Asbestos Exposure – its Related Disorders

KIMON CONSTANTINIDIS, MD, *Medical Research Council, Pneumoconiosis Unit, Penarth, Glamorgan.*

SUMMARY – Unlike most other inhaled dusts, asbestos can produce at least three distinct diseases: asbestosis, lung cancer and mesotheliomas of the pleura and peritoneum. Workers with asbestosis are at greater risk of developing lung cancer than their healthy contemporaries and some studies have suggested that asbestos exposure without asbestosis increases the risk of lung cancer. Mesotheliomas of the pleura and peritoneum is a rare tumour but it has been found with ever-increasing frequency in persons exposed to relatively small amounts of asbestos; the latent period between exposure to asbestos dust and development of the tumour usually exceeds 20 years.

GENERAL AND HISTORICAL ASPECTS

Asbestos is the generic name given to certain varieties of fibrous mineral silicates which vary considerably in physical properties and chemical composition. Although asbestos has been known since antiquity, in recent years there has been an increased interest in the biological effects of exposure to asbestos dust. The commercially important types of asbestos are the serpentine chrysotile, which is the most widely used, and the hornblende (amphibole) group of minerals, crocidolite, amosite and anthophyllite. Around 3,000 BC anthophyllite was being used in Finland to strengthen earthenware pots, the first asbestos composite; the Chinese and Egyptians used cloth and mats of woven asbestos. The ancient historian Plutarch first used the name *asbesta*, a Greek word meaning inextinguishable or inconsumable, and it was then in use in lamp wicks as in the perpetual lamps of the Vestal Virgins. The Romans in ancient times found several uses in spinning and weaving for asbestos mined in Italy and Cyprus and Pliny referred to the use of respirators to avoid the inhalation of asbestos dust and made mention of asbestos shrouds used in cremations for the Roman *élite* to permit easy collection of the ashes for burial. In 1250 Marco Polo recorded that in the Tartar Empire he was shown textiles which resisted the might of fire. The modern asbestos industry dates from the 1880s, when large-scale development of huge deposits in Canada and Russia began.

CHEMICAL AND PHYSICAL DATA

The chemical composition of different types of asbestos from various localities has been reported by several authors (Sinclair, 1959; Timbrell, 1970; Morgan and Cralley, 1973). Chrysotile (white asbestos) is a hydrated magnesium silicate which usually occurs in seams close to the earth's surface ($Mg_3Si_2O_5(OH)_4$). The fibres may be long and flexible because of unique structure of tubular microfibrils. It is heat-resistant and some fibres may be heated to 3,000°F without being visibly affected. Chrysotile does not resist sea water, acids and alkalis. The mean value of the fibril diameters are generally in the range of 30 – 40 nm (Atkinson, Gettins and Richards, 1971). The fibril morphology is so unique that the mineral species can be identified on this basis alone with the use of a transmission electron microscope (Langer, Rubin and Selikoff, 1972). The largest commercial deposits are in the Ural Mountains and in Quebec Province. It is also mined in China, Cyprus, Italy, British Columbia, Southern Africa and the USA.

Crocidolite or blue asbestos is a hydrated sodium ferroso – ferric silicate ($NaFe(SiO_3)_2 FeSiO_3$). It is also known as Cape blue, because formerly it was mined only in Cape Province, South Africa. Its commercial value is mainly determined by its chemical properties. It is highly resistant to acids and alkali solutions, and is remarkably strong. The fibres may be soft or harsh but they always possess a high degree of elasticity.

Amosite, $(MgFe)0.SiO_2$, which occurs only in South Africa, is named after the initial letters of Asbestos Mine of South Africa, the name of the mine where it was first worked. The fibres possess superior heat resistance. It is unaffected by immersion in acids and it is fairly resistant to alkalis and salt water. Anthophyllite ($7Mg0.\ 8SiO_2.\ H_20$) is mainly produced in Finland and it is the least com-

mercially useful of the amphiboles. The fibres are brittle and short, sometimes soft and flexible. It is infusible, and resistant to acids and alkalis.

USES OF ASBESTOS

The uses of asbestos are multiple and more than 1,000 different uses in industry have been reported (Hendry, 1965). Asbestos is used in heat insulation (boiler and pipe packing, insulation blocks and boards, pot holders, gloves lining, ironing board covers, fire-fighting suits, sheets and ropes, firemen's helmets), in friction materials (clutch plates, brake lining, bearing packings), in the building industry (pipes for water and sewage, floor tiles, pipes for gas, ceiling board, artificial wood, cements, paint, roof coating), in electrical installations (insulating cables, electrical wires, switch boxes, tapes, condensers, spark plugs) and miscellaneous uses (automobile undercoating, life-jackets, clay for pottery and sculpture, cigarette filters, artificial snow, fire hose, mail bags, airplane wings, etc). From 1900, crocidolite was in demand in the shipbuilding industry because chrysotile was not a good insulating material when exposed to sea water, but it has now been replaced by amosite.

OCCUPATIONAL AND ENVIRONMENTAL EXPOSURE

Until recently large amounts of asbestos fibre escaped into the air from the mines and mills so that not only the workers but the whole population of the nearby towns and countryside have been exposed. Obviously the greatest exposure to airborne asbestos dust is likely to occur in the industry: mining, crushing, carding, spinning and formulation, all offer opportunities for heavy exposure. Asbestos is obtained from both deep and surface mines and most of it is bound into the parent rock in clumps and this, together with the use of dust suppression, has minimized the danger of asbestos exposure for the miners. The raw asbestos is crushed in mills to release the fibres suitable for spinning. Bagging of fibres used to be a very dusty process until the recent introduction of pressure-packing methods and leak-proof bags. Asbestos cement spraying has often been documented as a significant source of environmental exposure and the process has been stopped in some places. Asbestos is virtually indestructible and, therefore, it eventually has to be removed from ships, buildings, etc, when it is often very dry and the proportion of respirable fibres in the dust high; removing old lagging material usually takes place in confined spaces, increasing the risks of exposure to asbestos.

Workmen not directly involved in asbestos applications may receive massive dust exposure; fitters, joiners and general labourers are not classified as 'asbestos workers' and they are unaware of the dangers of dust inhalations and do not use protective overalls and respirators.

The risks attached to children living and playing near to asbestos processing factories has been well demonstrated by Wagner (1965), and housewives have developed mesothelioma as a result of undusting asbestos-contaminated overalls of their husbands (Newhouse and Thompson, 1965).

PHYSICAL AND CHEMICAL FACTORS AS AETIOLOGICAL MECHANISMS OF ASBESTOS DISEASES

Physical factors play a major role in the aetiology of asbestos diseases since they govern the respirability of the fibres and the efficiency of penetration of the different types of asbestos to various parts of the lungs. The first study on the aerodynamic properties of the fibres was carried out by Timbrell (1965) and subsequent inoculation experiments (Burger and Engelbrecht, 1970) have re-emphasised the importance of fibre length in relation to fibrosis; recent studies (Wagner *et al*, 1970) have indicated a relationship between fibre size and the development of mesotheliomas. Timbrell's hypothesis (Timbrell, 1973) explains why there is: 1) a higher risk of mesothelioma in mining and milling crocidolite than amphiboles; 2) a high asbestosis and lung carcinoma risk in mining anthophyllite but no mesothelioma; and 3) a low mesothelioma and low bronchial carcinoma risk in chrysotile mining and a higher mesothelioma and bronchial carcinoma risk in insulation workers exposed to a mixture of fibres (Gilson, 1973). So it has been found that the most important factor influencing the entry of the fibres into the lungs is the falling speed of the particle. It is a feature of a cylindrically shaped particle that the falling speed is related to the square of the diameter but not closely to the length. Fibres more than 3 μm in diameter mostly fall and

impact in the upper respiratory tract and are removed with the sputum. Fibres thinner than this, though they may be longer, can penetrate to the respiratory bronchioles and alveoli where they will be retained. Fibres longer than 200 μm tend to be thick and settle out quickly and are not inhaled. In Fig. 1 are shown the different sizes and shapes of the asbestos fibres. Chrysotile and the amphibole fibres will exhibit different aerodynamic behaviour if they are long but similar behaviour if they are short. Anthophyllite has the largest diameter of all and, therefore, less of it will penetrate into the alveoli and pleura; because of its size it cannot enter into the cells (except phagocytes) and produce mesothelioma. Crocidolite has the smallest diameter and has more chance of penetrating the alveoli and pleura than the amphiboles. Chrysotile has a small diameter but it is curly and, therefore, much less will reach the alveoli than would be anticipated from its diameter.

In South Africa the North Western Cape Province produces crocidolite and the Transvaal produces both crocidolite and amosite. The paradox is that in the NW Cape more than 100 mesotheliomas due to crocidolite have been seen, whereas in the Transvaal only one possible case of mesothelioma was shown in the 10 years preceeding 1969 (Wagner *et al*, 1971). Transvaal fibres, both crocidolite and amosite, are on average 27 times the volume of Cape fibres and therefore have a higher fibre settling rate and shorter time available for inhalation and less efficient penetration into the deeper parts of the bronchial tree.

The modes of action of asbestos as a chemical carcinogen have been analysed by Harington (1973), who considered two possible mechanisms: 1) asbestos in the pure state may act as a carcinogen, possibly as a macromolecular iron or metal complex in an analogous way to iron-dextran; and 2) asbestos fibres in the impure state may act in conjunction with trace metals known to be carcinogenic, with oils and other organic matter or with a combination of both.

CARCINOGENICITY STUDIES IN ANIMALS

In inhalation experiments carcinoma of the lungs was observed in rats repeatedly exposed to chrysotile dust at a mean concentration of 86 mg/m³ for 30 hours per week (Gross *et al*, 1967). Within 16 months 20 out of 72 rats developed adenocarcinoma and 4 squamous cell carcinoma, while no tumours occurred in 39 controls. In another experiment (Wagner, 1972), 415 rats were exposed to all types of asbestos dust at different lengths of exposure, 233 rats for 7 hours for only one day and 182 rats for 5 hours a day for 90 days, at a concentration of 12 mg/m³. At the end of the 90-day period of exposure, the amount of dust in the lungs of the animals exposed to chrysotile was approximately one-sixth of that found in the animals exposed to amphibole samples. One squamous carcinoma of the lung was seen in the long exposure to crocidolite group and mesotheliomas were observed in three rats, one in the group with long exposure to crocidolite and two in the shorter period group, one with amosite and one with crocidolite.

Intratracheal injection in rats (Pyler and Shabad, 1973) has shown that chrysotile promotes the carcinogenicity of benz (a) pyrene.

Intrapleural administration of asbestos in rats (Wagner and Berry, 1973) has produced mesotheliomas in varying numbers: crocidolite 61%, amosite 36%, anthophyllite 34%, Canadian chrysotile 30% and Rhodesian chrysotile 19%. The authors concluded that it seemed unlikely that the presence of oils and waxes played a significant part in the development of mesothelioma.

Intraperitoneal injection of crocidolite and chrysotile (Reeves *et al*, 1971) can produce mesothelioma while injection of amosite failed to do so.

Mesothelioma in pleura and peritoneum has also been produced by other workers in rats and rabbits (Gross *et al*, 1967) and hamsters (Smith *et al*, 1965).

MEDICAL MANIFESTATIONS OF ASBESTOS DISEASES

Exposure to asbestos dust can produce pulmonary fibrosis, bronchial carcinoma, mesothelioma and pleural plaques. Laryngeal carcinomas have also been reported (Newhouse and Berry, 1973) and benign pleural effusions (Gaensler and Kaplan, 1971).

PULMONARY FIBROSIS (ASBESTOSIS)

The frequency with which asbestosis occurs in the exposed population depends on the length and degree of exposure and probably on the size and type of fibre. The

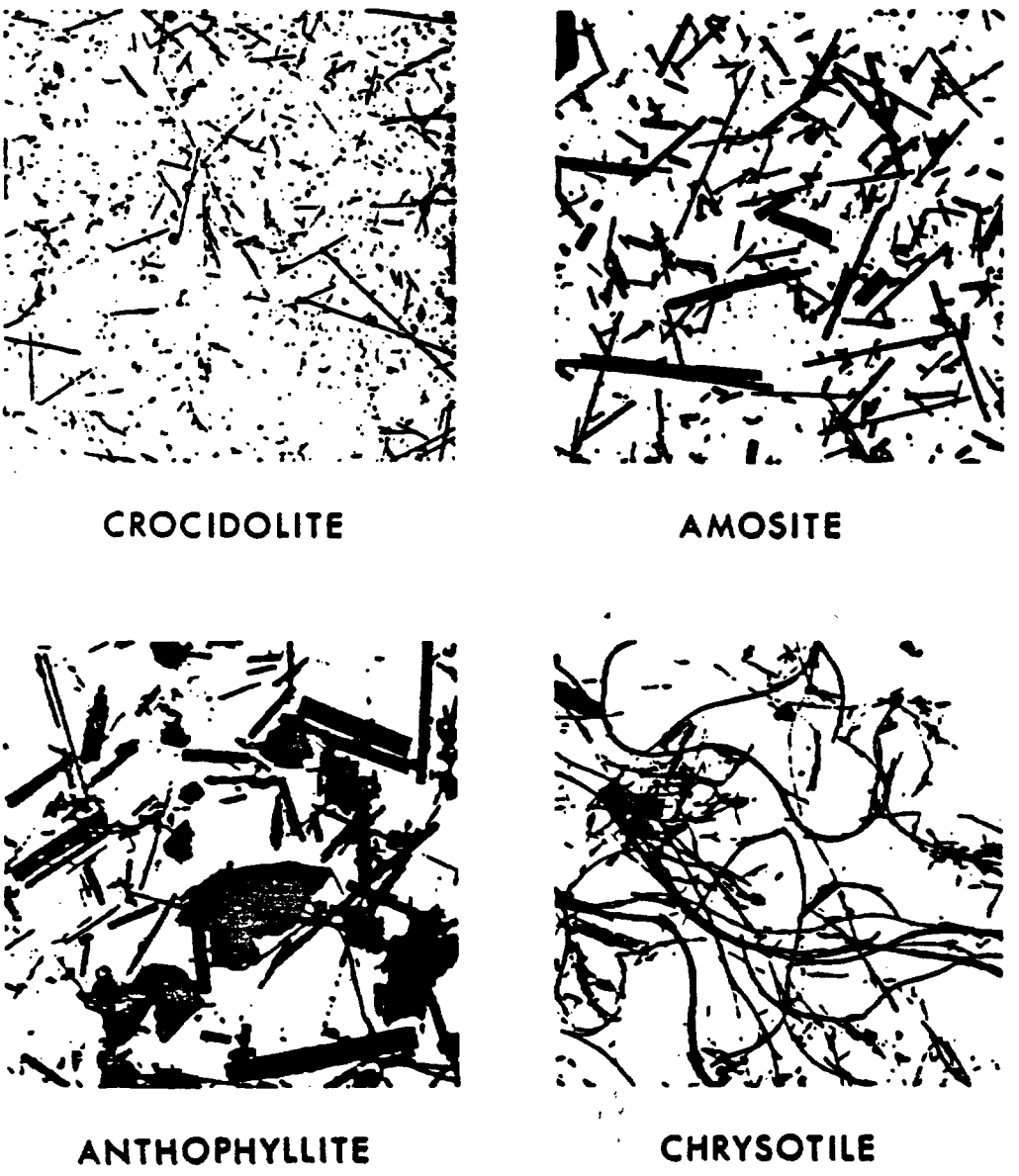

Fig. 1. Electron micrographs of crocidolite, amosite, anthophylite and chrysotile at the same magnification (x 1,7000). Characteristic features are the curved flexible chrysotile fibres in contrast to the rectilinear shape of the amphibole fibres and the small size of the diameter of the crocidolite fibres. (Courtesy of IARC and V. Timbrell.)

haze reco 20th pulm that (Mer reco prev althc effec torie each 196· take occu 197(grea (ferr auto Unit are dust of a num large

A posu betw of th gene remc evide stage arres at dc from repc 57.

CLI Th henc diag tion, finge bing asso occu muc sput and tight occa vanc (redu the f

hazards due to exposure to asbestos were first recognised in Europe at the beginning of the 20th Century. The first recorded case of pulmonary asbestosis in Great Britain was that reported by Murray (1907) and in 1930 (Merewether and Price) asbestosis was recognised as an industrial disease and preventive measures were taken. But although improvements in dust control were effective in most of the asbestos textile factories, the new cases of asbestosis reported each year are steadily increasing (Gilson, 1966). On the other hand, in a study undertaken in New York City in a non-occupational setting (Selikoff and Hammond, 1970), the authors failed to demonstrate a greater frequency of the finding of asbestos (ferruginous) bodies in the lungs of routine autopsies between 1934 and 1967. In the United States approximately 40,000 workers are exposed to asbestos in the insulation industry and about 50,000 in the manufacture of asbestos products (Seaton, 1975). The numbers exposed to demolition work are large but unknown.

Asbestosis can occur after quite short exposure but in recent years the average length between exposure and development of signs of the disease has been 10 years or longer. In general the disease is progressive even after removal from contact, but there is some evidence that if exposure ceases at an early stage progression may be slow or even arrested (Newhouse, 1967). The average age at death from asbestosis has gradually risen, from around 30 at the time of the original report of the disease to 41 in the 1930s and 57 in 1965 (Gilson, 1965).

CLINICAL FEATURES OF ASBESTOSIS

The onset of the disease is gradual and hence difficult to define. The main criteria for diagnosis include cough, dyspnoea on exertion, basal crepitations and clubbing of fingers and toes. Rapid development of clubbing may herald the development of an associated bronchial carcinoma. Cyanosis occurs in advanced stages. The sputum is mucoid. Asbestos or ferruginous bodies in the sputum indicate exposure to asbestos dust and not necessarily asbestosis. Chest tightness, inability to breathe in deeply and, occasionally, to yawn are common in advanced disease, due to increased stiffness (reduced compliance) of the lungs caused by the fibrosis (Parkes, 1973).

In general both the symptoms and physical signs of asbestosis are those of a diffuse interstitial fibrosis and have no pathognomonic features.

Asbestosis may be associated with an increased incidence of abdominal tumours, particularly ovarian neoplasms (Keal, 1960), peritoneal tumours (Br med J, 1964), gastrointestinal tumours (Selikoff *et al*, 1964) and with bronchial carcinoma (Dull, 1955). Some of the ovarian carcinomas were subsequently shown to be peritoneal mesotheliomas (Hourihane, 1964). The accepted evidence is that the bronchial carcinoma occurs in cases of definite asbestosis and that excessive exposure to all major types of asbestos used commercially are implicated (Wagner, 1975).

RADIOLOGY

The early changes appear mainly at both bases and spread upwards into the middle and upper zones (Fig 2). Accentuation of the normal vessel markings and a horizontal linear pattern resembling Kerley-B lines might appear (Fletcher and Edge, 1970). A "honeycomb" appearance may be seen in advanced stages of the disease. The area of both lung fields decreases due to contraction of the lungs and elevation of the diaphragm. Rheumatoid Caplan's nodules in asbestosis

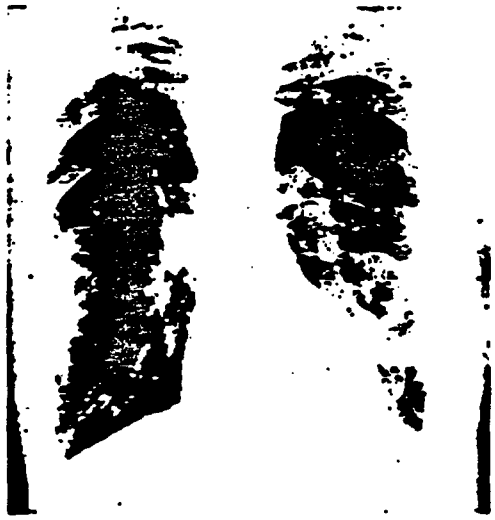

Fig. 2. Chest radiograph of a patient with asbestosis. There is evidence of pleurisy at the left base, plaques and irregular opacities spreading upwards.

have been reported (Richards and Barrett, 1958; Tellesson, 1961; Morgan, 1964; Mattson, 1971). Pleural plaques, calcified or non-calcified, may be present but are evidence only of asbestos exposure (Meurman, 1968).

The ILO U/C International Classification of Radiographs of Pneumoconiosis (1971) provides a means of systematically recording the radiographic changes in the chest provoked by the inhalation of various dusts including asbestos and takes into consideration the different sizes, shapes, profusion of opacities and the number of zones affected.

PHYSIOLOGY

In the diagnosis of asbestosis lung function tests are of particular value as the radiological findings are not specific. Characteristic functional abnormalities include progressive reduction in vital capacity and total lung capacity and reduction in diffusing capacity for carbon monoxide. Increased static recoil pressure and a decrease in lung compliance are usually found. Exercise tests show hyperventilation and arterial desaturation. Airways obstruction was not considered a feature of asbestosis (Williams and Hugh Jones, 1960; Thomson *et al*, 1965), though recent reports (Fournier-Massey *et al*, 1971; Muldoon and Warwick, 1972; Becklake, 1973) express the view that an obstructive function profile is not uncommon in the presence of asbestosis. A short clinical description and comments on lung function tests on a patient with asbestosis (the patient in Fig. 2) as a typical example are given below:-

A 52-year-old insulation engineer presented with increasing breathlessness on exertion and symptoms of chronic bronchitis with frequent chest illnesses during the winters of the preceeding six years. Because of these he had spontaneously reduced his cigarettes from 20 to 10 per day and avoided industrial fumes where possible. On examination he was short of breath, exhibited clubbing of the fingers, and bilateral wheeze and crepitations at the bases were present. The bronchogram was normal. Lung function tests were:-

	Observed	Expected
Forced Expiratory Volume (1)	0·9	3·1
Forced Vital Capacity (1)	2·2	4·1
FEV_1 X 100 - FVC%	41	72
Total Lung Capacity (1)	6·2	6·2
Residual Volume	3·9	2·0
RV X 100 - TLC%	63	35
Transfer factor (ml/min/torr)	11	27
Exercise ventilation a/c/O_2 (1/min)	0/28	23
Arterial blood Pco_2 rest/ex (torr)	71/70	90
Arterial blood Pco_2	49/38	40
A - aDO_2 rest/ex (torr)	19/35	20
Vd X 100 - Vt rest/ex	67/55	35/25

Comment: The low FEV_1 and increased residual volume are evidence of airways obstruction which is the main cause for the patient's breathlessness, which in turn is aggravated by exercise hyperventilation. The low transfer factor and increased alveolo-arterial oxygen tension during exercise indicate impaired pulmonary gas transfer which, in the absence of features of emphysema, is due to interstitial fibrosis. The high resting Pco_2 and physiological dead space suggest that the disturbance to gas exchange is aggravated by hypoventilation which may be a consequence of the airways obstruction.

These tests are sometimes difficult to interpret when applied to individuals with early disease because of the wide range of predicted normal values and the smoking habits and the polluted atmospheres where most asbestos workers live. Nevertheless, sequential studies, even using the simple ventilatory parameters of FEV and FVC at yearly intervals, will reveal deviation from normal and add precision to the diagnosis (Elmes, 1972).

PATHOLOGY AND IMMUNOLOGY

The distribution of the fibrosis in cases of asbestosis is predominantly in the lower part of the lungs, which is helpful in the differential diagnosis; in sarcoidosis, tuberculosis and allergic alveolitis it is predominantly in the upper zones and in fibrosing alveolitis it is more generalised. In mixed cases of asbestosis and silicosis, fibrosis may occur in the upper zones. Associated pleural thickening may help in the differentiation.

Microscopically in the early cases the lesions are confined to the respiratory bronchioles of scattered acini. Their walls are thickened by an increase in reticulin fibres. Asbestos bodies and fibres can be seen in the bronchioles and lumina (Fig. 3) lying free and ingested by phagocytes which may be multinucleate. Asbestos bodies consist of asbestos fibres which have been coated by iron and protein.

Demonstration of asbestos bodies in the sputum will provide confirmation of previous exposure. In experimental animals and probably in man they are found within a few weeks of exposure. In the established cases they are extraordinarily persistent and may be found 20 years or longer after exposure has ceased (Hinson, 1965). A whole-lung section with marked asbestosis is shown in Figure 4.

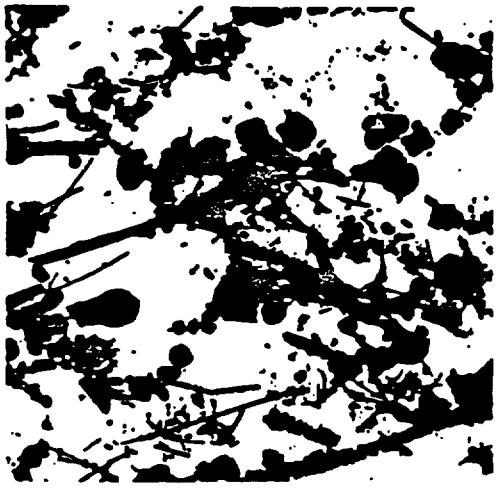

Fig. 3. Electron micrograph (x 3,000) showing asbestos (ferruginous) bodies and fibres in lung tissue. (Courtesy of V. Timbrell.)

Fig. 4. Whole lung section with marked asbestosis.

In the late stages of asbestosis the fibrosis spreads out into distal alveoli and eventually a widespread fibrosis occurs more marked at the bases with dilation of the uninvolved small airways (Webster, 1970). Histological studies would probably show asbestos bodies aggregated in areas of fibrosis. Lung biopsy is rarely indicated in the diagnosis of asbestosis (Scott and Hunt, 1975). Non-organ-specific autoantibodies, especially antinuclear autoantibodies, are found with increased frequency in asbestos workers and this appears to be related to the development of asbestosis and not to exposure to asbestos dust alone (Warwick, 1973).

CARCINOMA OF THE LUNGS

Carcinoma of the lungs was first reported in cases of asbestosis in 1935 (Lynch and Smith). The incidence of this tumour has increased rapidly and by 1964 60% of those workers in the United Kingdom diagnosed as having asbestosis to a degree warranting compensation developed carcinoma (Wagner, 1975). The excess of lung cancer varied considerably between surveys. In some of the surveys the workers were exposed to a mixture of fibres (Elmes and Simpson, 1971), or to chrysotile (Manusco and El-Attar, 1967) or amosite (Selikoff *et al*, 1972). The incidence of bronchial carcinoma was relatively low in a population of chrysotile miners in Quebec (McDonald *et al*, 1971) and particularly high among insulation workers exposed to amosite (Selikoff *et al*, 1972). The fact that cigarette smoking and asbestosis have a multiplicative carcinogenic effect has been established (Berry *et al*, 1972). The increased risk of developing carcinoma of the lungs appears to be related to the dose of asbestos dust inhaled (Newhouse, 1961). The commonest type of lung cancer appears to be adenocarcinoma (Whitwell *et al*, 1974). The primary site of origin of carcinoma in asbestosis was investigated in the United States of America (Isselbacher *et al*, 1953) and it was shown that about four-fifths arose in the lower lobes, whereas in the normal population more than 50% arise in the upper lobes. Some authors (Selikoff *et al*, 1964; Manusco and Coulter, 1965) suggested that an excess mortality from bronchial carcinoma may occur in workers exposed to asbestos who do not have clinically detectable asbestosis.

MESOTHELIOMA OF THE PLEURA AND PERITONEUM

The relationship between malignant mesothelioma and exposure to asbestos was first suggested by Wagner and his colleagues

(Wagner *et al*, 1960), who reported 33 cases from workers exposed to North West Cape of South Africa crocidolite asbestos. Mesothelioma was not found in the chrysotile or amosite mining areas of South Africa nor in the crocidolite area adjacent to the amosite deposits. An interesting finding was the long latent period, a mean of approximately 40 years between initial exposure and subsequent development of the tumour. The development of the malignancy was not related to the amount of asbestos dust inhaled. Since then reports from various countries have described several mesotheliomas in relation to asbestos exposure (Selikoff *et al*, 1965; Elmes *et al*, 1965; Thompson, 1970; Dels *et al*, 1971). Malignant mesotheliomas in childhood have also been reported; (Kauffman and Stout, 1964; Lieben and Pistawka, 1967; McDonald *et al*, 1970; Whitwell and Rawcliffe, 1971). In a review of 42,597 death certificates for children who died of cancer in the United States between 1960 and 1968, 31 had a diagnosis of mesothelioma and, of these, 13 were confirmed by data from hospital records. The illness presented with acute pleural effusion and encasement of the lung by tumour, with survival usually of less than six months (Grundy and Hiller, 1972). The case histories gave no information on environmental exposures.

Some of the patients may give a history of continuous exposure to asbestos over many years though a significant proportion gave a history of only transient exposure sometimes amounting to a few weeks only, several years previously. In a small proportion there is no history of exposure to asbestos dust. Unlike carcinoma there is no correlation between cigarette smoking and mesothelioma of the pleura and peritoneum. Mesothelioma is not associated with exposure to anthophyllite asbestos mined in Finland.

Clinical Features

In the majority of cases of pleural mesothelioma the patients appear in good general health when first seen at the hospital (Elmes and Simpson, 1976). Their usual presenting complaints are of chest pain and dyspnoea. Cough and haemoptysis are occasionally present. The pain may be localised or of a diffused generalised or pleuritic type. The shortness of breath is progressive and is related to lung compression and restriction of the chest wall by the tumour itself and associated pleural effusion and atelectasis. When the pleural effusion is small the fluid is usually non-haemorrhagic; however, during the course of the illness the patients develop at some time a haemorrhagic effusion, thickening first of the parietal and then of the visceral pleura, gross clubbing of fingers and toes, a raised sedimentation rate and a polymorph leukocytosis (Elmes, 1973). At the late stages the pleura becomes thickened, adherent and contracted. The contraction leads to a kyphosis towards the affected side, with a drooping shoulder and overlapping of the ribs (Stumphius, 1971). Clinical evidence of metastasis to other organs is rarely present, though local spread may occur to involve lymph nodes, ribs, mediastinum and pericardium with resulting enlarged supraclavicular lymph nodes, rib tumours or rib fractures, superior vena caval obstruction and cardiac tamponade. Local spread may lead to pleural effusion on the opposite side. Attempts to aspirate the effusion result in rapid re-accumulation and occasionally in subcutaneous lumps. Extension through the diaphragm is often followed by free spread throughout the peritoneal cavity with ascites and at autopsy it may be difficult to define which was the primary site. Hypertrophic pulmonary osteoarthropathy is not encountered frequently. Paraplegia may develop due to the impairment of the blood supply to the spinal cord.

Peritoneal tumours are more likely to occur in men with heavy exposure (Elmes and Simpson, 1976). A full but not distended abdomen with equivocal signs of ascites are commonly seen. Diffuse abdominal pain, loss of weight and symptoms of intestinal obstruction may occur. There is no clinical characteristic which distinguishes mesothelioma from other tumours with diffuse peritoneal spread, except evidence of past exposure to asbestos (Elmes, 1973). Symptoms and signs of a co-existent asbestosis may be detected. The average survival period in pleural or peritoneal tumour does not usually exceed the one year.

Radiology

Pleural mesothelioma presents as a pleural effusion or an irregular pleural thickening or more usually with a combination of both, where the irregular pleural thickening may be seen above the fluid level. The diaphragm may be raised and some shift of the

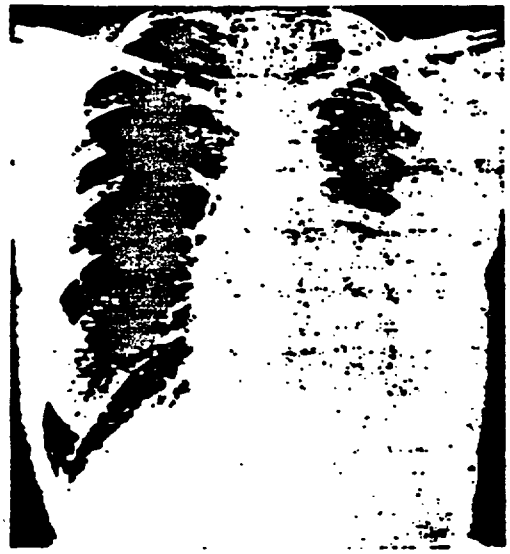

Fig. 5. Malignant mesothelioma of the lung in a patient exposed to asbestos dust.

mediastinal structure to the affected side usually occurs, suggesting the existence of an atelectasis (Fig. 5). In the early stages the lesion is unilateral but in the late stages it may spread across the mediastinum to the opposite side. A peritoneal mesothelioma may also spread through the diaphragm to both pleural cavities. Hydropneumothorax may occur either spontaneously or as a result of aspiration (Fig. 6). Pleural calcification may by visible, as may the pulmonary lesions of asbestosis.

Fig. 6. Hydropneumothorax in a case of pleural mesothelioma.

Pathology

Macroscopically the mesothelioma appears as a thick grey or white mass encasing the lung (Fig. 7). The tumour may vary in size from a very small mass to one that may occupy the entire hemithorax. The small ones tend to project freely into the pleural cavity, whereas many of the large ones develop adhesions to neighbouring tissue. There may be foci of degeneration, necrosis, haemorrage or calcification (Shabannah and Sayegh, 1971).

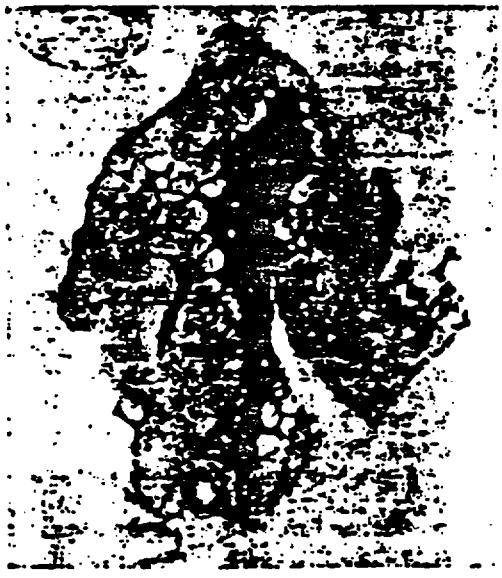

Fig. 7. Section of lung showing mesothelioma. (Courtesy of J. C. Wagner.)

Mesothelial tumours are characteristically pleomorphic in that they appear to be derived from both epithelial and connective tissue cells. Because of the resemblance of the histological appearances of malignant mesothelioma to the other malignant types it is very difficult to diagnose it with certainty by biopsy and to distinguish it from adenocarcinoma or fibrosarcoma. The presence of different elements in the tumour is strongly in favour of a diagnosis of

mesothelioma (Parkes, 1973). Hyaluronic acid in the fluid may help in the diagnosis (Wagner *et al*, 1962), though this is not always present and it may occasionally be found in pleural effusions associated with other tumours. Tumour cells in the lung and the hilar lymph nodes may contain dust particles, a phenomenon rarely appearing in carcinoma cells (McCaughey, 1979). Asbestos bodies and fibres are present in the lungs in the majority of cases.

Management

In an analysis of 300 cases of pleural and peritoneal mesotheliomas. Elmes (1976) concluded that conventional treatment by surgery, cytotoxic drugs and radiation is ineffective at relieving symptoms and may encourage the spread of the tumour; conservative treatment offers the best quality of life. Intrapleural administration of ribonucleic acid in cases of pleural mesothelioma with good results has been reported (Forbes and Mackaness, 1963).

PLEURAL PLAQUES

Pleural plaques associated with asbestos exposure are found predominantly on the parietal and diaphragmatic pleura. They are bilateral, most prominent in the lower halves of the pleurae, well circumscribed, irregular in shape, distributed beneath the surface of the ribs, sometimes spreading over the intercostal spaces (Fig. 8). They are not associated with adhesions (Meurman, 1966) and are better seen on anterior oblique views taken at 45°. Asbestos fibres may be seen but not asbestos bodies. Plaque formation does not appear to occur in the peritoneum. Microscopically the plaques consist mainly of avascular, acellular fibrohyaline connective tissue made up essentially of thick bundles of collagen fibres. Calcification of the pleural plaques occurs commonly and they should be distinguished from tuberculous pleurisy, calcified haematoma, silicosis, talc pneumoconiosis and old pneumothorax. A strong correlation exists between plaque formation and exposure to asbestos dust of all types, but an immediate cause-and-effect relationship has not been established. A latent interval of 20 years between first exposure and evidence of plaque formation is usual. Those environmentally exposed from birth develop plaques at an earlier age than those occupationally exposed. (Jones and Sheers, 1973). A higher than expected incidence of bronchogenic carcinoma when plaques are present has been reported (Fletcher, 1972).

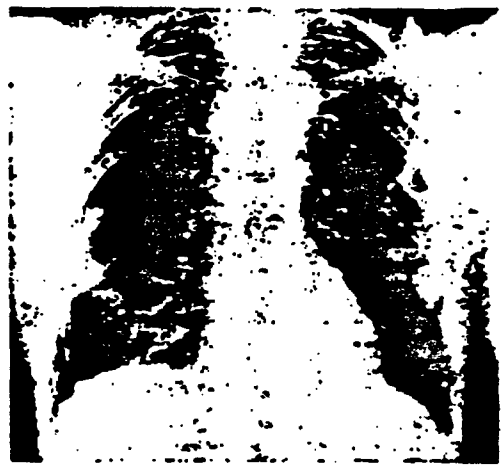

Fig. 8. Chest radiograph with bilateral extensive pleural plaques in a patient exposed to asbestos dust.

DISCUSSION

Asbestos exposure is now widespread and asbestos fibres have been found in the lungs of people without industrial asbestos exposure (Um Chang, 1971). Evidence of haematogenous spread of asbestos fibres was provided by several authors who reported this finding of asbestos fibres in the urine (Wyss, 1953) and spleen (Keal, 1960) and asbestos bodies in the thyroid (Keal, 1960) in cases of asbestos exposure, though these are chance findings without any pathological significance. There is no doubt that all the major commercial types of asbestos are able to cause carcinoma and the production of lung carcinomas in certain animals by all types of asbestos supports this conclusion. The epidemiological evidence in man, however, shows that there are clear differences in risk with the type of fibre and nature of exposure. There is also evidence that all commercial types of asbestos except anthophyllite may cause mesothelioma. The risk is greatest with crocidolite, less with amosite and apparently less with chrysotile. Population studies have shown that a proportion of cases of mesothelioma have no known association with exposure to asbestos. The successful management of the asbestos problem depends on the prevention of exposure of the workers to asbestos dust.

In the United States of America (NIOSH, 1972) and United Kingdom (DEP, 1970) have been laid down various standards for working with asbestos in industry. Measurement of asbestos dust concentrations in the atmosphere can be made by using the Royco Electronic Counter which has the advantage of eliminating human error in counting or by the gravimetric method using for example the Hexlet sampler or with the use of a microscope by counting the number of dust particles or asbestos fibres deposited from a measured sample of air.

So far there has been no evidence of an increased incidence of mesotheliomas in the general public as a result of asbestos air pollution and studies of the geographical distribution of cases of mesothelioma in the United Kingdom over a 10-year period (Gilson, 1970) indicate that the new cases are nearly all from areas where there has been a recognised occupational exposure to asbestos in the past. There is no evidence either that exposure of the general population to asbestos from beverages, drinking water, food or pharmaceutical preparations increase the risk of asbestos-induced diseases.

Acknowledgement

This review was mainly based on research work and surveys of my colleagues in the Research Pneumoconiosis Unit, J. C. GILSON, *former Director of the Unit,* P. C. ELMES, *Director of the Unit,* J. C. WAGNER *and* J. E. COTES. *The description of the physical properties and characteristics of asbestos fibres was based on research work of* DR V. TIMBRELL. *I wish to thank* MRS J. HENLEY *for her secretarial assistance and* MR R. HARRIS *for the prints of the chest x-rays.*

REFERENCES

Atkinson, A. W., Gettins, R. B., Richards, A. L. (1971): Morphology of chrysotile, presented at the second International Conference on the Physics and Chemistry of Asbestos minerals, Louvain.

Becklake, M. (1973): Lung function. In: *Biological effects of Asbestos.* P. Bogouski, J. C. Gilson, V. Timbrell, J. C. Wagner, Eds. Lyon: IARC, 31.

Berry, G., Newhouse, M. L., Turok, M. (1972): Combined effect of asbestos exposure and smoking on mortality from lung cancer in factory workers. *Lancet,* 2, 476.

British Medical Journal (1964) *Asbestos and Malignancy, (Leading Article).* 2, 202.

Burger, B. F., Engelbrecht, F. M. (1970): The biological effects of the International Standard reference asbestos samples (UICC) on the lungs of rats. *S Afr med J,* 44, 1271.

Criteria for a Recommended Standard, Occupational Exposure to Asbestos (1972): US Department of Health, Education and Welfare. National Institute for Occup Saf and Health. Washington.

Department of Employment and Productivity (1970): Asbestos: Health Precautions in Industry. *Health and Safety at Work,* 44, London: HMSO.

Doll, R. (1955): Mortality for lung cancer in asbestos workers. *Br J ind Med,* 12, 81.

Donna, A. (1970): Tumori sperimentali da amianto di crisotilo, crocidolite e amosite in ratto. Sprague – Dawley, *Med J Lavoro,* 61, 1.

Elmes, P. C. (1972): Asbestos. In *Clinical Aspects of Inhaled Particles.* D. C. F. Muir, Ed London: Heinemann, p 84.

Elmes, P. C. (1973): The natural history of diffuse mesothelioma. In *Biological Effects of Asbestos.* P. Bogouski, J. C. Gilson, V. Timbrell, J. C. Wagner, Lyon: IARC. 267.

Elmes, P. C. (1976): Management of mesothelioma, Report of Meeting. *Br J Dis Chest,* 70, 67.

Elmes, P. C., McCaughey, W. T. E., Wade, O. L. (1965): Diffuse mesothelioma of the pleura and asbestos, *Br med J,* 1, 350.

Elmes, P. C., Simpson, M. J. C. (1971): Insulation workers in Belfast. 3. Mortality 1940 – 66. *Br J ind Med,* 28, 226.

Elmes, P. C., Simpson, M. J. C. (1976): The clinical aspects of mesothelioma. *Q J Med,* XLV, 179, 427.

Fletcher, D. E. (1972): A mortality study of shipyard workers with pleural plaques. *Br J ind Med,* 29, 142.

Fletcher, D. E., Edge, J. R. (1970): The early radiological changes in pulmonary and pleural asbestosis, *Clin Radiol,* 21, 355.

Forbes, I. J., Mackaness, G. B. (1963): Mitosis in macrophages. *Lancet,* 2, 1203.

Fournier-Massey, G. G., Becklake, M. R., Rossiter, C. E., Gibbs, G., McDonald, J. C. (1971): Lung function patterns in relation to questionnaire, dust exposure and radiologic changes in Quebec asbestos workers. Presented at the Annual Meeting of the Canadian Thoracic Society, Toronto.

Gaensler, E. A., Kaplan, A. I. (1971): Asbestos pleural effusion. *Ann Intern Med,* 74, 178.

Gilson, J. C. (1965): Problems and perspectives, the changing hazards of exposure to asbestos, *Ann NY Acad Sci,* 132, 696.

Gilson, J. C. (1966): Wyers memorial lecture, 1965. Health hazards of asbestos. Recent studies on its biological effects. *Transactions Society for Occupational Medicine,* 16, 62.

Gilson, J. C. (1970): Asbestos health hazards, recent observations in the United Kingdom. In *Pneumoconiosis,* Proc Int Conf. H. A. Shapiro, Ed Hohannesburg, Cape Town: Oxford Univ Press, p173.

Gilson, J. C. (1973): Asbestos cancer, past and future hazards. *Proc roy Soc Med,* 66, 395.

Gross, P., De-Treville, R. T. P., Tolker, F. B., Kaschak, M., Babyak, M. A. (1967): Experimental asbestosis, the development of lung cancer in rats with pulmonary deposits of chrysotile asbestos dust. *Arch envir Hlth,* 15, 343.

Grundy, G. W., Miller, R. W. (1972): Malignant mesothelioma in childhood. *Cancer,* 29, 1216.

Harington, J. S. (1973): Chemical factors (including trace elements) as etiological mechanisms. In *Biological Effects of Asbestos.* P. Bogouski, J. C. Gilson, V. Timbrell, J. C. Wagner, Lyon: IARC, p304.

Hendry, N. W. (1965): The geology, occurrences and major uses of asbestos. *Ann NY Acad Sci,* 132, 12.

Hinson, K. F. W. (1965): Cancer of the lungs and other diseases after exposure to asbestos dust. *Brit J Dis Chest,* 59, 121.

Wagner, J. C., Gilson, J. C., Berry, G., Timbrell, V. (1971): Epidemiology of asbestos cancers. *Br med Bull.* 27, 71.
Wagner, J. C., Munday, D. E., Harrington, J. S. (1962): Histochemical demonstration of hyaluronic acide in pleural mesotheliomas. *J Path. Bact.* 84, 73.
Wagner, J. C., Sleggs, C. A., Marchand, P. (1960): Diffuse pleural mesothelioma and asbestos exposure in the North-West Cape Province. *Br J ind Med.* 17, 260.
Warwick, T. M. (1973): Immunology and asbestosis. In *Biological Effects of Asbestos.* P. Bogouski, J. C. Gilson, V. Timbrell and J. C. Wagner, Lyon: IARC, 258.
Webster, I (1970): The pathogenesis of asbestosis. In H. A. Shapiro, Pneumoconiosis, *Proceedings of an International Conference, Johannesburg.* Cape Town: Oxford Univ Press, p92.
Whitwell, F., Newhouse, M. L., Bennett, D. R. (1974): A study of the histological cell types of lung cancer in workers suffering from asbestosis in the United Kingdom, *Br J ind Med.* 31, 298.
Whitwell, F., Rawcliffe, R. M. (1971): Diffuse malignant pleural mesotheliomas and asbestos exposure. *Thorax.* 26, 6.
Williams, R., Hugh-Jones, P. (1960): The significance of lung function changes in asbestosis. *Thorax.* 15, 109.
Wyss, V. (1953): Presenza di aghi di amianto nelle urine di operai esposti al rischio asbestosico. *Rass Med Indust.* 22, 53.

Contributions to this Journal

Clinical articles, reports of clinical trials and contributions to the Skin Clinic and Spot Diagnosis are welcomed by the Editors. When accepted, this is on the understanding that they are not submitted to another journal.

Manuscripts should be typewritten, using double spacing, with a wide margin. Illustrations should be in the form of black and white glossy prints and should bear the figure number and author's name on the back. Each figure should be mentioned in the text, the legends being typed on a separate page. References should be listed in alphabetical order at the end of the paper, the abbreviations following the style of *World Medical Periodicals.* Every article which is accepted becomes the copyright of the publishers, Messrs Harvey & Blythe Ltd.

The Editors are not necessarily in agreement with opinions expressed by contributors.

THE BRITISH JOURNAL OF CLINICAL PRACTICE
216 CHURCH ROAD, HOVE, SUSSEX

Subscription Order Form

To HARVEY & BLYTHE LTD, Lloyd's Bank Chambers, 216 Church Road, Hove, Sussex BN3 2DJ

Subscription rates: ONE YEAR – UK: £10; Overseas: £15; USA and Canada: $30. All post free.

Please enter my subscription to The British Journal of Clinical Practice for One/Three years and continue until cancelled.

I wish to start with the ..... issue

NAME IN FULL .....
ADDRESS .....
.....
DATE .....

The Journal will be mailed free on written request to doctors in the United Kingdom and EEC countries on the NHS list, or the equivalent, and to postgraduate medical centres.

PRINTED BY GALE & POLDEN, ALDERSHOT, HANTS.