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PATHOLOGICAL ASPECTS OF ASBESTOSIS

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WIDESPREAD recognition of asbestosis dates from the work of Merewether and Price in 1930. They investigated 363 asbestos workers and concluded that there was a pneumoconiosis resulting from asbestos inhalation, that this condition shortened life, and that measures to diminish the atmospheric concentration of asbestos dust would reduce the incidence of the disease. In 1931 asbestosis was accepted as a compensatable disease in Great Britain and steps were taken to reduce the risk in the asbestos industry. 18 years later Wyers (1949) found that the age at death in this disorder had increased and that finger-clubbing had become more common. He suggested that these changes were due to a more chronic form of the disease resulting from improved dust control in the industry following the legislation of 1931. Currently however, the number of new cases of asbestosis in Great Britain is increasing, their frequency suggesting an incidence rate of at least five per thousand of those occupationally exposed (McVittie, 1965). Though earlier reports indicated that tuberculosis was common in asbestosis (Wyers, 1949; Gloyne, 1951; Bonser, Foulds and Stewart, 1955) it appears to be a rare complication at the present time (Buchanan, 1965).

Within the past few years it has become increasingly apparent that exposure to asbestos is associated with a further hazard. This is the development of malignant disease in the lung and serosal membranes and possibly the gastrointestinal tract. These neoplastic complications have given rise to much concern in view of the widespread use of asbestos in industry, its almost ubiquitous distribution in the modern urban community and the fact that current information does not permit the definition of safe levels of exposure.

Pathological studies have made an important contribution to knowledge of the effects of asbestos exposure and are reviewed in this paper.

Pathology of Asbestosis

The main pathological characteristics of asbestosis have been described in a series of papers by Gloyne (Wood and Gloyne, 1930; Gloyne, 1932 - 33; Wood and Gloyne, 1934; Gloyne, 1938). Our own experience is based upon pathological material from 69 cases who had been found to have clinical asbestosis in the London Hospital. Details of each patient are accessible (Hourihane, 1965a).

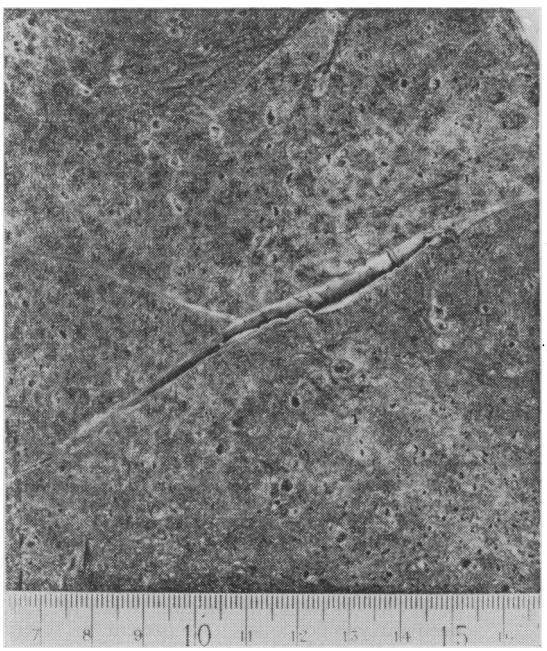

FIG. 1—Cut surface of lung showing moderately severe fibrosis. Confluence of fibrotic foci in lower right has given rise to an area of interstitial fibrosis.

The lung from an uncomplicated fully-developed case of asbestosis is typically small and firm with a dry cut surface. A fine nodular fibrosis can often be appreciated (Fig. 1), usually most severe in the lower parts of the lung and subpleurally where the fibrotic nodules may become confluent. Less frequently solid areas of fibrosis may develop in other parts of the lung (Gough, 1965). Cystic changes may be found in the air spaces between fibrotic areas giving rise to so-called "honeycomb lung," but this is rarely extensive. Bronchiectasis may also occur, and right ventricular cardiac hypertrophy is a common finding at necropsy.

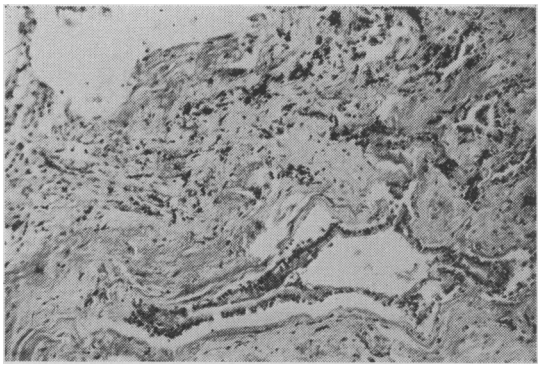

FIG. 2—Peribronchiolar fibrosis extending into alveoli from a case of asbestosis. H. & E. × 120.

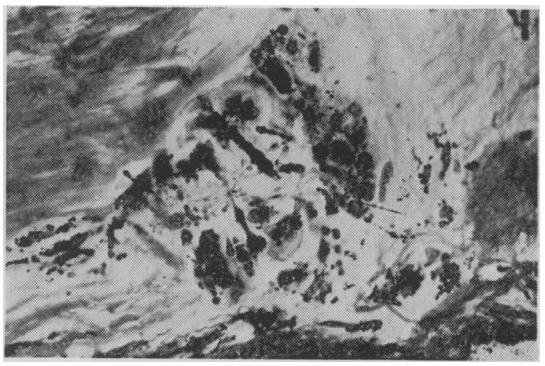

FIG. 3—A central clump of intracellular asbestos bodies is partly surrounded by laminated haematoxyphylic collagen. H. & E. × 480.

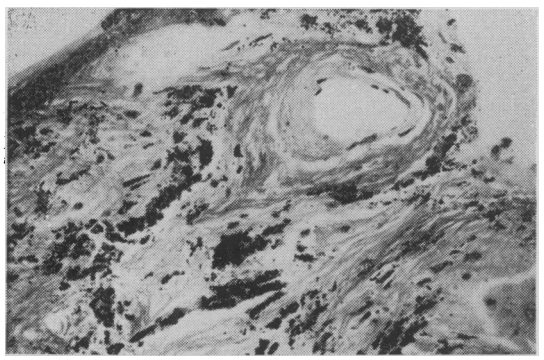

FIG. 4—Sclerotic vessel in asbestotic lung. Asbestos bodies are indistinct below and to the left, and haematoxyphilic collagen is present in several parts of the field. H. & E. × 200.

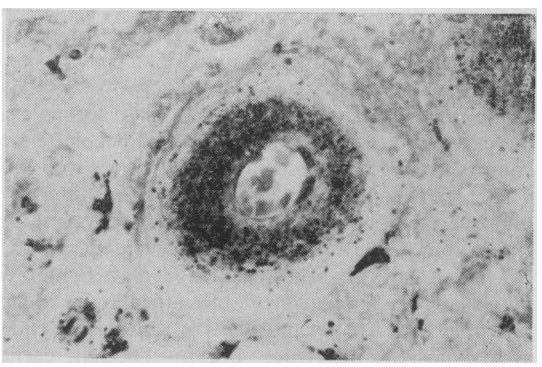

FIG. 5—Dark granules in the wall of a small pulmonary blood vessel. H. & E. × 200.

Histologically, the basic lesion is a peribronchiolar fibrosis which obliterates surrounding alveoli as it extends outwards from the bronchiole (Fig. 2). In zones of solid fibrosis laminated collagen replaces the entire parenchyma (Fig. 3). Alveolar cell hyperplasia may be prominent in zones of severe fibrosis, and the vessels in such areas are frequently sclerotic (Fig. 4).

The fibrous tissue within asbestotic lungs may show an unusual haematoxyphilia (Figs. 3 and 4), and dark granules may surround the lumina of small blood vessels in fibrotic areas (Fig. 5). This material does not stain as DNA or calcium, but it reacts weakly for iron, and gives intense reactions for neutral and acid mucopolysaccharides.

Asbestos fibres and bodies are generally present in large numbers and the bodies are readily detectable in routine sections (Fig. 3). They may occur singly or in clumps and may be associated with a macrophage or giant-cell reaction, especially when there has been recent exposure to asbestos. They may lie free in the air spaces or may be buried in and partly obscured by scar tissue. Asbestos fibres are usually numerous in cases of recent (6 - 12 months) exposure but are difficult to see without special techniques.

The lungs often contain much carbon, and short asbestos fibres appear to be especially numerous within carbon aggregates, being made visible by incineration which drives off the obscuring carbon (Hourihane, 1965 b). The impression has been gained that long fibres (>20μ) became converted into asbestos bodies and tend to remain in the vicinity of the bronchiole, whereas short fibres (5 - 20μ) are transported to local lymphoid aggregates where they remain as fibres, largely masked from view by carbon pigment.

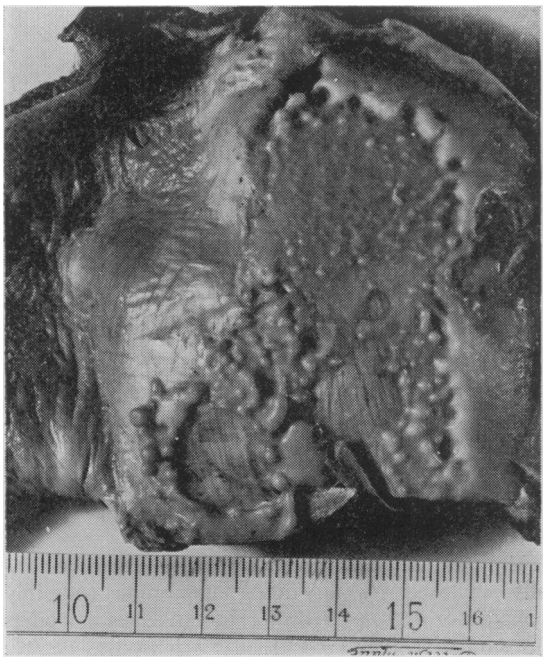

FIG. 6—Typical hyaline plaque on diaphragmatic pleura. The small projections at lower left and the smooth cartilaginous appearance at upper right are both common features.

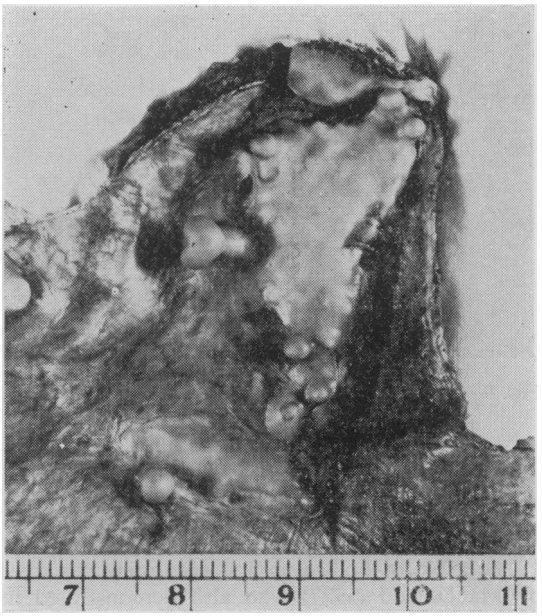

FIG. 7—Close-up view of a small plaque of parietal pleura. The combination of "knobbly" projections and smooth surfaces is again clearly shown.

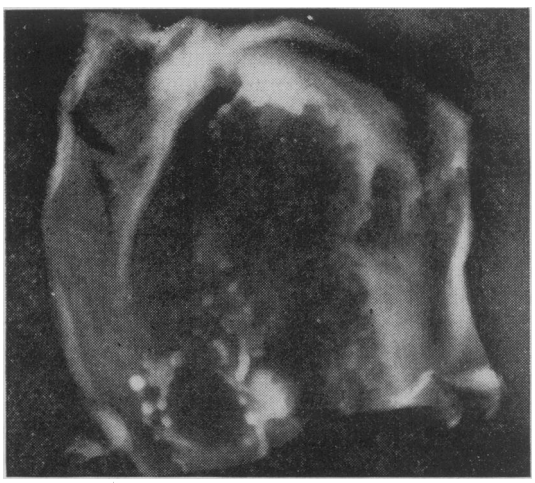

FIG. 8—Radiograph of specimen shown in Fig. 6 shows distribution of calcium within the plaque.

Pleural Changes

The pleura in a case of asbestosis is nearly always abnormal. Terminally, a primary diffuse pleural neoplasm may develop, (see below) or rarely, there may be diffuse fibrosis of both layers obliterating the pleural cavity but without histological evidence of neoplasia. However, hyaline plaques are the commonest pleural lesions found, and were noted by one of us (D. O'B. H.) in all of 16 cases in which they were specifically sought.

Hyaline pleural plaques occur as slightly elevated, firm, glistening areas of thickening, preferentially affecting the parietal pleura in its lower halves. (Figs. 6 and 7). Plaques vary from 10 cm to 1 cm in diameter, and are generally of almost cartilaginous consistency. Focal calcification may occur within the laminated, hyaline, acellular collagen of which they are composed, (Fig. 8) and such calcification may be visible radiologically. (15% of plaques detected at necropsy had been seen in radiographs during life).

These plaques are not neoplastic and may represent reactive fibrosis to contained asbestos fibres (Hourihane, Lessof and Richardson, 1966). Identical lesions occur in the absence of asbestosis although evidence of asbestos exposure can generally be found, and experience suggests that their incidence in a population probably reflects the extent to which a community is exposed to asbestos (Kiviluoto, 1960; Hourihane and others, 1966).

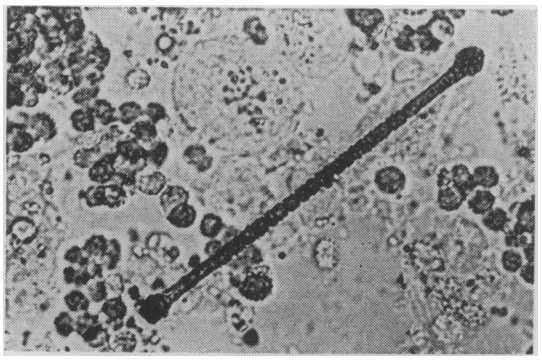

FIG. 9—Asbestos body in fluid squeezed from lung surface. This structure shows the classical segmentation of its shaft, and the bulbous terminations. Unstained × 1000.

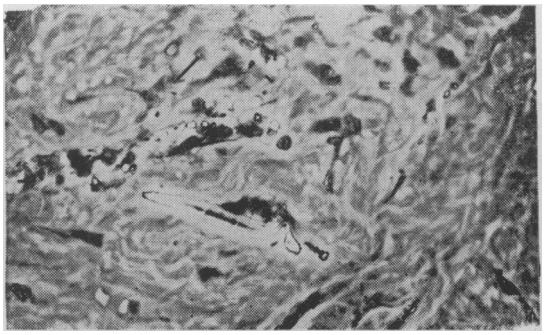

FIG. 10—Fibrotic area of lung from a case of asbestosis. The cigar-shaped body in the centre of the field shows a smooth refractile envelope. Its central dark fibre can be seen to be discontinuous. H. & E. × 590. Phase Contrast.

The Asbestos Body

The asbestos body was first accurately described by MacDonald (1927) who also demonstrated its iron content. Gloyne (1932) studied the nature of the bodies and concluded that they were composed of an envelope of iron and protein surrounding a central asbestos fibre, and that their presence in lung merely indicated a previous exposure to asbestos and did not necessarily mean that the disease asbestosis was present. Simson and Strachan (1931) had already shown that 90% of asbestos workers had such bodies in sputum and that they might be present after as little as 4 months employment.

Asbestos bodies typically are elongated structures of yellowish-brown or golden-yellow colour which give a positive Perl's reaction for iron. They may have a smooth outline, but commonly show segmentation and bulbous extremeties (Fig. 9). As illustrated by Gloyne (1932) many different shapes may be found. Their resistance to acid (Gloyne, 1932) and heat (Hourihane, 1965b) suggest an inorganic composition.

The fibres lose their intrinsic birefrigence when coated, but the presence of a central asbestos fibre can be readily seen using phase-contrast microscopy (Fig. 10). The absence of a visible fibre within some bodies suggests that the fibre silicate may be utilised in the formation of the body envelope, perhaps to form iron silicate. Gardner and Cummings (1931) after producing structures similar to asbestos bodies *in vitro* postulated that the coating of the fibre contained silicate.

Davis (1964a) has studied the formation of asbestos bodies in guinea pigs. Using electron microscopy bodies were seen to begin as an aggregation of dark granules (possibly ferritin) around phagocytosed fibres, while a formed body showed similar granules occasionally alternating with pale layers (possibly protein). The whole was occasionally enclosed by an outer membrane (possibly collagen or fibrous ferritin). Human asbestos bodies are similar (Davis, 1964 b).

Asbestos bodies usually represent only a fraction of the total asbestos in a lung, and there is experimental evidence to support the concept that fibres and not bodies are the fibrogenic agent (Gardner and Cummings, 1931; Gardner, 1942; Vorwald, Durkan and Pratt, 1951).

However, the suggestion of Knox and Beattie (1954 b) that bodies may fragment within lung and that the resulting small particles may be the fibrogenic agent should be borne in mind. It is possible that the type of segmentation shown in Fig. 9 might be the initial stage in fragmentation, and it is certainly the case that tiny particles derived from asbestos bodies would be indistinguishable from haemosiderin with light microscopy and that haemosiderin-like granules are common within intra-alveolar macrophages and in scar tissue in asbestosis.

In cases of substantial or heavy asbestos exposure, typical bodies may be present within hilar lymph nodes in addition to those in the lung. A case has been recorded where an asbestos body was present in the spleen (Stewart, Bucher and Coleman, 1931), and probable asbestos fibres have been found within pleural and peritoneal mesotheliomas (Hourihane, 1965 b). Their appearance in the latter site could be due to penetration of gut by swallowed fibres in sputum, as it has been shown that such penetration may occur in rats (Westlake, Spjut and Smith, 1965).

The specificity of the asbestos body has been questioned but most reports of confusion with other particulate matter may be readily dismissed. Rouleaux of erythrocytes and graphite particles

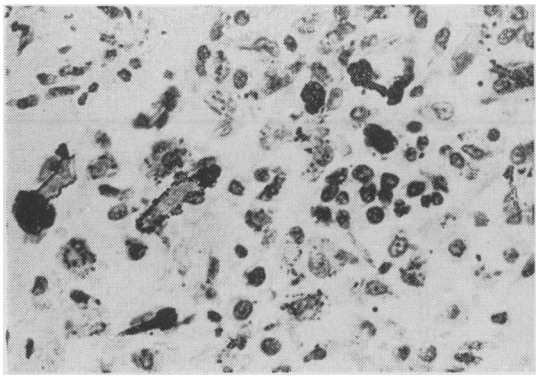

FIG. 11—Thick squat bodies in the lung of a case of talc pneumoconiosis. The resemblance to asbestos bodies is close, but is detectable as a resemblance. Occasionally, structures indistinguishable from classical asbestos bodies may be found in the lungs of a talc worker. H. & E. × 480.

FIG. 12—Same field as previous Fig. The enormous number of bi-refrigent plates of talc are clearly shown. H. & E. × 480. Crossed Nicols.

should never lead to error with an experienced microscopist. However, similar (Fig. 11) or even identical bodies may be seen in the lungs of talc workers, but in such cases, examination with crossed Nicols will usually demonstrate large numbers of talc fragments (Fig. 12), far greater in number and of different shape from the fibres found in asbestos workers. With this possible exception, asbestos bodies would appear to be specific for asbestos exposure. Much less reliance can be placed upon the recognition of asbestos fibres by traditional light microscopy, although X-ray diffraction and possibly electron microscopy permit accurate identification.

Incidence of Asbestos Bodies in Population Surveys

Necropsy studies of the prevalence of asbestos bodies in the lungs of urban dwellers have shown that they may occur with remarkable frequency. Thomson, Kaschula and McDonald (1963) reported that about one quarter of the adult necropsy population in Cape Town showed asbestos bodies in lung fluid, and similar results have been obtained from surveys in Miami, Florida (Thomson, 1965), Pittsburgh, Pennsylvania (Cauna, Totten and Gross, 1965) and in London, (Hourihane, 1965 a). In the majority of cases, fibrosis is absent, and asbestosis is therefore not present (2 out of 127 cases showed asbestosis in the London series.)

The bodies may be found in fluid squeezed from the cut-surface of the lungs or in routine histological preparations. The yield of cases with asbestos bodies rises when unstained, histological sections of 20 - 30 μ thickness are substituted for the routine, stained sections of 5 μ thickness (27% of 127 cases showed bodies in 30 μ unstained preparations, compared with 3% of 100 cases in stained 5 μ preparations in the London Hospital Series.

It has been stated (Thomson and others, 1963) that the lung bases contain the largest number of asbestos bodies and fibres. This finding would serve to explain why fibrosis is most severe in this area in cases of asbestosis, and the particular tendency for lung cancer to occur in the lower lobes in this disease. The most widely used type of asbestos is chrysotile and there is experimental evidence that it may disappear from lung and subcutaneous tissue (Gardner, 1942; Wagner and Skidmore, 1965). It is therefore possible that surveys of lung tissue for asbestos may underestimate the incidence of exposure to this type of dust.

Widespread asbestos contamination of urban communities may be reflected in a high incidence of hyaline pleural plaques in the same population; four and eleven per cent of the consecutive necropsy subjects showing such plaques in 2 separate series in London (Hourihane and others, 1966). It is likely that radiological surveys to assess the incidence of plaques would be a useful adjunct to post-mortem studies, in epidemiological investigations of asbestos exposure.

Asbestos and Neoplasia

Most reports dealing with lung cancer and asbestos exposure have been concerned with the incidence of cancer at necropsy in subjects with severe (compensatable) asbestosis. In such cases the incidence of lung cancer has ranged between 13 and 17.5 per cent (Merewether, 1955; Wyers, 1949; Gloyne, 1951; Bonser and others, 1955). Doll (1955) found the incidence of lung cancer in persons with long-continued heavy exposure to asbestos to be in the region of ten times the expected rate. Buchanan (1965) has observed that currently over 50 per cent of males dying with asbestosis in the United

TABLE 1

CANCER OF LUNG IN ASBESTOSIS

FEMALE PATIENTS

Case No.	Sex	Age	Cigs/Day	Histological Type
118	F	62	0	Adeno
119	F	43	—	Adeno
127	F	44	0	Adeno
128	F	70	0	Squamous
131	F	58	0	Adeno
132	F	50	0	Adeno
142	F	63	0	Adenoacanthoma
145	F	38	10	Adeno
155	F	56	10	Squamous
160	F	64	20	Oat-cell

Mean age of these cases 54.6 years.
7 of 9 tumours arose in lower lobes (77.7%)
4 of 9 tumours arose in right lung (44.4%)

Of a total 26 tumours in both sexes 65.3% originated within lower lobes (compare with 24.4% of 866 cases presented by Bryson and Spencer (1951)).

TABLE 2

CANCER OF LUNG IN ABSESTOSIS

MALE PATIENTS

Case No.	Sex	Age	Cigs/Day	Histological Type
115	M	46	40	Oat-cell
116	M	54	0	Undifferentiated
124	M	60	5	Squamous
126	M	67	20	Squamous
130	M	66	10	Adeno
137	M	63	10	Oat-cell
139	M	63	20	Adeno
141	M	53	0	Oat-cell
149	M	55	+	Squamous
150	M	71	5	Adeno
151	M	49	30	Oat-cell
152	M	57	20	Squamous
154	M	57	80	Squamous
158	M	53	60	Adeno
159	M	60	0	Adeno
163	M	66	20	Undifferentiated
125	M	50	0	Adeno

Mean age of these cases 58.2 years.

9 of 17 in lower lobes (52.9%)
11 of 17 in right lung (64.7%)

Kingdom also have an intrathoracic neoplasm. He also notes that "the incidence appears to be increasing and that this, if true, is a disturbing state of affairs especially as there has been in operation for upwards of 30 years a stringent system of statutory precautions for the traditional uses of asbestos."

Also significant in relation to modern industrial and occupational conditions is the finding that building insulation workers in New York have an incidence of lung cancer 6 - 7 times the expected rate. These workers were considered to have had relatively light intermittent exposure to asbestos (Selikoff, Churg and Hammond, 1964).

The distribution of lung cancer associated with asbestosis is unusual in that the lower lobe is more frequently involved than the upper lobe (Bohlig and Jacob, 1956) and our own experience confirms this (Tables 1 and 2). There is no clear indication as to whether asbestos exposure predisposes to any particular type of lung cancer. Our impression based on personal experience and informal discussion with others is that adenocarcinoma occurs with unexpected frequency.

Recently evidence has been rapidly accumulating that asbestos may be a major factor in the aetiology of diffuse mesothelioma, an uncommon tumour which is believed to arise from the lining cells (mesothelium) of the serosal cavities. These tumours show a striking tendency to spread extensively over the affected serosal membrane (Fig. 13). They infiltrate adjacent tissues and frequently metastasise to regional lymph nodes and less frequently to more distant sites. Accurate diagnosis of this tumour during life must usually be based on biopsy and the criteria have recently been reviewed (Hourihane, 1965b; McCaughey, 1965). Differentiation from metastatic carcinoma may be difficult. These tumours are often associated with an effusion and cytological examination of the fluid by an experienced observer may permit confident identification of the tumour. The presence of hyaluronic acid in the fluid may also be a helpful pointer to likely cases.

Groups of diffuse mesotheliomas of the pleura and peritoneum associated with asbestos exposure have now been reported from South Africa (Wagner, Sleggs and Marchand, 1960), Germany (Konig, 1960), the United Kingdom (Hourihane, 1964; Owen, 1964; Elmes, McCaughey and Wade, 1965) and the United States (Selikoff, Churg and Hammond, 1965). In many of these cases exposure has been light and frequently not associated with pulmonary fibrosis. Although diffuse mesothelioma has accounted for only a small proportion of recorded intrathoracic neoplasms in cases of asbestosis the experience of one of us (D. O'B. H.) at the London Hospital would suggest that it may be common. Thus among 43 deaths in male asbestosis patients 17 had diffuse mesotheliomas (8 pleural, 9 peritoneal), as opposed to 17 with lung cancer; while in 26 deaths in female asbestosis patients, 9 had diffuse mesotheliomas (1 pleural, 8 peritoneal), and 10 had lung cancer. The interval between the first exposure to asbestos and the development of mesothelioma had usually been at least 20 - 30 years.

Table 3 gives the details of asbestos exposure in those cases in a total series of 76 patients with asbestosis where data were available. It can be seen that the time from first known exposure to death is fairly constant around 30 years, for each sex and for each major diagnosis. This is surprising in view

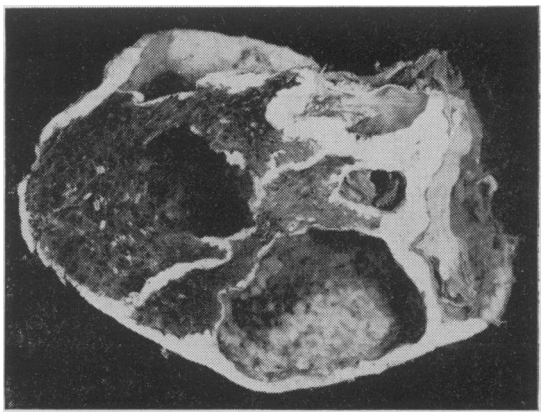

FIG. 13—Pleural mesothelioma showing diffuse spread with collapse of underlying lung. The loculated effusion in the lower part of the specimen is a common feature.

of the shorter exposure time in women and their correspondingly longer survival times from last known exposure to death, and immediately reminds one of Knox and Beattie's (1954 a) similar observation with regard to factors influencing the degree of pulmonary fibrosis in patients with asbestosis. It may well be that once a critical level of asbestos has been inhaled, the time of subsequent fibrosis or neoplasia is relatively fixed, and is predetermined many years in advance.

However, at lower levels of asbestos exposure there is evidence of a dose-response relationship between the amount of asbestos inhaled and the proportion of subsequent mesotheliomas. In the London Hospital general necropsy population the incidence of diffuse mesotheliomas is 0.3%, and most subjects with this tumour have small amounts of asbestos in the lung, with no more than 10% having any knowledge of absestos exposure (often non-industrial). In classical asbestosis, with large amounts of asbestos in lungs and a history of industrial exposure, the proportion of subjects who develop diffuse mesotheliomas rises to 37%. Subjects with pleural plaques at necropsy and without classical asbestosis occupy an intermediate position (Hourihane and others, 1966).

A similar consideration of lung cancer is of interest. Lung cancer occurs in about 40% of patients with classical asbestosis, and in 12% of unselected necropsy subjects in the same hospital. It is possible that a dose-response relationship might exist here also, as Knox, Doll and Hill (1965) have shown a decreasing rate of lung cancer with improved dust control.

Although evidence from South Africa would suggest that blue asbestos (crocidolite) is particularly

TABLE 3

DETAILS OF ASBESTOS EXPOSURE AND SURVIVAL IN ASBESTOSIS

Cause of Death	Asbestos Exposure (Average in years)	Last Exposure to Death (Average in years)	First Exposure to Death (Average in years)	Age at Death (Average)
MALES				
Lung Cancer	20.2 (14 cases)	15.0 (12 cases)	32.5 (11 cases)	59.2 (17 cases)
Mesothelioma	19.3 (13 cases)	14.4 (7 cases)	28.9 (12 cases)	51.6 (17 cases)
Heart Failure	—	14.9 (3 cases)	26.3 (3 cases)	57.0 (7 cases)
FEMALES				
Lung Cancer	4.2 (9 cases)	26.5 (9 cases)	29.2 (9 cases)	53.1 (10 cases)
Mesothelioma	8.1 (4 cases)	13.2 (4 cases)	24.0 (4 cases)	52.8 (9 cases)
Heart Failure	—	27.0 (4 cases)	36.3 (6 cases)	52.5 (6 cases)
BOTH SEXES				
Alive and Well	4.25 (5 cases)	23.1 (4 cases)	22.8 (5 cases)	57.8 (7 cases)
Heart Failure	5.5 (11 cases)	21.0 (7 cases)	30.3 (9 cases)	54.8 (13 cases)

likely to produce diffuse mesothelioma (Wagner and others, 1960), not enough evidence is available on a world-wide basis to assess the relative carcinogenicity of the main types of asbestos in this respect or in the production of lung cancer. Experimental evidence (Wagner, 1965) however, would suggest that mesothelial tumours can be readily induced by intrapleural inoculation of any of the three main types of asbestos (Chrysotile, crocidolite or amosite). Harington (1965) and Harington and Roe (1965) have reviewed the chemistry of asbestos and the possible mechanisms of carcinogenesis.

The survey of insulation workers by Selikoff and others (1964) has produced evidence of a possible connection between gastro-intestinal malignancy and exposure to asbestos dust.

Discussion

The present century has witnessed an enormous expansion in the use of asbestos by industry for a wide range of products. Current world production is estimated at over 3 million tons, (Hendry, 1965) and because of the widespread use by the building industry in particular this virtually indestructible material has become widely distributed. Although some of the hazards of occupational exposure to asbestos have been apparent for many years and active measures have been taken to reduce industrial exposure it is clear that in spite of a few encouraging reports (Knox and others, 1965) the measures taken in general have been far from effective in eliminating asbestosis or lung cancer. The report of the Ministry of Pensions and National Insurance for the year 1964 in fact shows that the number of new cases of asbestosis receiving compensation each year is rising. The recognition of a close association between asbestos exposure and diffuse mesothelioma of the pleura and peritoneum and the fact that in many cases of this tumour exposure has been slight, emphasises that even low levels of exposure cannot be considered safe. In this light it is disturbing that low-grade environmental exposure appears to be common in several parts of the world.

It must also be remembered in relation to the neoplastic complications of asbestos exposure that the interval between first exposure and the develop-

ment of lung or pleural cancer is usually at least 20 years and especially in the case of diffuse mesothelioma may be as much as 40 - 60 years. The significance of present levels of exposure may not become apparent therefore for at least several decades.

The question of compensation in cases with the neoplastic sequelae of asbestosis raises a difficult problem. The Pneumoconiosis Medical Panels in Great Britain accept lung cancer as a sequela of asbestosis and therefore compensatable. What however can be regarded as a significant degree of asbestosis in this respect? Both of us have seen many cases of bronchogenic carcinoma with asbestos bodies in the lung. In some of these there was no obvious pulmonary fibrosis, in others only slight fibrosis which might not necessarily have been due to asbestos. The question is complicated not only by the high incidence of bronchogenic carcinoma in the community generally but by the existence of other aetiological factors, notably smoking. In view of the high (over 80%) incidence of asbestos exposure in cases of diffuse mesothelioma and the relative rarity of these tumours there is clearly a much stronger case for regarding slight asbestos contamination of the lung as significant when associated with this tumour in either the pleura or peritoneum. It is worth emphasising that some subjects with mesothelioma and asbestos bodies give no history of industrial exposure to asbestos, and appear to have contracted a fatal disease through residence in an urban community.

It has been suggested in this paper that the incidence of mesotheliomas and possibly lung cancer also, is affected by the dose of asbestos introduced to the body, and consequently that a "safe" level of exposure might be achieved. What this level is one cannot say, but it is clear that information on this point is urgently required, both from industrial and epidemiological points of view.

The mechanism or mechanisms whereby asbestos damages tissues have not yet been clearly established. Mechanical and chemical factors have been implicated in the production of fibrosis. Neoplasia in the lung and possibly also in the serosal membranes could be a direct complication of this fibrosis. However, it has been shown that carcinogens occur in asbestos. These include natural and contaminating oils, iron, nickel and chromium (Harington and Roe, 1965). Further investigation of this subject combined with studies of cancer rates associated with pure exposure to individual types of asbestos are obviously of great importance in devising effective safety regulations for the treatment and handling of this material.

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