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REVIEW

Recent advances in the pathogenesis and clinical assessment of mineral dust pneumoconioses: asbestosis, silicosis and coal pneumoconiosis

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ABSTRACT: Recent investigations of the fundamental mechanisms of the mineral dust diseases have substantially increased our understanding of the pathogenesis of the pneumoconioses. In all the mineral dust pneumoconioses, the initial early lung lesion is a fibrosing macrophagic alveolitis. The additional contribution of other lung cell populations is currently under investigation and may identify specific processes for each of the pneumoconioses. Clinical investigations have also progressed with new tools such as Gallium-67 lung scanning, bronchoalveolar lavage analyses, and CT scanning of the thorax; their established values are reviewed in this paper, and areas where progress is needed are considered. The clinical progress in the mineral dust diseases is clearly linked to the basic understanding of the mechanisms of these diseases.

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The long term inhalation of inorganic mineral dusts in the work place can lead to the development of interstitial lung disease, with associated lung function derangements. Over the last ten years, it has been well documented that the pneumoconioses are associated with chronic inflammatory processes in the lower respiratory tract which have been well characterized in several independent laboratories. The recognition of an inflammatory component to the pneumoconioses has permitted the improvement of the sensitivity and specificity of methods of disease detection.

These newer understandings of biological mechanisms of the pneumoconioses and the recent associated advances in the clinical assessment of mineral dust pneumoconioses are summarized in this review article.

Fundamental pathogenesis of mineral dust disease

General concepts

The magic in bioactive minerals. The vast majority of minerals known to man have very little toxicity to the lung, thus one cannot attempt a review of the subject without asking the obvious question: what makes some of the minerals more toxic than others? What is the magic in some of these minerals?

There are at least three fundamental groups of factors that are known to influence the character and severity of lung tissue reaction to the mineral dusts.

The amount of dust retained and duration of exposure. The exposure factor has been extensively discussed in several epidemiological studies where it has been well documented that in an industrial setting with dust exposure at risk of pneumoconiosis, the risk is related to the intensity and years of exposure (dose × time) [1–4]. However, within an industry, among a group of workers apparently exposed to the same dust (dose × time), only a fraction of the group will develop the pneumoconiosis. This common clinical and epidemiological observation [1–8] has been explained at least in part by the so-called individual susceptibility factor.

The individual susceptibility. To investigate the individual susceptibility factor, immunologic background, lung structure and clearance capacity have been considered. Reports on human immunologic histocompatibility have failed to document definite markers identifying the more susceptible workers [9, 10] and our own work with asbestos workers appears to agree with these earlier reports [7].

BECKLAKE [11] has suggested that lung structure may be a risk factor in the adverse pulmonary response to asbestos exposure.

Alveolar dust clearance capacity in humans has not been directly studied in asbestos-exposed workers as a determinant factor for individual susceptibility to the disease. Lung tissue burden of fibres has been found to be increased in asbestos workers compared with that in

the general population [12]. In the exposed workers, it has been documented that workers with isolated airway disease have twice the fibre content of the lungs of workers without airway disease but only 50% of the fibre content of patients with asbestosis [13]. In the lung tissue of patients with asbestosis, the lung fibre burden appears to correlate with severity of the disease [14–17]. Analysis of bronchoalveolar lavage (BAL) fibre content in workers with asbestosis have yielded results in the same range as that of our sheep with asbestos alveolitis, but lower values were found in exposed workers without asbestosis [18, 19]. In human studies, the amount of exposure is difficult to determine with precision, and it has not been possible to compare groups of workers with similar exposures but different disease activity. We have evaluated the alveolar dust clearance capacity in our sheep model of asbestosis.

Given that all our exposed sheep had similar exposures, BAL fibre content can be seen as an index of alveolar dust retention [20] and hence assesses the individual alveolar clearance capacity. In the sheep with alveolitis, we found a four-fold increase in the number of fibres retained in the alveolar space without difference in type, size distribution, width, or aspect ratio of the fibres [21]. These data in the sheep model clearly link the individual susceptibility to develop asbestos alveolitis to alveolar retention of the dust and thereby to the individual dust clearance capacity. In addition, cigarette smoking has been documented to impede asbestos fibre clearance [22], which may explain the increased disease rate seen in asbestos workers who smoke.

The nature and properties of each specific dust. The nature and physical properties of mineral dusts constitute the third factor under consideration. For each individual mineral, the 3 following elements have to be considered: geometric and aerodynamic properties, chemistry, and surface properties. Each of these physical aspects of a mineral will not be reviewed in detail but we will only summarize the most important observations on fibres or particles relevant to the pneumoconioses of interest in this review.

Fibres

Geometric and aerodynamic properties of fibres through their effects on deposition and retention in lung tissue will influence the amount of dust retained in the lung and thus will clearly influence the intensity of biologic reaction to the dust. Fibres less than 0.25 μm in diameter and longer than 8 μm in length will be the most active. The wide fibre will not reach the distal respiratory unit and it will be the same for the majority of larger fibres. The length of fibre appears to be important, as fibres that cannot be completely phagocytosed by the alveolar macrophage will increase the permeability of cell membranes and facilitate leakage of enzymes and other cell products which would activate the alveolar macrophage population to release factors implicated in the development of a fibrogenic process [23–26]. Short fibres will have reduced fibrogenic activity but are not necessarily completely inert as recent studies have demonstrated [27–29]. Thus the dimensional aspect cannot completely explain biological activity, but in general, it can be said that it constitutes a major determinant of biological activity.

Chemistry of fibres also has been considered of importance, as the high magnesium of chrysotile and anthrophyllite is considered toxic to the cell membrane and its replacement through acid treatment appears to reduce cell membrane injury [30, 31]. Experimental studies with phosphorylated chrysotiles also appear to reduce somewhat the toxicity of the fibre [32, 33]. This effect, however, may be of limited practical importance as the phosphorylation process affects only the outer layers of chrysotile fibre bundles (P. SÉBASTIEN, personal communication).

The experimental data gathered to date on fibre toxicity cannot be completely explained by the dimensional and chemical aspect of fibres, so surface properties had to be considered [34–36]. It is acknowledged that interactions between solid particles and molecules in the biologic medium are controlled by the surface reactivity of the solid. There is no solid surface which is chemically inert. Surface breaking of the bonds between atoms constituting the inorganic solid leads to the appearance of atoms in low co-ordination states which are carriers of residual charges, as a function of their nature and the environmental configuration. These surface atoms correspond to the active surface site and the activity of the minerals in different media is related to the nature, strength and density of these surface sites. The surface activity of a solid can lead to: 1) modification of existing equilibria in biologic media by adsorption phenomena, and 2) the appearance of new chemical species [34]. Adsorption of carcinogens on chrysotile fibres is well-known and may enhance the toxicity of the latter [35]. Similarly, catalytic activity of chrysotile may release free radicals, molecules known for their biologic activity [36].

Surface properties of fibres have been studied particularly in relation to carcinogenicity. Also in relation to fibrogenicity, aluminium coating of the surface has been shown to reduce significantly the biologic properties of chrysotile, although similar but less intense peribronchiolar alveolitis occurred in the animals exposed to aluminium treated chrysotile as compared to untreated chrysotile [33].

Particles

The geometric and aerodynamic properties of particles have been quite thoroughly studied. It is well established that most inhaled particles are deposited in the upper airways before reaching the respiratory bronchiole. Nearly all particles larger than 5 μm will not reach the terminal respiratory unit, whereas most particles below 5 μm will reach the respiratory bronchiole with a large fraction deposited either in them or in the alveoli. Particles of diameter less than 0.5 μm will largely remain suspended in the airstream and be exhaled [37].

The chemistry of mineral particles

This is an extremely complex field of knowledge in constant evolution, where most of the work has been related to quartz toxicity. One major theory is that hydration of quartz results in the formation of silanol groups, the hydrogen bonds of which would react with phospholipids of the cell membrane to cause haemolysis or cytotoxicity [38, 39]. The bonding of the hydrogen of silica by the polymer PVNO or compound 40/80 would effectively reduce the toxicity of quartz. The proton-donating groups can form hydrogen-bonded complexes with the phosphate ester groups of membrane phospholipids and thus disrupt the cell membrane. On the other hand, extracellular phospholipids in the alveolar space may reduce this cell toxicity. This formation of hydrogen bonds would be absent in amorphous silica. One argument against this hypothesis could be the observation of pneumoconiosis in patients working in silicon factories [40]. However, a significant amount of cristobalite is known to be generated during the process.

Another possible chemical aspect of silica toxicity of quartz to consider is the observation that silica may be the source of free radicals which would induce peroxidation changes in the lipids of cell membranes and thus disruption. CHRAPIL [41] has conducted experiments on the subject and concluded that haemolysis by silica is an independent process not related to induction of lipid peroxidation (accumulation of degradative products of peroxidation was not found). Also, we have conducted *in vivo* experiments and studied the release of superoxide by lung inflammatory cells exposed to silica [42]. The spontaneous release of superoxide was not increased but the inflammatory cells were primed with marked enhancement of their capacity to release toxic oxygen radicals. This effect was significantly attenuated after exposure cessation although quartz particles were still in the lung. Thus it is felt that the release of free radicals is more likely to be the effect of the inflammatory process or immunologic process (lymphokine secretion) rather than the effect of the quartz itself.

Two other theories of the toxicity of quartz have been developed in the past: the piezo-electric effect and the solubility theory. The work relating to the pros and cons of the theories is well reviewed in PARKES' textbook [43]; it is sufficient to say that at the present time, there has been no satisfactory evidence to support them.

The surface properties of mineral particles

The initial observations of HALDANE [44] documented that the silicogenic potential of mine dusts is not only related to its silica content but also related to variable nonsilica content. This was further investigated and the capacity of coal, illite or kaolin minerals to inhibit the toxicity of quartz was documented [45–47]. This was apparently related to surface fixation of these minerals on quartz. Aluminium compounds were later documented to be adsorbed onto quartz surfaces and to reduce the biological activity of the mineral. This point is of particular importance as it is conceivable that aluminium lactate inhalation could be used eventually in selected silicotic patients.

The quartz Minusil-5 has been documented to adsorb up to 11 mg of aluminium per 100 mg Minusil-5. The aluminium fixation was verified by: grazing incidence electron diffraction technique [45] which documents altered surface diffraction of quartz particles by aluminium treatment; colourimetric titration of aluminium in the Si-Al sample with ammonium aurintricarboxylate (11 mg% *vs* 0 mg% in untreated silica sample) [48–50]; modification of solubility of quartz [45]; haemolytic activity on sheep red blood cells which was 93% with untreated Minusil-5 and 0% with treated Minusil-5 [51, 52]; electron spectroscopy for chemical analyses (ESCA) which documented the surface location of aluminium [53].

The quartz particles so treated did not induce silicosis in exposed animals [54] and it was further documented that aluminium inhalation significantly reduced the biological activity and intensity of the silicotic process in the animal models [53]. The surface properties of other mineral dusts have been less well-investigated.

The bridge between mineral matter and biological substances determining the pneumo-nocivity of various minerals remains by and large incompletely understood [55]. Whereas most toxic mineral matter can induce acute cytotoxicity, this avenue does not appear to be the major pathway of the pneumoconioses. The fundamental process appears to occur with viable cells after internalizing the mineral fibre or particle. Intracellular lysosomal rupture occurs with damage to the surrounding structures [56]. The biochemical and functional consequences of intracellular lysosomal rupture have not been clearly identified but it is conceivable that this may lead to the sequence of molecular secretions which would have chemotactic activity for macrophages, lymphocytes and neutrophils with activation of these cells at the site of tissue injury.

From inhalation to retention

Inhalation of mineral dust, particulate or fibrous, will be followed by deposition of some of the inhaled materials in the lung tissue. This is largely controlled by the geometric and aerodynamic properties of the minerals, which will not be reviewed here. The complexity of this aspect of mineral dust disease is more completely discussed in other reviews [37, 57–59]. It is enough to note that particles smaller than 5 μm diameter and larger than 0.5 μm are most likely to be deposited below the respiratory bronchiole, the larger being deposited higher in the bronchial tree and cleared away, whereas the smaller would remain largely in the airstream and be exhaled. With regard to fibrous material, the diameter of the fibres appears to have the major role in the control of deposition. Most fibres thinner than 3 μm will reach the respiratory bronchiole and beyond with the highest fraction of deposition for those between 1 and 2.5 μm. Fibres of all lengths can reach the alveolar airspace but in the terminal lung unit, fibres shorter than 8 μm appear to be capable

of being easily and completely phagocytosed by alveolar macrophages and cleared away more rapidly than the longer fibres. Larger fibres do not reach the terminal respiratory unit, and are cleared rapidly from the upper airways as are most particles of diameter larger than 5 μm. Thus, long and thin fibres will be retained in the distal lung unit [20, 60] and will initiate the disease process.

Lung tissue reactions

Following mineral dust exposure, the macrophage is the major effector cell in defence of the integrity of the lower respiratory tract. After mineral dust inhalation, macrophages are chemoattracted to the site of dust deposition [61–64], initially at alveolar duct bifurcation [62]. In addition, enhanced local proliferation of the *in situ* macrophage population may also contribute to the accumulation of the mononuclear phagocytes [65]. Thus lungs chronically exposed to mineral dusts have an excessive early accumulation of macrophages in the lower respiratory tract, which can be recognized at lung biopsy [5, 66] or lung lavage [6, 67, 68].

However, this initial macrophage alveolitis does not necessarily lead to interstitial lung fibrosis. Indeed, it has been documented in long term asbestos or silica workers [69] that the macrophage population of the lower respiratory tract may be expanded in the absence of interstitial lung fibrosing disease; in the animal model, it is a well-recognized early lung tissue reaction to inert dust particles which usually disappears without residual scar in the months after exposure cessation [70, 71]. This type of "transient macrophagic alveolitis" has been observed following exposure to latex beads, carbon, graphite, and carborundum particles [70–72]. Pathological characteristics of this lesion are the absence of distortion of the normal histological lung structure and the clearance of the phagocyte accumulation after arrest of exposure [70–72].

In terms of cell biology of the macrophage, what differentiates the macrophage of the transient dust alveolitis from that of the normal lung or that of a fibrosing alveolitis? First, the macrophage of the normal lung is a permanent component of the lung defence mechanisms which, under normal healthy conditions, are in a quiescent state, producing minimal amounts of secretions [73, 74].

When the lower respiratory tract is exposed to various particles, the deposition of the particles initiates *in situ* chemotactic activity for the macrophage which accumulates at the site of particle deposition [61–64]. Basal metabolic activity is increased, it displays pronounced ruffling of its surface, phagocytosis and cell size increases, function is enhanced and usually within hours, most particles deposited are phagocytosed [73–74]. If the particle or fibre phagocytosed is "inert", limited secretory activity of the alveolar macrophage occurs, and the macrophage alveolitis is more or less intense according to the amount of dust deposited in the distal lung unit, the outpouring of cells is transient, lung structure remains normal (as in simple pneumococcal pneumonia), and within 3 to 6 months, the alveolitis completely disappears with little or no lung scar tissue [70–72]. Under the circumstances of exposure to inert dusts such as the latex beads, particulate carborundum, carbon or graphite particles, alveolar macrophages phagocytose the vast majority of particles rapidly, but they do not increase secretion of molecules known to contribute to the pathogenesis of chronic lung disease [70–72].

Exposure of the lower respiratory tract to fibres or particles known to cause lung injury, *i.e.* bioactive, can lead to the specific lung tissue responses which will be discussed under the following separate headings: asbestosis: pathology, pathogenesis; silicosis: pathology, pathogenesis; coal pneumoconiosis: pathology, pathogenesis.

Asbestosis

Pathology

The recent comprehensive review of asbestosis pathology [75] recognized that asbestos seems to be deposited first in the respiratory bronchiole and alveolar duct. This is followed by an early transient reaction characterized primarily by macrophage accumulation at the site of dust deposition followed by thickening of the bronchiolar wall due to reticulin and collagen accumulation. In typical cases, only occasional pulmonary subunits are affected. These morphological changes constitute minimal changes, which constitute asbestos-related disease and should be called asbestos airway disease according to Churg [13]. In a more advanced stage of disease, the interstitium of the lung becomes involved in an inflammatory and fibrosing process gradually affecting all lung tissue and generally accompanied by fibre and asbestos bodies in the tissue. In the late stage of the disease, honeycombing occurs and the pathological process becomes similar to that of idiopathic lung fibrosis [75].

Pathogenesis

Studies in several animal models, including sheep [76–83] and in humans [5, 66–68] have clearly documented that the macrophage is the major effector cell in defence of the integrity of the lower respiratory tract following mineral dust exposure. The initial events have been summarized above. However, this initial macrophage alveolitis does not necessarily lead to interstitial lung fibrosis.

Exposure of the lower respiratory tract to fibres or particles known to cause lung injury (bioactive), can lead to the following lung tissue responses:

1. The no-retention reaction: most fibres appear to be cleared away from the lung tissue rapidly without any lung scar tissue. This is the case in several experimental conditions of low exposures to chrysotile [84]. Also it is the case in some of the long term asbestos workers which may be estimated in our clinical work to be up to 50% of all workers [5–8]. Under these circumstances, the

minerals would be rapidly cleared from lung tissue without lung scar tissue. This has been observed in the animal model [84] as well as in long term chrysotile miners [13].

2. The low-retention reaction: deposition and retention are low because of the so-called "individual susceptibility factor", and lung tissue reaction is limited to the site of deposition where macrophages accumulate and eventually are replaced by fibrotic scars limited to the distal airways [13, 14]. In studies of chrysotile lung injury in sheep, this limited distal airway reaction has been observed in the low fibre retainer sheep [21].

3. The high-retention reaction: deposition and retention are significantly higher, lung tissue reaction is more intense, and diffuse alveolitis can be recognized. There is chemo-attraction of macrophages at the site of dust retention. In the alveoli and interstitium, the resident macrophage may also proliferate locally and the macrophage is activated. Its secretory activity is enhanced. Oxidant production is increased [42], fibronectin production [67–69], neutrophil chemotactic activity [85, 86] and fibroblast growth activity [67, 87] are increased, and plasminogen activator [88] is secreted at higher levels. If these secretions are sustained, diffuse lung damage would occur with the development of a chronic interstitial lung disease. The latter observation has been particularly well documented in animal models.

The high-retention reaction is clearly the case in individuals with interstitial lung disease associated with chronic inhalation of inorganic dust, asbestos in particular [67, 68]. The men with asbestosis have, in general, a significantly higher fibre content of their lung tissue than men with disease limited to the airways [13–17]. These individuals with established asbestosis have a well-described fibrosing alveolitis where macrophages are clearly activated, producing excessive amounts of oxidants, fibronectin, neutrophil chemotactic factors and fibroblast growth factors. This type of reaction has also been well characterized in animal models. In the sheep model [21, 82], we have previously documented that this high retention reaction has all of the secretory characteristics reported in humans and becomes a progressive interstitial lung fibrosing disease even in the absence of further dust exposure. The animal models have demonstrated that these macrophage secretions need to be sustained to initiate and maintain the development of a fibrosing lung process.

Silicosis

Pathology

The fundamental lesion is the silicotic nodule [43, 89]. In its early stage, the quartz induced lung injury is composed of birefringent particle-laden macrophages and other mononuclear cells which accumulate in excess in the alveolar and intersitial spaces, aggregate and make-up the initial quartz-induced alveolitis. The developing nodule which follows has a distinct architecture centred around cells and dust. Fibroblasts and collagen tissue begin to surround the central zone of mononuclear cells and intermingle with them. Somehow this pathological process organizes itself into a nodular form which is highly cellular initially and chiefly located around vessels. Gradually, the contents of the nodule become less cellular: reticulin, proteins, phospholipids and collagen tissue are deposited in a concentric arrangement with some hyalinization. Eventually, the resulting near spherical nodule consists of concentrically arranged zones of a cellular hyalinic substance enclosed in a collagenous capsule. In this advanced stage, the nodule contains an excess of collagen but little dust. The nodules located around vessels and small airways may obliterate the lumen of these structures. The nodules tend to occur in clusters and may subsequently fuse into conglomerations. These conglomerations result from coalescence and fusion of nodules which collapse into one another. Extensive type 2 pneumocyte hyperplasia and epithelial cell injury are seen. Conglomerations are not amorphous masses, for individual nodules do not wholly lose their identity. A central vascular necrosis may occur. Sometimes, for unknown reasons, the quartz induced disease may lack the compact pattern of typical nodules. Silica content of normal lung tissue is 0.1 to 0.2% of dried tissue. The content of the silicotic lung is commonly 2–3% and up to 20%.

Pathogenesis

The inhaled silica dust particles are deposited in the bronchoalveolar space depending on size, shape, mass, aerodynamics and other physical properties. Particles smaller than 5 μm reach the lower respiratory tract and are deposited in the small airways and alveoli. Within hours of deposition, the particles are found predominantly at the alveolar duct bifurcations and the randomly distributed alveolar macrophages regroup and are concentrated at the site of dust deposition [90–92]. This process is apparently initiated by activation of complement present in the alveolar lining fluid with generation of the powerful chemotactant, C5a, which recruits macrophages to the sites of dust deposition. This chemo-attraction may be amplified by the on-site macrophage [93].

Within 48 hours of deposition, the majority of quartz particles have been ingested and are found within the macrophages. These particles will by and large remain in the macrophage throughout the time the particles remain in the lung, although occasional particles can be found extracellularly, in other cell types or sequestered in dense layers of collagen in the silicotic nodules. Once the macrophage has ingested the particles, intracellular lysosomal rupture would occur with damage to the surrounding structures [55], which may lead to the sequence of biological events [89, 94–97] to be considered in the following pathways: cytotoxicity, release of oxidants; enhanced fibroblast growth factors by alveolar macrophages; macrophage influence on lymphocytes; macrophage influence on neutrophils; type 2 pneumocyte hyperplasia and activation.

Cytotoxicity

ALLISON *et al.* [98] were the primary proponeants of this hypothesis based on the observation that alveolar macrophages were injured and ruptured soon after phagocytosis of silica added to their culture medium. It was hypothesized that injury, inflammation and ultimately silicosis develop as a result of the release of toxic substances, proteolytic enzymes and lysosomal hydrolases from dying macrophages.

Recent work in the rat and sheep models [54, 92, 99] and in humans [100, 101] have documented that this immediate cell toxicity is more evident *in vitro* than *in vivo*, as alveolar macrophages of dust exposed animals or humans have normal viability and basal function, although containing up to four birefringent particles per cell.

It is thus likely that *in vivo* exposures are not as intense as *in vitro* and it seems likely that *in vivo*, the immediate toxicity of quartz is partially attenuated by the coating of the minerals with surfactant lipids and other alveolar lining fluid materials. This apparent delay in the time course of cell injury reduces cell mortality and disruption but could nonetheless alter the various functions of the macrophage.

Release of oxidants

Alveolar macrophages, as polymorphonuclear cells when activated, can release large amounts of superoxide and hydrogen peroxide which may react with other molecules such as iron or a halide in the presence of myeloperoxidase to form the hydroxyl radical and the hypohalous anion. Although oxidants play an essential role in defending the lung against inhaled microorganisms, they also can inactivate extracellular proteins such as alpha$_1$-antitrypsin, induce lipid peroxidation in cell membranes, cause cytogenetic injury and mediate cell death [102–104].

In humans exposed to a variety of inorganic dusts, spontaneous release of oxidants by lung lavage cells has been found to increase in 50% of cases [68]. In the sheep model of silicosis, it was also documented that the resident alveolar macrophages have enhanced capacity to release superoxide upon additional stimulation [42]. These reactive oxygen intermediates (ROI) can induce degradation of connective tissue components of the lung, damage the lung interstitial matrix and cause marked alterations of lung parenchymal architecture consistent with alveolar epithelial cell injury [105]. The ROI production following silica exposure is reversible, as stopping exposure can restore the normal lung inflammatory cell superoxide metabolism [42] but can be reactivated by cigarette smoking or lung infection.

Enhanced fibroblast growth factors by alveolar macrophages

It has been demonstrated in humans and in the experimental animals that alveolar macrophages of silica-exposed subjects were spontaneously releasing exaggerated amounts of fibronectin and other fibroblast growth factors [67–69, 101, 106, 107]. These factors provide a mechanism to chemoattract the fibroblasts, attach them to the connective tissue matrix and serve as a "competence" signal moving the fibroblast into the early portion of G1 of the replication cycle. Factors other than fibronectin act later in the G1 portion of the cell cycle signalling fibroblasts to synthesize DNA and replicate. It has been documented that in the alveolar space of silica-exposed subjects, the accumulation of fibroblast growth modulating molecules may precede and direct the accumulation of fibroblasts and fibroblast products (procollagen 3) in advanced silicosis [101] and recent experimental data support the latter observation [108].

Macrophage influence on lymphocytes

Multiple bidirectional communication between the two cell types is well-known in other systems and could play an important role in the pathogenesis of silicosis. Here the macrophage would influence and activate lymphocytes. This probably occurs through release by the macrophage of interleukin-(IL-1) which is known to stimulate receptive helper/inducer T-lymphocytes to secrete interleukin-2 and induce proliferation of an expanded and activated population of helper T-cells. We currently have no proof of this hypothesis but SCHMIDT *et al.* [109] have reported that monocytes treated with quartz *in vitro* secrete a factor that caused thymocytes to proliferate (the standard IL-1 bioassay). This effect could be counter-balanced if suppressor/cytolytic T-cells were stimulated and the activity of IL-1 countered by prostaglandin E-2 release from alveolar macrophages, which is not the case *in vitro* at least.

Expansion of the lymphocyte population has been observed in lung lavages of silicotic humans and animals [100, 101, 106]. These activated lymphocytes could in turn secrete a wide range of mediators directed toward the macrophage: macrophage activating factor, interferon-gamma, macrophage migration-inhibition factor and macrophage fusion factor. Some of the effects of these factors may occur as the macrophages have morphologic and functional evidence of increased activity, and increased numbers of multinucleated cells are observed.

Some of the lymphocyte group, the B-cell line, may be increased as it has already been documented, that at least an increase in immunoglobulin accumulation occurs in silica-exposed workers with or without silicosis [101, 110]. This alveolar space increase in immunoglobulin occurs in the absence of alveolar-capillary membrane leakage and precedes the systemic elevation of these proteins. This increased production of immunoglobulins by B-lymphocytes may be a direct effect of a macrophage mediator or it may be brought on through an activated T-lymphocyte intermediary. The specific role of these accumulated immunoglobulins in the pathogenesis of silicosis is currently undetermined.

Macrophage influence on neutrophils

Excessive accumulation of neutrophils has been observed in silica-exposed workers with or without

silicosis [101]. In the animal models, immediately after exposure, there is a surge of neutrophils to the site of dust deposition and this excess of polymorphonuclears is known to persist up to 7 months after the last exposure [54]. In that regard, LUGANO *et al.* [111] reported that macrophages exposed *in vitro* to silica released a chemotactic factor for neutrophils which could be leucotriene-B_4 [112]. The presence of an excess of neutrophils in the alveolar space of silicotics cannot be ignored as this cell population is known to be capable when activated, of secreting collagenase, elastase, several other proteolytic enzymes and reactive oxygen intermediates that are capable of degrading the extracellular connective tissue matrix to induce cell and tissue damage. This type of injury is particularly well appreciated in situations of intense silica exposure experimentally and in the human condition known as "acute silicosis" associated with high level quartz exposure. Under these circumstances, damage to the respiratory epithelium and lung tissue is readily seen as airspaces are filled with neutrophils, epithelial cells, proteinous and lipoproteinous materials [113].

Type 2 pneumocyte hyperplasia and activation

In silica-exposed workers with intense exposures and severe clinical conditions known as acute silicosis and silico-proteinosis, type 2 pneumocyte hyperplasia has been noted on lung tissue and an excess of these cells can be retrieved on bronchoalveolar lavage [114]. These alveolar type 2 epithelial cells are probably activated, producing an excess of lipids which, in extreme cases, may accumulate to completely obliterate the airspace which gives rise to the condition known as silico-proteinosis [113], a disease well-reproduced in an animal model under conditions of high intensity exposure [115]. Under conditions of less intense quartz exposure, we have documented that activation of the type 2 cell also occurs, producing an excess of phospholipids in the alveolar space, which can be readily detected by lung lavage, although not evident on lung histopathology [52–54]. The excess of phospholipids is known to be a fundamental constituent of the silicotic nodule but the precise roles of phospholipids in modulating the cytotoxicity of quartz, influencing clearance of the particles or inhibiting/facilitating the silicotic nodule formation are completely unknown. Similarly, it is possible that type 2 epithelial cells activated directly or indirectly by quartz also secrete an excess of surfactant associated proteins which may contribute to the development of the disease. Further work is obviously needed in this area.

Coal pneumoconiosis

Pathology

Simple pneumoconiosis is composed of dust macules and nodules [43, 116–119].

Dust macules consist of intra and extra-cellular dust particles concentrated mainly around and near respiratory bronchioles. Some proliferation of reticulin fibres is demonstrated by silver impregnation but collagenous fibrosis is absent.

Nodular lesions consist of dust, macrophages, collagen and reticulin fibres which run in random direction in contrast to the characteristic concentric arrangement of collagen in silicotic nodules. The ratio reticulin/collagen is higher than in the silicotic nodules. Coal bodies may be found in areas of dust concentration.

Centrilobular emphysema is seen with the dust but does not constitute an integral part of the disease process and is not disabling in simple pneumoconiosis.

Progressive massive fibrosis (PMF) has been arbitrarily defined as a massive lesion or nodule with a diameter in excess of 1 cm. The microscopic feature of PMF is the same as the nodule with, in some cases, necrosis. Coal PMF is readily distinguished from a silicotic conglomeration by the excess of black dust and the absence of identifiable silicotic nodules. The microscopic features of PMF consist of a large quantity of coal dust, lymphocytes, dust-laden macrophages and dense bundles of reticulin and collagen fibres, some of which are hyalinized. The collagen elaborated in PMF appears to be of a similar type to the hyaline pleural plaque associated with asbestos exposure. In most of these PMF lesions, the extracellular material contains fibronectin [120].

Pathogenesis

The rank of coal does not influence the features of coal pneumoconiosis. However, high rank coals, chiefly anthracite, are associated with a greater prevalence of pneumoconiosis: the higher the rank, the higher the coal content and in general the lower the content of silica and other minerals [43, 117]. High rank coals may be fragmented more easily and yield a greater mass concentration of respirable particles.

The role of quartz content of coal dust can be summarized as follows: pure carbon black and/or quartz free artificial graphite can produce simple pneumoconiosis and PMF. In mixed dust exposures, when the quartz content of dust does not exceed 10%, the probability of developing pneumoconiosis is not enhanced [43].

Fibrogenesis in coal pneumoconiosis appears to be determined chiefly by the amount of total dust lung burden [43, 117–119]. Macrophage activation, oxidant and fibronectin excess production have been documented in long-term workers [121, 122].

Recent advances in diagnostic methods

Over the last decade, several investigations in pulmonary medicine have been oriented towards early detection of lung disease and prevention of late invalidating sequelae. In the field of mineral dust pneumoconioses, several groups of investigators have oriented their studies toward early detection and prevention of late scars and have applied the newer technologies available in

parallel with traditional clinical methods of investigation of these pneumoconioses. These studies have clarified the interest of each new technique and have contributed to improving the sensitivity and specificity of our evaluations of workers at risk of pneumoconioses and of those with pneumoconioses.

Rales

It is well recognized that the finding of rales on auscultation can be a very useful indicator of the presence of asbestosis, particularly for the physician in charge of health surveillance of a plant using asbestos. Recordings and spectral analyses of the auscultatory findings can be used to confirm clinical findings when needed [123, 124]. However, in our own experience [6] of chest auscultation and rales recording of workers of the chrysotile mines and mills of Québec, we find that rales on auscultation are the initial indicator of disease in less than 5% of cases. Most of the time, when rales are heard on auscultation, the chest radiograph and lung functions are abnormal and confirm our clinical impression.

In workers exposed to silica or coal dust, rales are usually absent in cases of simple pneumoconiosis and in most cases of complicated disease.

Chest radiograph

The standard postero-anterior chest radiograph is definitely, and will remain, the major, simplest indicator of mineral dust pneumoconiosis. However, it is well-documented that in more than 10% of symptomatic patients with interstitial lung disease, the plain chest radiograph is normal [125]. In asbestos workers, we have documented in a similar proportion of patients the presence of a subclinical alveolitis [5].

In silicosis, CRAIGHEAD and VALLYATHAN [126] have seen pathologic changes in men with normal chest radiographs; our group and the Burlington VT group [100, 101] have reported abnormal lung lavage in several workers exposed to silica, without radiographic abnormalities.

Thus, the chest radiograph will probably remain one of the major instruments of disease detection in mineral dust exposed workers, but it can not be considered a very sensitive indicator of disease, particularly at the subclinical stage of alveolitis.

CT scan of the thorax

In the clinical investigation of pleuropulmonary disease computed tomography of the thorax (CT scan) often yields information not available by other methods [127–130].

In asbestos related pleuropulmonary diseases, earlier clinical studies [131, 132] on relatively small populations of patients have found that a CT scan was significantly more sensitive than conventional chest radiograph in the detection of disease. In 1984, we reported on 127 long term asbestos workers of the mines and mills of the Eastern Townships of Québec [133]. The CT scan with 10 mm cuts did not detect significant parenchymal disease which had not been seen by the standard radiograph, but provided a better spacial view of the disease process and identified significantly more pleural calcifications than the chest radiograph of patients at risk of developing asbestosis.

Since that report, the 2 mm thin cut scan has been introduced and may be more sensitive for parenchymal disease [134–137]. Further studies are needed to determine more precisely the role of thin cut high resolution CT scans in the early detection of asbestosis.

We studied the CT scan from 58 long-term silica-exposed workers [138]. The major finding of the study was that in the presence of simple silicosis (category 1, 2, or 3) without coalescence or large opacities on plain chest radiograph, CT of the thorax revealed conglomerations in 10 of 30 cases, 70% of which could not be seen with the addition of lateral and oblique chest films. Such coalescence constitutes replacement of normally aerated lung tissue by a functionless mass of fibrous tissue [139] and is associated with the appearance of respiratory symptoms, and leads to deterioration of lung function [140].

Again, with the recent technical improvements of thin cut high resolution CT scan, additional studies are needed.

The value of CT scan in the evaluation of coal pneumoconiosis has yet to be investigated but will probably reveal information similar to that of our study of silicotic patients.

Gallium-67 lung scan

In interstitial lung disease, ^{67}Ga lung uptake reflects the inflammatory activity of effector cells in the lung [141]. Gallium-67 lung accumulation is primarily determined by the number and state of activity of the macrophage population in the lung [142–144], and it correlates well with the intensity of the inflammatory process as graded on lung biopsies [141, 143].

In long term asbestos workers without the usual criteria for asbestosis [145, 146], some 65% of the men have normal ^{67}Ga lung uptake. However, 35% have enhanced lung uptake which is usually associated with rigid lung pressure-volume curves and abnormal exercise gas exchange [5, 6]. When lung biopsies were obtained in such cases, a peribronchiolar fibrosing macrophagic alveolitis was observed. In the men with criteria for asbestosis, 70% have increased ^{67}Ga lung uptake and their rate of decline in vital capacity is faster than that of asbestosis patients with normal ^{67}Ga scans. Differences in ^{67}Ga lung uptake score between groups are not related to pleural disease [147] but rather with the yearly fall in vital capacity: the workers with abnormal scans have the highest yearly decline in vital capacity [148].

In 98 patients with silicosis, SIEMSEN *et al.* [149], reported a high incidence of positive gallium lung scans.

Only overt cases with definite radiographic abnormalities were included.

We reported the study of 46 long-term workers exposed to silica dust in the granite industry [69]. The study showed in the control subjects, a mean ^{67}Ga scan index of 1.77±0.46; the index was 3.05±0.69 in the 11 workers exposed to silica dust without silicosis; in 12 workers with simple silicosis, it was 3.75±0.70; in eight workers with silicosis and coalescence, it was 7.25±2.23, and in 15 workers with large opacities, it was 7.97±1.03. These data suggested that ^{67}Ga lung scanning may provide additional information to establish an early diagnosis of simple silicosis with borderline radiograph in the ILO/UC categories 0/1 or 1/0, where the finding of an abnormal scan would support early positive diagnosis. Also, when silicosis is well established, a highly increased ^{67}Ga uptake would strenghten the radiographic suspicion of complicated silicosis.

In coal pneumoconiosis, it was found in 22 Utah coal workers with more than 20 years of underground coal mining that ^{67}Ga scans were generally abnormal in most of the studied patients [150]. There was no significant difference in the uptake index between subjects with or without radiographic pneumoconiosis. The degree of abnormality correlated with total coal dust exposure.

Bronchoalveolar lavage

Bronchoalveolar lavage (BAL) has been introduced to the clinicians of pulmonary medicine as an investigative tool to evaluate the biology, disease activity and stage of interstitial lung diseases. In the clinical evaluation of patients at risk of occupational lung disease, BAL analyses appear to be particularly indicated: 1) to eliminate other causes of lung disease such as tuberculosis, mycosis, allergic alveolitis, sarcoidosis or lung cancer; 2) to document mineral dust exposures; 3) to support other clinical information such as a positive ^{67}Ga lung scan; and 4) to study the biological mechanisms of mineral dust disease [151].

Asbestos-exposed workers

Following our initial report on a substantial number of long term workers with abnormal ^{67}Ga scans in the absence of other criteria for asbestosis [5], we investigated several asbestos workers [6–8, 66] and similar studies were conducted by the National Institute of Health [65, 68]. In the studies of Rom *et al.* [65, 68] and in our own [6–8, 66], it was documented that macrophages of the bronchoalveolar space of asbestos exposed workers demonstrated marked structural changes, were producing excessive amounts of fibronectin, fibroblast growth factor, and increased γ–interferon, which could participate in the pathogenesis of asbestosis. These were confirmed by another study [86]. In our experimental studies in the sheep model we have fully reported similar evidence of activated macrophages producing excessive amounts of fibronectin, fibroblast growth factor, and neutrophil chemotactic factors, and we have also reported the multifaceted action of asbestos on local and systemic immune lymphocyte responses [21, 33, 42, 66, 67, 152].

The study of asbestos fibres and bodies in the BAL fluid has also been considered in relation to past exposure and indicators of disease activity [153–156]. The detection of asbestos bodies in the BAL fluid, although not a marker of disease, may be of interest particularly in patients with asbestos related disease without clear occupational history.

Silica-exposed workers

In silica-exposed workers from Vermont without radiographic changes of silicosis, Craighead and Vallyathan [126] found on postmortem several foci of macrophage accumulation and fibrosis associated with local accumulation of quartz particles in the lesions. In a similar population of Vermont granite workers without radiographic changes, Calhoun *et al.* [110] and Christman *et al.* [100] have observed elevated lymphocyte and immunoglobulin concentrations in BAL, suggesting a subclinical immune-inflammatory response. Similarly, in the sheep model of the disease, we have documented a quartz alveolitis [52–54] that has the same cellular and biochemical alterations as the human quartz alveolitis.

To characterize this chronic inflammatory process in silica-exposed humans, Schuyler *et al.* [114] have performed bronchoalveolar lavage (BAL) on eight patients with complicated silicosis. They have documented normal viability and phagocytic ability of the macrophages and observed increased numbers of type 2 pneumocytes in the lavages. The authors stressed the role of the type 2 cell in the disease process.

In a recent paper [101] detailed clinical, functional, and BAL analyses were reported in a group of 22 long-term silica-exposed workers with a broad spectrum of disease which ranged from exposed workers without clinical disease to simple silicosis and complicated silicosis.

The study of our workers with relatively high intensity silica exposures and with clinically distinct manifestations of disease documents that the cellularity of lung lavage is increased in all subsets of our silica-exposed workers, as are the elevated levels of the immunoglobulin, IgM; BAL biochemical markers of fibrogenic activity are increased only in workers with coalescence/conglomeration; and whereas silica-exposed workers without silicosis have BAL fluid which inhibits the proliferation of lung fibroblasts, the workers with simple or complicated silicosis have BAL fluid which enhances the proliferation of fibroblasts. This latter observation is of particular interest in relation to the frequent finding of CT scan conglomeration in patients with radiographically simple silicosis.

Coal exposed workers

The largest lung lavage study of coal workers has been carried out by the Lille group of Voisin, who have documented the presence of a macrophage alveolitis in

men with simple or complicated coal pneumoconiosis [121, 122, 157–161]. They also documented the long term retention in the macrophage of coal dust. The macrophages were found to have normal viability but were clearly activated to produce more oxidant, fibronectin and other fibroblast growth factors [157]. These functional abnormalities were primarily observed in the complicated forms of pneumoconiosis, the progressive massive fibrosis of the coal workers. In the study by ROM *et al.* [68], some 15 American coal workers were studied. Ten had simple coal pneumoconiosis and 5 had progressive massive fibrosis. All had a macrophagic alveolitis and again the spontaneous release by alveolar macrophages of oxidants, fibronectin and alveolar macrophage-derived growth factors were primarily seen in the workers with progressive massive fibrosis (ROM W., personal communication, July 28, 1988).

Conclusion

It is now well-established that long-term inhalation of mineral dust in the workplace leads to a macrophage alveolitis which may or may not progress to a classic form of pneumoconiosis. Activation of the alveolar macrophage to release fibronectin and other macrophage-derived fibroblast growth factors, neutrophil chemotactic factors and oxidants constitutes the common apparent denominator for all pneumoconioses. This sequence of events will occur in the most susceptible individuals (dust retainers).

The specific mineral dust disease will develop with the additional participation of other cells lining the lower respiratory tract. Epithelial cell injury may be more important in high intensity exposure; type 2 cells will be activated in silicosis. The B- and T-cell lymphocytes have yet an incompletely understood role.

We can use this fundamental knowledge of the common denominator mechanisms of mineral dust diseases to better characterize early disease. It is expected that the forthcoming investigations in the field of mineral dust disease will be oriented to clarify the specific mechanisms which make a silicosis pathologically different from an asbestosis or a coal pneumoconiosis. An understanding of the specific mechanisms of each pneumoconiosis will also contribute to improving our clinical assessment of mineral dust-exposed patient.

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Progrès récents dans la pathogénie et l'appréciation clinique des pneumoconioses minérales (asbestose, silicose et pneumoconiose du charbon). R. Bégin, A. Cantin, S. Massé.

RÉSUMÉ: Des investigations récentes sur les mécanismes fondamentaux des maladies dues aux poussières minérales ont augmenté substantiellement notre compréhension de la pathogénie des pneumoconioses. Dans toutes les pneumoconioses à poussières minérales, la lésion pulmonaire initiale précoce est une alvéolite macrophagique fibrosante. La contribution complémentaire d'autres populations cellulaires pulmonaires est actuellement en cours d'investigation et pourrait identifier des processus spécifiques pour chacune des pneumoconioses. Les investigations cliniques ont elles aussi progressé grâce à des nouvelles techniques comme le scanning pulmonaire au Gallium 67, des analyses du produit de lavage broncho-alvéolaire et le CT scan du thorax. Ce document reprend la valeur bien établie de ces techniques et signale les zones où des progrès sont encore nécessaires. Tout progrès clinique, dans le domaine des maladies dues aux poussières minérales, est évidemment lié à compréhension des mécanismes de base de ces affections.
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