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The Pneumoconioses: Silicosis and Silicatosis

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Evidence of the effects of dust can be found as early as 3500 B.C. in the lungs of miners from Egypt, India, and China; Hippocrates described "miner's dyspnea" in 400 B.C.[1] In 1866, Zenker proposed the term pneumonokoniosis as a name for all forms of pathologic changes resulting from dust accumulation in the lung.[2] The exposure of workers to dust was dramatically increased at the beginning of the twentieth century because of the invention of the pneumatic hammer drill and sandblasting. The pneumatic hammer drill was often referred to as "the widow maker" because of the marked amount of dust it generated and the number of workers who developed lung disease from such exposure.[3]

Perhaps the most significant event in the modern history of dust-related disease occurred in 1936, in West Virginia. In the construction of the Gauley Bridge, tunnelers, after drilling through a nearly pure alpha quartz stone formation, developed acute silicosis. A number of workers died soon after this exposure from what is presently known as alveolar proteinosis; others died later from the development of fibrous lung disease. This tragedy heightened awareness in the United States of dust-related lung disease and resulted in the establishment of dust-control standards in 1937.[4] The permissible levels of dust in the workplace have been revised many times since, and in 1986 the World Health Organization limit of 40 $\mu g/m^3$ for respirable quartz was established.[5]

In the United States, diseases related to dust inhalation now tend to be sporadic, but silicosis remains a major health problem in China, Eastern Europe, Africa, and South America.

Factors important in determining the pathologic response to a dust exposure include the number, size, and physicochemical properties of the inhaled particles.[6] All of these factors will determine deposition of these particles in the respiratory tract, the potential for their clearance from the lung, the initial inflammatory response, the pathologic changes, and the ultimate development of symptomatic disease.

Mechanisms of particle deposition include sedimentation, inertial impaction, diffusion, electrical forces, and interception.[7] Sedimentation refers to the gravitational settling of particles with a density greater than that of air. Inertial impaction occurs primarily when particles hit branch points of airways in the lung, rather than going with the airstream. The term diffusion refers to random collisions of gas and particles by brownian movement, which causes them to come in contact with and deposit on surfaces. Particles may have electrostatic charges and can induce an image charge on the lung surface, thereby depositing electrostatically. Van der Waals forces can also cause attraction between particles and surfaces by fluctuation in the position of electrical charges. Interception is most important for fibers. Deposition occurs when a point along the length of a fiber touches the wall of an airway; fibers attach at bifurcations by this mechanism.[8]

Additional factors influencing deposition include hygroscopicity,[9] breathing pattern,[10] the anatomy of the respiratory tract, and preexisting pathologic changes.[11–13] Eighty percent of particles greater than 10 μm in diameter will deposit in the nasopharyngeal tract, 5% to 40% of all particles will deposit in the tracheobronchial tract, and 60% of submicron particles will deposit at the bronchiolar and alveolar surfaces.[6] Breathing pattern determines the velocity of airflows in the lung and the extent of penetration in inhaled air. A slow, deep pattern gives more alveolar deposition. A rapid, shallow pattern results in airway deposition.[10]

Particles are cleared from the lung by mucociliary transport and intracellular sequestration. Particles landing on airway mucus can be transported out as free particles or ingested by lung macrophages. Experimental observations indicate that not all particles landing on the mucociliary tract clear immediately, but may in fact remain in the lung and be cleared slowly[14]; the mechanism of this slow clearance from the airway is not known.

At the alveolar level, particles are sequestered intracellularly in macrophages.[15] These particles may remain in macrophages a very long time, usually in the interstitial tissue in the distribution of lymphatics. Particles may be carried by macrophages to regional lymph nodes and more distal sites. Relatively insoluble particles

may be slowly dissolved, their ionic constituents released and cleared by way of the blood in the urine and other excreta.[16]

SILICOSIS

Silica is a term used for silicon dioxide, SiO_2, which occurs in both amorphous and crystalline forms. Amorphous forms include natural glasses, synthetic glasses, and fume silica. Crystalline forms include alpha quartz, which is found in granite and sandstone, and cristobalite and tridymite, which are formed in industrial processes.[17] Quartz is one of the most common components of the earth's crust. Exposure occurs in workers involved in mining, drilling, and stone cutting, as well as sandblasting, molding, and grinding work. Silicates are higher oxide forms of the element silicon (SiO_4) that are usually combined with various metal cations.

The biologic activities of silica particles depend on a number of particle and host factors. Crystalline forms of silica are more toxic than amorphous forms.[18] Quartz particles may have a soluble amorphous surface layer, the Beilby layer, which reduces their biologic activity.[19] Toxicity is enhanced when this layer is removed by acid washing or when freshly cleaved crystal surfaces are exposed.[20] Tridymite, the most fibrogenic form of crystalline silica, lacks a Beilby layer.[21]

Mechanisms of tissue injury by crystalline silica have focused on the surface activity of the crystal and interactions with lung macrophages. SiOH groups on the surface of quartz are thought to form bonds with cellular macromolecules, including phospholipids and proteins. These may be hydrogen bonds[22] or electrostatic bonds.[23] The bonding is thought to lead to denaturation of proteins and damage to lipid membranes. Injury to lysosomal membranes of the macrophage leads to cell injury and death.[22] Injured or dying macrophages release soluble protein factors that stimulate inflammation, fibroblast proliferation, and collagen synthesis.[23,24] Production of active oxygen metabolites may also be a mechanism of cell injury.[25,26]

Silicic acid is not important in the production of tissue injury because amorphous silica, which produces silicic acid most readily, is the least biologically active silica.[20] Cell membrane injury and cell death may actually play a smaller role in the development of pathologic changes related to silica than previously thought. There appear to be important roles for a number of cytokines in the pathogenesis of this disease. These cytokines, including interleukin-1 and macrophage-platelet–derived growth factors, are produced by viable macrophages in response to their interaction with silica.[27]

Macrophages ingesting silica also produce eicosanoids, including PGE_2, TXA_2, and LTB_4, in response to silica.[28] Tumor necrosis factor (TNF) is also synthesized by macrophages in response to silica, and LTB_4 can modulate TNF production.[29] Cytokine-mediated expansion of lymphocyte populations and the resultant production of humoral immune factors may account for the associations of silicosis with rheumatoid disease and scleroderma.[30] Fibrosis may be a consequence of cytokine effects on fibroblasts,[27,31] and TNF also appears to play a major role.[32]

Silicosis is the pulmonary disease that results from exposure to crystalline silica. There are three basic pathologic patterns of response to silica: silicotic fibrotic nodular lesions, interstitial fibrosis, and alveolar proteinosis. The nodules may not become clinically apparent for more than 20 years after exposure. Interstitial fibrosis is observed in workers exposed to dust containing combinations of silica and silicates.[17] Alveolar proteinosis occurs acutely after very large exposures to silica dust.

Silicotic nodules are the most common pathologic response to silica. They are illustrated in Figures 35-1 and 35-2. These nodules, when individual, are called simple silicosis or chronic silicosis and are usually less than a centimeter in diameter. The lesions are hard, spherical, and often slate gray to black in color, depending on the dusts inhaled along with silica. The nodules are relatively acellular masses of dense collagen in granulomalike formations in the lung and hilar lymph nodes. They may be found anywhere in the lung, although they tend to be more numerous in the upper lobes. They may coalesce to form irregular, firm masses 2 cm or more in diameter, which are termed conglomerate silicosis (Color Fig. 35-1). Central cavitation in these larger masses is common and is thought to be due to ischemia. However, with cavitation, superimposed tuberculosis should be suspected. Perifocal emphysema may also occur adjacent to the fibrotic nodules.

Hilar lymph nodes are almost always involved in silicosis, and in some patients they may be found in the absence of parenchymal nodules. The lymph nodes are very hard, blackened, and enlarged. Calcifications may be present and may be seen radiographically as eggshell calcifications. Silicotic nodules may be found outside the thoracic cavity, including the abdominal lymph nodes, liver, and spleen;[33] rarely, silicotic nodules have been reported in the bone marrow.[34]

Progressive massive fibrosis (PMF) is a form of silicosis characterized by dense agglomeration of nodules causing massive scarring usually in the upper lobes (Color Fig. 35-2). Radiographically, over time, this is often described as lesions moving toward the hilum. Simple silicotic nodules are seen throughout the lung and pleura in PMF.

Alveolar proteinosis is a pattern of lung injury that may be caused by inhalation of large amounts of silica. As noted, this was the cause of death of many workers in the Gauley Bridge tragedy.[4] Alveolar proteinosis is characterized by the accumulation of proteinaceous material in the air spaces (see Chap. 33). Acellular material accumulates in the air spaces with macrophages that ingest this material and have a foamy appearance. Alveolar proteinosis associated with silica inhalation is morphologically identical to idiopathic pulmonary alveolar proteinosis in the air space;

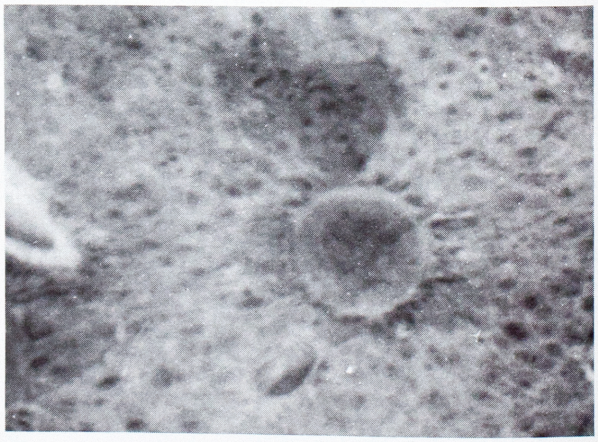

FIGURE 35-1. A silicotic nodule is seen in the lung of a granite worker. Black pigment also is present in the center of the lesion.

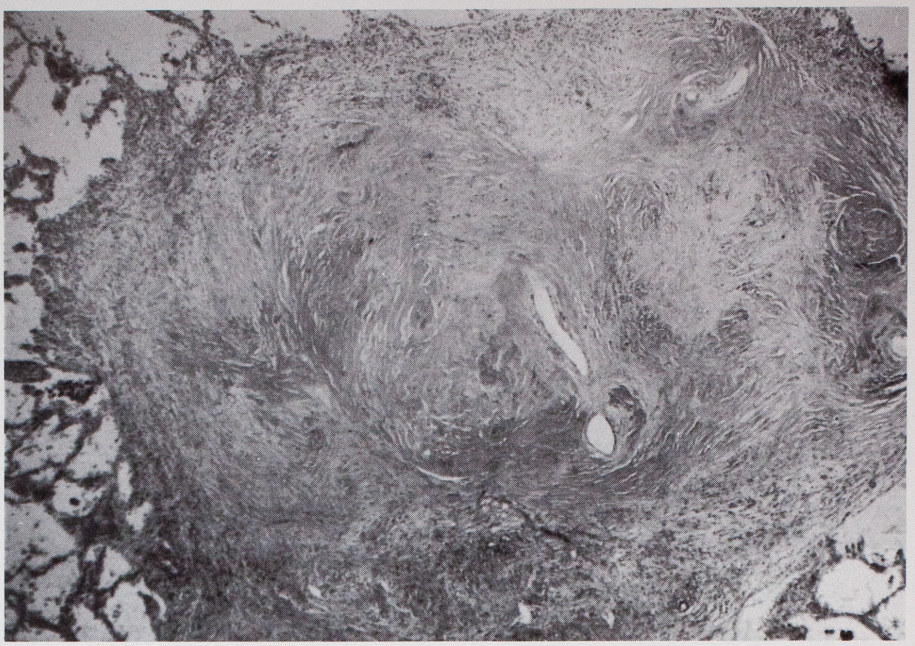

FIGURE 35-2. Cellular dense collagen is seen in most of a silicotic nodule. A few lymphocytes and macrophages are visible at the margin. (H & E stain; low magnification.)

however, there is usually more inflammation in the interstitium with silica exposure (Color Fig. 35-3).

The eosinophilic material of alveolar proteinosis stains positively with periodic acid-Schiff but negatively with alcian blue. Cholesterol clefts are seen in the eosinophilic material and in foamy macrophages. These lesions have been reproduced in experimental animals with exposure to high levels of silica dust.[35] The proteinaceous material filling the alveolar space chemically resembles surfactant but lacks surface tension–reducing properties.[36] This material contains increased amounts of surfactant protein (SP-A)[37] and has been shown to contain large quantities of the collagenous surfactant-associated carbohydrate binding protein SP-D.[38]

Tuberculous complications of silicosis occur in 0.5% to 5% of patients, and conglomerate silicosis may be complicated by tuberculosis in 40% to 60% of patients.[39] Studies from Sweden continue to show high risks of the development of tuberculosis in patients with silicosis;[40] therefore, cavitary lesions in silicosis should always raise the possibility of tuberculosis. Impaired resistance to tubercle bacilli may be caused by silica-induced injury to macrophages, which are then unable to contain and kill the organisms.[41,42]

The role of silica as a carcinogen in the respiratory tract has been controversial.[43] The International Agency for Research in Cancer concluded that crystalline silica should be regarded as a potential carcinogen[44–47] based on definite evidence of carcinogenicity in animals,[48–53] and weaker, yet continuously accumulating data suggest that silica increases the risk of lung cancer in man as well.[40–57] However, a well-controlled autopsy study from South Africa did not find an association between lung cancer and silica exposure.[58]

Pathologic identification of silicosis involves primarily the identification of the characteristic lesions described above. Identification of silica within the lung tissue is confirmatory. Polarized light may be helpful to suggest silicosis, but usually the most birefringent particles are silicates. Silica is only weakly birefringent.

Definitive identification is usually done by energy-dispersive x-ray analysis (EDXA) and x-ray diffraction.[17,19,59] These techniques can be applied to digests of lung tissue, which is usually done with commercial Clorox followed by concentration and extraction of the mineralogic content.[60] The mineral particles on a filter used for light microscopic counting are placed on a carbon planchet and studied by scanning electron microscopy (SEM). Alternatively, they may be placed on carbon-coated grids for study by transmission electron microscopy.

With SEM it is possible to detect the surface morphology of the particles as well as to do EDXA. SEM offers the additional advantage of using paraffin-embedded tissue. Histologic sections are mounted on carbon planchets, and the paraffin is removed with xylene. SEM is then used in the backscatter mode to detect particles followed by EDXA. Stained light microscopic sections may be used by removing the cover slip, and the section from the glass slide is transferred to a SEM planchet for further study of the same areas that were seen histologically.[61] Figure 35-3 is an example of an energy-dispersive analysis spectrum of pure alpha quartz.

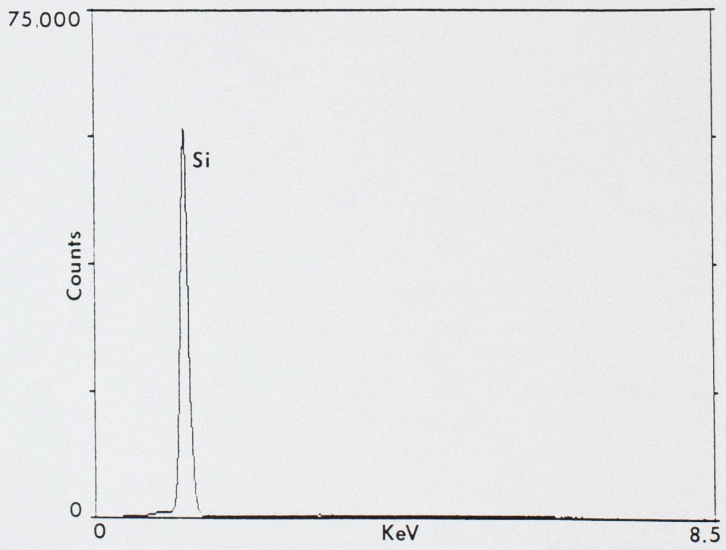

FIGURE 35-3. Energy-dispersive analysis spectrum of silica.

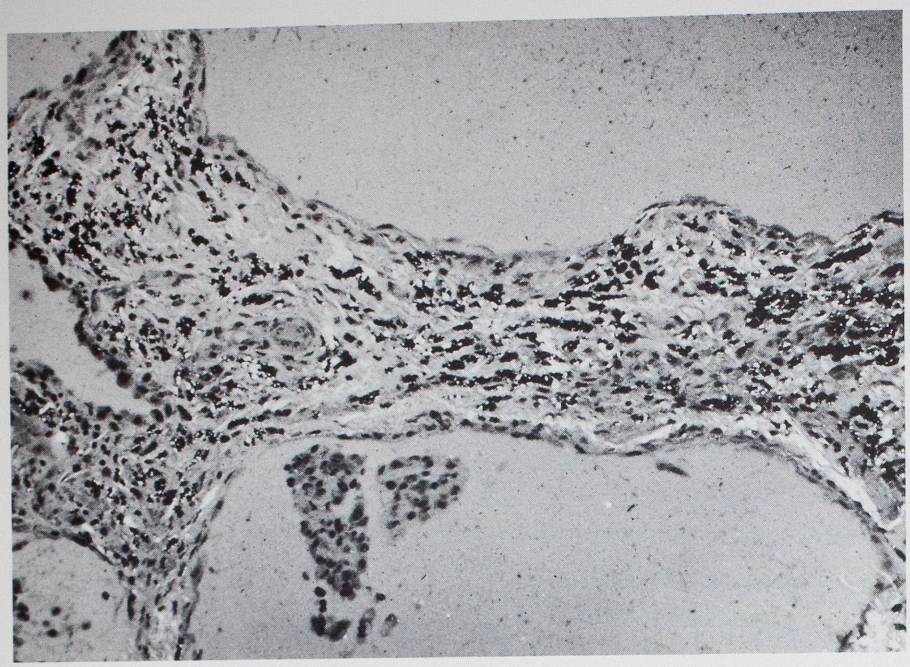

FIGURE 35-4. A microscopic section of silicatosis viewed with polarized light reveals interstitial fibrosis and numerous silicate and carbonaceous particles in the interstitium. (H & E stain; intermediate magnification.)

SILICATOSIS

Silicates have various anions and cations substituted into the crystalline-silica matrix. These compounds are extremely common in the environment because they are components of soil and rocks. Examples of silicates that may be inhaled in occupational settings include talc, kaolin, feldspar, mica, and muscovite. Pathologic patterns of response to silicates are characterized by the accumulation of large amounts of dust in the interstitium resulting in interstitial fibrosis. Silicates often accompany silica. In silicate pneumoconiosis, they represent the overwhelming numbers of particles. Figure 35-4 is an example of silicate pneumoconiosis in which the large number of particles seen by polarized light in the interstitium of the lung have widened the interstitium and produced a fibrogenic response. A similar particle burden with accompanying fibrosis is seen in hilar lymph nodes (Fig. 35-5). EDXA revealed a mixture of silicates. The spectrum of a particle is illustrated in Figure 35-6, which is an aluminum silicate containing potassium as well as trace amounts of titanium and iron.

Talc Inhalation

Talc inhalation may result in pneumoconiosis. It is a hydrated magnesium silicate that occurs as platy, granular, and fibrous particles. With polarized light, it is seen as brightly birefringent needle-shaped particles. Exposure occurs in a number of manufacturing processes; talc is used as a lubricant in many situations. Occupational exposure results from mining and milling operations. Another form of talc may be found in the lung vasculature when tablets containing talc as filler are crushed and injected intravenously (Color Fig. 35-4). There is a granulomatous response similar to that seen in an intravenous drug abuser's lung (see Chap. 22).

In heavy talc dust exposure, pleural plaques are seen, and the

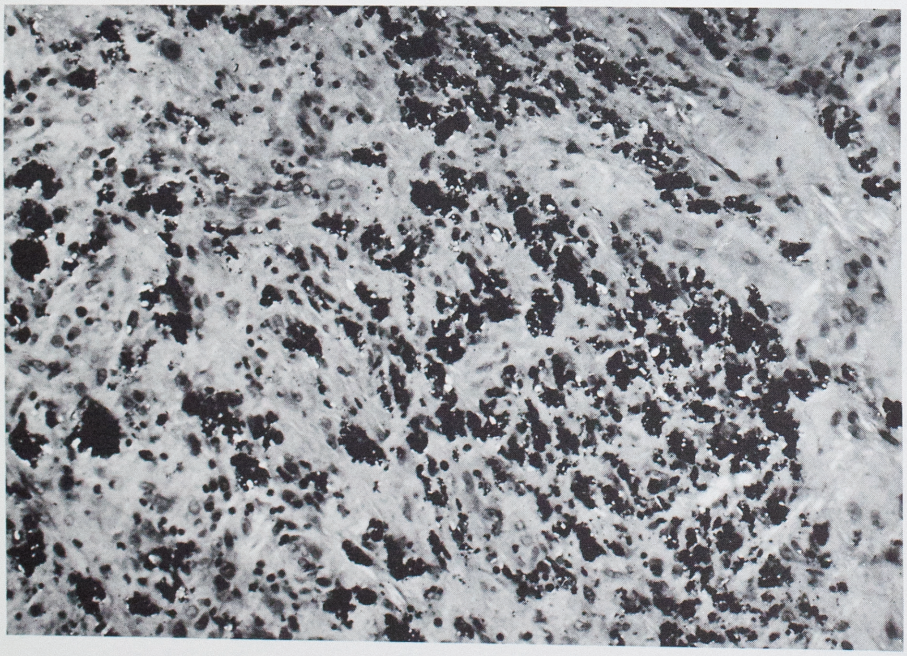

FIGURE 35-5. A lymph node with fibrosis and silicatosis is present in the same patient as in Figure 35-4. (H & E stain; intermediate magnification.)

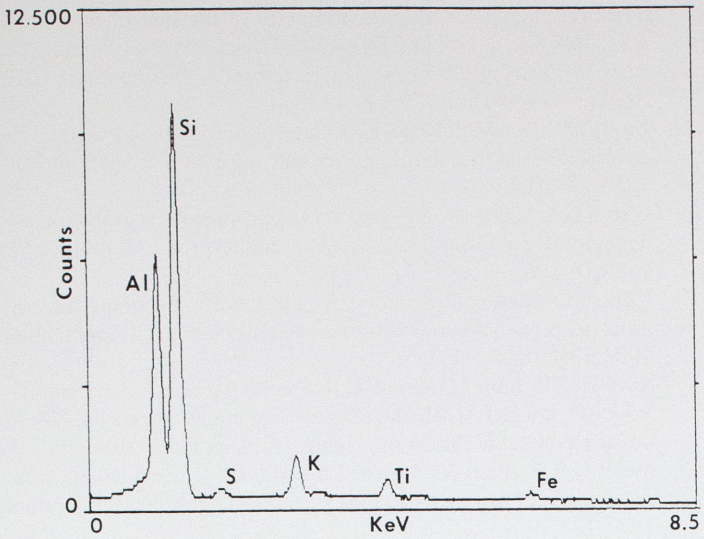

FIGURE 35-6. Energy-dispersive analysis spectrum of an aluminum silicate with potassium and trace amounts of sulfur, titanium, and iron.

lung contains discrete palpable nodules as well as diffuse interstitial fibrosis.[62] In some cases, PMF may occur; the lesions often involve the upper portions of the lung, similar to the distribution of silicosis.[63] An increased risk of lung cancer in talc miners from New York State has been reported.[64]

Kaolinite

Kaolinite is a hydrated aluminum silicate. It is the major component of kaolin (*i.e.*, China clay), which in the United States occurs in deposits from central Georgia to western South Carolina. Deposits are also found in other parts of the world. Kaolin is used in the manufacture of paper products and ceramics, as well as in fillers in plastics and rubber. Occupational exposure to kaolin dust occurs in persons employed in these industries, but the largest exposure occurs in the mining and processing of kaolin. Pneumoconiosis has been reported in kaolin workers.[65–67] The lungs show brown discoloration and numerous firm, gray-brown nodules ranging in size from 0.5 cm to 12 cm in diameter. The hilar lymph nodes are often enlarged, secondary to the accumulation of dust-laden macrophages.

Microscopically, the lesions consist of massive intracellular and extracellular deposits of fine, golden brown particulates, primarily in peribronchial distributions. Most kaolin deposits in the United States are relatively free of quartz. Pulmonary fibrosis and granulomatous responses to other silicates have been described in a number of reports, including mica-associated pulmonary fibrosis.[68]

Coal Worker's Pneumoconiosis

Coal worker's pneumoconiosis is discussed in detail in Chapter 34. Because of the role of silica and silicates in this disease, a few remarks are warranted here.

Coal dust is made up of amorphous, noncrystalline carbon with varying amounts of crystalline silica (*i.e.*, quartz) and silicates (*e.g.*, kaolin, mica). The amount of quartz in coal dust is an important determinant in the pathologic response in coal worker's pneumoconiosis and varies considerably from one mine to another. Anthracite coal usually contains higher percentages of silica than bituminous coal. Quartz exposure also varies with different jobs within a mine. Workers drilling into the ceiling of the shaft and making communicating shafts between adjacent coal seams are exposed to higher levels of crystalline silica than individuals working at the coal face, or those loading coal.

A number of responses to the inhalation of coal dust may be seen. Anthracosilicosis is the accumulation of both carbonaceous dusts and silica. The presence of palpable nodular lesions in coal worker's pneumoconiosis indicates a change in pathologic response most likely related to silica content of the inhaled dust. The spherical nodules are generally similar in appearance and distribution to those observed in pure silicosis, except that they are generally more darkly pigmented. The nodular lesions of coal worker's pneumoconiosis are classified into micronodules, which are as large as 0.7 cm in diameter, and macronodules, which range from

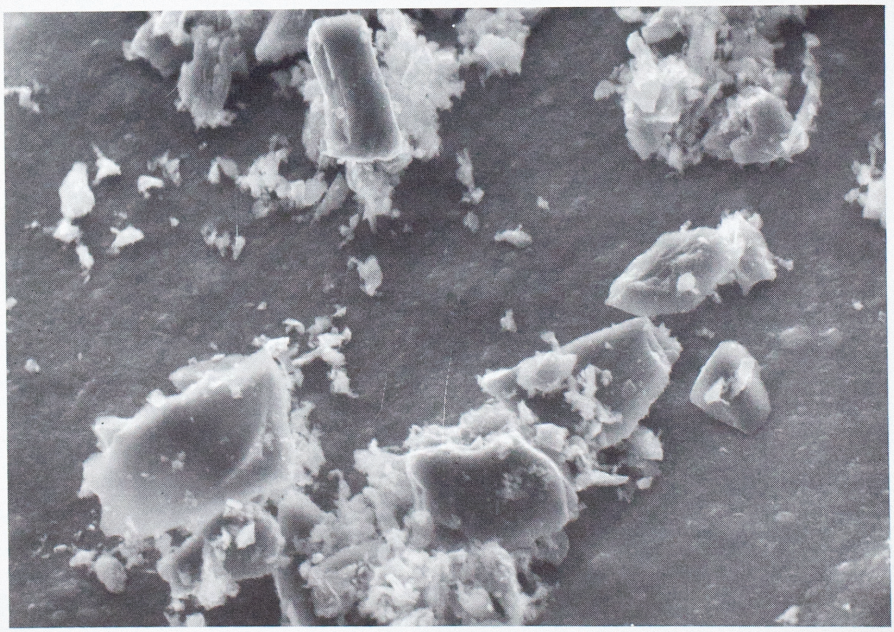

FIGURE 35-7. A scanning electron micrograph reveals silicate in anthracite coal dust.

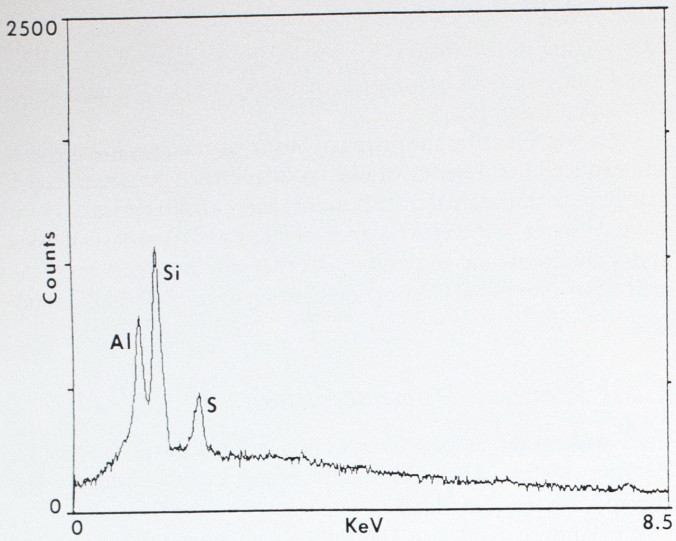

FIGURE 35-8. Energy-dispersive analysis spectrum of the anthracite coal dust in Figure 35-5.

0.7 cm to 2 cm in diameter. PMF is more asymmetrical in distribution and irregular in shape with lesions that, by definition, are at least 2 cm or more in diameter. The latter resembles conglomerate silicosis and PMF of pure silicosis. It most often involves the upper lobes and may extend across fissures to adjacent lobes. Cavitation may occur, as well as superimposed tuberculosis. Coal dust and silicates extracted from the lung of an anthracite miner are illustrated in Figures 35-7 and 35-8.

Caplan syndrome may be seen in the lungs of some coal miners who have rheumatoid arthritis. These appear as giant silicotic nodules up to 5 cm or more in diameter with a smooth border and concentric internal laminations. Microscopically, they may show pallisading of macrophages at the periphery and focal areas of necrosis, as occur in rheumatoid nodules in other sites. Caplan lesions are thus a peculiar combination of silicotic nodules and rheumatoid nodules (see Chap. 34).

Nonasbestos mineral fibers may cause lung disease. These include man-made mineral fibers, zeolite, wallastonite, and vermiculite. In many cases it is the combination of these asbestos fibers that causes fibrotic lung disease. Among this group, wallastonite is known to cause fibrotic lung disease (see Chaps. 36 and 37).

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