A REVIEW OF SOME OF THE PROBLEMS FOUND IN THE PATHOLOGY OF THE PNEUMOCONIOSES

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If all the dust were to be removed from the atmosphere of a mine or a factory, pneumoconiosis, defined in South Africa as permanent damage of the cardiorespiratory organs from the inhalation of mineral dust, would disappear. This has not yet been done and in 1962 the pneumoconioses are still a hazard of mining and industry.

Since 1556, when Agricola published *De rea metallica,* the results of many investigations into the pathogenesis and pathology of the pneumoconioses have been recorded, but unsolved problems are still associated with this group of diseases. How silica produces fibrosis is still not known, nor is the part it plays in coal workers' pneumoconiosis and massive fibrosis. Increasing numbers of silicates, long considered to be non-toxic, have been shown to produce an interstitial fibrosis of the lungs.

Mining operations produce, apart from silica, toxic

substances such as nitrous and diesel oil fumes in the atmosphere, but the part played by these substances in increasing or decreasing the toxic action of silica is not known. Wet mining methods have reduced the dust hazard considerably, but the hazard still exists even with the axial feed drills. The amount and character of 'drilling dust' will depend on the amount of energy expended during drilling, and will vary according to the hardness of the rock, the amount of pressure on the drill and the power of the machine. Not only is the miner using a drill exposed to a variable dust cloud, but different mining operations, such as scraping, produce a dust cloud which may differ considerably from drilling dust.

Although Vorwald[1] has shown that silica particles, from 0·009 to 0·1 microns, produce a diffuse interstitial fibrosis and emphysema in rabbits, there is no definite evidence that sub-microscopic particles are toxic in man. Davies[2] did not consider that these very fine particles contributed to silicotic fibrosis in miners, because a rock drill will not exert enough energy to produce sufficient of them. Considerable numbers of such particles have been demonstrated in the dust in South African gold mines by Talbot and Kempis[3] and the possible toxic actions of these are under investigation.

DUST IN THE LUNGS

Particles of dust above 10 microns in size will be trapped in the nasal cavities and prevented from reaching the lower respiratory tract, but the dust escapes this filtration mechanism during mouth breathing. Hatch,[4] in human volunteers, and Davies,[5] using models of the bronchial tree, showed that dust particles below 5 microns only were retained in the alveoli in significant numbers. The alveolar retention curve, however, applies to a normal chest, and the effect of any abnormality in the respiratory tract on such retention has not been determined.[6] The presence of fibrosed root glands and emphysema may cause the retention curve to be altered, and particles above 5 microns in size may then be retained and play a part in the production of silicotic fibrosis.

This retention curve assumes that the diameter of a dust particle is the parameter which is a measure of fibrogenic activity. The surface area or the mass of the dust in the lungs may be of greater importance. Using the surface area of the particles as the common denominator, Nagelschmidt *et al.*[7] found, by intratracheal inoculation, that particles of less than 5 microns in diameter were fibrogenic and those in the range of 1 - 2 microns were most toxic. Goldstein,[8] however, found that particles in the 3·5 micron group produced more fibrous connective tissue than those in the 0 - 2 micron range. In another series of experiments, King[9] has confirmed the findings of Nagelschmidt and his co-workers.

According to Heppleston,[10] dust is taken up by the alveolar phagocytes and carried to the second order of respiratory bronchioles, where the dust-containing phagocytes enter the interstitial tissue. In the guinea-pig, Gross[11] considered that dust particles could penetrate the walls of the alveoli, but both Heppleston[12] and Gross[13] indicated that further investigation of the mechanism by which dust enters the interstitial tissue is necessary. Duguid[14] considered that, in coal workers' pneumoconiosis, foci of fibrosis are produced by organization of those alveoli that are packed with dust-laden phagocytes, and that the lesion is not essentially in the interstitial tissues. Although coal dust is easily demonstrated in histological sections, the relation of silica particles to different parts of the respiratory system is difficult to determine, since these particles can only be shown up with dark-field illumination or by using polarized light.

During the last few years, Heppleston[15] and Gross[16] have shown that the deposits of dust in the lung are by no means static, and that dust can move from one part of the lung to another. Heppleston[15] has demonstrated that inhaled iron particles can enter an existing focus of collagenization. Gough[17] has shown that coal dust is removed from bronchiectatic areas of lung tissue.

Not all dust which is inhaled is retained, and the effectiveness of the dust-clearing mechanism varies from one individual to another. Such variation has been well demonstrated in monkeys, where a silica suspension was introduced into the right lower lobe through a bronchoscope. After 6 months, 2 of 18 monkeys did not show any evidence of dust deposition or of a tissue reaction to dust.[59] Cartwright and Nagelschmidt[18] suggested that dust clearance depends on particle size; the smaller the particles the higher is their chance of being retained. In an examination of the dust in lung residues of coal miners with pneumoconiosis, the mean mass size distribution, converted to Stokes diameters, had a maximum in the 2·3 micron range and ended at about 5 microns.

Using the amount of dust in the regional lymph nodes, Policard and his co-workers[19] showed that a non-toxic dust (titanium oxide) was cleared more slowly from the lung than was quartz. Le Bouffant,[20] however, considered elimination of dust *via* the lymphatic system to be negligible, and did not find any significant difference between the clearance of a toxic and non-toxic dust.

THE PNEUMOCONIOSES

Pathogenesis of Silicosis

It is well known that silica possesses a specific fibrogenic action. Many theories have been developed to account for this, but at the present time none is generally accepted. For over 25 years it was considered that silicic acid, which is produced when silica is in a fluid medium, was the fibrogenic agent, but in 1953 King *et al.*[21] and in 1956 Zaidi *et al.*[22] showed that, although different forms of quartz produced the same amount of silicic acid in solution, the amount of fibrosis found in animals injected with tridymite was far greater than in animals inoculated with fused quartz. Curran and Rowsell[23] showed that, when silica was enclosed in a membrane which would not allow the particles to come into contact with peritoneal tissue, fibrous tissue was not laid down even though any silicic acid produced could leave the membrane.

The extended solubility theory[24] does not explain why different forms of quartz produce varying amounts of connective tissue, but postulates that the cytoplasm of quartz-containing phagocytes has in it a collagen precursor and

that the polymerized form of silicic acid (polysilicic acid) changes pro-collagen to collagen. This suggests that early collagen fibrils might be found in the cytoplasm of the phagocyte, but Policard and his co-workers[25] have demonstrated in electron microscopical studies that the early fibres are extracellular in distribution.

Much work has been done in different countries on a possible immunological factor in the production of silicotic fibrosis. It is considered that silica alters the basic components of tissue sufficiently for them to become antigenic. This may occur in the phagocytes[26] or in the interstitial tissue.[27] As yet there is no definite proof that silicotic fibrosis is produced by an antigen/antibody interaction or as a type of auto-immune disease, but there are indications that silica affects certain immunological reactions. The properdin level in the serum of animals, exposed to a silica-dust cloud, drops during the first few weeks of exposure.[27] Vigliani and Pernis[28] have shown that there is an increased amount of beta and gamma globulins in the fully formed silicotic islet, and Pernis[28] has demonstrated that, when a phagocyte containing silica dies, the cytological features are similar to phagocytes exposed to a serum containing high amounts of gamma globulin. The sera of miners attending the South African Pneumoconiosis Bureau partially inhibit the haemolysis produced by silicic acid in the presence of complement.[27] Recently, Vigliani and Pernis[29] suggested that the action of silica is that of an adjuvant to other immunological processes, and that there is no specific antigen formed or antibody produced.

Many other theories have been suggested to explain the fibrogenic action of silica; according to Nagelschmidt[30] these 'range from the reasonable to the bizarre'. It is only since 1956 when Zaidi *et al.*[22] showed that the solubility theory of silicosis (as postulated) was no longer tenable, that intensive work into the action of silica started. It is known that the surface of the silica particles possesses well-marked oxidative properties and that amino acids can be altered by shaking them well with silica.[31] This finding defines more accurately than before the nature of the activity of the silica particle and may lead to a better understanding of the fibrogenic action of quartz.

Pathology of Silicosis

The lesions of silicosis found in South African gold miners were fully described by Watt *et al.*[32] in 1916, by Strachan and Simson[33] in 1930 and by Strachan[34] in 1946. Simson and Strachan did not find the diffuse thickening of the alveolar walls described in 1916, but it is probable that the improvements in mining methods may have reduced the type of dust causing this lesion. In 1930 Simson and Strachan[33] examined the lungs of miners who worked before 1928, when it was probable that the major improvements in ventilation and methods of drilling were complete. A comparison of the pathology described by these 2 authors with that found in miners who had worked wholly in improved mining conditions was reported by Webster[35] in 1959, when it was noted that the distribution of the silicotic lesion was different. The lesion is now mainly a perivascular one, instead of being primarily peribronchiolar. The perivascular lesion was also noted by Rüttner and Grassman[36] in German industrial workers.

The nature of the lesion may depend on the type of dust inhaled. Vorwald[1] has already demonstrated that the sub-microscopic particles produce a diffuse fibrosis, and it is possible that the size of the dust particle may determine whether the lesion is peribronchiolar or perivascular. As will be shown, some of the combined forms of silica (silicates) produce a diffuse fibrosis. Sericite and other silicates are found in the atmosphere of the gold mines and, indeed, Jones[37] maintained that the fibrous forms of sericite were the causative factor in silicosis. Not only particle size, but also the nature of the dust, therefore, may determine the type of lesion produced.

From animal experiments it is known that guinea pigs exposed to a silica-dust cloud, in which the average airborne particle is 1 micron, show a diffuse thickening of the alveolar walls, whereas in monkeys exposed to a similar dust cloud the lesions are nodular and resemble those found in man.[59]

As yet no satisfactory explanation has been found to account for the symptoms of disability of which some of the miners complain. It has been demonstrated that exposure to a silica-dust cloud will affect certain enzyme systems in lung tissue,[38] and Pernis[28] has suggested that the toxic action of silica in macrophages may be from the interference of the esterase group of enzymes. The lipid content of the lung also increases when animals are exposed to silica,[39] but these changes are only now being assessed as possible factors in the pulmonary disability of gold miners.

Mixed-dust Pneumoconioses

McLaughlin[40] found that the pneumoconiotic lesions in foundry workers differed from those of classical silicosis in that they were less discrete and the fibrosis extended into the adjacent alveolar walls in a stellate arrangement. These lesions were produced by a dust containing a mixture of iron and silica, and the histological features of the lesion varied according to the amount of silica present. With a high percentage of quartz there is concentric fibrosis in the centre of the lesion.

Lesions of the mixed-dust type have been found in South African gold miners, but the amount of 'inert' minerals in mine dust is not sufficient to produce this type of lesion. During discussions with McLaughlin,[41] it was suggested that the less active combined forms of silica (silicates) could act in the place of iron, and that the findings of mixed-dust lesions on histological examination were compatible with service in gold mines. It is possible that the lesions found in miners from other South African mines are basically of the mixed-dust type, where iron has been replaced by one of the other more inert minerals.

Some of the lesions, previously described as tuberculo-silicotic, have features which are very similar to the mixed-dust lesion, and the criteria for such a diagnosis should be reviewed.

Coal Workers' Pneumoconiosis

The nodular lesions of coal workers' pneumoconiosis are of the mixed-dust type, but there is no uniformity of opinion on the pathogenesis. In Germany[42] it is considered

that the fibrosis is caused mainly by the presence of silica in the coal dust, but in Great Britain an infection, probably, but not necessarily, tuberculous, is considered to be the cause of the fibrosis.[42]

Massive fibrosis can occur in any of the pneumoconioses, but most of the work done on its aetiology has been related to coal workers. In Germany,[42] although it is admitted that a few cases are caused by tuberculosis, in many there is no evidence of this disease and silica is thought to be the causative factor. In Great Britain, Gough[43] and Hinson[44] are of the opinion that most of the massive fibrous lesions are tuberculous in origin. Cochrane,[45] in 1960, reported on a large-scale survey of the incidence of tuberculosis and massive fibrosis, and showed that there was little difference in the attack rate of massive fibrosis in one valley which had been intensively 'combed' for tuberculosis. He summarized the 4 current theories of the aetiology of massive fibrosis, and indicated that there had been some tendency to underestimate the importance of dust itself as a factor.

Emphysema may be marked in the pneumoconioses and appears to be a feature in coal workers' pneumoconiosis. Although the dust deposits are associated with areas of centrilobular emphysema, the exact parts played by aging and by dust have not been established. Does inhalation of mineral dust, especially silica, cause a more rapid aging of lung tissue?

Silicatosis

For many years it was considered that silicates were not fibrogenic, and in 1960 Nagelschmidt[30] expressed the view that silicates do not produce fibrosis. One of the possible reasons for disregarding dusts containing silicates as an industrial hazard was that, with the exception of asbestos, they do not produce silicic acid. Now that the chemical or solubility theory has been shown to be untenable, this property of a dust cannot be regarded as evidence of toxicity.

It has been shown, however, that after long exposure a diffuse fibrosis of the lungs occurs in kaolin and talc workers. This was ascribed to the small amounts of free silica present, but the lesions do not have the features of a mixed-dust lesion. In 1960 Barrie and Gosselin[46] described a pneumoconiosis in a nepheline-ore worker; nepheline consists of silicates, but no free silica.

It is considered that the silicates can no longer be regarded as non-fibrogenic dusts, and that exposure to dust containing silicates may constitute an industrial hazard, but further cases will have to be examined.

Asbestosis

The pathogenesis of asbestosis is obscure and much attention has been paid to the asbestos fibre and to the asbestos body. It is still considered by some that the fibrosis of asbestosis results from mechanical trauma from the asbestos fibre.

Recently, Beattie[47] has shown that the 'asbestos body' consists of a protein coating of the fibre, and that this coating is gradually impregnated with iron salts which are responsible for the yellow and brown staining. After a number of years the 'asbestosis body' undergoes segmentation and eventually particles of the body are engulfed by phagocytes. The fibrosis of asbestosis occurs at this time. Disruption of the fibre is accelerated by pulmonary infection and chronic cardiac failure.

Experimental work in South Africa[48] does not support the findings of Beattie, since the fibrosis produced in animals exposed to an asbestos-dust cloud is not related to segmentation of the bodies nor is there a long latent period before it occurs.

The presence of the bodies, more correctly known as asbestosis bodies, does not appear to be directly related to the presence or degree of fibrosis, and it is considered that more attention should be paid to the silicate nature of asbestos and that asbestosis may be another example of the silicatoses.

The incidence of asbestosis is far greater than has been thought, and it is apparent that only short exposure to the dust may produce the disease. The wide use of asbestos in industry and the methods which are necessary to prepare the fibre as a commercial product indicate that many people are exposed to this hazard.

The fibrosis in asbestosis is diffuse and not nodular, and it is to be expected that those suffering from it will complain of more severe dyspnoea than those with silicosis. The incidence of cor pulmonale should be higher than in the other pneumoconioses, but no exact figures are available.

Gloyne[49] showed that the incidence of bronchogenic carcinoma in patients with asbestosis is much higher than that expected in the general population, and Keal[50] has described abdominal tumours in women working with asbestos. In South Africa, a relatively large number of tumours of the pleura (mesotheliomata) has been found.[51] All except 7 of the patients quoted had some association with the north-western region of the Cape Province. Of the 7 patients, 5 had definite industrial exposure to asbestos mined in that area. Cases of mesothelioma have been reported in other countries in people who have been exposed to asbestos.[43,44,52-54]

Other Pneumoconioses

The increased interest in industrial medicine has resulted in the correlation of cases of pulmonary fibrosis with the inhalation of toxic substances in the atmosphere of the working place. The concept of a mixed-dust lesion has enlarged the pathological criteria upon which a diagnosis of pneumoconiosis was made, and has resulted in a number of cases previously considered as not typical of a pneumoconiosis being classified as such.

Other diagnostic criteria are being revised and it is now suggested that the characteristic granuloma of beryllium disease is not a specific histological feature. Indeed, the cellular infiltration of the alveolar walls is considered to be more important in this pneumoconiosis than the granuloma. It is possible that some other factor besides beryllium is required before beryllium disease can occur.[55]

ANIMAL EXPERIMENTS

Most of the work on which our knowledge of the pathogenesis of the pneumoconioses is based has been carried out in animals. There are different methods of introducing dust into an animal and, since no one method is widely used, it is apparent that difficulties have been encountered in the use of each method.

The intratracheal inoculation of a dust suspension, developed and used extensively by King and his co-workers, was the method which should have given consistent and reasonably quick results. Many workers, however, are unhappy about this technique. There may be unequal retention of the suspension and also difficulty in the correlation of histological findings and collagen content. Although this method is of great value in a qualitative study of fibrogenicity of dusts, relatively large numbers of animals are required to obtain reproducible quantitative results.

The subcutaneous inoculation of dust suspension is criticized because the tissue into which the inoculum is injected is not the same as that in which a pneumoconiosis occurs. In addition, the factors of stress and change in temperature will affect the development of any subcutaneous dust granuloma, as they do in other experiments of a similar nature.[56] Although a number of suspensions can be injected into one animal, the reaction to the inoculum will depend on the blood supply at the site of injection. Nodules produced in the subcutaneous tissue of the lower abdomen cannot be compared with those in the upper abdomen or back.

The intravenous injection of the dust suspension is used, but because the dust is not retained in one organ, the amount of fibrous tissue in the liver is correlated with the amount of dust found there. This method of estimating the fibrogenic effect of a dust is criticized because it is not known whether the dust found in the liver is the only part of the suspension which has caused a reaction in the tissue. It is possible that some of the sample may have been removed by the defence mechanisms of the liver.

The most acceptable method is the exposure of animals to a cloud of dust, since this is the method by which dust enters the lungs. Using this method, lesions take a relatively long time to develop, and intercurrent infections may affect the experiments. As has been shown, the properdin levels of the serum drop considerably when the animals are first exposed. As properdin is associated with the natural defence mechanisms of the body, an infection at this stage will spread widely. With adequate care of the animals, however, this method is of great value. In South Africa lesions, very similar to those described as acute silicosis in man, have been produced in monkeys after 16 months' exposure to a silica-dust cloud.

The optimum dust concentration in such a dust cloud is not known, and although in South Africa the concentration is maintained between 25,000 and 30,000 particles per c.mm., this is considered by Nagelschmidt[57] to be too high. Much discussion has centred on whether the animals should be exposed to the dust cloud continuously or intermittently. Vorwald,[1] exposing animals to high concentrations for 15 - 30 minutes every 7 - 10 days, has produced lesions in guinea pigs in a reasonably short time.

Other methods of inoculation, such as intra-ocular, are used in specific experiments, but it is often difficult to prevent infection of the eye. The phagocyte-culture technique developed by Marks[58] is used to assess the effect of dust in macrophages, but the peritoneal macrophage differs from the alveolar phagocyte, and studies on the histochemistry of dust-containing phagocytes have to be carried out on cultures of the defence cells of the lung.

CONCLUSION

This review indicates that there are still many problems associated with the pathogenesis and pathology of the pneumoconioses and that the particular property of a dust to produce fibrosis is obscure.

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