain zeolite minerals and rutile. These materials are all silicates, with the exception of rutile which is a titanium dioxide mineral. When examined visually, many of these minerals cannot be recognized as being fibrous in character, and normally the fibrous particles they produce can be observed only at high magnification. The size characteristics of the fibres of these minerals often vary with their geological source. As well as being used industrially, some of them also occur very widely distributed over the earth's crust in many rocks and the soil, where they act as a local source of fibrous dust which can contaminate the environment, especially if the local climate is arid and the rock or soil is used for building or agricultural purposes. This is the case in certain areas of Turkey, where fibrous zeolite minerals and volcanic glass particles can be found in air-borne dust samples and have been related to an increased incidence of chest diseases (Baris et al. 1978). The similarity in morphology of one of these minerals and asbestos is illustrated in Plate II; at the same magnification, comparison is made between crocidolite, chrysotile, amosite, anthophyllite and sepiolite fibres.

2 Asbestos and Cancer

a Epidemiological Investigations

The evidence on carcinogenesis and asbestos has recently been documented (International Agency for Research on Cancer, 1977). It is established that exposure to all three commercial asbestos types—chrysotile, crocidolite and amosite—results in an increase in deaths due to lung cancer, and that this increase is dose related. For exposures to high concentrations the death rates relating to lung cancer may be increased over the background rates by a factor of five or more (e.g. in the UK: Doll, 1955; Newhouse, 1969; in the USA: Selikoff et al. 1964). This increase does not occur until at least 10 years after first exposure, as would be expected on the basis of the natural history of the disease (Geddes, 1979), and is not detectable epidemiologically until at least 15 years have elapsed.

The relationship between asbestos exposure and mesotheliomas is also established. The original association was with crocidolite mining (Wagner et al. 1960) and was confirmed by studies of populations exposed in factories manufacturing asbestos in the USA and the UK, which showed that mesotheliomas occurred after exposure to mixed dust containing amphibole (Selikoff et al. 1964; Newhouse, 1969). Mesotheliomas have been observed in a group of workers employed in an amosite factory (Selikoff, 1976), but there were seven excess lung cancers for each mesothelioma. In contrast, in the two groups of insulation workers studied by the same author there were two to three excess lung cancers for each mesothelioma, whilst for another factory there were almost as many mesotheliomas as excess lung cancers—a result also obtained by Newhouse & Berry (1979) in a group of factory workers exposed to mixed dust in London. Evidence of an association between exposure to chrysotile and mesothelioma comes from the study of chrysotile miners in Quebec (McDonald, 1978), but only seven mesotheliomas out of over 4500 deaths could be definitely attributed to chrysotile. Many of the men had not been exposed to heavy concentrations of chrysotile, but the relative scarcity of mesotheliomas leads to the conclusion that exposure to amphibole is much more likely to result in mesothelioma than in exposure to chrysotile. Exposure to amosite results in a risk probably not so high as that with crocidolite; this view-point is supported by the finding of Timbrell et al. (1970) that crocidolite is finer than amosite.

Mesotheliomas have been observed to occur after a very short or slight exposure to asbestos and this led to a belief that these tumours may not be dose related. However, this is an argument that cannot be sustained on scientific grounds and its weakness is illustrated by the fact that, after careful inquiry, Greenberg & Lloyd Davies (1974) were unable to find any evidence of asbestos exposure in 15% of the mesotheliomas occurring in England, Wales and Scotland in 1961-68. The mesothelioma risk is, in fact, dose dependent; this has been shown by Newhouse & Berry (1976) for both intensity and duration of exposure, and by Selikoff (1976) for duration of exposure. There is no evidence that short or slight exposure to asbestos does not result in a small increase in lung cancer risk.
Electron micrographs of dispersed samples of asbestos and absorbent clay; the latter was collected from a garage in South Wales. Note that the magnification of the absorbent clay sample is 10 times that of the other samples.
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but the excess cases, if they occur, could not be detected against the background of a high lung cancer mortality.

Selikoff et al. (1968) were the first to investigate the joint action of cigarette smoking and occupational exposure to asbestos in producing lung cancer. Their data were consistent with the two carcinogens acting multiplicatively or synergistically. A study in the UK (Berry et al. 1972) supported the view of a multiplicative effect, and Saracci (1977), in a review of all the evidence, has concluded that this is the most plausible hypothesis. The recent results of Selikoff & Hammond (1979) strongly support this. They found that, relative to men who neither worked with asbestos nor smoked, the death rate for lung cancer was five times higher for men who worked with asbestos but did not smoke; it was 11 times higher for those who smoked but had not worked with asbestos, whilst for those who both worked with asbestos and smoked it was 53 times higher. Men and women working with asbestos have even more reason to give up smoking than have smokers in the general population.

Since both mesotheliomas and lung cancer in excess are not detectable until 15 years, and usually longer, after exposure to asbestos, the epidemiological results are always relevant to levels of exposure that occurred at some time in the past. As an example, Knox et al. (1968) could not detect any excess lung cancer in workers in an asbestos factory who began their employment there after conditions had been improved in about 1933. In a continuation of this study Peto et al. (1977) showed that there were about twice as many deaths due to lung cancer as were expected. Thus it had taken 40 years to demonstrate the excess risk in the improved conditions. Another example was given by Newhouse & Berry (1976) who predicted that, amongst a group employed at an asbestos factory that closed in 1968, the number of deaths due to mesothelioma would reach its peak during the 1980s and would be similar at the turn of the century to that observed in the early 1970s.

b Animal Experiments

At the same time as epidemiological investigations were being carried out, animal experiments were being conducted to explore the relationship between asbestos and cancer. All the main types of asbestos, including anthophyllite, were shown to be capable of producing mesotheliomas in rats after intrapleural inoculation (Wagner et al. 1973). This method of application was criticized as being artificial, and experiments have also been carried out in which rats were exposed to asbestos dust by inhalation in specially designed cabinets (Wagner et al. 1974). These experiments produced some surprising results: in particular, although the crocidolite sample had produced more mesotheliomas than did the chrysotiles after intrapleural injection, after inhalation the sample of chrysotile from Canada produced as many mesotheliomas as did crocidolite; this was in spite of the fact that the retention of chrysotile dust in the lungs was very much less than that of crocidolite. This experiment has cast some doubt on the epidemiological evidence that crocidolite is much more hazardous than chrysotile as far as mesotheliomas are concerned.

As a result of work carried out during the 1960s, there was increasing support for the hypothesis that the carcinogenic effect of asbestos was mainly attributable to its size and shape rather than to its chemical characteristics. This led to the inclusion of fibres other than asbestos in animal experiments. Stanton & Wrench (1972) were the first to demonstrate that fibrous glass, when implanted into the pleura of rats, could produce mesotheliomas of the same form as occurred with asbestos. A similar result was obtained by Wagner et al. (1976), who produced mesotheliomas after the injection of a glass fibre mostly finer than 0.5 μm in diameter, but did not obtain tumours with a coarser fibre. Pott et al. (1976) extended this type of experiment to include other mineral fibres and they also obtained tumours. Stanton et al. (1977) gave results of an experiment in which 17 different samples of fibrous glass had been tested. These samples had been specially prepared and covered a wide range of diameters and lengths. Some of the samples produced pleural sarcomas in more than half the rats, and an analysis of the tumour response in terms of the size distribution of the fibres showed that the fibres responsible were fine in diameter and long in length. They suggested that the fibres found to be most carcinogenic were those less than 1.5 μm in diameter and greater than 8 μm in length.

The experimental results showing that glass fibre and other mineral fibres produced cancer in animals led to concern as to the safety of mineral fibres in industry. This concern was heightened by the fact that, because of the awareness of the health hazards brought about by using asbestos, there was a trend for substituting glass fibre for uses which had previously involved asbestos.

In these experiments it was possible to challenge some of the hypotheses that had been suggested. The idea that primitive oils and waxes adsorbed on to the fibres could be a possible cause of these tumours was put forward by Harington (1962). These oils did contain aromatic hydrocarbons including benzolepyrene. However, in a series of animal experiments with the use of asbestos samples free from oils and untreated fibres, we were able to show that the removal of the oils did not affect the tumour rate (Wagner et al. 1973). Another hypothesis put forward by Sunderman (1968) and supported by Webster (1965) was that the trace elements such as nickel and chromium, occurring with the fibres, played an important part. It was shown that chromium and nickel were present in greater quantities with amosite than with crocidolite. Amosite produced fewer mesotheliomas than did crocidolite after implantation experiments.

Using the consistent results from the intrapleural inoculation of crocidolite as a model, attempts have been made to alter the rate of mesothelioma production. The only significant result has been obtained by Margaret Wagner using newborn Wistar SPF rats. Sham thymectomies will significantly reduce the mesothelioma rate if the animals are subsequently inoculated intrapleurally with crocidolite; total thymectomies have no effect (Wagner, 1979).

3 Man-Made Mineral Fibres and Cancer

The effects that man-made mineral fibres have on health were reviewed by Hill (1977). There have been only two epidemiological studies providing data relating to the question of a possible association between occupational exposure and cancer. Enterline & Henderson (1975) studied a group of 416 men who retired between 1945 and 1972, after being engaged in the manufacture of fibrous glass insulation for, on average, 23 years. Of these men, 111 had died, including 20 who died of cancer compared with an expectation of 23, and five who died of cancer of the lung compared with an expectation of six. Bayliss et al. (1976) studied a group of 1448 men who were first employed in the 1940s and who worked for at least five years in
a fibrous glass insulation plant. A total of 376 men had died; 54 of these deaths were due to cancer compared with 64 expected, and 16 deaths were due to lung cancer compared with 20 expected. Analysis of the lung cancer deaths did not show any increase, relative to expectation, as the time since first exposure increased; for example, after more than 20 years since first exposure there were eight lung cancers compared with 12 expected. A survey showed that the mean concentration of glass fibres in the air of the plant was 0.08 fibres/ml, with a median length of 1.8 μm and a median length of 28μm, and that 20% of the fibres had a diameter of less than 1 μm.

Hill (1977) commented that “…the commercial production of fibres with nominal diameters of 1 μm or less has only been introduced to any extent in the last 10 years or so…” and also that there was evidence that much higher dust levels could occur with these dusts. Therefore, there is a need for further epidemiological research. A study is being co-ordinated by the International Agency for Research on Cancer (1978) covering 13 factories in seven European countries, and results are expected in 1981.

Although the possibility that occupational exposure to glass fibre might produce lung cancer or mesothelioma remains, the indications are that the risk is less than with asbestos and that the use of glass fibre and mineral wools as a substitute for asbestos—where this is technically feasible—is in the interest of the health of those involved in both production and use of the product. However, this will be true only if the manufacturers avoid the production of small-diameter fibres.

### 4 Naturally Occurring Fibres and Cancer

Baris et al. (1978) published details of an outbreak of pleural mesothelioma in Karain, a village in Turkey. In the period 1970–76, when the total population of the village averaged less than 700, there were 35 deaths from pleural mesothelioma; this cause was responsible for over 40% of the deaths. In a group of nearby villages, only two deaths due to pleural mesothelioma were found. Both deaths were of women who had emigrated from Karain, where they had spent their early years. Baris et al. (1978) considered various hypotheses, including the possibility of the causative agent being asbestiform fibres in the drinking-water.

Mesotheliomas have also been found in Tuscoy, another village in Turkey. Both Tuscoy and Karain are situated in an area of volcanic origin in which there was an abundance of soft rock of volcanic tuffs. This rock has been cut and used for building and some of the villagers use caves in the tuff for storage. A detailed analysis (International Agency for Research on Cancer, 1978) has shown that rock samples from the two villages in which mesotheliomas occurred contained fine erionite fibres—erionite is a type of zeolite. Fine erionite fibres were not found in samples from other areas. This study is continuing in order to try to establish the causative agent. The results are important, not only because of the public health problem in the villages concerned, but also because zeolite is being mined increasingly in other countries.

The realization that naturally occurring mineral fibres, if of certain size characteristics, are possibly carcinogenic has opened up new fields for investigation.

## Acknowledgements

We would like to acknowledge the help we have received from Dr P C Elmes, Dr Margaret Wagner, Dr M Chamberlain and Dr R Brown; and especially our thanks are due to Mr M Griffiths for providing the illustrations for Plate II.

### References

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