Fibrosis of lung—an environmental disease?

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Environmental lung diseases are due to a number of different agents. The most important are the fibrous and non-fibrous mineral dusts and the organic dusts. Gases and aerosols can affect the airways or cause an acute toxic pneumonitis. Recovery from such acute damage sometimes leaves an obliterative bronchiolitis. Exposure to cadmium fume may lead to emphysema. But pulmonary fibrosis rarely results from acute or chronic exposure to gases or aerosols. As in renal disease, by the time organ failure leads to death the pathological findings in the lung consist of a combination of scars and secondary accelerated age changes that do not reveal the primary disorder. As with the kidney, biopsy in the early stages may be only partially informative and is too hazardous a procedure to use in large-scale survey work.

The mechanism leading to fibrosis in environmental lung disease is shown by correlating sequential clinical, radiological, and physiological studies and comparing them with the pathological findings at various stages in the development of the disease. Only rarely are biopsy information in an early stage and detailed follow-up studies culminating in a full necropsy available for study in a single case. It is dangerous to assume a spectrum of change from the examination of individual patients in apparently different stages of the disease, just as it is dangerous to translate experimental pathological findings to human disease.

Environmental lung fibrosis is due to the failure of the dust-handling mechanism when the lung is exposed to a fibrogenic dust. One would expect the pattern of the disease to be more or less the same irrespective of the nature of the fibrogenic dust. One would also expect the pattern of disease to be different from lung fibrosis due to infection, and different again from that due to systemic disorders such as rheumatoid arthritis and disseminated lupus erythematosus. As our knowledge of dust disease increases, however, it becomes apparent that there are considerable differences between the pattern of illness produced by different fibrogenic dusts. In some dust diseases the lesion is diffuse and primarily affects the lower part of the lung. In others the

lesion is discrete or nodular and affects the upper zones first. The pattern of environmental lung disease can mimic that produced by infections and by systemic diseases.

Mechanisms of alveolar dust clearance

Dust particles of effective diameter between 0.2 and 3 μm are not removed as the air passes down the airways. A proportion are precipitated below the lower end of the mucociliary system to lodge in the respiratory bronchioles and alveoli. Here they stimulate the production of surfactant by the type II cells and the phagocytic activity of the alveolar macrophages.

Unless the system is overloaded the alveoli remain aerated. The macrophages engulf the dust and carry it either directly up the airway or through the lymphatics in the connective tissue space around the terminal airways and into the airway lumina proximally. These loaded macrophages (dust cells) are either coughed up or swallowed, and should remove all inhaled dust. If the system is overloaded or if the dust damages the macrophages they may reach only the peribronchiolar connective tissue. Some may remain there indefinitely or move on to the hilar lymph nodes. Others may die and leave their load to other macrophages which also die.

Repeated cell damage of this sort, due either to continued overloading of the system by high levels of exposure or to a particularly cytotoxic dust, leads to an inflammatory reaction and fibrosis in the centre of the lung lobule. The laden macrophages with the inflammatory reaction and scarring, and rarely the dust itself (tin and iron), become visible on x-ray films as discrete shadows (simple pneumoconiosis). Depending on the amount of scarring, these shadows may not be associated with any disturbance of lung function.

One of the major problems is the association between dust deposition, fibrosis, and emphysema. A popular concept is that they are merely geographically related and the emphysema is of non-industrial origin. Another view is that the presence of dust within macrophages is associated over the years with

the release of hydrolytic proteases that are partly responsible for the destructive centrilobular emphysema. The development of patchy 'interstitial' fibrosis in this so-called 'simple' pneumoconiosis is also ill-understood and has been ignored in the past. These lesions impair the elastic movement of the lung and over the years concentrate and accentuate the age damage, yielding centrilobular emphysema. This may obscure the x-ray appearances and produce a progressive failure of the gas exchange function of the lung.

Long fibrous particles may get caught across smaller airways or trapped in alveolar sacs arising directly from the respiratory bronchioles: they may be forced into the interstitial tissue. They are incompletely engulfed by the phagocytes, which are damaged and die. Some naked fibres remain in the alveolar lumen; however, they may become coated with ferritin. Others migrate through the interstitial tissues. Both experimental and human epidemiological studies indicate that it is these fibres that cause the lung scarring. Smaller fibres, short enough to be engulfed by macrophages, travel free or within macrophages to the hilar lymph nodes, the visceral and parietal pleura, and beyond.

Although some organic dusts are insoluble and can be handled in the same way as mineral dust danger arises from the soluble component. This tends to cause inflammation and tissue damage by hypersensitivity reactions, by activating the alternate complement pathway, or by a non-specific foreign body reaction. When these reactions occur in response to dust caught in the alveoli alveolitis develops, followed by fibrosis.

Specific dust diseases

Study of the pattern of individual dust disease reveals different ways in which the normal defence mechanism fails and tissue damage occurs.

SILICOSIS

Freshly fractured quartz particles in the size range 2-5 μm in diameter are cytotoxic to phagocytic cells. If the level of exposure is high both the alveolar macrophages and the type II cells may be rapidly destroyed in the alveolar lumen, leading to acute alveolitis and rapidly progressive fibrosis. This kind of exposure is now rare because symptoms occurred within a few months of first exposure and, even after brief exposure, death took place within five years.

At lower levels of exposure the macrophages clear the alveoli but die in the peribronchiolar interstitium or in the lymph nodes. Successive macrophages engulf the particles and die, causing

an inflammatory reaction which leads to the characteristic whorled, discrete nodule. The parenchymal lesions are said to remain discrete without seriously disturbing lung function until the lesions in the lymph nodes interfere with lymphatic drainage. Once this occurs the continued exposure must lead to an accelerated production of nodules that coalesce. This process, *progressive massive fibrosis*, occurs first in the upper and mid-zones of the lungs, although the early discrete lesions are evenly distributed.

The relationship between silica dust and *Mycobacterium tuberculosis* in causing progressive massive fibrosis is still not clear. Not surprisingly, the involvement of the cellular defence mechanism by

Fig. 1 *Progressive massive fibrosis in silica exposure. Note upper lobe distribution of massive lesions against background of discrete whorled nodules in remainder of lung.*

Fig. 2. *Progressive fibrosis in a coal worker. Notice upper zone distribution of massive fibrosis, which shows areas of necrosis and cavitation. Rest of lung shows background of simple pneumoconiosis with centrilobular emphysema. The simple pneumoconiotic lesions consist mainly of dust-filled macrophages and little fibrous tissue.*

silica dust impairs the mechanism's ability to deal with *M. tuberculosis*. Overt silico-tuberculosis may result. More often it is difficult both for the clinician and the histopathologist to define the role of *M. tuberculosis* in individual cases of progressive massive fibrosis. When upper lobe tuberculosis with spontaneous recovery was common in the community it may have accounted for the upper zone localisation of progressive fibrosis.

Simple pneumoconiosis due to pure silica exposure progresses for some years after exposure ceases, probably because the particles do not become coated but remain cytotoxic (Fig. 1). Once massive fibrosis has started it progresses indefinitely. The upper two-thirds of the lung contracts towards the apex and the patient becomes dependent on the over-stretched, scarred lower zones which become progressively more emphysematous. Death is

usually due to respiratory failure. It is not clear whether the fall in the incidence of tuberculosis will alter the distribution of massive fibrosis in pure silicosis, but active tuberculous infection is not now a necessary part of fatal progressive disease (Fig. 1).

COAL WORKER'S PNEUMOCONIOSIS

Mixed inorganic dust exposure causes a pattern of simple pneumoconiosis similar to early silicosis. There is a dose/response relationship. In coal workers, however, the disease is less extensive than would be expected either from the amount of crystalline quartz present in the inhaled dust or in that recovered from the lung at necropsy. The other dusts (carbon, kaolin, mica, etc.) seem to reduce the toxicity or fibrogenicity of the quartz. The dust accumulates both around the terminal bronchioles

and in the lymph nodes but tissue damage and scarring is initially less severe (Fig. 2). Foci of dust-laden macrophages create the discrete shadows seen in the x-ray picture when there is minimal disturbance of lung structure and none of function.

In coal miners the lesions do not progress in the absence of further exposure. In contrast to silicosis, work at low levels of exposure can be safely continued. The lesions are evenly distributed through the lung fields. Continued heavy exposure leads to a gradual increase in the number and size of the micronodular shadows and to progressive tissue damage with the coalescence of the lesions. The progressive massive fibrosis is again concentrated in the upper and middle zones with contraction towards the apex (Fig. 2). Arteritis with central necrosis, and the evacuation of large quantities of liquid black

Fig. 3 *Progressive massive fibrosis in Caplan's syndrome. Note typical discrete Caplan lesions in middle and lower zones where some areas are almost free of simple pneumoconiosis. The massive lesion consists of an aggregation of small round Caplan lesions.*

material, is quite common and in some patients recurs repeatedly. It may be accompanied by serious haemorrhage.

Neither the aetiology nor the pathogenesis of progressive massive fibrosis in coal workers is clearly understood. Its pattern was thought to be related to past tuberculous infection, although active infection is no longer an important factor in the disease in Britain. The amount of simple pneumoconiosis necessary before progressive disease develops varies considerably. Investigation of this problem led to the recognition of Caplan's syndrome as a distinct entity. The massive shadows in Caplan's syndrome are smaller and rounder and appear against a trivial background of simple disease. (Fig. 3). The dust exposure is less and there is little respiratory disability until very late in the illness. The rheumatoid joint disease that may precede or follow the lung lesion is relatively benign. The lung lesions may remain stationary for a period and then progress rapidly. Eventually they coalesce, with the development of a picture indistinguishable radiologically from progressive massive fibrosis unassociated with rheumatoid disease. Central necrosis with black sputum and haemoptysis may occur. The early round lesions have a characteristic pallisade arrangement of cells with cellular evidence of immunological activity and the presence of aggregated rheumatoid factor and immunoglobulins. Central necrosis is followed by extension of the lesion and the older coalescent lesions show a laminated structure with evidence of immunological activity round the periphery (Fig. 3).

Although the typical case of Caplan's syndrome is obviously different initially from other cases of coal worker's lung the end-result is very similar. Surprisingly, a reinvestigation of non-rheumatoid progressive massive fibrosis in both coal workers and after pure silica exposure has shown that collagen fibrosis forms only a small part of the lesion. The bulk of the material appears to be formed of fibrin and immunoglobulin. Evidently these dusts initially cause a benign nodular lesion which triggers a progressive lesion provoked by an immune mechanism. The stage at which triggering occurs depends partly on the 'cytotoxicity' or 'fibrogenicity' of the dust, partly on the immune 'constitution' of the worker.

ASBESTOSIS

Asbestos dust contains relatively large fibrous particles which may be trapped in the lung parenchyma, causing cell damage and leading to scarring different in pattern and distribution to that due to other inorganic dusts. The lesion is diffuse; it affects the lower and peripheral part of the lung first and

spreads proximally (Fig. 4). It interferes early with the elastic movement of the affected area. Ventilation ceases and the lining of the peripheral air-spaces is replaced by cuboidal (mainly type II) cells and even by goblet cells.

Impairment of lung function and rales audible at the end of full inspiration may precede obvious x-ray changes. The lesion may progress for a time after sudden cessation of heavy exposure but may remain stationary for many years if exposure is very low. The clinical and pathological result in this type of disease is essentially the same as in idiopathic and extrinsic fibrosing alveolitis. The evidence of increased individual susceptibility related to tissue typing is not clear but cigarette smoking may be an adjuvant.

Even at a level which cannot be detected during life this fibrosis is associated with a much increased risk of cigarette-induced bronchial cancer. It differs in this respect from all other forms of lung fibrosis. Mesothelioma, which may also be caused by other

Fig. 4 Asbestosis in patient who had packed asbestos into quilts for many years. Disease is diffuse, mainly peripheral, and greatest in posterior and basal parts of the lower lobe where it has progressed to a honeycomb change. Death was due to respiratory failure.

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fine mineral fibres, is not epidemiologically linked either to lung fibrosis or cigarette smoking.

TALC

Prolonged exposure to high levels of talc dust, particularly the coarse material used in industry, has given rise to pulmonary fibrosis. The pattern of fibrosis closely resembles that produced by asbestos (Fig. 5) and examination of the fibrosed areas under polarised light reveals numerous plate-like birefringent talc particles. However, there is now doubt whether pure talc of the kind used for cosmetic or toilet purposes will produce this lesion. Electron microscope examination of the dust causing 'talc' fibrosis and of the dust in the damaged lung reveals the presence of asbestiform fibres, usually tremolite, not present in the pure talc. These may be the fibrogenic agents.

ORGANIC DUSTS

Exposure to organic dusts leads to a diffuse interstitial pneumonitis in which mononuclear cells predominate. It is associated with bronchiolitis and with evanescent sarcoid-like granulomata. Resolution is usually complete but in about 10% of cases fine nodules are seen on x-ray examination to persist. This persistence is possible after repeated exposure or more rarely after a single severe episode. Fibrotic changes may progress with contraction of the affected lobes. Whereas one would expect this extrinsic disease to affect the most-used parts of the lung first, in most cases of farmer's lung, bagassosis, and bird fancier's lung the permanent damage is greater in the upper lobes (Fig. 6). The distribution is similar to that seen in ulcerative colitis and associated with long-term sulphasalazine medication.

Although the pattern of disease in pigeon fanciers

Fig. 5 Diffuse fibrosis of lung in talc worker. Note distribution similar to that in asbestosis and the honeycomb change.

Fig. 6 *Chronic farmer's lung. Note diffuse change affecting upper and peripheral parts of lung, producing gross cystic change as well as honeycombing.*

is different on the whole from that seen in mushroom pickers and in farmers there is a distinct overlap and an even more distinct individual variation. The disease may start with hay fever and asthma in one patient and with mill fever and pneumonitis in another. Although prolonged high-level exposure after the first onset of symptoms seems to cause permanent damage in all patients, there is evidence of marked difference in individual susceptibility. As

in all diseases associated with an immune response, the immunological constitution of the individual patient is very important in determining the response to this extrinsic hazard.

BERYLLIUM

Acute, high exposure to beryllium causes an acute pneumonia with systemic symptoms. It is usually fatal. Chronic exposure produces a lesion which is both clinically and pathologically similar to sarcoidosis. The granulomatous disease has a mid-zone distribution, spreading out from the hilum. It may be associated with narrowing of the airways as well as stiffening of the lung periphery and impairment of gas transfer. The disease regresses in response to corticosteroid therapy, and this may delay or prevent fibrosis. But in most cases the treatment must be continued indefinitely. Whether the disease is related to the continued presence of beryllium in the tissues or whether the metal initiates a self-perpetuating disease is not clear. The onset of symptoms and signs is not directly dose-related and may occur on withdrawal or some time afterwards. The relationship to an inherited tendency to autoimmune disease has not yet been explored.

Conclusions

The pattern of lung fibrosis due to inhaled material can mimic the patterns produced by idiopathic and by infectious disease. This might be taken as an indication that all lung fibrosis is due to extrinsic factors. However, closer study of the processes involved indicate that the pattern of disease is determined as much by the inherited characteristics of the patient and by concomitant disease as by the nature of the causative agent.

Detailed references to the work on which this paper is based are given in Wagner (1977).

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Reference

- Wagner, J. C. (1977). Pulmonary fibrosis and mineral dusts. *Annals of the Rheumatic Diseases*, **36**, Supp. 2, 42-46.