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REPORT OF A MEETING

TISSUE RESPONSE TO ASBESTOS

A MEETING of 75 invited doctors and scientists was held in Cardiff from April 7th to 9th, 1970 under the auspices of the National Research Council, the Asbestos Research Council and International Union Against Cancer (UICC).

The intake of asbestos by man is almost entirely as an inhaled aerosol of industrial origin; recently the ubiquity and stability of asbestos fibres has raised the possibility of its significance in general air pollution. The consequences of breathing it into the lungs may be fibrosis, bronchial carcinoma and mesothelioma of the pleura or other tissues.

Industrial uses of asbestos started in 1878; asbestosis dates from 1900, lung cancer from 1935 and mesothelioma from 1955. The number of reported cases of mesothelioma in Britain has increased from 4 in 1962 to 800 in the current year. Carcinoma of the lung occurs in lungs severely damaged by fibrosis, but mesothelioma, which is particularly associated with crocidolite asbestos, is found when there is no fibrosis of the lungs, although asbestos fibres and asbestos bodies may be present.

The value of asbestos lies in its fibrous crystalline form. There are two kinds, chrysotile and amphibole; the latter includes crocidolite or blue asbestos, amosite, anthophyllite which represents only 1 per cent of the total production, and two rare varieties, tremolite and actinolite. The largest production is Russian chrysotile followed by chrysotile from Quebec. Chrysotile is mined from open holes, often on the bench system; amphiboles occur in seams or reefs, like coal, associated with non-fibrous rock of similar constitution.

Chrysotile fibres are flexible, they consist of bundles, about 30μm in diameter, of huge numbers of tubular fibrils. The fibres occur in tangled clumps. Amphiboles have stiff, needle-like fibres which may be very long. There are no fibrils. Deposits of crocidolite are sedimentary, from primeval seas, and contain up to 0.5 per cent of oil from organic residues. Oil is not found in chrysotile. Traces of the carcinogen benzpyrene occur in the oil; there is some doubt as to whether it comes from slow pyrolysis of indigenous plant oils or whether it is a contaminant from fuel oil in blasting explosives, mining lubricants or fuel smoke. Another trace constituent, originating from polythene bags, is a yellow oil containing diphenoquinone.

There are differences between asbestos of the same type from different deposits; for example, magnetite and brucite may occur with chrysotile, either as impurities or else incorporated in the lattice.

Cationic dispersing agents open up the fibres of chrysotile, and the fibres also tend to open up in the lungs. The surface of the fibrils is magnesium hydroxide with a positive charge which decreases as the pH of the surrounding liquid decreases. Amphiboles are more resistant than chrysotile to chemical attack; they have a high

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proportion of silica in the surface. Solution is affected by the metals present in the lattice, a metal more active in the electrochemical series suppressing the solution of a less active one. The leaching rate of magnesium in acid solution gives an indication of the origin of unknown fibres.

Asbestos can be identified by electron and X-ray diffraction, even single fibres by using an electron probe. Tissue can be burnt away from lung sections at only 100°–150°C to reveal the asbestos deposits by exposure to monatomic oxygen; the oxygen probe is activated at 35 MHz by an oscillator. This gives better results than direct heating which has to be at 450°C followed by acid irrigation.

It was suggested that 90 per cent of the asbestos fibres found in lungs were submicroscopic, electron microscopy being essential for their study. Nevertheless, using visual microscopy without oil immersion objectives, several million fibres per gram of lung tissue can be removed from cases of severe asbestosis. As well as fibres, asbestos or ferrugenous bodies are found in the lungs. There has been speculation about these for many years. After asbestos fibres have been inhaled and deposited in the lungs, some of them acquire a coating of iron-containing protein which appears to be conveyed to the fibres in ferritin granules from the blood. This builds up in a variety of forms and may be more or less uniform along the length, or thicker at the ends of the ends of the fibre, or grooved at regular intervals along the length, sometimes deeply; electron microscopy indicates that no bare patches of fibre are exposed at the base of the grooves and all fibres in the lungs soon receive a thin coating. It is noticeable that only a small proportion of fibres are treated by the lungs to form thick bodies. Whether the coating invariably takes place on fibres which have been engulfed by macrophages is uncertain. It has been suggested that a macrophage can only deal with one fibre and will coat just one of the several it may contain. Many fibres are too long for complete engulfment by macrophages and excellent photographs were shown of several macrophages tackling different parts of a single long fibre. It seems that a fibre longer than 7–9 μm would be too great for a single phagocyte to pick up. Certainly, the mobility of a long fibre which is being handled by several cells must be negligible.

The suggestion was put forward, and received some support, that the formation of an asbestos body was a defence mechanism of the lungs against inhaled and deposited fibres. After a time the body appears to have eroded away the fibre that was originally its core; the body then breaks up and the fragments disappear, apparently doing no further damage. The form of the bodies may be associated with the type of asbestos, the most deeply segmented ones being favoured on fibres of crocidolite. Asbestos bodies do occur on chrysotile, but they are rare compared with the occurrence on amphiboles.

Just as the length of the fibres inhaled affects both the distribution of fibres which are deposited in the lungs and the possibility of movement of deposited fibres by phagocytes, so also is there an important influence of length on the site of deposition.

To a first approximation, the rate of fall of an asbestos fibre depends on its diameter, not its length, since changing the length changes both weight and air resistance proportionately. When an aerosol of asbestos fibres is inhaled, therefore, deposition due to sedimentation is independent of the most obvious characteristic of a fibre, its length. On the other hand, deposition by interception or wall collision, which is very

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important in narrow airways, depends almost entirely on the length of the fibre. Chrysotile fibres, which are curled, are readily deposited by interception since the curvature increases the collision cross-section area; this holds, too, for loose clumps of chrysotile fibres which may be of large size but of very low effective density, because of the air entrained in the clump. Deposition by interception, during inhalation, is especially favoured at a carina where the bifurcation of an airway occurs.

Experiments in which the weight of dust remaining in the lungs of rats exposed to clouds of asbestos was determined, showed that the retention of amphibole asbestos was six times greater than that of chrysotile. The amphibole and chrysotile dusts had similar length distributions and it is thought that the curliness of the chrysotile fibres had caused many of them to be deposited by sedimentation and interception in the ciliated region of the respiratory tract. They were subsequently removed from the lungs on the mucous film by ciliary action, swallowed and excreted in the faeces. The needle-like fibres of amphibole were less affected by interception and many penetrated to the respiratory bronchioles, beyond the ciliated epithelium, and stayed in the lungs. Similar conclusions were reached when asbestos aerosols were sucked through models of pigs' lungs prepared by filling the airways of the lung with wax, removing the tissue and electroplating the wax and then finally melting the wax out of the metallic tubes.

These findings are paralleled by the results of dust sampling in relation to the incidence of disease in South Africa. In the North West Cape area, a fine-fibred crocidolite is produced and there is a high incidence of mesothelioma. In the Transvaal there is no mesothelioma but a lot of asbestosis. Samples of airborne dust from Transvaal mines show that the average fibre diameter for amosite and crocidolite is three times that found in North West Cape samples. It is thus likely that fibrosis is linked with fibres having a greater falling speed and a more efficient interception. Fine, slowly settling dust of the North West Cape mineral has access to the lung alveoli and from these works its way, aided by the movements of the lung, to the pleura where it causes mesothelioma. The ratio of 3:1 in diameter of fibre means that for the same dust count the Transvaal aerosol has 27 times the weight of that in the North Cape workings.

Several pathologists were of the opinion that asbestos fibres, when inhaled, deposit in the respiratory bronchioles of the lung. It was claimed that fibres were found in freshly killed animals only in these regions where there are relatively few alveoli opening directly upon the airway. Only after some delay were fibres found in the depth of the acini, in the more peripheral alveoli. There was some disagreement with this view and no backing was given to it from fibre counting and sizing observations, which are certainly necessary to decide how far the fibres can penetrate. It must also be remembered that the proximal alveoli are exposed for a longer part of each breath than are the more distal alveoli, because the tip of the parabaloid of inhaled tidal air advances into and then recedes from the alveolar ducts and occupies the centre of the lumen of the respiratory bronchioles for longer than it does in the more remote parts of the alveolar ducts.

Some beautiful time-lapse cinematography and many splendid electron micrographs contribute to the understanding of phagocytosis, the primary process for cleansing the walls of the alveoli of the lungs by wandering cells which engulf foreign particles. Whereas silica particles rapidly kill phagocytic cells in the lungs, the toxicity

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of asbestos fibres is less. If the asbestos is shorter than about 9 μm the cells should be able to dispose of it, but the possibility of some fibres working through to the pleura and causing mesothelioma remains. Large fibres can certainly get into the lung parenchyma, though probably not very often, by being breathed into the depths of the alveoli. Such particles cannot be moved by phagocytes, they congregate in the basal regions of the lung lobes, perhaps because of their weight, and cause asbestosis.

Why they cause asbestosis or the increased production of collagen, is far from being agreed upon. A few people regard this as the result of mechanical irritation. Another view is that the proliferation of collagen, which to a limited extent is also seen in other parts of the body, is the result of an immune reaction. In support of this view it has been found that people exposed to asbestos often have in their serum a circulating anti-nuclear reagent, which can be detected by a fluorescence test with nuclei from the liver of the rat.

Part of the fibrosis reaction is the passage of red blood cells from the capillaries between adjacent alveoli; these may provide the iron which is needed for asbestos bodies. It is suggested that there may be a region around each body which is deficient in red cells, as a result of removal of all the available iron. The total number of asbestos bodies in a lung with severe asbestosis may approach 10^8; a good many normal lungs also contain a few. Presumably the defence mechanism can cope with the odd fibres of adventitious exposure to asbestos, but not with the gross abuse of excessive industrial exposure with the result that fibrosis develops.

Collagen occurs all over the body as the structure supporting element of connective tissue. This contains only a few cells, the fibroblasts from which collagen is believed to originate; there are also elastin and reticulin threads embedded in ground substance. The importance of collagen in life is considerable; it increases in fibrosis or in ageing and it is laid down to repair wounds and the lesions of disease such as tuberculosis, where it fills space, in what was formally functional tissue. The ground substance consists of mucopolysacharides; the long threads of collagen are built up from protein subunits in an extremely regular way and are somehow stimulated by dust particles, or by products discharged by cells which are injured by dust particles, or by disease.

There is a characteristic macroscopic appearance of lung sections due to asbestosis. The respiratory bronchioles and nearby alveoli are affected, the walls being thickened and the lumen of the air spaces decreased; the lower parts of the lobes are most affected. The peripheral parts of the acini, and some complete acini are not involved. There is no emphysema. Airways adjacent to fibrosed areas are dilated and the lung section has a honeycomb appearance. A principal feature which contrasts with silicosis is the much smaller content of dust in the lymph nodes, only the smaller asbestos particles being seen. In asbestosis most dust is in the periphery of the lung, especially in the lower lobes. The behaviour of very small asbestos particles seems to resemble that of silica dust in some respects. The largest fibres found in the lymphatics are about 7μm long, thus supporting the view that they can only get there through the agency of mobile phagocytes. There is little fibrosis in the lymph glands, again in contrast to silicosis, which presumably expresses the considerably lower fibrogenic action of asbestos and the effectiveness of the rapid coating of the fibres in the lung,

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Experimental adenomas and mesotheliomas have been induced in animals by exposure to asbestos dust, mesotheliomas being infrequent. Lung dust loads of 3·6 g of amosite and 0·6 g of chrysotile were attained in rats after exposure to 5000 mg/hr/m³; the difference in lung dust is again due to removal of chrysotile by the bronchial epithelium where the greater curliness of the fibres favoured deposition. Direct inoculation into the pleura produced an increase in the number of mesotheliomas for each dust. No evidence was found for the significance of residual oil in asbestos. The UICC standard sample of Canadian asbestos is a blend of fibres from several different sources; tumour production from this was less than the figure from any one of its constituents. World distribution of standard blended samples for laboratory work has earlier been criticized on the grounds of fractionation during experimental procedures.

An interesting point, revealed by electron microscopy of tumour cells, was that in mesothelioma the cells looked like macrophages, having very similar processes growing from the cell wall. Metastatic spread was not marked from mesotheliomas unless the growth was disturbed. Possible lines of treatment were chemotherapy, immunology or injections of white cells from the patient himself into the tumour.

There is some feeling that synergistic action or co-carcinogenicity might be important in promoting tumour growth. Choking of the microlymphatic system and inhalation of other dusts and smoke were suggested as contributory factors. It is common practice to discourage smoking in asbestos factories.

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