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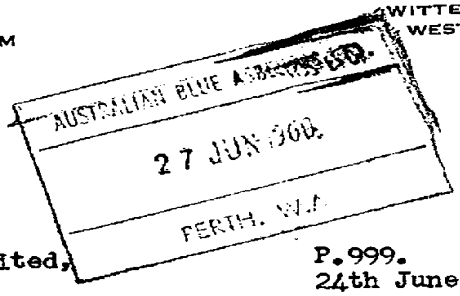
86

AUSTRALIAN BLUE ASBESTOS LIMITED

ASBESTOS

TELEGRAPHIC ADDRESS
"BLUEASBESTOS" WITTENOOM

WITTENOOM GORGE
WESTERN AUSTRALIA



PRIVATE

General Superintendent,
Australian Blue Asbestos Limited,
PERTH, W.A.

P.999.
24th June, 1960.

Dear Sir,

ASBESTOSIS: We are enclosing an extract taken from the British Medical Journal recently. It is the report of a discussion on the result of a post mortem on a man with asbestosis with fatal complications. We have not included the first part but only the summing up. You could, no doubt procure a copy of the Journal if necessary. I have underlined several passages which have been stressed by Dr.Oxer. It is quite interesting and gives some information previously not known to me.

Yours faithfully,

O A Allan.

Manager.

OAA/MS.

has been made that, while the tongue is probably the most sensitive site for the observation of central cyanosis, intelligent guessing does not replace thorough estimations of arterial oxygen saturation or oximetry.

...

CANCER IN FIBROTIC LUNG

The difficulty of diagnosing pulmonary shadows in the radiographs of coal-miners has recently been emphasized by R. Abbey Smith.[1] He notes in particular the single fibrotic nodule unaccompanied by radiographic evidence of simple pneumoconiosis and "the slowness in growth of certain lung cancers in miners." In a review of 320 cases operated on for lung cancer at one hospital, and drawn from the general population of town and country, he records that 36% survived two years or more after operation. This figure compares with 34% reported by A. B. Taylor and J. M. Levi[2] in 1954 in relation to 512 resections, and with 42% by J. R. Bignall and A. J. Moon[3] in 1955 in relation to 205. It appears that the "industrial" group of workers fared better than the "agricultural and rural," evidently because of the inclusion in the former of a number of coal-miners, coal-miner being defined as a person "who has worked five years or more underground at the coal face" (no account of geographical situation of the mines was taken). "During the same period with the same criteria of operability," he found that of 21 miners who had undergone resection only three died in the first two years after, which is a survival rate of 86%—a statistically significant difference from the whole.

He offers two possible explanations: first that the coal-miner develops a slowly-growing tumour specific to him; and secondly—which he finds the more probable—that growth of tumour is "retarded by the effects of prolonged inhalation of coal dust on the lung parenchyma and lymphatics." Against the first he quotes W. R. L. James[4] as finding no difference in the frequency of different histological types of carcinoma between miners and non-miners. But it may be that the histological type is not important in this respect, that in fact there may be some factor which operates in coal-miners to slow down the rate of growth of all tumours. If this is so, the factor which improves their prognosis could be akin to that which explains why patients with longer duration of symptoms pre-operatively fare better than those with a short history.[2,5] But Abbey Smith favours the second explanation, the blocking, referred to by F. G. Kergin,[6] of the lymphatics by carbon-laden macrophages and the choking of the glands by heavy carbon deposits and fibrosis, making lymphatic metastasis difficult. Kergin has drawn attention also to the fibrous tissue binding glands to blood vessels and bronchi, so often found in the lungs of coal-miners. It may be that lymphatic[7] as well as vascular[8] invasion and metastasis are hindered, though James found no difference in the incidence of metastasis to different organs in the miner and non-miner except for the brain, in which secondary deposits were found in only 9% of miners and 27% of non-miners.

This paper shows that experience is better distilled to statistics than to *obiter dicta*. It is a reminder of the theory that previous damage may mitigate later disease, as has been suggested in times past by clinicians who said that healed tuberculosis, by the blocking of lymphatics, reduced the spread of cancer and the toxic effect of empyema. More information on this problem would be welcome, and the higher survival rate among this group of miners, together with the lower incidence of lung cancer among coal-miners reported by Kennaway and Kennaway,[9] certainly points to the usefulness of further inquiry into the factors which may be responsible.

[1] Abbey Smith, R., *Brit. J. industr. Med.*, 1959, 16, 318.
[2] Taylor, A. B., and Levi, J. M., *Annual Cancer Report, United Birmingham Hospitals*, 1954, 9, 14.
[3] Bignall, J. R., and Moon, A. J., *Thorax*, 1955, 10, 183.
[4] James, W. R. L., *Brit. J. industr. Med.*, 1955, 12, 87.
[5] Steinberg, A., Lubliner, R., and Robin, P. H., *Dis. Chest*, 1951, 20, 257.
[6] Kergin, F. G., *J. thorac. Surg.*, 1952, 24, 545.
[7] Nohl, H. C., *Thorax*, 1956, 11, 172.
[8] Ballantyne, A. J., Clagett, O. T., and McDonald, J. R., *ibid.*, 1957, 12, 294.
[9] Kennaway, E. L., and Kennaway, N. M., *Brit. J. Cancer*, 1951, 5, 10.

KING GEORGE'S JUBILEE TRUST APPEAL

In 1935 a grateful people subscribed £1m. as a national thank-offering for the twenty-five years' reign of King George V, and the offering was dedicated to the cause, always dear to the king's heart, of advancing the physical, mental, and spiritual welfare of the younger generation in his kingdom. The fund inaugurated for this purpose—King George's Jubilee Trust—is now celebrating its own silver jubilee, and it has just launched its first national appeal for funds since its foundation. Over the past twenty-five years the Trust has given more than £1m. in grants for the welfare of the young, but the income at the council's disposal, even with the help of legacies and other gifts, barely exceeds £40,000 a year. The funds are chiefly used to help those who leave school at the age of 15; there were 610,000 of these in 1948, and there will be 852,000 in 1961 and 927,000 in 1962. With the increasing calls upon it, the Trust needs an additional income of £110,000 a year.

Many of the Trust's grants are well known: it gives bursaries, for example, to enable young people who could not otherwise afford to do so to join the Outward Bound Trust courses at sea and mountain schools; to the British Schools Exploring Society; or to the courses on the old sailing ship *Foudroyant*, moored in Portsmouth harbour. It also gives a great deal of unseen support to the day-to-day work of the national voluntary youth organizations. As the Trust's council says, the appeal is a national appeal in support of a national cause, and it is described as a call to the nation to accept again as it did in 1935 its responsibility for those on whom the future of the country will depend. Those who are interested in the work of this very practical organization should send their inquiries to the secretary, King George's Jubilee Trust, 166, Piccadilly, London, W.1.

The Queen has conferred the Order of Merit on Sir Cyril Hinshelwood, President of the Royal Society and Dr. Lee's Professor of Chemistry in the University of Oxford.

Clinicopathological Conference

COMPLICATIONS OF ASBESTOSIS

DEMONSTRATED AT THE
POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is the case of a man with asbestosis with a fatal complication (Case No. 215526; P.M. No. 8556). He presented with haemoptysis, and exemplified the problems of diagnosis of the cause of haemoptysis and the nature of the lung changes associated with the asbestosis.

Clinical History

Dr. Philip Hugh-Jones: This man was aged 50 years at death. His medical history starts in 1922, when at the age of 14 years he got rheumatic fever. He apparently made a good recovery from this. However, he was graded in group IV at an Army medical examination in 1940 at the age of 32, though he himself felt perfectly well. In 1943 he had a gradual onset of swelling, aching, and stiffness of the metacarpophalangeal joints of both hands and of the wrists, shoulders, knees, and ankles. This continued for five years; there was little constitutional upset, but the illness left him with a residual stiffness of his shoulders and wrists and with deformity of the hands typical of rheumatoid arthritis.

From 1938 to 1949 he worked in an asbestos factory. There he felt well, but on routine radiological examination of his chest in 1949 he was told he had asbestosis, was certified, and subsequently became a storeman. From that time onward he noticed increasing shortness of breath on exertion. In May, 1958, he got worse, had a brisk haemoptysis, and was admitted to Hammersmith Hospital for investigation.

Fig. 1.—Chest radiograph (posterior view) on first admission. The fracture of the sixth rib is not visible

Examination and Investigations

He had marked clubbing of the fingers and toes; rheumatoid changes in his hands, elbows, and shoulders; enlarged axillary glands; and two small, mobile, cutaneous nodules on the medial side of the right arm. There were persistent scattered râles over both lungs. His blood-pressure was 120/65, his pulse was regular, and he had a grade 3 aortic systolic murmur, an accentuated pulmonary second sound, with an opening snap and mid-diastolic murmur at the heart apex. A radiograph of the chest (Fig. 1) showed a fracture of the sixth rib on the right, large pulmonary vascular shadows, and a reticular mottling over the lower zones of both lung fields, with a "shaggy" outline to the heart. On barium swallow there was slight enlargement of the left atrium. The changes at the right hilum could be those of an enlarged pulmonary artery, or those associated with a right hilar neoplasm. Tomography (Fig. 2) confirmed the right hilar mass.

His sputum was examined on numerous occasions for tubercle bacilli, malignant cells, and asbestos bodies, but nothing abnormal was found. Bronchoscopy showed the left-hand side of the bronchial tree to be normal. The right upper lobe was normal, but there was blood-stained mucopus in the region of the right middle lobe, with a granular appearance of the right descending and lower lobe bronchi. However, a biopsy from the granular areas showed no evidence of malignant change. Biopsy of lymph glands and of the skin nodules showed only changes compatible with rheumatoid arthritis.

The electrocardiogram gave little support for the clinical diagnosis of mitral stenosis, despite the slight enlargement of the left auricle seen on barium swallow. The blood count was normal except that the haemoglobin was 11.5 g./100 ml. Blood cultures were persistently negative. The E.S.R. was 125 mm./hour. The differential agglutination test was positive for rheumatoid arthritis, and electrophoresis of the serum proteins showed high α_2 and β peaks.

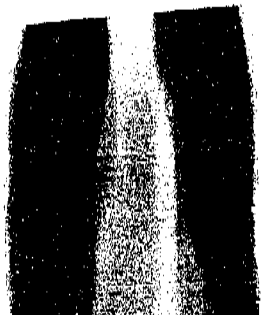


Fig. 2.—Tomograph confirming right hilar mass.

Lung function tests showed the changes typical of an interstitial fibrosis [illegible] to alveolar-capillary block—namely, [illegible] oxide diffusing capacity, [illegible] with arterial oxygen desaturation on [illegible] respiratory capacity, a maximum breathing [illegible] of 95 litres/min., [illegible] capacity, and a [illegible] of F.V. 1.0 [illegible] forced [illegible] response [illegible] (F.V. [illegible]

During the [illegible] he haemoptyses steadily decreased and he [illegible] having rheumatic heart disease (mitral stenosis and [illegible] with probably [illegible] ever it was [illegible] associated with the [illegible] pulmonary artery [illegible] bronchiectasis associ[illegible] event, further investig[illegible] was unlikely to alter [illegible] bronchial neoplasm [illegible] therefore discharged [illegible]

Readmitted in [illegible] 10 g. (West radio[illegible] [illegible] showed markedly

FIG. 2.—Chest radiograph, [illegible]

increased shadowing on the right, with collapse of the tenth thoracic vertebra. Sputum examination for malignant cells was negative.

During this time in the ward he had two attacks of involuntary jerking of the right leg which were thought to be possibly a form of Jacksonian fit associated with a cerebral metastasis from lung carcinoma, although E.E.G. examination gave no positive support to this diagnosis. In view of the radiological findings the diagnosis of lung cancer associated with [illegible] was much more [illegible]

again discharged. After that he deteriorated steadily with increasing haemoptyses, though he was in no pain. He was finally admitted again in September, 1958, when he showed signs of consolidation of the right chest and a swelling over the left clavicle. He died on September 29.

Clinical Diagnosis

1. Carcinoma of right lower lobe bronchus, with metastases to spine, brain, and elsewhere.

2. Asbestosis.

3. Rheumatic heart disease (quiescent aortic incompetence and mitral stenosis).

4. Rheumatoid arthritis.

Post-mortem Findings

Dr. B. E. HEARD: The body was wasted; weight 6 st. 10 lb. (42.6 kg.), height 5 ft. 7 in. (1.68 m.). Both hands showed ulnar deviation and the fingers and toes were clubbed. There were two small nodules 1 cm. in diameter over the right elbow and there was one 4 cm. in diameter over the left. They contained caseous material and histologically showed incisive-looking fibrous walls lined by macrophages and enclosing amorphous material with many cholesterol clefts. There was no certain evidence of active rheumatoid disease here. The chest measurements were: antero-posterior diameter 20.5 cm., lateral 25 cm., circumference 72 cm. This is within the normal range and excludes a barrel-shaped chest. Both *pleural sacs* were completely obliterated by dense fibrous adhesions. The *pericardium* was also obliterated and showed a plaque of calcification over the pulmonary conus. The *peritoneum* was normal.

STATE OF THE LUNGS

The *trachea* and *main bronchi* contained a large quantity of blood-stained mucus and both lungs were oedematous. There was bronchiectasis in the fibrosed areas to be described. The *right lung* weighed 1,370 g. (normally 400–450 g.). There was a carcinoma 7 cm. in diameter in the posterior basal segment of the lower lobe adherent to the diaphragm and invading it. The cut surface was pale and granular and there was central necrosis. The lower lobe also showed some subpleural fibrosis. There were secondary deposits in the hilar lymph nodes. The middle lobe was heavily infected, all bronchi being filled with mucopus and the

LEGENDS TO SPECIAL PLATE

FIG. 3.—The left lung showing honeycombing of the anterior parts of the lingular and anterior segments of the upper lobe, and also of a thick subpleural zone commencing half-way down the back of the lower lobe and involving the costophrenic angle and the whole of the diaphragmatic surface.

FIG. 5.—A higher magnification (×1.4) of the left lower lobe, showing the subpleural zone of honeycombing and dense overlying adhesions.

FIG. 6.—A higher magnification (×1.4) of the postero-apical segment of the upper lobe to show a little apical scarring, a bulla (marked by an arrow), and numerous black foci of centrilobular emphysema, separated from septa (and veins) by zones of unpigmented lung at the periphery of each lobule. The fine white lines mark the edges of secondary lobules and the black foci mark their centres approximately. Between septa and foci are peripheral zones of unpigmented lung. Two pale deposits of carcinoma near the top of the picture are indicated by arrows.

FIG. 4

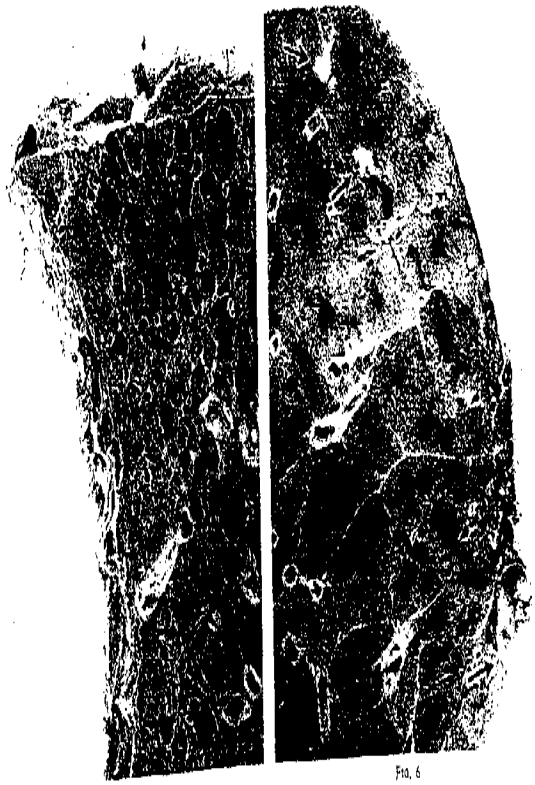


FIG. 5

FIG. 6

FIG. 7

FIG. 8

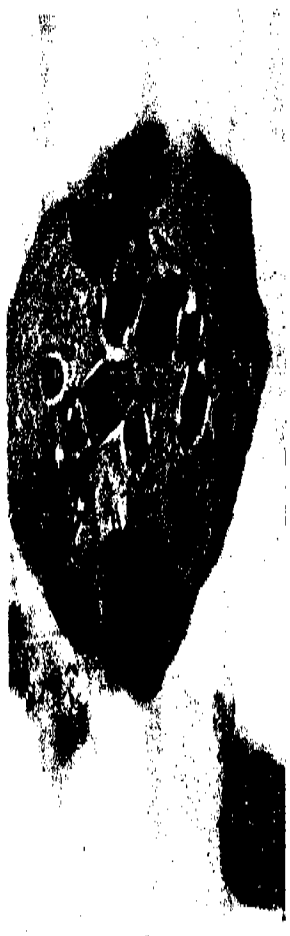


FIG. 9

FIG. 10

lung yellow and consolidated. There was some honeycombing of the anterior part of this lobe. The upper lobe showed slight apical fibrosis associated with two bullae 1.5 cm. in diameter, but no calcification. In all parts of the lung unaffected by fibrosis there was mild centrilobular emphysema. (The appearance in the left lung is shown in Figs. 4 and 6.) Respiratory bronchicles well away from the interlobular septa were heavily dust-pigmented and moderately dilated. Histologically these emphysematous foci were shown to be pigmented by black dust in macrophages lying mostly within the walls of the dilated respiratory bronchioles, and in the same situation were numerous small asbestos bodies. There was no notable increase of reticulin in these areas. The tumour was a moderately well-differentiated columnar-cell carcinoma with tubular and papillary patterns. Most reports stress the frequency of squamous carcinoma with asbestos, so the present case is somewhat unusual. There is no question of this being a mesothelioma. The *left lung* weighed 885 g., and was prepared by pressure fixation and barium sulphate impregnation* (Fig. 4) to demonstrate emphysema. The volume of the lung (2.2 litres) was at the lower limit of normal. There was honeycombing (Fig. 5) in a thick subpleural zone of lung commencing half-way down the back of the lower lobe, including the costophrenic angle and the whole of the diaphragmatic surface. Also honeycombed were the anterior parts of the lingula and a little of the anterior part of the anterior segment of the upper lobe. Honeycombing was accompanied by bronchiectasis.

Histologically the detail of the respiratory tissue was considerably simplified. Most of the airways consisted of small bronchi or bronchioles which were dilated (Fig. 7). There were no alveolated passages. Between the holes were thick walls of moderately dense collagen, lightly infiltrated in places by lymphocytes but as a rule having an inactive appearance. Stains for elastic tissue showed no alveolar shadows, most of the elastic being confined to the walls of blood vessels (Fig. 8). The larger arteries in the fibrous areas of lung showed considerable intimal fibro-elastosis, but elsewhere in the lung intimal thickening was only slight. Most of the dilated bronchi were lined by cubical or flattened epithelium, but in some areas macrophages were present in moderate numbers, sometimes accompanied by amorphous debris. Some of the macrophages were in the form of multinucleate giant cells (Fig. 9), well-known in recognized asbestosis. Asbestos bodies (Fig. 10) were lying free in the lumen, often in clumps. They had the characteristic golden-brown colour, and stained intensely for iron by Perls's reaction. Some of the bodies were smooth and rounded. Others were sausage-shaped with a variable amount of segmentation. Some sharp-ended crystals accompanied the bodies and may have been asbestos fibres. Elsewhere in the lung there was centrilobular emphysema of a mild grade.

*Heard, B. E., *Thorax*, 1958, 13, 136; ibid., 1959, 14, 58.

LEGENDS TO SPECIAL PLATE

FIG. 7.—A focus of centrilobular emphysema showing asbestos bodies with other pigment in the walls of dilated respiratory bronchioles. (×245.)

FIG. 8.—A section of a fibrosed juxtapleural zone stained to show elastic fibres. On the left is a thin layer of pleural fibrous tissue lying outside the elastic lamina which marks the original border of the lung. Within the lung, finer air spaces have been replaced by dense fibrous tissue. The minimal elastic content is related to small blood vessels. (×95.)

FIG. 9.—A multinucleate giant cell containing fragments of asbestos bodies. (×1,012.)

FIG. 10.—A clump of asbestos bodies showing wrinkled encrustations over the asbestos fibres. (×1,012.)

The low volume of the lung and the encasing effect of the honeycombing correlate well with the lung-function studies, which showed a small inspiratory capacity. This may be what has been referred to as a "tight" lung. The adhesions were moderately dense over the lung but were not cartilage-like.† There was no evidence of Caplan's change despite the coincidence of rheumatoid arthritis and asbestosis as described by Rickards and Barrett.‡

Heart and Other Organs

The *heart* weighed 370 g. (normally 281–361 g. for a man of 5 ft. 7 in.—1.68 m.). The increase in weight was partly due to dense adhesions, described above, and partly to a trace of hypertrophy of the left auricle and possibly the right ventricle (L.V. 1.5 cm. thick, R.V. 0.4 cm. thick). The pulmonary and tricuspid valves were normal, but the mitral valve was 70 mm. in circumference (normally 90–110 mm.). The chordae tendineae were fibrous but not shortened. The edge of the valve was straight. The valve cusps were fused and thickened by fibrosis and the valve admitted one and a half finger-tips. Histologically there were no signs of active rheumatic fever, but at one point there was a small mural thrombus as described by Magarey,§ who attributes the fibrosis to the organization of successive layers of fibrin on the surface. The aortic valve was normal in circumference but showed adhesion of the commissures for distances up to 7 mm. The cusps themselves were slightly fibrosed. There were no vegetations. The coronary arteries showed moderate atherosclerosis and the aorta a mild degree. The heart changes were consistent with an old history of rheumatic fever. There was no sign, histologically, of rheumatic activity.

The *oesophagus* and the rest of the *alimentary tract* were normal, but the *liver* was slightly increased in weight (1,630 g.; normally 1,400–1,600 g.), and contained some scattered secondary deposits of growth up to 1 cm. in diameter. It showed centrilobular congestion throughout, confirmed histologically. The *gall-bladder, biliary ducts,* and *pancreas* were normal. The *spleen* was normal, but the bone-marrow of the sternum, ribs, and vertebrae contained numerous large secondary deposits. There was a fracture of the middle of the sternum and collapse of the tenth thoracic vertebra. The *adrenals* (right 15 g., left 20 g.; normally 6–7 g. each) were enlarged by metastases but the other endocrine glands were normal. The *genito-urinary* system was normal. The *brain* showed secondary deposits (Fig. 11) up to 1 cm. in diameter in the left occipital lobe and in both cerebellar hemispheres.

Pathologist's Diagnosis

1. Carcinoma of the lung with metastases in the hilar lymph nodes, adrenals, liver, brain, and bones.
2. Honeycomb lung due to asbestosis.
3. Old rheumatic heart disease.
4. Old rheumatoid arthritis.

†Gloyne, S. R., *Tubercle*, 1933, 14, 445.
‡Rickards, A. G., and Barrett, G. M., *Thorax*, 1958, 13, 185.
§Magarey, F., *Brit. med. J.*, 1951, 1, 856.

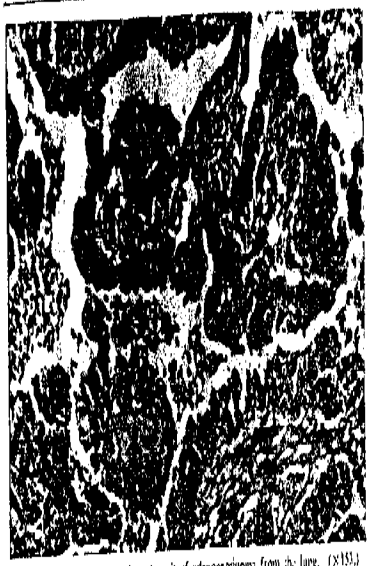


FIG. 11.—A cerebral secondary deposit of adenocarcinoma from the lung. (×135.)

Asbestosis Reviewed

Professor J. McMICHAEL: Dr. Hugh-Jones, would you sum it up?

Dr. HUGH-JONES: The case is of great interest, as it demonstrates so many of the problems associated with asbestosis which we should review. Asbestos itself is chiefly a double silicate of magnesium and iron. It occurs in a number of mineralogical forms, one of the most valuable being chrysolite. Asbestosis is a pneumoconiosis arising from the inhalation of asbestos dust during the manufacture of asbestos goods, such as asbestos sheeting, fireproof clothing, brake-linings, lagging for boilers and pipes, etc.

One way of thinking of the pneumoconioses is in relation to the chemical toxicity of the different dusts. At one extreme are those, such as iron, which are entirely non-toxic and simply produce a characteristic radiological appearance of the lungs with no change in bodily function. Then come others, such as coal, which do this but also have a pathogenic action by altering the reaction of the lungs to tubercle. Next there are dusts, such as silica, which produce a local reaction in the lungs and pulmonary fibrosis. Finally there are others, such as beryllium, of such toxicity that they can be regarded as general tissue poisons, which produce widespread effects in the body as well as local fibrosis in the lungs. Asbestosis is very toxic and produces not only pulmonary fibrosis but reactions in the pleura and even in other organs. Dr. Heard has excellently demonstrated the pathology of asbestosis in our patient, but by way of summary here is a picture (Fig. 12) of a whole-lung section of another patient who died from asbestosis. There is an interstitial fibrosis, as in the present case, gross pleural thickening, and some patchy bronchiectasis. Besides these three features, which are common in asbestosis, there may be associated tuberculosis, as there was in this second case, or, even more important, associated lung cancer, as in our patient. Sometimes the interstitial fibrosis gives rise to the formation of bullae, or occasionally even to a widespread "honeycomb lung"—i.e., that which occurs with other rare forms of pulmonary interstitial fibrosis, such as the sarcoidoses.

Radiological Appearances

These are typically those of a fine lace-like reticular pattern, particularly affecting the lower lung fields and causing a "shaggy" border to the heart, as in our patient. Besides this, cystic changes may be seen and very often the pleural thickening. Although the x-ray picture is typical and almost pathognomonic in a few advanced cases, there are many patients who have undoubted asbestosis (as judged by a history of exposure and the clinical features of clubbing, rales in the lungs, and typical changes in lung function) who do not have specific changes in their chest radiograph. That is extremely important in relation to the diagnosis, as we shall see later, because in general the diagnosis of pneumoconiosis depends on an appropriate industrial history and a characteristic x-ray appearance. There is a characteristic x-ray appearance in asbestosis, but unfortunately from the medico-legal standpoint not all patients with asbestosis have the characteristic radiograph. Finally, the radiological appearances of asbestosis cannot be classified in the same categories as those accepted internationally for the other pneumoconioses.

Clinical Features and Course

Gross clubbing of the fingers and persistent rales in the chest are the characteristic clinical signs of the condition. Exertional dyspnoea is the main symptom as in other pneumoconioses. Patients suffering from

FIG. 12.—Large lung section, prepared by Professor Gough's technique, from another patient with asbestosis, showing diffuse pleural thickening, patchy fibrosis, and bronchiectasis, and an accompanying tuberculosis at the lung apex.

asbestosis may die either from the complication of tuberculosis (more common in past years), or more particularly from that of carcinoma of the lung. Those not killed by chest infection or cancer may finally get cor pulmonale.

The disease usually makes its appearance rather suddenly, over the course of a few months, often long after the initial exposure to the asbestos inhalation. It has been suggested that the asbestos lies dormant as an asbestos body, which has to "ripen" over many years before it can break down and liberate its toxic contents. In this respect asbestosis is again like beryllium, which may also lie dormant in the body and then suddenly produce its effects concurrently with some other infection.

Carcinoma of the lung is a serious and well-recognized complication in asbestosis. Its frequency in asbestosis is difficult to determine, for it is now a common condition in the general population. Moreover, exposure to asbestos may have occurred many years before the cancer develops. Nevertheless, the paper by Doll[1] makes it fairly clear that a patient with asbestosis has a risk about 10 times that of the general population of getting carcinoma of the lung. Another hazard is mesothelioma of the pleura. This rather rare tumour may draw attention to the fact that a patient has worked in asbestos dust. Finally, in women who work with asbestos there is a high incidence of cancer of the ovary.

Functional Effects

There is a diminution of the inspiratory capacity which fits in with the "shrunken lung" demonstrated by Dr. Heard in this case. In contrast with other pneumoconioses there is often little disturbance to air flow, so that all the movement of the lungs there is is used to good advantage, and the maximum breathing capacity (M.B.C.) is often surprisingly well maintained. Thus if a patient suffering from asbestosis is assessed by the M.B.C. or forced expiratory volume (F.E.V.) test, he is unfairly assessed for compensation compared with a man suffering from silicosis or coal-workers' pneumoconiosis. The essential cause of the breathlessness in asbestosis is the difficulty of transference of oxygen across the altered alveolar membrane, more so than the reduced maximum breathing capacity, which is the cause in, say, coal pneumoconiosis. Carbon dioxide, being soluble, diffuses 20 times as rapidly as oxygen and is unaffected. Oxygen transfer is usually adequate at rest, so that the patients are rarely cyanosed, but when they start to exercise there is a rapid fall in oxygen saturation and gross hyperpnoea.

The diagnosis is made on a history of exposure, the presence of clubbing and rales, and usually by means of a radiograph. There is, however, evidence that the radiograph may not show changes as early as do the lung-function tests. Although the latter are not specific to asbestosis, they are only seen in other uncommon diseases which cause alveolar-capillary block and interstitial fibrosis (such as sarcoid, scleroderma, microlithiasis, and other rare conditions). Thus lung-function tests are useful for making the pathological diagnosis, for, if it can be shown that the patient has an interstitial fibrosis causing alveolar-capillary block, has gross clubbing and rales, and a history of exposure to asbestos dust, it seems reasonable that he has asbestosis whether the radiograph is specific or not.

[1] Doll, R., *Brit. J. Industr. Med.*, 1955, 12, 81.

Asbestos Dust

The asbestos bodies simply prove exposure to asbestos dust and of themselves do not mean asbestosis. Anyone may cough up asbestos bodies who has inhaled dust, without necessarily having the changes of asbestosis in the lungs. Vice versa, a patient may have definite and gross asbestosis without asbestos bodies necessarily being found in the sputum during life. Since, medico-legally, the diagnosis depends on a history of dust exposure together with the appropriate x-ray and other changes, the finding of asbestos bodies is of importance in proving exposure.

It seems probable that asbestos fibres, once inhaled, are coated with collagen. Over the course of years the collagen cover "ripens" by forming transverse cracks, and then the asbestos body can break down, liberating the toxin and causing the reactive fibrosis in the lungs. The nature of the toxin is uncertain. It is, however, presumably the same substance which is carcinogenic.

Asbestosis was first described in this country by M. Murray in 1907. After that, in 1930, Merewether and Price[2] reported the dangers of asbestos dust in the lungs and made recommendations for dust suppression. Thereafter there was a great improvement. In the factory where our patient worked the utmost precautions are now taken to prevent asbestosis occurring. It is a disappearing disease. Nevertheless, asbestos dust is most toxic, and the amount needed to cause asbestosis is not known, so constant vigilance and new preventive methods are needed if this disease is to be abolished.

Discussion

Professor McMICHAEL: There are many other facets to this patient, but before we go on to them are there any other points or queries which could be raised on the pathogenesis of asbestosis?

Dr. R. S. WILLIAMS: I think there is one point in support of the mechanical theory that is worth raising. If experimentally you give asbestos ground up into a fine dust, fibrosis does not occur, and it seems that asbestos fibres between 20 and 50 microns in length are necessary to produce the typical peribronchiolar fibrosis.

Distribution of Fibrosis

Professor E. G. L. BYWATERS: What is the explanation of the distribution of fibrosis? Does it correspond to the distribution of asbestos in the lung, or is there some other explanation?

Dr. HEARD: As a matter of fact, it doesn't seem to correspond. Although some of the best asbestos bodies in this case were in fibrosed areas, there were plenty surrounded by perfectly normal lung in other parts. Dr. Nagelschmidt, from Sheffield, was here two days ago and he was saying that they have recently examined chemically a number of lungs from cases of asbestosis. In some there was a lot of fibrosis and practically no asbestos. However, he did point out that there was a possible error because the asbestos content was estimated as the percentage of the dried weight and the dried weight of fibrosed lung is not altogether comparable to the dried weight of the normal lung. It is quite a problem, and, so far as I know, the peripheral distribution of the fibrosis has not been explained. It is not restricted to asbestosis, being seen in other forms of honeycomb lung.

[2] Merewether, E. R. A., and Price, C. W., *Report on Effects of Asbestos Dust on the Lungs*, 1930. H.M.S.O., London.

ASBESTOS IN THE PERICARDIUM

Professor McMICHAEL: Dr. Plotz, you have a question?

Dr. PLOTZ (New York): I've got a couple of questions. In reading the case history I was surprised—pleasantly surprised and greatly relieved—to find that no mention was made of this man's smoking habits. Some of our surgical friends are putting asbestos rather than talc into the pericardial cavity to produce adhesions, on the grounds that chemically they are both silicates and the adhesions grow much more quickly with asbestos. This does not meet with my approval on other grounds, but I am wondering what Dr. Hugh-Jones and Dr. Heard would have to say about that. One other minor point that bothered me a little in the case history—perhaps I am getting a little touchy at the age of 50 and a little over—but you said that his age was a factor in determining whether or not to operate on him, and you decided not to operate on him because of his age. I am wondering if he was too old, or too young.

Dr. HUGH-JONES: I couldn't agree with you more about age. But the thing we debated in his particular case was the patient's general condition, including his age. He was a man of 50 who had gross rheumatoid arthritis and was considerably disabled and deformed by it. He had severe breathlessness from his asbestosis, and his general condition was such that we didn't think it was justifiable to do an exploratory thoracotomy on a very small chance of being able to eradicate the carcinoma permanently. I am afraid I am not all that optimistic about the effects of surgery in carcinoma of the lung.

He did smoke, but incidentally he had an adenocarcinoma, which is not a kind particularly related to smoking so far as one knows. We believe, from the work that is being done both in this country and in the United States in relation to smoking, that it is the squamous and the oat-cell carcinomas which have arisen since the 1900s and could be correlated with smoking. Way back in the 1900s carcinoma of the lung was equally common in men and women, and it was predominantly an adenocarcinoma then. It is the recent emergence of the squamous and oat-cell types which gives the male preponderance and which various people have related to smoking.

Professor McMICHAEL: What about the dangers of asbestos in the pericardium?

Dr. HUGH-JONES: I think that's a very interesting point, because asbestos and talc are similar chemically. On general principles I would be a little worried about the possible ultimate effects of asbestos in the pericardial cavity. Talc is used in the pleural cavity to produce adhesions after many spontaneous pneumothoraces, but I don't know if anyone has put asbestos in the pleural cavity. I would be a little worried about asbestos, but I've got no reason for saying that it's a bad thing.

Dr. C. L. COPE: Is there any lung trouble in talc manufacturers?

Dr. HUGH-JONES: Oh, yes.

RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS

Professor McMICHAEL: Professor Bywaters, would you like to comment on the recurring sequence of alleged acute rheumatic fever followed by progressive rheumatoid arthritis? This is the second example we have seen to-day.

Professor BYWATERS: I think they are both fairly common diseases. And when you get a difference here of, say, 21 years between the two, with the rheumatic fever occurring in childhood, I think a coincidence is possible. We have seen a number of people with both diseases, and one disease doesn't seem to confer immunity from the other. I think we are always happier that the first diagnosis is correct when there are no intervening symptoms. Here there is no doubt about the rheumatoid arthritis. I didn't see the patient during life, nor I think did Dr. Dixon, so I am not quite happy about the nodules which Dr. Hugh-Jones described. It's a very unusual place he pointed to on his own arm.

Dr. HUGH-JONES: That was where they were on this patient's arm.

Professor BYWATERS: I would think it's quite likely that they weren't rheumatoid nodules. Dr. Heard didn't seem any too happy either on the pathological side, but I haven't seen the sections. I think this is of some importance from the point of view of the lung, because the Caplan type of lesion seems to occur mainly in rheumatoid patients with nodules elsewhere. In fact the Caplan lesion is a modified rheumatoid nodule occurring in the lung substance or the pleural fissures, perhaps as a result of the abnormal stresses from fibrosis. You can trace in early specimens the palisade layer round the necrotic fibre which is the hallmark of the rheumatoid nodule. I am not saying that these are not nodules, I haven't seen them; but it might be the reason why he didn't develop further changes in his lungs.

Professor SHEILA SHERLOCK: When I first came to this School in 1942 I used to sit back admiringly while Professor Bywaters thought of another good reason why rheumatoid arthritis and rheumatic fever were unrelated diseases. Is there really no relation between these diseases?

RHEUMATOID ARTHRITIS AND DISSEMINATED LUPUS

Dr. COPE: I've commented at a previous conference on the relative frequency with which we've seen acute rheumatism followed by rheumatoid arthritis and then followed by disseminated lupus. When somebody wrote to me about this and inquired for details I quoted the two cases I knew of, and the same day, whilst I was doing the letter, the Records Department turned up five others which were diagnosed "rheumatoid arthritis" and then subsequently disseminated lupus.

Professor BYWATERS: We feel there is no real relation but often close clinical, and sometimes even pathological, similarities. Unless you have got bona-fide heart lesions, it is sometimes extraordinarily difficult to differentiate the early stage of rheumatic fever from the very early episodes of lupus, ankylosing spondylitis, or rheumatoid arthritis. If you get adequate heart lesions, you can be fairly certain about it sometimes!

Professor McMICHAEL: It's very interesting to see these "arrested" valvular lesions. The minimal adhesion of the mitral valve and aortic valve cusps indicates that, even although the valves may be damaged, progression is not inevitable. There are some who think that progression of rheumatic valvulitis is inevitable, but this man, presumably with valve damage at 14, got through to 50.

FRACTURED RIB

Professor BYWATERS: Was there any evidence at necropsy of any metastasis in the fractured rib that might have given us an earlier clue to the diagnosis?

Dr. HEARD: There were very widespread metastases. I didn't examine that particular rib, but I expect it was affected.

Dr. COPE: What about this heavy intimal thickening, is it characteristic of asbestosis? Does it lead to pulmonary hypertension, or what happens?

Dr. HEARD: The gross intimal thickening of the pulmonary arteries that I showed was in the fibrous areas. Elsewhere there was only a little thickening. With this and the normal right ventricle, I doubt whether there was much in the way of pulmonary hypertension here.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to the photographic department of the Postgraduate Medical School for the illustrations.

Drug Treatment of Disease

INFECTIONS OF THE EYE

BY

ARNOLD SORSBY, M.D., F.R.C.S.

Research Professor in Ophthalmology, Royal College of Surgeons of England and the Royal Hospital, London

Infections of the interior of the eye are grave emergencies and call for immediate and expert treatment. Relatively uncommon, they are seen after intraocular operations, perforating injuries, or in severe infections of the cornea. In contrast, infections of the outer eye are of daily occurrence. When the infection is bacterial in origin, treatment by antibiotics is generally efficacious, but virus infections still present a considerable problem.

The poor penetration into the interior of the eye of many of the antibiotics greatly limits the value of systemic administration of these drugs in the treatment of intraocular infections. Fortunately, subconjunctival injection of some of the antibiotics is a feasible procedure in expert hands and gives excellent results. For the external infections of the eye, local application is so eminently satisfactory, and so readily given, that neither systemic administration nor subconjunctival injections often need to be considered. The newer agents thus carry forward an older tradition of both ophthalmology and dermatology, in which local applications have always had a greater vogue than systemic therapy.

AVAILABLE DRUGS

Sulphonamides

The classical sulphonamides are all highly insoluble. When sulphacetamide as a soluble sodium salt became available it was used widely as a local application in all forms of ocular infection, including infected corneal ulcers. Some of the claims put forward for sulphacetamide were untenable: the experimental and clinical results claimed for corneal infections due to *Pseudomonas pyocyanea*—organisms insensitive to sulphonamides—merely reflect the early and rather uncritical enthusiasm for the sulphonamides. It may be taken that the limited range of action of the sulphonamides, together with the fact that the sulphonamides locally are inactivated by pus and breakdown products of tissue, make sulphacetamide of little value in ocular therapeutics.

There is, however, an unquestioned place for the sulphonamides given systemically in treating some of the external infections of the eye; in ophthalmia neonatorum it is possibly still the agent of choice. The causative organism in ophthalmia neonatorum is commonly *Staphylococcus aureus*; a virus closely allied to that of trachoma is responsible for another substantial group in which inclusion bodies can be found in epithelial scrapings taken from the conjunctiva; the gonococcus accounts for a relatively small proportion of the total—possibly as little as 20% or less in present-day series—and the pneumococcus accounts for a further substantial proportion. All these organisms are fairly readily susceptible to the modern sulphonamides in adequate concentration, so that most cases of ophthalmia neonatorum respond quickly to systemic administration.

Apart from ophthalmia neonatorum, and the somewhat similar purulent ophthalmia of adults, the sulphonamides systemically are useful in the after-treatment of septic affections in the lid and orbit dealt with surgically. In the treatment of intraocular infections the sulphonamides systemically are of little use owing to their poor penetration.

Sulphonamides administered locally are of value in only one disease: trachoma free from secondary infection. It is, however, likely that this isolated indication for the use of sulphacetamide has already been superseded by the greater efficacy of some of the antibiotics.

Antibiotics for Systemic Administration

Penicillin, streptomycin, chloramphenicol, and the tetracyclines are widely used systemically, and are all valuable as local applications in ophthalmology. The extensive use of penicillin ointment as a prophylactic measure after removal of corneal foreign bodies and after other minor injuries of the eye has greatly reduced the incidence of infected corneal ulcers and mucopurulent conjunctivitis. Ointments of penicillin and of chloramphenicol, as also of tetracyclines, are used commonly in the treatment of subacute and acute conjunctivitis, and of blepharitis, replacing almost entirely all the older remedies. Penicillin and streptomycin, being very soluble, can also be used as subconjunctival injections for infected corneal ulcers and intraocular infections generally, so that there is a broad field for the use of these agents in ophthalmology.

Recently it has been questioned whether it is justifiable to give any of these antibiotics for relatively minor infections. It is held that some patients may become sensitized, making the systemic administration

EXHIBIT 164

SIMPSON

~~144~~ 36 Ex 164

AUSTRALIAN BLUE ASBESTOS LIMITED

TELEGRAPHIC ADDRESS
"BLUEASBESTOS" WITTENOOM

WITTENOOM GORGE
WESTERN AUSTRALIA

PRIVATE

Managing Director,
Australian Blue Asbestos Limited,
SYDNEY, N.S.W.

P.826.
24th June, 1960.

Dear Sir,

ASBESTOSIS. We enclose for your information two copies of an extract taken from the British Medical Journal. It is quite an interesting article and reveals several facts not known to us before. There is quite a lengthy clinical description of the case also in this issue of the Journal.

Yours faithfully,

Manager.

OA/HS.

EXTRACT taken from the British Medical Journal of 30th April, 1960 headed "Complications of Asbestosis".

ASBESTOSIS REVIEWED.

Professor J.McMichael: Dr.Hugh-Jones, would you sum it up?

Dr. Hugh-Jones: The case is of great interest, as it demonstrates so many of the problems associated with asbestosis which we should review. Asbestos itself is chiefly a double silicate of magnesium and iron. It occurs in a number of mineralogical forms, one of the most valuable being chrysolite. Asbestosis is a pneumoconiosis arising from the inhalation of asbestos dust during the manufacture of asbestos goods, such as asbestos sheeting, fireproof clothing, brake-linings, lagging for boilers and pipes, etc.

One way of thinking of the pneumoconioses is in relation to the chemical toxicity of the different dusts. At one extreme are those, such as iron, which are entirely non-toxic and simply produce a characteristic radiological appearance of the lungs with no change in bodily function. Then come others, such as coal, which do this but also have a pathogenic action by altering the reaction of the lungs to tubercle. Next there are dusts, such as silica, which produce a local reaction in the lungs and pulmonary fibrosis. Finally there are others, such as beryllium, of such toxicity that they can be regarded as general tissue poisons, which produce widespread effects in the body as well as local fibrosis in the lungs. Asbestos is very toxic and produces not only pulmonary fibrosis but reactions in the pleura and even in other organs. Dr.Heard has excellently demonstrated the pathology of asbestosis in our patient, but by way of summary here is a picture (Fig.12) of a whole lung section of another patient who died from asbestosis. There is an interstitial fibrosis, as in the present case, gross pleural thickening and some patchy bronchiectasis. Besides these three features, which are common in asbestosis, there may be associated tuberculosis, as there was in this second case, or, even more important, associated lung cancer, as in our patient. Sometimes the interstitial fibrosis gives rise to the formation of bullae, or occasionally even to a widespread "honeycomb lung" - i.e., that which occurs with other rare forms of pulmonary interstitial fibrosis, such as the xanthomatoses.

RADIOLOGICAL APPEARANCES.

These are typically those of a fine lace-like reticular pattern, particularly affecting the lower lung fields and causing a "shaggy" border to the heart, as in our patient. Besides this, cystic changes may be seen and very often the pleural thickening. Although the X-ray picture is typical and almost pathognomonic in a few advanced cases, there are many patients who have undoubted asbestosis (as judged by a history of exposure and the clinical features of clubbing, rales in the lungs, and typical changes in lung function), who do not have specific changes in their chest radiograph. That is extremely important in relation to the diagnosis, as we shall see later, because in general the diagnosis of pneumoconiosis depends on an appropriate industrial history and a characteristic X-ray appearance. There is a characteristic X-ray appearance in asbestosis, but unfortunately from the medico-legal standpoint not all patients with asbestosis have the characteristic radiograph. Finally, the radiological appearances of asbestosis cannot be classified in the same categories as those accepted internationally for the other pneumoconioses.

CLINICAL FEATURES AND COURSE.

Gross clubbing of the fingers and persistent rales in the chest are the characteristic clinical signs of the condition. Exertional dyspnoea is the main symptom as in other pneumoconioses. Patients suffering from asbestosis may die either from the complication of tuberculosis (more common in past years), or more particularly from that of carcinoma of the lung. Those not killed by chest infection or cancer may finally get cor pulmonale.

The disease usually makes its appearance rather suddenly, over the course of a few months, often long after the initial exposure to the asbestos inhalation. It has been suggested that the asbestos lies dormant as an asbestos body, which has to "ripen" over many years before it can break down and liberate its toxic contents. In this respect asbestos is again like beryllium, which may also lie dormant in the body and then suddenly produce its effects concurrently with some other infection.

Carcinoma of the lung is a serious and well recognised complication in asbestosis. Its frequency in asbestosis is difficult to determine, for it is now a common condition in the general population. Moreover, exposure to asbestos may have occurred many years before the cancer develops. Nevertheless, the paper by Doll makes it fairly clear that a patient with asbestosis has a risk about 10 times that of the general population of getting carcinoma of the lung. Another hazard is mesothelioma of the pleura. This rather rare tumour may draw attention to the fact that a patient has worked in asbestos dust. Finally, in women who work with asbestos there is a high incidence of cancer of the ovary.

FUNCTIONAL EFFECTS.

There is a diminution of the inspiratory capacity which fits in with the "shrunken lung" demonstrated by Dr.Heard in this case. In contrast with other pneumoconioses there is often little disturbance to air flow, so that all the movement of the lungs there is is used to good advantage, and the maximum breathing capacity (M.B.C.) is often surprisingly well maintained. Thus if a patient suffering from asbestosis is assessed by the M.B.C., or forced expiratory volume (F.E.V.) test, he is unfairly assessed for compensation compared with a man suffering from silicosis or coal-workers' pneumoconiosis. The essential cause of the breathlessness in asbestosis is the difficulty of transference of oxygen across the altered alveolar membranes, more so than the reduced maximum breathing capacity, which is the cause in, say, coal pneumoconiosis. Carbon dioxide, being soluble, diffuses 20 times as rapidly as oxygen and is unaffected. Oxygen transfer is usually adequate at rest, so that the patients are rarely cyanosed, but when they start to exercise there is a rapid fall in oxygen saturation and gross hyperpnoea.

The diagnosis is made on a history of exposure, the presence of clubbing and rales, and usually by means of a radiograph. There is, however, evidence that the radiograph may not show changes as early as do the lung-function tests. Although the latter are not specific to asbestosis, they are only seen in other uncommon diseases which cause alveolar-capillary block and interstitial fibrosis (such as sarcoid, scleroderma, microlithiasis, and other rare conditions). Thus lung-function tests are useful for making the pathological diagnosis, for, if it can be shown that the patient has an interstitial fibrosis causing alveolar-capillary

block, has gross clubbing and rales, and a history of exposure to asbestos dust, it seems reasonable that he has asbestosis whether the radiograph is specific or no

ASBESTOS DUST

The asbestos bodies simply prove exposure to asbestos dust and of themselves do not mean asbestosis. Anyone may cough up asbestos bodies who has inhaled dust, without necessarily having the changes of asbestosis in the lungs. Vice versa, a patient may have definite and gross asbestosis without asbestos bodies necessarily being found in the sputum during life. Since, medico-legally, the diagnosis depends on a history of dust exposure together with the appropriate X-ray and other changes, the finding of asbestos bodies is of importance in proving exposure.

It seems probable that asbestos fibres, once inhaled, are coated with collage Over the course of years the collagen cover "ripens" by forming transverse cracks, and then the asbestos body can break down, liberating the toxin and causing the reactive fibrosis in the lungs. The nature of the toxin is uncertain. It is, however, presumably the same substance which is carcinogenic.

Asbestosis was first described in this country by M.Murray in 1907. After that, in 1930, Merewether and Price reported the dangers of asbestos dust in the lungs and made recommendations for dust suppression. Thereafter there was a great improvement. In the factory where our patient worked the utmost precautions are now taken to prevent asbestosis occurring. It is a disappearing disease. Nevertheless, asbestos dust is most toxic, and the amount needed to cause asbestosis is not known, so constant vigilance and new preventive methods a needed if this disease is to be abolished.

DISCUSSION.

Professor McMichael. There are many other facets to this patient, butbefore we go on to them are there any other points or queries which could be raised on the pathogenesis of asbestosis?

Dr.R.S.Williams. Ithink there is one point in support of the mechanical theory that is worth raising. If experimentally you give asbestos ground up into a fi dust, fibrosis does not occur, and it seems that asbestos fibres between 20 and 5 microns in length are necessary to produce the typical peribronchiolar fibrosis.

DISTRIBUTION OF FIBROSIS.

Professor E.G.L.Bywaters. What is the explanation of the distribution of fibrosis? Does it correspond to the distribution of asbestos in the lung, or is there some other explanation?

Dr.Heard. As a matter of fact, it doesn't seem to correspond. Although some of the best asbestos bodies in this case were in fibrosed areas, there were plenty surrounded by perfectly normal lung in other parts. Dr.Nagelschmidt, fro Sheffield, was here two days ago and he was saying that they have recently examined chemically a number of lungs from cases of asbestosis. In some there

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