15 SILICOSIS AND COAL WORKER'S PNEUMOCONIOSIS

DAVID N. WEISSMAN, M.D.
DANIEL E. BANKS, M.D.

Silicosis and coal worker's pneumoconiosis are occupational lung diseases caused by inhalation of mineral dusts. Despite similar radiographic appearances, these diseases are very different from the standpoints of pathology, clinical presentation, and natural history. Even though both diseases are preventable, they continue to exist. It is, therefore, critical that respiratory physicians continue to be familiar with these diseases and have a high index of suspicion for their presence in appropriate clinical settings.

SILICOSIS

Silicosis refers to a spectrum of pulmonary diseases caused by inhalation of the various forms of free crystalline silicon dioxide or silica. This occupational lung disease has been recognized since antiquity, with written documentation of silicosis dating to the ancient Egyptians and Greeks.[1,2]

Forms of Silica

Silicon dioxide or silica is the most abundant mineral on earth. It is formed from the elements silicon and oxygen under conditions of increased heat and pressure, and exists in the crystalline and amorphous forms. Crystalline forms are based on a tetrahedral structure in which the central atom is silicon, and the corners are occupied by oxygen. Two adjacent tetrahedrons share two oxygen atoms. Examples of crystalline silica are quartz, cristobalite, and tridymite. The most common form is quartz, a typical component of rocks. Quartz-containing materials used in industry include granite, slate, and sandstone. Granite contains about 30% free silica; slate about 40%, and sandstone is almost pure silica.[3] Crystobalite and tridymite occur naturally in lava and are formed when quartz or amorphous silica is subjected to very high temperatures. They may also be formed in silica bricks used in industrial furnaces. Amorphous silica is noncrystalline and is relatively nontoxic after inhalation. It exists as diatomite (skeletons of prehistoric marine organisms) or as vitreous silica (the result of carefully melting and then quickly cooling crystalline silica). Heating diatomite with or without alkali (a process known as calcining) forms cristobalite, a material that is highly toxic after inhalation.

"Free" crystalline silica is that which is unbound to other minerals; "combined" forms are compounds in which silica is bound to other minerals. The latter are also known as silicates. Examples of silicates that have been widely used in industry include asbestos, talc ($Mg_3Si_4O_{10}(OH)_2$), and kaolinite ($Al_2Si_2O_5(OH)_4$) which is a major component of china clay, or kaolin.[4]

Occupational Exposure to Silica

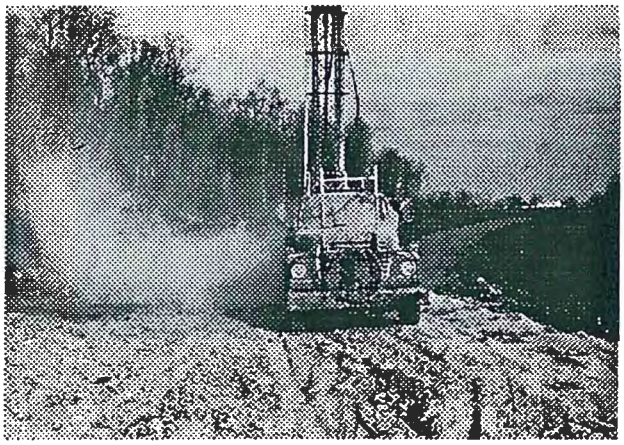
A wide variety of industries are associated with generation of particulate aerosols with sufficient silica content to induce silicosis. Essentially any occupation that disturbs the earth's crust or exposes the worker to use or processing of silica-containing rock or sand has potential risks.[5] Occupations mentioned in this brief overview are of major importance, but this list is not complete and continues to change over time. New reports of silicosis in industries and work settings not previously recognized to be at risk continue to occur.[5] Thus, a high index of suspicion for risk of silicosis should be maintained when the clinical history indicates a dusty work environment.

Mining has been known to be associated with silicosis since antiquity. Hippocrates reported that miners developed dyspnea with exertion. Ramazzini and Agricola recognized the relationship between rock dust exposure and the development of dyspnea in those who worked in this trade.[1] Underground mining for metals often involves removal of quartz-rich ores from the earth with generation of respirable quartz-containing aerosols. Silicosis may be caused by gold, tin, iron, copper, nickel, silver, tungsten, and uranium mining. Mining for other types of minerals can also cause silicosis. For example, underground coal mining can be associated with silicosis, particularly when tunneling through or roof-bolting

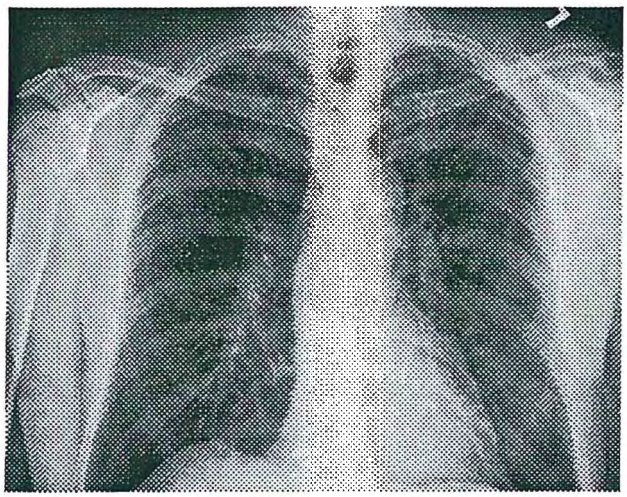
Supported by the U.S. Bureau of Mines, Generic Mineral Technology Center for Respirable Dust.

into rock with high silica content, or when using sand as a friction material on rails. Although dust exposure levels are generally lower in surface or strip mining, silicosis has been reported in workers who operate the large drills to make holes in which explosives are placed to expose coal deposits (Figure 15–1).[6]

Tunneling through rock with high silica content, such as granite or sandstone, can also generate very significant aerosol exposure to silica. In fact, the worst outbreak of silicosis in the USA occurred during the construction of the Gauley Bridge tunnel in West Virginia in 1930 and 1931. In this catastrophe, more than 400 of the estimated 2000 men engaged in rock drilling died, and about 1500 contracted silicosis and were eventually disabled.[1] Other occupations involving disruption of the earth's crust, such as quarrying and stone cutting, are also associated with risk of silicosis.[7]



A



B

Figure 15–1 *A*, Drilling at a surface coal mine. Note the cloud of dust generated by dry surface drilling. Operator is exposed to dust as he must be positioned at the back of the truck to monitor drill pressures and change bits as needed. *B*, Simple pneumoconiosis in a bulldozer operator who worked at surface coal mines for 42 years. In the early stages of his career, his bulldozer had an open cab allowing high exposures to dust. Although the risk associated with surface mining appears primarily related to drilling, clearly others working in the area of drilling are also at risk.

Foundry work is another potentially hazardous occupation.[7] Metal castings are produced in foundries by making a mold into which molten metal is poured. A core may also be used to produce a hollow casting. After it is cooled, the solidified casting is then knocked out of the mold. Silica exposure can occur in the production of the molds and cores, which are made of quartz sands bonded by clays or resins, but the greatest risks are associated with knocking out castings and with the process of cleaning and polishing of the product. This latter process is especially dangerous and is known as "fettling" or "dressing." It may be done with hammers, grinding wheels, mills, or abrasive blasting. These activities aerosolize the silica, especially cristobalite, burnt onto the casting. Foundry workers may also inhale silica when knocking out the linings of furnaces, often of quartz.

Sandblasting generates respirable aerosols of silica and is associated with a great risk for silicosis even when respiratory protection is used.[5,8-10] Sandblasting occurs in ship building, oil rig maintenance, preparing steel for painting, and many other applications where abrasive cleaning of surfaces is required. Sandblasting continues despite the availability of a number of substitute materials for abrasive blasting. Although the UK has strict restrictions on the use of abrasives containing silica since 1949, the USA allows virtually unrestricted use of sand for abrasive blasting, except in the underground mining environment.[11]

Production of silica flour, or finely milled crystalline silica, is associated with risk of silicosis.[12] This abrasive powder is used in the production of scouring powders, polishes, toothpastes, and sandpaper. It is also used as a filler in paints, woods, surfacing materials, rubbers, and plastics.

Production of ceramics has historically been associated with risk of silicosis. Traditionally, a mixture of crushed flint and siliceous clays has been used to produce china and earthenware, and the products are polished or fettled prior to glazing. Substitute materials, however, are now reducing the risk of silicosis in this industry.

Diatomaceous earth is amorphous silica; in its native state it does not entail a great health hazard. However, when it is calcined it is converted into cristobalite and tridymite, which are hazardous. Exposure to calcined material used in filters, abrasives, insulation materials, and absorbents may result in silicosis in unexpected settings.[7]

Although occupation is the major risk factor for inhalation of crystalline silica and development of silicosis, simple silicosis has been reported after environmental exposures in regions where the soil silica content is high, and dust storms are common.[13]

Biologic Consequences of Silica Inhalation

For inhaled silica to affect the lungs, inhaled crystalline silica particles should have favorable characteris-

tics for intrapulmonary deposition, the most important being size. Particles less than 1 μm are believed to be the most pathogenic; the median diameters of silica particles retained in the human lung range from 0.5 to 0.7 μm.[14] Over time, particle burden within the lung is the result of an equilibrium between dust deposition and dust clearance. Clearance mechanisms include removal through expired air, mucociliary clearance from the upper airways, and phagocytosis by alveolar macrophages with subsequent clearance via either the mucociliary escalator or via pulmonary lymphatics.

Interactions between alveolar macrophages and inhaled silica play a major role in the pathogenesis of silicosis. Early work on the pathogenesis of silica-induced lung injury focused on cell damage and cell death occurring after ingestion of silica by alveolar macrophages.[15,16] Lung injury was believed to be related to the release of intracellular proteolytic enzymes following the disruption and death of the alveolar macrophage. Intracellular silica released in this process was taken up by other macrophages. This was proposed to start a vicious cycle of macrophage phagocytosis, cell death, release of intracellular enzymes, lung injury, and reuptake of silica. Current work continues to support this hypothesis, as silica was recently demonstrated to induce apoptosis in human alveolar macrophages via interactions with the scavenger receptor.[17]

Interactions between inhaled silica and alveolar macrophages can also generate pulmonary inflammation and fibrosis through a process of cytokine networking between macrophages, lymphocytes, neutrophils, fibroblasts, epithelial cells, and potentially a number of other cell types.[18] The ability of silica to stimulate cytokine secretion by alveolar macrophages may relate to the ability of silica particles to react with water to form hydroxyl radicals leading to cell membrane lipid peroxidation.[19,20] In this regard, it is of interest that freshly crushed silica forms more hydroxyl radicals than does similar amounts of aged silica. It has also been demonstrated to be more cytotoxic, produce more lipid peroxidation, and induce alveolar macrophages to produce more superoxide and hydrogen peroxide than does stored or "aged" silica. Signal transduction leading to cytokine production is likely to be mediated at least in part by calcium, as exposure to silica increases cytosolic-free calcium in alveolar macrophages.[21,22]

Alveolar macrophages stimulated in vitro by silica or evaluated ex vivo after in vivo exposure to silica secrete proinflammatory and profibrogenic mediators. For example, enhanced production of interleukin-1β (IL-1β),[23,24] IL-6, tumor necrosis factor-α (TNF-α),[25,26] transforming growth factor β, (TGF-β),[27] fibronectin,[28] platelet-derived growth factor (PDGF), and insulin-like growth factor-1 (IGF-1)[18] by silica-activated alveolar macrophages have all been demonstrated. Pulmonary stromal cells such as endothelial and smooth muscle cells have the potential to amplify local inflammation by secretion of chemokines such as IL-8 after stimulation by macrophage-derived IL-1β and TNF-α.[29] Silica may also stimulate chemokine secretion by aveolar epithelial cells by direct action on these cells.[30]

Tumor necrosis factor-α may play a particularly important role in the pathogenesis of silicosis. Increased levels of lung TNF messenger RNA (mRNA) can be demonstrated by in situ hybridization in mice after intratracheal instillation of silica.[25] Deposition of extracellular matrix protein (expressed as increase in hydroxyproline) can be prevented in this model by pretreatment with anti-TNF antibodies or soluble TNF receptors.[25,31] An inbred strain of TNF-deficient mice shows less inflammation and collagen accumulation in the lungs after instillation of silica when compared to appropriate controls.[32]

The profibrogenic cytokine TGF-β also appears to be important in the pathogenesis of silicosis. It has been demonstrated by immunohistochemical staining in experimental silicosis.[27] In human specimens, TGF-β has been localized in peribronchiolar fibrotic lesions, hyaline centers of nodules, progressive massive fibrosis (PMF) lesions, fibroblasts, and alveolar macrophages of silicotic lungs.[33]

The pathogenesis of acute silicosis is different from that of classic or chronic silicosis. In acute silicosis, the alveoli fill with an amorphous lipoproteinaceous exudate. Animal models of this condition show a dramatic increase in the amounts of intracellular and extracellular phospholipids.[34-36] The composition of lung surfactant is also altered.[37] A distinct population of hypertrophic type II pneumocytes has been observed in experimental acute silicosis. These cells appear to be responsible for the marked increase in the amount of pulmonary surfactant in the silica-treated animals.[38,39] In addition to the increased activity of metabolic pathways involved in surfactant production, increased biosynthesis of surfactant protein A (SP-A) and augmented levels of SP-A messenger ribonucleic acid (mRNA) have also been shown.[40]

A variety of factors can modify the host response to inhaled silica. The duration and amount of exposure as well as content of free crystalline silica are critical determinants of the progression of silicosis.[5,7,14,41] As previously mentioned, particle size in the respirable range increases toxicity. Furthermore, freshly fractured silica particles have greater ability to interact with water and generate oxygen radicals, and thus may be more toxic than older particles.[19] In the case of mixed dust exposures, the nature of the mixture along with relative silica content is important.

Host factors appear to be of less importance than dust characteristics, but also play a role in modifying the biologic response to inhaled silica. Specific human leukocyte antigen (HLA) haplotype associations with silicosis have been reported in a Japanese population.[42] In addition, HLA haplotype associations with coal worker's pneumoconiosis have been reported in a German population.[43] Thus, genetic factors linked to HLA might play a role in the development of silicosis.

Previous environmental exposures might also alter the host response to inhaled silica. There is an interest-

ing report of experimental exposure to a high concentration of quartz dust producing an alveolar proteinosis response in specific pathogen-free (SPF) rats but resulting in the typical granulomatous and fibrotic changes in ordinary stock rats.[44] The only difference seemed to be an inadequately developed lymphatic system in the SPF rats. How previous environmental exposures impact on human responses to silica is unknown; however, there are reports of differences in responses of smokers and nonsmokers to hard rock mining exposures.[45]

Pathology of Silicosis

A detailed review of the pathology of silicosis has been published elsewhere.[14] The following is a brief overview.

On inspection, the silicotic lung is firm, and is blacker than the normal lung. The surface is coarse and nodular. The visceral pleura has areas of fibrosis and may be covered by plaque-like lesions. Peribronchial and hilar lymph nodes are typically enlarged. On sectioning, these enlarged nodes show concentrically arranged fibrous tissue, and the lung reveals palpable intrapulmonary nodules, especially in the upper lobes. In simple silicosis these nodules are usually 2 to 6 mm in diameter. In conglomerate silicosis or progressive massive fibrosis, the lesions are typically 10 to 20 mm in diameter, a result of the coalescence of smaller nodules. Nodules vary in color, depending on the presence of other dusts; the extent of nodule calcification is also variable.

The earliest histopathologic lesion in workers with relatively low-dose, chronic exposure to free crystalline silica is a collection of dust-laden macrophages and loose reticulin fibers in the peribronchial, perivascular, and paraseptal or subpleural areas. Later, these lesions become more organized and may appear whorled. The silicotic nodule, the pathologic hallmark of silicosis, has a histologic appearance analogous to a tornado (Figure 15–2). The central zone, like the eye of the storm, shows little activity. It is hyalinized and composed of concentrically arranged collagen fibers. The peripheral zone is whorled and becomes less organized toward the edges. It contains macrophages, lymphocytes, and lesser amounts of loosely formed collagen. Under polarized light microscopy, a few weakly birefringent particles may be seen in the center of the nodule, likely the result of trapped crystalline silica mixed with other dusts. In the periphery of the nodule, the amount of dust and the degree of birefringence differ dramatically. Needle-shaped, strongly birefringent material is intermingled with cells and dust. This is the site of active enlargement of the nodule and of ongoing inflammation. As the disease progresses, the periphery of the silicotic nodule moves farther from the hyalinized center, enmeshing small airways, pleura, and blood and lymphatic vessels in the fibrotic process.

Coalescence of silicotic nodules forms the progressive massive fibrotic lesion, a mass of dense, hyalinized

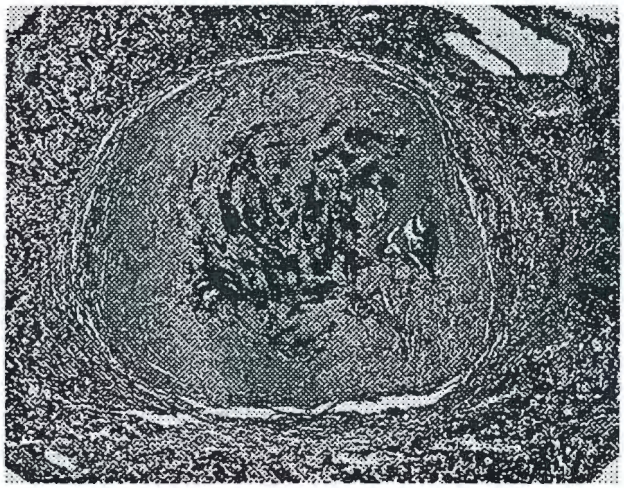


Figure 15–2 Histology section from a patient with silicosis showing a typical silicotic nodule.

connective tissue with minimal silica content, a small amount of anthracotic pigment, minimal cellular infiltrate, and negligible vascularization. Typically, the centers of these conglomerate lesions cavitate, the result of mycobacterial infection or ischemic necrosis, when the lesions exceed a certain size.

The histologic pattern of acute silicosis differs from that of chronic silicosis. Silicotic nodules are rarely seen and, if identified, are usually poorly developed. The interstitium is thickened with inflammatory cells. There is alveolar filling with proteinaceous material consisting largely of phospholipids or surfactant (or surfactant-like material) which stain with periodic acid–Schiff (PAS) reagent. Since the histologic appearance resembles that of idiopathic alveolar proteinosis, this process occurring in a clinical background of overwhelming silica exposure has also been called "silicoproteinosis."[46] On electron microscopic examination, the alveoli are lined by prominent epithelial cells, the majority of which are hypertrophic type II pneumocytes.[47] The alveolar exudate is most likely the result of overproduction of phospholipids and surfactant-associated proteins by these hypertrophic type II cells. In addition, desquamated pneumocytes, macrophages, and silica particles are found in the alveolar spaces. Typically, a minimal amount of pulmonary fibrosis is present. Although the term "silicoproteinosis" may reflect one of the pathologic changes present, there are other features of acute alveolar damage syndromes and even of desquamative interstitial pneumonitis as part of the recognized lung injury.

Epidemiology of Silicosis

It is difficult to obtain precise estimates of the prevalence of silicosis because of the many different occupations involved, the participation of transient workers, the variability of disease detection methods (e.g., autopsy versus compensation, or screening data), and differing reporting

practices from place to place. Although not systematically studied, it is common for silicosis to be diagnosed after a worker has left the silica-exposed industry and for it to continue to progress slowly over many decades of life after exposure has ended. Thus, there are reports with higher prevalence levels and estimates of exposure risk when these studies included retired workers.[48]

In 1956, Trasko[49] obtained estimates of silicosis prevalence by examining records of workers in 20 states who were compensated for silicosis, and identified about 6000 cases. The largest numbers of silicosis cases were found among metal miners (1637) and foundry workers (1645). Because of the nature of case identifications, these numbers most likely are underestimates of the actual frequencies. Autopsy records of 3365 underground miners, submitted to the U.S. National Coal Workers' Autopsy Study between 1971 and 1980, revealed the presence of classic silicotic nodules in 12.5% of the cases.[50] In an investigation of worker health at two silica flour mills, 16 (26%) of the 61 workers who were exposed to microcrystalline silica had radiographic evidence of simple silicosis, and 7 (11%) had progressive massive fibrosis.[51]

With an estimated 200,000 miners and 1.7 million nonmining workers in the United States having occupational exposures to inhaled silica, silicosis continues to be a significant problem.[52] New cases of silicosis are still reported sporadically in both developed and developing countries.[53] Silicosis was identified in 577 workers in the state of Michigan alone between 1987 and 1995 through a state surveillance system.[54]

The prevalence of silicosis increases with increasing silica dust exposure.[41] The risk of silicosis can therefore be decreased by appropriate engineering controls to decrease inhalation exposure. The Vermont granite industry is an excellent example of effective prevention. Historically, workers had been enduring heavy silica dust exposures as a result of activities such as granite grinding and chipping. Earlier this century, two studies evaluating this population documented serious dust-induced lung disease and premature death.[55,56] However, beginning in the 1950s, there was evidence that institution of dust control measures had produced a safer workplace.[57,58] These data serve as the backbone for current federal regulations for permissible silica exposure. More recent results of longitudinal radiographic surveillance of this population shows convincingly that the mandated current level of permissible granite dust exposure in these workers has proved to be protective.[59] However, others have suggested that these levels may still be associated with an unacceptable lifetime risk of silicosis.[48,60]

Diagnosis of Silicosis

There are three requisites for the diagnosis of silicosis. First, the worker must provide a history of silica exposure sufficient to cause this illness. Second, the chest radiograph has to show opacities consistent with silicosis. Third, there must be no underlying illnesses present capable of imitating silicosis, such as a miliary distribution of mycobacterial or fungal organisms, or in the unusual circumstance, sarcoidosis. Although respiratory symptoms and lung function impairment are commonly present, neither is necessary for the diagnosis of silicosis.

The first diagnostic criteria to be addressed by the physician, determining whether the worker's occupational silica exposure is sufficient to cause silicosis, can be difficult. This requires information about the workplace environment and the worker's exposures. The most important history includes details regarding the length of employment, exposure measurements (if available), and recognition of whether the worker was provided effective respiratory protection. Silicosis being caused by industrial processes where silica particles of respirable size are generated and aerosolized are the common thread among occupations (e.g., sandblasting, drilling into siliceous rock, or exposure to finely milled silica flour) where this disease is a clearly recognized risk. Without manipulation of the silica particle to respirable size (an aerodynamic diameter of less than 10 microns), the particle is trapped and cleared from the upper airways, and silicosis does not occur.

The efficacy of respiratory protection devices is highly variable.[10] For various reasons, silicosis can certainly occur in workers even though they use personal respiratory protection: (1) each respirator has a limit beyond which the dust level exceeds the protective capacity, and the worker may be using a respiratory protective device inadequate for the amount of dust present; (2) respiratory protective devices are designed to protect for specific exposure, and the worker may be using the wrong type of respirator. If a solvent mask was used for dust protection, the effectiveness would be compromised; (3) the respiratory protection may be improperly fitted; and (4) because these protective devices are associated with an increased work of breathing (which makes it more difficult to do work), the worker may decide not to use effective available protection, to avoid the discomfort. How only some workers develop silicosis (or greater or lesser extents of this illness) while employed in the same general work area may be related to the adequacy of respiratory protection.

Information regarding silica dust levels in the workplace can be useful in diagnosis; however, such levels may not represent the complete picture. Cases of acute silicosis in surface coal mine drillers have been reported where the measured dust levels were within normal limits.[6] In this report, the measurements were not representative of the overwhelming dust exposures, which induced very aggressive silicosis. Furthermore, the percentage of free crystalline silica in the measured mine dust had not been determined. Thus, although dust measurements can be helpful, it is essential to understand the conditions under which the samples were collected and be sure that these measurements accurately represent the workplace environment. Sometimes the

relevance of the exposures can only be validated by going to the workplace and observing the conditions in which the work is performed.

When the three clinical requirements for the diagnosis of silicosis are met, additional evaluation of the worker is not necessary to make the diagnosis. In some occasions, it is not possible to make the diagnosis clinically, for example, when the exposure history is uncertain or when the differential diagnosis includes a malignant tumor (sometimes considered when the coalesced lesions of progressive massive fibrosis are unilateral or asymmetric. This consideration may arise more frequently because of the interest in silica as a potential carcinogen[5,61]). Other illnesses have radiographic features which mimic silicosis. These include rheumatoid nodules[62] (referred to as Caplan's syndrome when this occurs in the presence of pneumoconiosis), infectious processes, or sarcoidosis. In these instances, histologic examination of lung tissue becomes necessary.

When tissue is required for diagnostic analysis, the traditional preference has been for an open lung biopsy, as there is a chance of pneumothorax after transbronchial lung biopsy.[63] The increased risk for pneumothoraces may be explained by the presence of stiff upper zones while there are emphysematous changes in the lower zones.

Although the small sample obtained by transbronchial lung biopsy may sometimes be inadequate for diagnosis of silicosis, bronchoalveolar lavage and transbronchial biopsy with energy dispersive x-ray analysis have been used in addition to aid in the diagnosis. In one report, a neutrophilic alveolitis and the presence of silica in alveolar macrophages were shown in a sandblaster by bronchoalveolar lavage and energy dispersive x-ray analysis, respectively, despite the absence of birefringent crystal particles. Transbronchial biopsy showed fibrocellular nodules in the parenchyma. Taken together, these findings were consistent with the diagnosis of silicosis.[64]

Approaches to Categorizing Silicosis

Silicosis can be commonly categorized into two types by findings on the chest radiograph: *classic silicosis* and *acute silicosis.* Classic silicosis is separated into *simple silicosis* and *progressive massive fibrosis.* These two presentations are radiographically different; however, they are grouped together under the category of classic silicosis because they are a part of the radiographic spectrum of this illness. On the chest radiograph, simple silicosis is recognized as a profusion of small (less than 10 mm in diameter), rounded opacities (nodules) predominant in the upper lung zones (for an unknown reason, retention of silica particles is favored in the upper lung zones) (Figure 15–3). In some, these small opacities gradually enlarge and coalesce to form larger, usually bilateral, upper-zone opacities of similar sizes (more than 10 mm in diameter) recognized as conglomerate silicosis or progressive massive fibrosis (Figure 15–4).

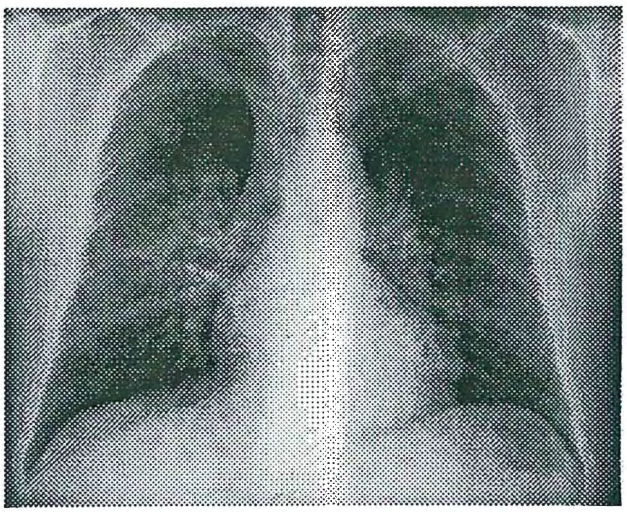
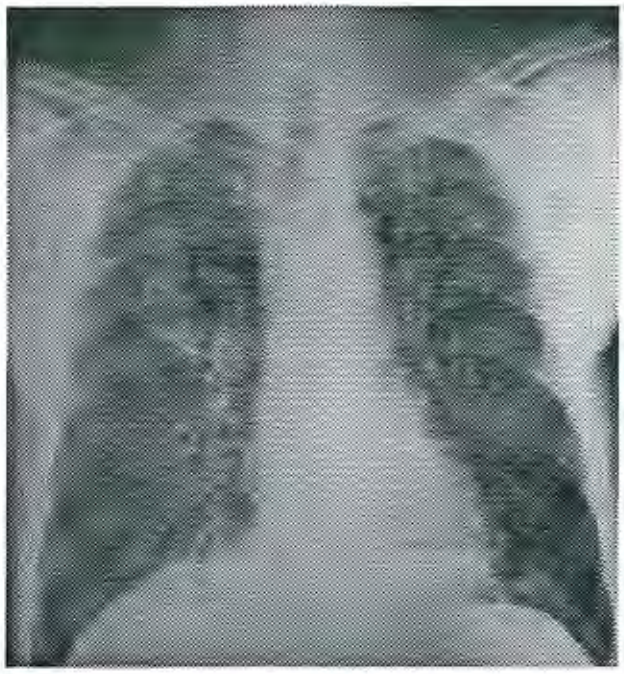


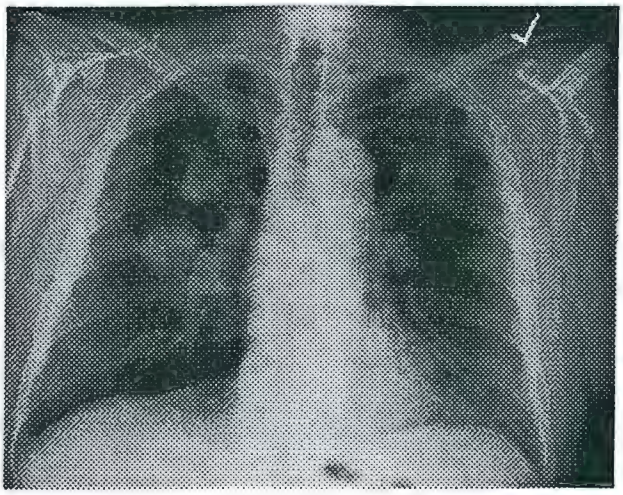
Figure 15–3 Chest radiograph from a patient with simple silicosis. Note the bilateral nodular interstitial process with prominent involvement of the mid and upper zones.

Acute silicosis, the other radiographic presentation, occurs rarely.[65-67] This is the result of an overwhelming exposure to free crystalline silica over a short time, typically less than a few years. In addition, it may also be that excessive exposure to "freshly fractured silica," material shown to have considerably more free radical oxygen species than "stale" or "old" fractured silica, is more fibrogenic.[19] In some with acute silicosis, the chest radiograph has a basilar alveolar filling pattern (identical to that seen in pulmonary alveolar proteinosis) without rounded opacities or lymph node calcifications (Figure 15–5). This is termed silicoproteinosis.[46] With time, these features progress from a pattern of lower-zone alveolar filling to large masses of coalesced parenchymal tissue, typically bilateral but not always symmetrical, in the middle and lower zones. In others with excessive silica exposures, the radiographic features are those of simple silicosis which progresses to conglomerate silicosis in a very short time-frame, consistent with acute silicosis. The explanation for the very different radiographic response of an alveolar filling pattern in some in contrast to a very aggressive nodular silicosis in others in the face of an overwhelming silica exposure is not known but might reflect an important difference in an individual's pulmonary lymphatic drainage.[44]

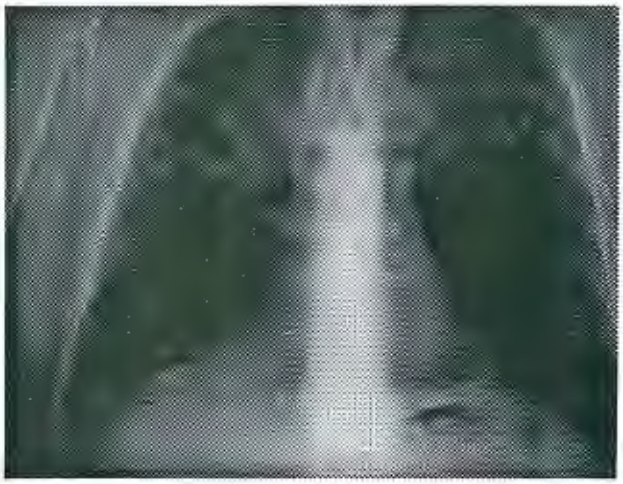
Silicosis can also be categorized on the basis of the duration from initial exposure to the recognition of the disease. The time frames are imprecise, but this approach is useful because of its relevance to prognosis. Classic silicosis develops slowly; usually 10 to 30 years (a working lifetime) are required from the beginning of exposure to the recognition of radiographic manifestations. In a minority, the nodules of simple silicosis coalesce to become progressive massive fibrosis. Accelerated silicosis occurs infrequently; it appears radiographically as simple silicosis which develops after less than 10 years of excessive silica exposure. The development of silicosis after such



A



B



C

Figure 15–4 Different appearances of conglomerate silicosis or PMF. *A*, A soft, fluffy process with coalescence is prominent in the right upper zone. The process is asymmetric as it is far less prominent on the left. In appropriate clinical settings, mycobacterial infection might need to be considered. A background of simple pneumoconiosis is also present. *B*, PMF is more advanced. The large, bilateral upper-zone nodules are more distinct than in Figure 15–4A. When asymmetric, such processes can be confused with lung cancer. *C*, Far advanced PMF. Hila and airways are distorted and pulled upward toward the process. Associated severe emphysematous changes are noted in the lower zones. This patient had severe airways obstruction and respiratory impairment.

a short time signals that the worker is at great risk for the immunologic sequelae of silicosis[5] and for the development of progressive massive fibrosis. On the other hand, acute silicosis occurs over a few years and is associated with an inexorable progression towards a premature respiratory death.

Simple Silicosis

Workers with simple silicosis are usually without chest symptoms. Some, however, report a chronic productive cough, a feature likely due to dust-induced bronchitis. Physical examination of the chest is usually unremarkable. Coarse adventitious sounds, when present, are the result of coexisting bronchitis.

Roentgenographically, simple silicosis presents as an upper-zone distribution of rounded opacities less than one centimeter in diameter. In miners, these opacities have the same distribution as the nodules described in simple coalworker's pneumoconiosis but are generally larger and more dense.[68] Peripheral "eggshell" calcifications are sometimes present in the hilar and mediastinal lymph nodes (Figure 15–6).

Pulmonary function studies in simple silicosis do not usually demonstrate functional impairment. Yet, there tends to be restriction in total lung capacity and compliance as the extent of profusion of small rounded opacities increases. This most clearly manifests as overt restriction in some patients with progressive massive fibrosis. As the disease progresses, reduction in compliance usually precedes reductions in vital capacity or forced ex-

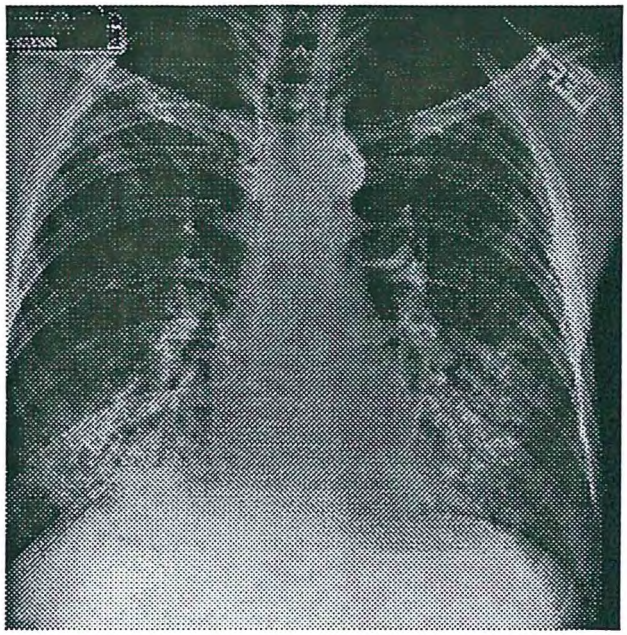


Figure 15–5 Acute silicosis in a surface coalmine driller. Note the biliateral lower zone alveolar filling processes with air bronchograms. Open lung biopsy ruled out the presence of an infectious process and confirmed the diagnosis. (Reprinted with permission from Thorax 1983;38:276.)

piratory flow rate. Few nonsmoking, dust-exposed workers with simple silicosis develop airflow abnormalities.[69,70] In a sophisticated study using high resolution CT scans of the chest to identify the presence of emphysema in workers with simple silicosis, Kinsella et al.,[71] noted that simple silicosis did not cause significant emphysema. Furthermore, it was the degree of emphysema rather than the extent of simple silicosis that determined the level of respiratory function. Emphysema occurred frequently in association with progressive massive fibrosis (see Figure 15–4C) but was not different among smokers and nonsmokers.

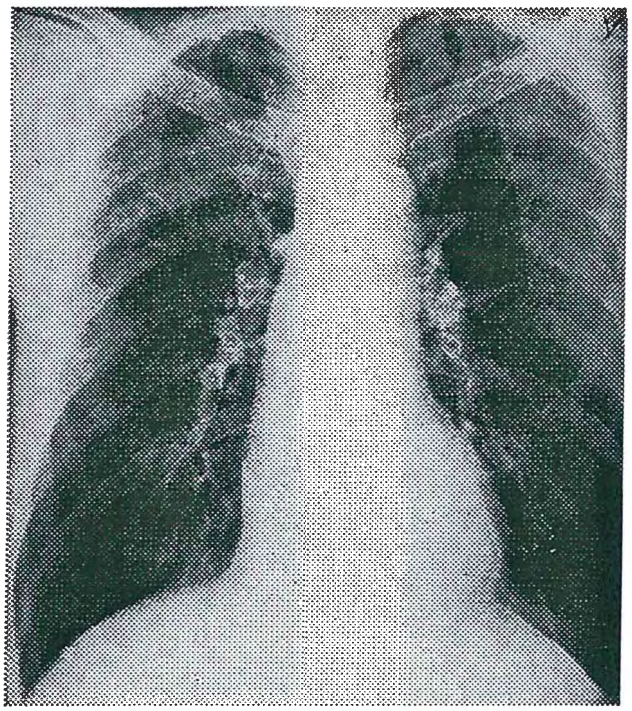


Figure 15–6 A chest radiograph demonstrating enlargement and prominent eggshell calcification of hilar lymph nodes. In addition, a minimal background of simple pneumoconiosis with a suggestion of coalescence of nodules in the right upper zone is present.

Progressive Massive Fibrosis

Progressive massive fibrosis is a conglomeration of small rounded opacities. The traditional view is that progressive massive fibrosis develops on a background of advanced simple silicosis. Yet, not all coal miners who develop progressive massive fibrosis have an underlying advanced degree of simple coal worker's pneumoconiosis.[72] Whether this is also the case in silicosis has not been described.

The respiratory symptoms present in a worker with progressive massive fibrosis are again variable. They range from only a chronic productive cough to exertional dyspnea and, in some, ultimately to respiratory failure. With time, however, the progressive coalescence of silicotic nodules impairs the function of the underlying pulmonary parenchyma and results in progressive respiratory impairment in all.

Physical examination demonstrates decreased breath sounds on auscultation (explained by the emphysematous changes associated with progressive massive fibrosis) and, if the illness is extensive, signs of cor pulmonale and impending respiratory failure. Crackles do not occur as a result of the fibrotic changes but adventitious sounds may be audible if bronchitis is present. Finger clubbing, if present, is attributable to other causes.

The chest roentgenogram reveals confluent nodules exceeding one centimeter in diameter on a background of small rounded opacities, which is recognizable as simple silicosis. The confluence of these nodules begins posteriorly and peripherally and migrates centrally. As with simple silicosis, progressive massive fibrosis develops most prominently in the upper lobes. As these upper-lobe fibrous masses progressively enlarge, the hila are retracted upward and the lower zones become hyperinflated and appear as bullous emphysema (see Figure 15–4). These upper-zone opacities, particularly if they are not symmetrical, often cause concern that neoplastic processes are present. Importantly, progressive massive fibrotic lesions are relatively thin and plate-like and are located in the peripheral and posterior aspects of the upper lung zones. These radiographic features are sometimes helpful in differentiating between progressive massive fibrosis and pulmonary malignancy.

Pulmonary function studies initially demonstrate a decrease in compliance, followed by decreases in lung volumes and diffusing capacity. If bronchial distortion and lower-zone hyperinflation are present, the forced expiratory time is likely to be prolonged, and airflow obstruction is measurable. Deterioration in lung function commonly occurs despite discontinuation of silica exposure.

The likelihood of progression directly correlates with the duration and concentration of silica exposure as well as the presence or absence of mycobacterial infection.

Accelerated Silicosis

Accelerated silicosis is radiographically identical to classic silicosis except that the interval between the initial exposure to silica and the development of radiographic and pulmonary function changes attributable to silicosis is shorter and the changes often exaggerated. Accelerated silicosis is associated with a relatively rapid progression from the radiographic changes of simple silicosis to progressive massive fibrosis resulting in severe respiratory impairment and a shortened lifespan.

Acute Silicosis

This most aggressive form of silicosis is caused by exposure to overwhelmingly high concentrations of respirable free silica. The interval between exposure and development of disease is short. The worker rapidly progresses to disabling chest symptoms and severe respiratory impairment. Respiratory failure and death invariably follow. Although patients with this form of silicosis may have some features of classic silicosis, there are distinct clinical, radiographic, and histologic differences.

In 1969, Buechner and Ansari[46] reported on four sandblasters with acute silicosis and coined the term silicoproteinosis. At autopsy, these sandblasters were found to have PAS positive-staining proteinaceous material filling the alveolar spaces; silica particles in the lung; and histologic changes of alveolar proteinosis. However, a review of the literature prior to Buechner and Ansari's description suggests that many earlier reported cases had similar histologic features. Suratt et al.,[73] reported the same presentation in tombstone sandblasters. Chapman[67] reported the histology to show localized areas of basilar "bronchopneumonia" in which the alveoli were filled with a pink-staining edema fluid with a high protein content. Gardner[74] confirmed the uniqueness of this presentation by showing that the most common lesion was an alveolar exudate which contained few if any cells. Silicoproteinosis is a descriptive term for the histologic findings in the lungs of those who develop silicosis over a very short period of time (acute silicosis) and is not a separate entity.

Workers with acute silicosis have been reported to present with an irritative, sometimes productive cough, weight loss, fatigue, and occasionally pleuritic pain. Symptoms begin usually 1 to 3 years after the initial exposure. Rarely, symptoms occurring less than a year after beginning sandblasting have been reported. Unlike in the chest examination of classic silicosis, crackles are usually present and likely reflect alveolar and airway fluid. Patients rapidly develop cyanosis, symptoms of cor pulmonale, and respiratory failure. Mycobacterial and fungal infections frequently complicate the clinical course. Survival after onset of symptoms is typically less than four years.

The chest radiograph typically reveals bibasilar alveolar filling with air bronchograms (see Figure 15–5).[66] The diffuse alveolar filling is best described as a ground-glass appearance. Histologically, small, rounded opacities can sometimes be identified, but they are not easily recognized on the chest radiograph. Progression of the chest radiograph occurs over a relatively short time. Areas of alveolar filling progress to large masses which are similar to those seen in the upper zones in progressive massive fibrosis but somewhat larger and often located in the middle zones. Tracheal distortion is common, and is a result of the parenchymal distortion with stress placed on the trachea. Radiographic progression can be accelerated in these workers by superimposed mycobacterial infection.

Acute silicosis can usually be diagnosed on the basis of a history of employment in an occupation where the opportunity for overwhelming silica exposure exists, and when the clinical features and chest radiograph are consistent with this illness. If review of lung tissue becomes necessary for an accurate diagnosis, an open lung biopsy is recommended. Despite appropriate therapy for any underlying chest infection, the worker's lung function continues to deteriorate. Perhaps the best differential diagnosis of these very unusual chest radiographs includes alveolar proteinosis, bronchiolitis obliterans with organizing pneumonia, desquamative interstitial pneumonitis, and lipoid pneumonia. These entities can usually be excluded on a clinical basis.

International Labour Office Classification and Chest Roentgenography in Silicosis

As discussed above, the chest x-ray plays a key role in the identification and characterization of silicosis. Appropriate and reproducible interpretation of the chest x-ray has therefore been an important concern of epidemiologists as well as clinicians and those involved in the processes of workmen's compensation and litigation. In response to these needs, the International Labour Office (ILO) has developed a series of classification schemes to characterize chest films in studies of pneumoconiosis.[75] The most recent was developed in 1980 and is described in the ILO publication *International Classification of Radiographs of the Pneumoconioses.*[76] In the United States, the National Institute of Occupational Safety and Health (NIOSH) maintains a training and certification program for physicians seeking to read chest films according to the ILO system. Physicians may qualify as "A" readers (attended training seminars) or "B" readers (passed a comprehensive examination based on 120 roentgenograms read into the ILO classification).

Briefly, in this classification scheme, the reader initially grades film quality and whether or not changes on the film might be due to pneumoconiosis. If small opacities are present, they are characterized according to shape and size. Small round opacities are characterized

according to size as "p" (up to 1.5 mm), "q" (1.5 to 3 mm), or "r" (3 to 10 mm). Irregular small opacities are classified by width as "s," "t," or "u" (same sizes as for small, rounded opacities). Level of involvement with small opacities, or profusion, is classified on a 12-point scale as 0/- to 3/+. Next, the large opacities are identified, and defined as any opacity greater than 1 cm present in a film in which there is sufficient evidence to indicate a diagnosis of pneumoconiosis. Large opacities are classified as category A (for one or more large opacities not exceeding a combined diameter of 5 cm), category B (large opacities with combined diameter greater than 5 cm but not exceeding the equivalent of the right upper zone), or category C (bigger than B). Pleural thickening is also assessed with respect to thickness, extent, and degree of calcification. Finally, other abnormal features of the chest x-ray can be commented upon.

The characteristic radiographic appearance of simple silicosis is the presence of rounded opacities, which tend to be of the "q" and "r" types. In the lower profusion categories these opacities are most often present in the upper lung zones. In the more advanced stages of the disease, typically the middle and lower lung zones are also involved.

Large opacities are found in complicated or conglomerate silicosis, also known as "progressive massive fibrosis." In this condition, smaller lesions coalesce into large ones; and the large opacities seen on the chest radiograph tend to retract toward the hilus, resulting in subpleural areas of air-space enlargement. The clear area between the outer border of the opacity and the chest wall appears as a bulla (Figure 15–7). Since coalescence of these nodules occurs in the upper zones, the result is loss of upper zone volume, elevation of both hila, and the development of basilar emphysematous changes. Cavitation of these coalesced lesions may be explained by ischemia, but tuberculosis, or carcinoma with necrosis should also be considered in the differential diagnosis. These distinctions are not always easy to make on a clinical basis.

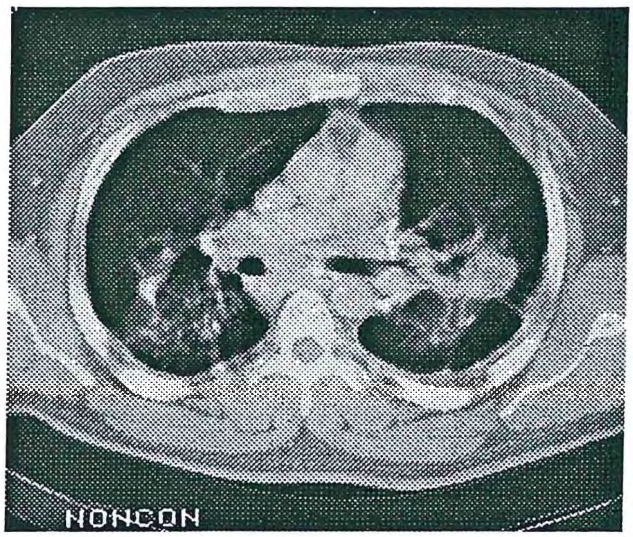


Figure 15–7 A computed tomography scan of the lung demonstrating conglomerate densities in the posterior aspects of both midzones. Note the associated subpleural emphysematous changes.

Enlargement of hilar lymph nodes is common. In 5 to 10% of cases, the hilar nodes calcify circumferentially, producing the so-called eggshell pattern of calcification (see Figure 15–6). This is not pathognomonic of silicosis, as it has also been described in sarcoidosis, postirradiation Hodgkin's disease, blastomycosis, scleroderma, amyloidosis, and histoplasmosis.[77] However, the presence of eggshell hilar calcifications in the presence of typically distributed nodular parenchymal opacities reinforces the clinical impression of silicosis when there is an appropriate exposure history.

Acute silicosis or silicoproteinosis presents radiographically with varying degrees of air-space filling (see Figure 15–5). The radiographic differential diagnosis includes pneumonias and other pulmonary infections, pulmonary edema, alveolar hemorrhage, alveolar cell cancer, and idiopathic alveolar proteinosis.

Several studies have examined the role of computed tomography (CT) of the thorax in the diagnosis of silicosis. Begin et al.,[78] studied a group of 58 granite or foundry workers in Quebec and compared their conventional chest radiography and CT. There was a good correlation between the two techniques for parenchymal profusion scores, although some workers without CT changes showed minimal parenchymal opacities on the chest radiograph. The advantage of CT scan was its ability to demonstrate conglomerate densities that were not detectable on the routine chest radiograph (see Figure 15–7). Kinsella et al.,[71] and Bergin et al.,[79] showed the same findings and demonstrated that decrements in pulmonary function correlated with the degree of emphysema and not with the profusion of parenchymal opacities attributable to silica exposure.

Complications of Silicosis

Mycobacterial Infections

The association between silicosis and pulmonary tuberculosis has long been recognized.[5] Epidemiologic studies suggest that the risk of pulmonary and extrapulmonary tuberculosis is increased about three-fold in workers with silicosis compared to exposed workers without silicois.[80,81] The incidence of tuberculosis increases with the profusion of radiographic opacities. The incidence of tuberculosis and nontuberculous mycobacterial disease appears to be highest in acute and accelerated silicosis.[63] Prolonged silica exposure without silicosis may be sufficient to increase the risk for tuberculosis. A recent Danish study of 5579 male foundry workers over a 19-year period showed increased incidence of pulmonary tuberculosis in silicotics and in nonsilicotics with long work histories and, presumably, large cumulative silica exposures.[82]

Infections with atypical mycobacteria such as *Mycobacterium kansasii* and *Mycobacterium avium-intracel-*

lulare must be considered in the patient with silicosis.[9] The frequency at which these atypical mycobacterial infections are found is probably related to the geographic distribution of the organisms.

Mycobacterial infection should always be suspected when a silicotic patient experiences appropriate constitutional symptoms, worsening of respiratory symptoms, or changes such as cavitation of PMF lesions in the chest radiograph. It has been recommended that silicotics, or those with more that 25 years' exposure to inhaled crystalline silica, should have a tuberculin test performed by intradermal injection of 5 tuberculin units (TU) of purified protein derivative (PPD).[5] Chemoprophylaxis for tuberculosis should be offered to all patients with reactions of greater than 9 mm in duration, regardless of their BCG vaccination status.[5] Because silicotic changes on chest x-rays can make radiographic evaluation for active tuberculosis difficult, it is critical to evaluate for active disease after a positive PPD skin test has been documented. If acid-fast smears are negative in the presence of a positive tuberculin test, the American Thoracic Society and the Centers for Disease Control recommends chemoprophylaxis with 300 mg of isoniazid daily for a year or a four-month multidrug regimen.[83] However, short course multidrug chemoprophylaxis may be ineffective in the presence of silicosis.[84]

Smear- or culture-postive silicotics should be treated with multiple antituberculous drugs. Effective regimens generally contain isoniazid, rifampin, and pyrazinamide. Older studies suggest that antituberculous chemotherapy should be given for an extended period, ranging from more than a year to a lifetime.[85] Recent papers show successful outcomes and acceptable relapse rates with shorter treatment regimens.[86,87] One study suggested that silicotics with tuberculosis do better when the usual multidrug regimen is given for 8 months.[88] Efficacy of therapy should be monitored using clinical and radiographic examinations as well as smear and culture responses.

Immune-Mediated Complications

Silicosis is associated with immune dysfunction, both systemically and in the lung.[89] A major feature of this immune dysfunction is dysregulated and increased immunoglobulin production.[90-94] Increased serum IgG and IgM concentrations have been reported in sandblasters;[90] increased serum IgG and IgA concentrations in silicotic stone masons;[91] increased serum IgG, IgM, and IgA concentrations in slate-pencil workers;[92] increased IgG in quartz crushers;[93] and increased IgG, IgA, and IgE in silicotic miners.[94] Silicosis is also associated with increased prevalence of serum autoantibodies, such as antinuclear antibody and rheumatoid factor, as well as with increased prevalence of circulating immune complexes.[14,89-91,93,94] Despite apparent activation of antibody immunity, silicosis is associated with impaired antimycobacterial defenses, an important cell-mediated immune function, as discussed above.

In additon to altered markers of immune function, silicosis also appears to be associated with several autoimmune diseases. There is persuasive evidence relating scleroderma to occupational silica exposures.[5] This observation was first made in 1914 in Scottish stonemasons.[95] Subsequent reports described increased prevalence of sclerodactyly (acrosclerosis) and progressive systemic sclerosis (PSS) in patients from dusty trades and in patients with silicosis.[96,97] More recent studies in South African miners have shown increased incidence of PSS[98] as well as an increased number of PSS cases relative to systemic lupus erythematosus (SLE) cases.[99] A potentially confounding factor in these studies is the induction of acrosclerosis and Raynaud's phenomenon in response to vibration injury encountered by many workers, including miners who drill rock.[100] However, the preponderance of evidence suggests an association between silica exposure and PSS.

A causal association between rheumatoid arthritis (RA) and silicosis is also possible but remains unproven.[5] A Finnish cohort of 1026 current and former granite workers had excessive numbers of individuals disabled by or taking treatment for RA, when compared to age-specific rates in the general population.[101] South African miners with RA were more likely to have silicosis than were miners not exhibiting RA, and their silicosis was more progressive. The study did not assess whether silica exposure increased the risk of RA.[102] Accurately defining the relationship between RA and silicosis is complex because of the difficulty in ensuring that individuals with arthritis actually suffer from RA, as well as the ability of silicosis to induce positive serum tests for rheumatoid factor in the absence of RA.[90,103]

Evidence for an association between SLE and mixed connective tissue disorders with silicosis is based on only several reports from populations of sandblasters and workers grinding and handling silica for use in scouring powder.[63,73,104] Current evidence can only support the suspicion of a causal relationship between SLE and silica exposure in the presence of acute or accelerated silicosis.

Lung Cancer

Many animal and human studies have addressed the issue of whether silica exposure or silicosis predisposes to the development of lung cancer.[5] In 1987, the International Agency for Research on Cancer (IARC) reviewed carcinogenicity studies and concluded there was *sufficient* evidence of carcinogenicity in experimental animals and *limited* evidence for carcinogenicity in humans.[105] In October 1996, a committee of the IARC reclassified silica as a Group I substance described as "carcinogenic in humans," concluding that there is "sufficient evidence of carcinogenicity in humans."

Animal studies have shown that rats given intrapleural silica develop malignant histiocytic lymphoma.[106,107] In addition, intratracheal administration of

silica can lead to respiratory neoplasms that resemble human bronchogenic carcinoma.[108] However, relatively high doses of silica were administered, and prolonged observation for almost the lifetime of the rats was needed before tumors appeared.

With regard to human studies, older reports reached conflicting conclusions regarding the association between silica exposure and lung cancer.[109] These studies were confounded by selection bias in the detection of cases of pneumoconiosis, and many of them did not account for the effects of other carcinogens such as cigarette smoke or radon exposure in underground mines.

Since 1986, a number of additional studies on whether silicosis predisposes to lung cancer have been reported.[110-115] These and other studies have been analyzed in a review by Weill and McDonald[116] and by the American Thoracic Society.[5] Overall, the available data support the conclusion that silicosis, whether induced by mining or nonmining dust-associated trades, produces increased risk for bronchogenic carcinoma. The most convincing evidence for increased cancer risk attributable to silica is in tobacco smokers with silicosis. Less information is available on those who never smoked, or workers exposed to silica but who do not have silicosis. Thus, silicosis should be considered a condition that predisposes workers to an increased risk of lung cancer.

Chronic Bronchitis and Airflow Obstruction

Studies from many different work environments suggest that exposure to environments with silica levels that may not cause roentgenographically visible simple silicosis can still cause more bronchitic symptoms than those expected from smoking alone.[5] A recent meta-analysis of 13 studies among coal and gold miners confirmed an excess of bronchitic symptoms and obstructive physiology, even among nonsmokers.[117] Pathology studies of such workers exposed to nonasbestos mineral dust have shown pigmentation and fibrosis surrounding small airways, a condition termed "mineral dust small airways disease."[118]

Airways obstruction in the presence of silicosis is also documented.[5] In moderate to severe silicosis, nodules occur in close proximity to small and medium airways causing narrowing and distortion of the lumen. Hypertrophy and scarring in bronchial-associated lymphoid tissue and intrapulmonary lymph nodes may compress the larger airways. Radiologic and pathologic emphysema also occurs in association with silicosis, particularly in progressive massive fibrosis.[119] In patients with more advanced silicosis, pulmonary function tests usually reflect a mixed pattern of nonreversible airflow obstruction as well as the features of volume restriction and impaired gas exchange expected with diffuse interstitial lung disease. Airways obstruction in dust-exposed workers has recently been reviewed in considerable detail.[120]

Renal Complications

A relationship between silica exposure and renal disease has been suspected since the 1930s. A report at that time documented a 45% increase in the death rate from chronic nephritis in English and Welsh men with occupations associated with silica exposure, relative to age-specific rates in the reference population.[121] A case control study of men with end-stage renal disease found elevated odds ratios for "regular occupational exposures to solvents or silica." It stated that other evidence of silica-related renal disease was limited to case reports.[122] Case reports have also suggested an association between acute silicoproteinosis and glomerular injury.[123,124]

Treatment and Prevention of Silicosis

Treatment of Silicosis

There is no proven specific therapy for silicosis. Symptomatic therapy includes measures such as treatment of airflow obstruction with bronchodilators, treatment of respiratory tract infection with antibiotics, and use of supplemental oxygen to prevent complications of chronic hypoxemia. As already noted, patients should be screened for tuberculosis infection, and a high index of suspicion for mycobacterial infection superimposed over silicosis should be maintained.

Corticosteroid therapy has been attempted as a measure to interrupt inflammation and cytokine networking which lead to progressive silicosis. In the largest study to date, a six-month trial of prednisolone was carried out in north India in 34 patients with chronic simple and complicated silicosis. Treatment resulted in statistically (although not clinically) significant improvements in lung volumes, diffusing capacity (DL_{CO}), and partial pressure of arterial oxygen (PaO_2). A significant decrease in total cells recovered by bronchoalveolar lavage was also noted.[125] Systemic steroid therapy has also been reported to be beneficial in accelerated and acute silicosis.[126] Unfortunately, no large randomized, double-blinded prospective clinical trials have documented the impact of steroid therapy on the long-term outcome of silicosis.

Other experimental treatment measures have been attempted in silicosis. Whole lung lavage (WLL) has been proposed as a therapeutic measure based on its ability to reduce the pulmonary dust burden and remove inflammatory cells from the lung.[127-129] While current data show the procedure to be safe and technically feasible, its usefulness remains unclear.

Additional therapies investigated in animal models and humans include modulation of silica-induced toxicity by inhalation of aluminum, and inhalational or parenteral administration of a polymer, polyvinyl pyridine N-oxide (PVNO).[130-132] Inhaled aluminum has been ineffective in human disease and in a sheep model of

chronic silicosis.[133] The PVNO has beneficial effects in some experimental models, but may be carcinogenic.[7]

Tetrandrine, an active component of the Chinese traditional medicine "hanfangii," has been reported in the Chinese literature to inhibit and even reverse pulmonary lesions in experimental silicosis.[134] An open clinical trial showed clinical and radiographic improvement in patients with pulmonary fibrosis from silica inhalation.[135] Tetrandrine appears to function as an anti-inflammatory agent. It has antiphagocytic and antioxidant properties,[136] is able to inhibit human neutrophil and monocyte adherence,[137] and inhibits particle-stimulated oxygen consumption, superoxide release, and hydrogen peroxide production by rat alveolar macrophages.[138]

As is currently the case for many end-stage lung diseases, lung transplantation is a potential option in end-stage silicosis. A case of unilateral lung transplantation in a 23-year-old man with acute silicosis was reported in 1972.[139] Lung function and gas exchange improved and the patient survived for 10 months. The option of lung transplantation should be seriously considered for the end-stage silicotic.

Prevention of Silicosis

Silicosis is a preventable disease. As a consequence of reduced dust standards and better industrial hygiene practices, silicosis afflicts far fewer people than in the past. The Occupational Safety and Health Administration (OSHA) has set the permissible exposure limit (PEL) for respirable silica at 10 mg/m^3 divided by (%SiO_2 + 2) or 250 million particles per cubic foot divided by (%SiO_2 + 5), superseding the previous standard of 0.1 mg/m^3 respirable silica.[140] Some authorities feel this exposure level is too high for long-term exposures, such as would occur over an entire working lifetime.[48,60] Thus, a lower PEL standard of 0.05 mg/m^3 is recommended by the National Institute for Occupational Safety and Health (NIOSH).[141] A number of NIOSH publications are available addressing such issues as silica as a workplace hazard, environmental controls, personal protection, and medical monitoring.[8,142,143]

COAL WORKER'S PNEUMOCONIOSIS

Coal worker's pneumoconiosis (CWP) is a disease distinct and separate from silicosis, and results from inhalation and deposition of coal dust in the lungs. Although the coal particle is not nearly as fibrogenic as the silica particle, excessive exposures over a period of time can overwhelm effective clearance mechanisms and initiate a spectrum of diseases including industrial bronchitis, simple CWP, and complicated CWP also known as PMF. In simple CWP, the chest x-ray shows only small rounded opacities (as previously discussed for silicosis). In complicated CWP or PMF, large opacities are present.

Simple CWP is clearly related to the amount of dust deposited within the lungs. Progressive massive fibrosis most often occurs on a background of simple CWP and is the result of dust deposition as well as other inadequately defined host factors. Immunologic and local cellular factors may contribute to the development of this form of the disease.

Progressive massive fibrosis is clearly associated with alterations in the ventilatory, mechanical, and vascular functions of the lungs. These abnormalities in PMF contribute to premature morbidity and mortality. Like silicosis, there is no specific therapy for CWP; prevention remains the cornerstone of eliminating this occupational lung disease. Education of workers and employers regarding the hazards of coal dust exposure, and measurement and effective control of dust exposure are the key elements in disease prevention.

Formation and Characteristics of Coal

Coal is not a pure mineral but is formed by the accumulation of vegetable matter covered by sedimentary rock (thereby sealing it from air) and subjected to pressure and temperature over the ages. This causes the physical and chemical properties of the matter to change. The matter dries, becomes warmer, and loses oxygen content, all the while increasing the relative carbon content.[144]

The first step in this conversion of vegetable matter to coal is the formation of peat, a moist spongy material. This transformation of organic deposit can occur in a stagnant water bed relatively quickly (at a rate of approximately one foot per hundred years). An approximately hundred-foot accumulation of peat compresses to form a one foot wide coal seam. In the simplest terms, coal comprises moisture (which decreases with time), pure coal (carbon), and mineral matter.[145]

The process of conversion (coalification) from organic matter follows a sequence from wood to peat, lignite, bituminous coal, and finally anthracite coal. Coal is classified primarily by *"rank,"* which describes the extent of change from vegetation to mineral-free coal. Rank is directly related to the percent of carbon in coal, the completeness of the transformation from vegetation to coal, and the geologic age of the deposit. New deposits form above the old, and according to Hilt,[146] "in a vertical sequence, at any one locality in a coalfield, the rank of the coal seam rises with increasing depth." The *"type"* of coal relates to the plant materials which form the coal. *"Grade"* refers to the purity of the coal — or the amount of inorganic material (including ash and sulfur) released in the burning of coal. Sulfur is a frequent contaminant of coal and is derived from sulfur in the plants which have formed the coal or is the result of infusion of water containing sulfur during the formation of coal. In today's world, sulfur released as a by-product of coal

burning is an important air pollutant and boiler corrosive, thus making coal with a high sulfur content less desirable.

Other important descriptive terms include a quantitative measurement of coal *"moisture"* (the percentage of water that is contained in coal and released with moderate heat) and the amount of *"volatile matter"* (the percentage of substances, mainly gases and coal tar, lost when a sample is well heated). The residue of combusted material remaining after a coal sample is completely burned is coal *"ash."* The ash content has two sources: the first is the inherent minerals in the decaying wood, and the second is material which entered the swamp or was blown in while the peat was being formed.[147]

The composition of coal mine dust varies with the coal seam. Most of the dust is composed of carbon, although in some seams it may only form 60% of the dust,[148] with more than 50 different elements and their oxides.[149] Dusts of higher rank typically have more silica than dusts of lesser rank because the anthracite seams often have roofs and floors of quartz which contaminate the coal during mining.

How Coal is Mined

Coal mining is inherently dangerous; in addition to its respiratory risks, there are other serious risks such as underground fires and explosions, toxic gas excess, and rock falls. Important safety measures include adequate ventilation so that methane is removed and the risk of explosion and fire minimized; protection from roof falls; and control of dust. Each of the different methods of mining presents its own safety challenges.

Coal may be found in outcroppings and in seams that are sometimes just a few feet below the surface. In these deposits coal can be obtained by scraping away the surface or overburden and extracting the coal with earth moving equipment. This is called "surface or strip mining."

On hillsides where the coal seam may be many feet below the surface of the hill but some outcropping occurs from the side of the hill, a feasible method of mining coal is to bore into the outcropping with an auger. Depending upon how far into the hillside the seam extends, this method of mining is a combination of surface and underground mining.

Where coal seams are buried deep, typically greater than 200 feet underground, it is not economically feasible to strip away the overburden. The only practical way of mining the coal is to sink shafts from the surface to the coal seam and then follow the seam with a series of more or less horizontal tunnels. This has been the most prevalent method of mining coal in this century.

Modern underground coal mines are categorized as "room-and-pillar mines" and "longwall mines." A room-and-pillar mine is a series of parallel rooms where mining has occurred separated by pillars of unmined coal. As mining goes on, this looks increasingly like a honeycomb. Two types of mining are performed in room-and-pillar mining. The first is *conventional mining*, which is the least mechanized, accounting for less than 10% of US coal mine production.[150] Here, incisions are cut in the sides and bases of the seam and charges inserted through holes drilled in these areas. The roof is first supported, then the charges are exploded, and the coal loaded and removed from the face. The cycle is typically performed sequentially in adjacent areas to maximize coal production.[151]

An alternative approach is *continuous mining*, which accounts for approximately 60% of US coal production. In this approach, a machine with a rotating head is used to break coal from the face. The operator advances this machine through the seam, moving the cutting head of the machine up and down to maximize coal breakaway from the face. A conveyor, incorporated into the continuous mining machine, moves the broken coal from the face to waiting underground shuttle cars. The continuous miner may include roof-bolter units located just behind the rotating cutter head or have a roof-bolting machine nearby. Workers remain here while mining is conducted.

In this method of mining, one-third to two-thirds of the coal remains within the pillars after the rooms are mined. To recover the coal within the pillars, each pillar is mined using timber for temporary roof support. The timber is then removed, allowing the roof in that area to collapse. This approach is called "retreat mining" because after mining of the pillars, no attempt is made to go back into the block. The roof caves in, and the mine is abandoned.[152]

Longwall mining is the most mechanized and the most productive means of underground mining. The number of underground mines employing longwall mining techniques continues to increase in the US (and is now used in approximately 100 mines). This accounts for approximately 30% of US coal production. Longwall mining produces up to 40 tons of coal per minute, and in some instances, nearly 4000 tons per work shift. In this process, the continuous miner cuts out a longwall of coal which may be 600 to 800 feet wide and 5,000 to 12,000 feet long. When the wall is formed, the hydraulically powered roof supports, the cutting machine or shearer (often with built-in water sprays to minimize dust generation), and the conveyors are put into place. The shearer moves across the coal face in a bidirectional manner with a depth of cut of about two feet. A conveyor belt, which runs the length of the longwall, captures the newly excavated coal. As each pass is made by the shearer (which requires one or two workers to operate and travels up to 60 feet/minute), the roof supports and the conveyor are advanced. As these supports are advanced, the roof behind these supports caves in, which provides another example of retreat mining.[153]

Although it is a very productive way to mine coal, *longwall mining* has several disadvantages. First, if the cutting machine or any machine necessary for the process fails, the entire system and thereby the production of coal comes to a stop. Second, a coal face of 600 to 800 feet may have numerous different characteristics,

and mining this extensive block may lead to difficulties. Third, developing and setting up a longwall requires considerable time and effort. Finally, the large number of roof supports required for a longwall are very costly. This has led to *shortwall mining* in which operators use fewer supports, and combine the roof support system of the longwall mine with the flexibility of the continuous mining machine. With this approach, the face is shortened to about one-third of the length of the longwall, production is increased relative to room-and-pillar mining, and the miner works under hydraulic roof supports the entire time, with fewer hazards of roof falls.

HISTORY OF COAL WORKER'S PNEUMOCONIOSIS

The earliest coal mines were outcroppings of coal along river banks, and as such, they could be described as surface mines. The drive for coal production on a large scale was associated with the manufacture of iron and the development of the steam engine in the early part of the 18th century. It was not until 1762 that a steam engine was used to work a colliery in Scotland.[154] Underground mining grew quickly as effective methods for ventilating fresh air into mines and removing toxic gases and water from mines were developed. By 1866, in Scotland alone, there were 472 coal mines, 41,000 miners, and 12 million tons of coal produced yearly.

Meiklejohn[154-156] has extensively reviewed the history of lung disease in miners. Lung disease in miners has been referred to as miners' asthma, phthisis, anthracosis, and in Scotland, miners' black lung. In 1831, the first published report of "black lungs" attributed to employment in coal mines[157] described a 59-year-old man who had been employed as a miner for 10 or 12 years and was hospitalized for generalized anasarca. He soon died from progressive heart failure. The lungs were examined and a picture consistent with PMF with cavitation of these large lesions on a background of simple CWP was described.

> "At necropsy, the lungs were universally adherent to the chest wall; the pleura was thickened and in places ossified. When cut into, both lungs presented one uniform black carbonaceous color, pervading every part of their substance ... The left lung did not appear to contain any cavities, but was condensed and loaded with black serum. Some minute hard points could be felt in various parts of both lungs."

Opinions regarding the explanation for this black pigment included gunpowder, inhalation of lamp-black, or soot from the oil lamps of the miners. Marshall (1833-1834),[158] just several years later, concluded that:

> "The true explanation of the origin of this disease in colliers seems to be that it is in consequence of the inhalation of fine coal dust, and its deposition in the substance of the lung. That coal may float through the air in particles sufficiently fine to be inhaled without immediate irritation and that it is thus inhaled is a matter of common observation."

Thoughout the 19th century, there was considerable controversy and disagreement regarding the impact of coal dust inhalation on the survival of miners. Overall, data showed that the mortality of coal miners only minimally exceeded the mortality of other groups such as farmers or agricultural laborers. The lack of coal dust effect on survival was felt attributable to better mine ventilation and lesser exposures to coal dust. Even at that time, the lesser fibrogenicity of coal dust compared to silica was well recognized.[155,159]

Early in the 20th century, Collis[160] opined that coal dust did not produce pneumoconiosis, and that it even served to protect against tuberculosis. He attributed the dust disease in miners to silica inhalation and felt that the disease present was silicosis. It was not until later when washed coal, free of silica, was recognized to produce dust disease in the lungs of stevedores who loaded and leveled coal in the holds of ships that CWP was widely accepted as being pathologically distinct from silicosis.[161-163] Later, King et al.,[164] showed that the radiologic and histologic severity of pneumoconiosis in coal miners was related to the total amount of dust and not the silica content of the coal.

Dust levels in the air at surface mines are generally considerably lower than in underground mines with few notable exceptions. In surface miners and coal plant cleaning workers in the anthracite mining area of the US, the mean FVC, FEV_1, and peak flow rates were not related to the number of years worked in coal-cleaning plants.[165] Yet, there is a group of these workers at special risk for pneumoconiosis. Workers at surface coal mines who operate the large drills (drillers and driller-helpers) to make holes in which explosives are placed to remove the overburden are exposed to silica and are at risk for the development of silicosis rather than CWP.[6]

Workers in some exclusively above-ground operations may be exposed to coal dust. These are the workers at the tipples where crushing, sizing, washing, and blending of coal is done; at surface coal mine sites away from the drilling operations; and at locations where coal is loaded into ships, railroad cars, or river barges. Although each case needs to be evaluated on an individual basis, the great majority of these exposures are relatively small and insufficient to cause disease.

With the development of standardized medical tools to monitor pneumoconiosis in miners, such as standardized questionnaires, measurement of lung function, and standardized interpretation of chest radiographs, the emphasis of CWP research from the 1930s to the present time has been on epidemiologic studies. These studies have been critical in the development of current

dust standards for coal mines, such as those mandated in the United States Federal Coal Mine Health and Safety Acts of 1969 and 1977.[75]

Epidemiology of Coal Worker's Pneumoconiosis

A series of studies in the 1960s showed that the prevalence of CWP varied by region of the country, the type (rank) of coal mined,[166] and the duration and intensity of exposure.[167,168] Among underground miners, those working at the face and exposed to higher concentrations of coal mine dust had a higher prevalence of CWP than surface workers or those whose jobs caused them to enter the face area only intermittently. For example, there was considerably greater prevalence of CWP among miners in Pennsylvania anthracite seams than among miners in the western plateau of Colorado and Utah where a lower rank of coal was mined.

The institution and enforcement of dust control measures have reduced the rate of CWP and may have retarded progression among those with radiographic opacities who continued to work in mines. The US dust standard was instituted in 1969 at 3 mg per m^3 and further reduced to 2 mg per m^3 in 1972.[169]

The US Public Health Service has performed a series of studies evaluating the prevalence of CWP. The first, round one of the US coal worker's surveillance program, was performed using data collected from 1970 to 1973. The most recent, round five of this same program, was undertaken from 1987 to 1991. Data from these studies have been presented in summary form in a series of reports.[170-172] Mines chosen for evaluation represented different geographic areas, coal seams, and coal mining methods. These studies appear to show a reduction in the prevalence of CWP over time. When comparing studies from the mid-70s to the mid-80s, the number of cases with both simple CWP and PMF declined in all groups with at least 10 years of mining. In one group of miners with tenures of 15 to 24 years, the prevalence decreased to less than half, and in those with a lifetime of coal mining, 11% had category 2 simple CWP in round one, compared to 2% in round 4. An important concern about these data is whether this decline is a true decrease or the effect of bias induced by self-selection. In the years 1970 to 1973, approximately 75% of the nation's 100,000 miners participated in the program. Participation decreased to approximately 15% of the mining work force in the study performed from 1987 to 1991.

Data from British studies have shown that the attack rate (incidence of new cases) and the probability of progressing to a higher category of simple CWP are related to the mass of respirable dust to which the miner is exposed during his lifetime.[173] When the miner with simple CWP is no longer exposed to dust, the chest radiograph is not likely to progress; however, the same cannot be said for PMF. The rate of progression to PMF appears to be influenced chiefly by the age at which the miner begins to show radiographic changes of CWP, and also by the presence of a rheumatoid diathesis.[174]

A number of studies have addressed mortality rates in coal miners and CWP. Perhaps the best to summarize mortality rates in the first part of this century was Enterline,[175] who noted that it was not until 1950 that relatively accurate death certificate data which described an individual's usual occupation were available. In the US Public Health Service data collected from death certificates for the year 1950,[176] there was a gross excess in mortality among coal miners of all ages, compared to the general population. For example, in miners aged 45 to 64 years, the Standard Mortality Ratio (SMR), the ratio between the actual number of deaths and the observed number of deaths, approximated 2.0.

To further emphasize the mortality risk faced by a coal miner between the years 1949 and 1963, the US Society of Actuaries published SMRs on 44 occupations, using life insurance policy data.[177] Of all of these occupations, coal mining had the highest SMR, which was 1.5. The SMR for death attributable to respiratory disease exceeded 40 using death certificate data, and 11 using life insurance policy information. Even when accidents and respiratory disease were eliminated as causes of death, the SMR for coal miners ranged between 1.4 and 1.7 times the death rate for all working men. Even as late as 1979, a coal miner was recognized to have a two-fold risk of being killed because of his work, compared to the risk faced by the average worker.[178]

Studies involving approximately 6000 miners and exminers residing in the Rhondda Fach,[179,180] a mining community in southern Wales, also showed an excess mortality. In the absence of pneumoconiosis, or when simple pneumoconiosis or even PMF of category A was present, the SMR approximated 1.2. The number of deaths did not vary by pneumoconiosis category, unless category B or C large opacities were present when the SMR nearly doubled that of the comparison group. Chronic bronchitis was twice as often a cause of death among the miners. Additionally, carcinoma of the stomach increased with the pneumoconiosis category, a feature frequently reported in other studies. Ortmeyer et al.,[181] reviewed the mortality rates for compensated Pennsylvania miners by category of opacity on the chest radiograph and recorded similar results.

Stocks[182] was one of the first to present the relationship between mining and gastric cancer, but his report made it clear that it was necessary to compare the mining risks for illness with local controls. He showed that the rate of gastric cancer among miners in the United Kingdom varied, with it being most frequent in south Wales, intermediate in Northern England, and least in the Midlands. The relationship between this malignacy and coal dust exposure was also suggested in a study of gastric carcinoma in Utah. Gastric malignancy increased nearly three-fold in residents of two Utah coal mining counties, leading the authors to speculate that

swallowed coal particles containing polyaromatic hydrocarbons such as benzpyrene increased cancer risk.[183]

More data about the mortality rates for US coal miners on the rolls of the United Mine Workers Health and Retirement Fund from 1959 to 1971 was presented by Rockette.[184] Of the 23,232 men enrolled, 7,741 died. The overall SMR for this population was 1.02, a dramatic improvement compared to the rates in the death certificate study cited above.[176] Yet, the SMRs for several specific categories remained elevated. Specifically, the SMR for nonmalignant respiratory disease was 1.6, and the SMR for accidents was 1.8. Although mortality due to all cancers had not increased, the SMRs for stomach and lung cancer were excessive (1.4 and 1.1, respectively).

In a mortality report of Appalachian coal miners and exminers who were monitored from 1963 to 1971, mortality among present miners was 7% less than expected and the exminer mortality was 24% greater than expected.[185] Simple pneumoconiosis did not affect life expectancy while the presence of PMF did.

Meijers et al.,[186] postulated that coal workers have a greater risk of lung cancer due to their exposure to coal mine dust, a material containing various potentially carcinogenic organic (i.e., hydrocarbons) and inorganic (i.e., trace elements such as cadmium and chromium) compounds. In support of this hypothesis, crystalline silica, a component of coal dust, had been declared a probable carcinogen.[105] The cause of death of 334 miners from a cohort of 5400 miners with CWP, employed in 11 Dutch coal mines from 1956 to 1960, was evaluated in 1983. Data showed a higher than expected mortality, primarily attributed to stomach or large and small intestine malignancy, as well as more frequent nonmalignant respiratory diseases.

Exposure data were available for 26,363 coal miners from 20 collieries in England and Wales, who first attended medical screening between 1953 and 1958.[187] A chest radiograph, respiratory questionnaire, and coal mining history were recorded and estimates of exposure made. An assessment of the causes of 8489 deaths was initiated in 1980. The general mortality was 13% less, on an average, than in the English and Welsh miners in the same region. The survival of miners with category A large opacities was less than that of men without pneumoconiosis, yet the mortality rate did not increase with increasing category of simple pneumoconiosis. Mortality due to all causes, as well as that attributable to pneumoconiosis, bronchitis, and emphysema, increased with cumulative dust exposure. Furthermore, a shorter survival was reported in those with greater dust exposures at the start of the evaluation, particularly those of an older age group. There was no association between lung cancer and coal mining, but the risk for cancer of the digestive system approached significance.

The mortality rate of US coal miners with exposure estimates was reported by Kuempel et al.[188] In this population, the mortality rate of 793 men among a population of 8878 miners, enrolled between 1969 and 1971 and monitored until 1979, was evaluated. Overall, the SMR for all causes was 0.85; the SMRs for bronchitis, emphysema, lung cancer, and stomach cancer were not higher, but the SMR for pneumoconiosis was 3.7. No statistical relationship between deaths due to lung cancer or stomach cancer was reported.

In summary, a series of mortality reports have not convincingly shown that simple CWP is associated with premature mortality. However, PMF adversely effects survival, especially when category B and C large opacities are present. Although there appears to be no clear difference in the SMR for lung cancer between miners and others,[189] a number of studies show an increase in the SMR for digestive cancer in general and stomach cancer in particular.

Industrial Bronchitis

Industrial bronchitis is diagnosed frequently among workers exposed to dusts, including coal dust.[190] It manifests as a productive cough which persists for at least 3 months in a year for at least 2 years (chronic bronchitis) and is associated with workplace dust exposure. The relationship between coal mining and bronchial mucus gland dimensions was presented in an autopsy study by Douglas et al.[191] Coal dust exposure resulted in an increase in the maximal gland/wall ratio independent of smoking, but no relationship between mucous gland size and lung dust or pneumoconiosis was found. This suggested that pneumoconiosis is related to respirable dust exposure, and mucous gland enlargement is related to the inhalation of larger (nonrespirable) dust particles which present a chronic burden to the mucociliary escalator and act as irritants to the airway.

Early reports showed that the prevalence of bronchitis in coal miners varied by smoking habit, age, and work history.[192] In all reports, miners who were smokers had bronchitis more frequently than did nonsmokers and, when studied, showed bronchitis to increase with age (a surrogate for years of dust exposure in the workplace). Marine et al.,[193] identified 543 lifetime nonsmokers among 14,888 British coal miners (3.6%) who were studied between 1953 and 1967 and were less than 65 years of age; they worked at the coal face in most instances, did not have PMF, and had participated in three surveys over 10 years. Of these, 17% were found to have bronchitis at the third survey. In another report of coal miners, 16% had bronchitis.[194] There is little information on the natural history of chronic bronchitis in nonsmoking miners once they are removed from dust exposure; however, the bronchitis is thought to resolve when dust exposure ends. In those who develop chronic bronchitis due to dust, there is often a measurable, but not clinically significant, decline in FEV_1.

Pathology of Coal Worker's Pneumoconiosis

When the normal dust clearance mechanisms of the lung are overwhelmed, dust deposition increases. With

the initiation and progression of fibrosis, the lung lesions increase in size and number. A focal collection of coal dust in pigment-laden macrophages, which tapers off toward the alveolar duct, is initially apparent around the dilated respiratory bronchioles.[195] This is the *coal macule*, the characteristic lesion of CWP (Figure 15–8). A fine network of reticulin within this collection of cells may be visible early on. Focal emphysema is a specific entity that is an integral part of the lesion of simple CWP. It is characterized by enlargement of the air spaces immediately adjacent to the dust macule.[196]

The impact of pathologic changes on lung function has been the subject of considerable discussion. In nonsmoking miners with nonobstructed airways, Morgan et al.,[197] showed an increase in the residual volume (RV). In miners without CWP, the RV was 105% of that of a group of nonminers. This increased to 108% and 114% of controls in miners with category 1 or category 2 and 3 simple CWP, respectively. Although Morgan considered that this might be attributable to focal emphysema, he thought it unlikely because pathologic disruption of the bronchioles was absent. Rather, he considered this hyperinflation to be the result of airways being narrowed by the coal macules located along the airway margins, with alteration of the peripheral flow rates by an increasing resistance.[197]

On gross examination of the lung, larger collections of dust are described as coal nodules, classified as "micronodular" if they are 7 mm in diameter or less, and "macronodular" if they are larger than this. These nodules are palpable, whereas coal macules are not.

Progressive massive fibrosis is diagnosed when one or more nodules attain a size of 2 cm or greater in diameter, typically on a background of simple CWP.[72,198] The 2 cm diameter is an arbitrary choice of minimal diameter that has allowed better correlation with clinical and radiographic measurements. Gross examination of the lung in PMF reveals a solid, heavily pigmented lung that is rubbery-to-hard in texture. These features are most common in the apical posterior portions of the upper lobes or the superior segments of the lower lobes. These lesions tend to occur asymmetrically, occasionally showing first in one lung and then in the other, leading to a suspicion of malignancy. When these lesions are ashed, they appear to be composed of varying amounts of coal, silica, calcium, and other substances. About 25% of the proteinaceous material in the center of these lesions is collagen.[199] These lesions may also cavitate and the worker may expectorate an ink-like fluid (a clinical sign described as "melanoptysis"); or, when these cavitary lesions are cut, they may drain ink-like fluid. Airways and vessels adjacent to the lesions are distorted and destroyed by the lesions.

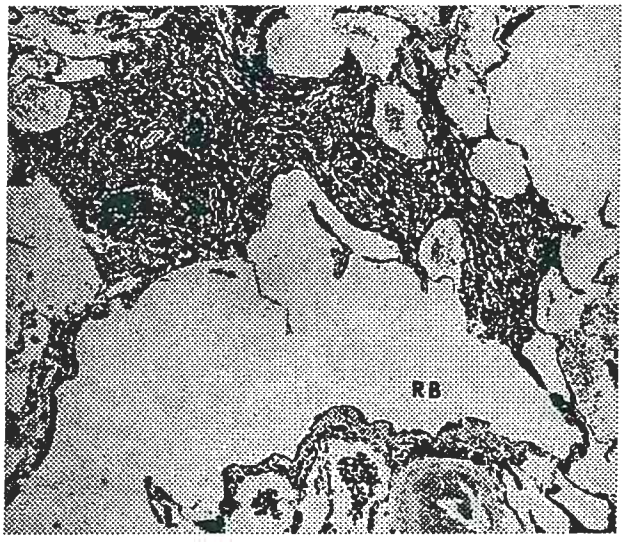


Figure 15–8 Histology section from a patient with coal worker's pneumoconiosis showing a typical coal macule.

Caplan's syndrome is also described with coal dust exposure. It is a nodular lung reaction that occurs in dust-exposed individuals who either have RA or develop RA within the subsequent 5 to 10 years.[62,200] The nodules vary in diameter from 0.5 to 5 cm, and are usually multiple, bilateral, and peripherally situated. Grossly, the lesions resemble a giant silicotic nodule. Microscopically, the amount of dust in the lesion is small, there is a necrotic area in the center, and there is a surrounding cellular zone infiltrated with lymphocytes and plasma cells. In many nodules, there is a peripheral zone of active inflammation with neutrophils and a few macrophages.

Pathogenesis of Coal Worker's Pneumoconiosis

Coal worker's pneumoconiosis is the result of coal-dust-induced cell damage with activation of the fibrotic process. Lapp et al.,[201] provided a well-outlined approach to addressing how coal dust causes lung damage. Potential mechanisms include: (1) direct cytotoxicity of coal dust; (2) release of oxidants, enzymes, and cell membrane constituents from alveolar macrophages in association with cell death after coal dust exposure; and (3) stimulation of cytokine release from alveolar macrophages with subsequent cytokine networking. Such cytokine secretion can lead to recruitment of effector cells to the lung such as neutrophils and monocytes as well as the stimulation of fibroblast proliferation and collagen synthesis in the area of coal dust deposition.

Coal dust is much less fibrogenic than silica. A mixture of 10% silica and 90% coal is far more cytotoxic to macrophages than pure coal dust.[202] However, both dusts, when cleaved, show surface radicals by electron spin resonance spectroscopy. The free radicals generated by crushing anthracite coal are more numerous than those generated from crushing bituminous coal, which has led to speculation regarding free radical release from different coal ranks and the suggestion that exposure to anthracite coal increases the risk for development and progression of disease.[203]

Long-term coal dust exposure in animals increases the number of alveolar cells recovered by lavage.[204] In addition, an elevation in the number of blood monocytes and an increased rate of mitosis have been recognized in cells from animals undergoing chronic coal dust inhalation.[205] This suggests that recruitment of cells into the lung from the alveolar capillaries and the interstitium of the lung occurs with dust inhalation. Recruited "young" macrophages appear to be more phagocytically active than are older macrophages. This may be a mechanism for more effective clearance of particles.[204]

Exposure of alveolar macrophages to dust particles can result in the release of proteolytic enzymes, reactive oxygen species (i.e., hydrogen peroxide, hydroxyl radical, and superoxide anion), and leukotrienes via breakdown of arachidonic acid in the cell membrane. Again, silica is a much stronger stimulus to the release of these agents than coal dust.[19] Excessive release of these reactive oxygen species has the potential to overwhelm the naturally protective antioxidant system within the lung and begin the process of inflammation and fibrosis.

Activated macrophages secrete a wide variety of mediators which can attract neutrophils into the affected area and then stimulate them to release reactive oxygen species and enzymes.[206] Similarly, the macrophage-derived inflammatory factors can act as chemotactic agents for neutrophils (e.g., TNF-α, IL-8, and leukotrienes), and increase neutrophil adherence and reactive enzyme release (PDGF and platelet-activating factor [PAF]). The presence of these factors escalates the inflammatory process. Finally, secretion of many of the above factors by activated macrophages also enhances fibroblast growth and/or stimulates the production of collagen.

Although the alveolar macrophages in animals are activated after chronic exposure to coal dust, there is little lung damage. The protein and lysosomal enzyme levels in the acellular lavage fluid of the animals are not increased.[204] However, when as little as 2% silica is added, the fibrotic process begins.[207]

A number of investigators have applied bronchoalveolar lavage (BAL) to evaluate the mechanisms of CWP. Lapp et al.,[208] using BAL, compared 12 asymptomatic, life-long nonsmoking coal miners without pneumoconiosis with a mean of 17 years of undergound mining exposure with the results from 18 controls.[208] There was no difference in the BAL mean total or differential cell counts, IgA or IgG concentration, or spontaneous or stimulated phorbol myristic acetate (PMA) stimulated alveolar macrophage chemiluminescence. The BAL total protein levels and particle stimulated chemiluminescence were decreased in the miners. Scanning electron microscopy showed a marked increase in alveolar macrophage cell surface ruffling consistent with activation. Transmission electron microscopy showed particles in macrophages consistent with coal.

Rom et al.,[28] studied 15 symptomatic, nonsmoking coal miners with simple CWP by BAL. They found no significant difference between miners with CWP and controls, in the number of cells recovered, BAL cell differentials, and in the release of superoxide anion or hydrogen peroxide from alveolar macrophages. This contrasted with findings in subjects with asbestosis and silicosis, whose values for spontaneous release of oxidant superoxide and hydrogen peroxide were significantly greater than those of controls. The BAL levels of fibronectin and alveolar macrophage derived growth factor (AMDGF) were elevated but not different from the values obtained in subjects with asbestosis and silicosis. While fibrosis has not been a major part of the pathology of simple CWP, there is evidence of the presence of fibronectin in pneumoconiotic lesions.[209]

In contrast to other reports, Wallaert et al.,[210] demonstrated a significantly increased number of total cells in the BAL fluid recovered from miners with simple and complicated CWP. Alveolar cells from miners with simple CWP and PMF spontaneously released significantly more superoxide, when compared to the levels generated in the comparison group. However, when these alveolar cells were stimulated with PMA, only the cells recovered from the miners with PMF showed significantly increased amounts of superoxide release.

Overall, coal dust is much less fibrogenic than silica dust; however, coal dust is a sufficient stimulus for the secretion and release of macrophage products. These activated macrophages can release enzymes, reactive oxygen species, cytokines, and growth factors which cause fibroblast proliferation. All are important factors in inflammation and the development of CWP.

The chest radiograph in simple CWP correlates with the amount of dust in the lung at autopsy.[211] This is not true of the complicated form of the disease, which suggests that inadequately defined host factors play a role in the development of this lesion. Hypotheses proposed to explain the differences in tissue response to coal dust in those who remain with simple CWP and those who progress to PMF include differing silica contents of inhaled dusts, development of mycobacterial infection, and differences in host immune responses to dust inhalation. None of these appear to be fully satisfactory explanations. Progressive massive fibrosis has been reported in carbon electrode workers, suggesting that silica exposure is not necessary for PMF.[151] Treatment of some Welsh miners with simple CWP with antituberculous drugs did not prevent PMF.[212] Host factors predisposing to development of PMF have been elusive. If such factors are present, they do not appear to be linked to the histocompatibility type.[213]

Relationships between autoantibodies and CWP have been explored extensively. Soutar et al.,[214] reported circulating ANA (antinuclear factor) and RF (rheumatoid factor) levels among 109 miners with radiographic evidence of pneumoconiosis. The authors did not identify the region of the country from which the miners came or in which mines they worked. They found positive ANA in 17% and RF in 10% of the miners. The expected prevalence in the male general population of a positive ANA approximates 2 to 3%. The prevalence of

ANA was least (9%) in simple CWP, and 27% in those with category C (PMF). A similar but less striking trend was seen with RF, ranging from 6% in simple CWP to 18% in category C. Combining both ANA and RF resulted in prevalence of positive results in 13% of the miners with simple and 45% of those with category C PMF.[214]

In 1973, Lippman et al.,[215] reported a prevalence study of circulating ANA and RF among coal miners in the United States. Sera from 207 coal miners were examined, and of the 196 miners with pneumoconiosis, 9 were positive for RF and 34% had positive ANA. There were regional variations in ANA that seemed to parallel the prevalence of radiographic changes, namely, a higher prevalence in the anthracite miners and a lesser prevalence in bituminous miners. These authors did not find the increased prevalence of RF in miners with PMF compared to simple CWP that Wagner et al.,[216] reported in Welsh miners.

Benedek et al.,[217] was unable to confirm findings reported by European investigators among miners in the US. These authors matched 55 pairs of coal miners with rheumatoid arthritis with others with RA. The miners and others did not differ in respect to serum concentrations of IgG or IgA. Elevated levels of IgM were more frequent among the miners but did not reach significance. Rheumatoid factor was positive in 82% of miners and only 64% of others ($p < 0.05$), but there was no correlation with category of pneumoconiosis.

Studies of serum immunoglobulins were also conducted by Hahon et al.,[218] among 155 US coal miners with chest radiographs demonstrating simple CWP, Caplan's syndrome, and PMF. They found significantly higher serum concentrations of C3, alpha-$_1$ antitrypsin, and IgA, and IgG in anthracite miners than in bituminous miners with PMF. There were few differences in these serum proteins among the miners with simple CWP. Compared to normal controls, C3, alpha$_1$ antitrypsin, and IgG values of the miners were elevated. The authors did not find an association between the elevated immunoglobulins and FEV_1.

Burrell[219] used an antiglobulin consumption test to identify autoantibodies in the sera of coal miners directed at lung parenchyma and basement membrane. The lung autoantibodies tended to reside in the IgA class. The role of these and other autoantibodies in the pathogenesis of CWP remains unclear.

Clinical Features of Coal Worker's Pneumoconiosis

Coal worker's pneumonconiosis results from the inhalation of coal dust, its deposition in the lungs, and the host response to its presence. Like silicosis, three criteria are necessary for the diagnosis of CWP.[220] They include:

1. A chest radiograph consistent with the features of CWP;
2. A work history (typically that of underground coal mining) which is sufficient in exposure and latency to result in pneumoconiosis; and
3. The absence of other illnesses which may mimic CWP.

Therefore, the diagnosis of CWP is a clinical and radiologic diagnosis which can be made with confidence without histologic confirmation. Clinical features such as dyspnea, cough, and sputum production are important in addressing the degree of a miner's overall respiratory impairment, but are not a part of the diagnostic criteria.

The radiographic appearance of CWP is indistinguishable from that of silicosis, and miners may develop disease from exposure to both dusts. As is the case for silicosis, the ILO classification scheme (described earlier in this chapter) is used in epidemiologic studies of CWP.[75,76]

Typically, CWP is described as either simple pneumoconiosis or PMF. The radiograph in simple pneumoconiosis shows small opacities, ranging in size from a pinhead to 1 cm in diameter. Rounded nodules predominate and tend to appear first in the upper zones and then the rest of the lung as the number of opacities increase. With prolonged and excessive exposure, these small opacities may coalesce and form larger opacities. They are recognized as PMF lesions and characterized by one or more large opacities greater than 1 cm in diameter. As the disease progresses, the upper-zone nodules begin to coalesce and distort the lung architecture, a feature which gradually becomes more prominent. This typically presents as deviation of the trachea and major airways to the side of the most prominent area of coalescence, loss of upper-zone lung volume, elevation of the hila, and basilar emphysema (typically of a panacinar type), attributable to traction placed on the lower lung zones by the elevation of the hila.

There are no symptoms or physical signs associated with simple CWP. The not-infrequent presence of a chronic cough and sputum production, even in the presence of CWP, is attributable to "industrial bronchitis."[190] Alternatively, these same clinical features in a smoking miner may be partially attributable to bronchitis caused by the inflammatory stimulus of cigarette smoke. Finger clubbing is not a feature of CWP, and if noted, should prompt further investigations.

When PMF is recognized on the chest radiograph, the worker frequently describes dyspnea, cough, and sputum production, although it is well recognized that the degree of impairment or the presence or absence of symptoms does not always correlate well with the extent of chest radiographic abnormalities.

The consultant may be requested to differentiate a primary or metastatic neoplasm from an unusual presentation of PMF. When large opacities of PMF occur bilaterally on a background of simple CWP, one can be reasonably confident that the lesions are less likely to represent neoplastic disease. When there is a sparse background of simple CWP or none, or there are crops of nodules (as in Caplan's syndrome), differentiation from neoplasm may be difficult.

The effect of pneumoconiosis on the heart has been described by several investigators. Lapp et al.,[221] performed cardiac catheterization during rest and exercise in 43 miners with CWP (23 with airways obstruction and 24 without). In 7 out of 12 miners, either chronic obstructive lung disease or PMF appeared to explain the increase in pulmonary artery pressures. The other five with increased pressures had the smaller type of pinpoint (p) opacity on their radiograph. It may be pertinent that the pinpoint type of opacity is associated with diminished diffusion and a diminution of the vascular bed.[222] A later autopsy study of 215 British coal miners (100 with simple CWP or no pneumoconiosis, and 115 with PMF) was designed to address the relationship between coal dust exposure and right ventricular hypertrophy (RVH). In this population, the prevalence of RVH was the same in those with simple CWP as in those without pneumoconiosis (approximately 15%) and was related to the extent of airways obstruction. Overall, RV enlargement did not occur unless the coal miner was a smoker with severe airflow obstruction or had developed PMF.[223]

Coal worker's pneumoconiosis alone does not appear to significantly increase the risk for development of coexisting mycobacterial infection. However, miners often have exposure to silica in drilling, a job typically associated with exposure to silica dust rather than to coal dust. Miners with silica exposure in the workplace may also be at risk for mycobacterial infection. The appearance of a cavity in a PMF lesion or an aggressive and unexplained rate of radiographic progression should prompt examination of the sputum for mycobacteria.

As already noted, CWP is associated with a variety of immunologic abnormalities. An increased prevalence of ANA and RF is present in populations with CWP. Caplan's syndrome can be present, often in association with RA or subcutaneous nodules. Lesions on chest x-ray are multiple, peripherally located, and between 0.5 and 5.0 cm in diameter. They usually appear on a background profusion of small opacities of 0 or 1, as opposed to PMF in which the background profusion is more advanced. The lesions appear within a short time, often weeks. The lesions can cavitate, develop fluid levels, calcify or even disappear, to be followed later by a fresh crop of lesions. Caplan's syndrome can predate RA by up to 10 years. Scleroderma may also be a risk of coal mining. In a group of 60 consecutive cases of scleroderma, Rodnan et al.,[97] described 26 with a history of employment as a coal miner or employment in an occupation where there was silica exposure. Although the course of scleroderma did not vary in the two groups, it appears that chronic fibrogenic dust exposure may be a risk factor for the development of scleroderma.

Management of Coal Worker's Pneumoconiosis

There is no proven therapy for CWP. The primary prevention of lung disease in miners must include continuing efforts at reducing coal dust exposure. Management is best directed at prevention, early recognition, and treatment of complications. The major challenges to the physician are the recognition and management of airflow obstruction, respiratory infection, hypoxemia, respiratory failure, cor pulmonale, arrhythmias, and pneumothorax.

Improved mining methods and lower dust levels appear to be reducing exposures and new cases of both simple and complicated pneumoconiosis in the US Medical surveillance programs, using chest radiographs, allow the early recognition of workers with simple pneumoconiosis. Workers with simple pneumoconiosis should be encouraged to transfer from jobs with high dust exposure to jobs with low dust exposure, or to leave the dusty workplace altogether. Any worker with the unexpected finding of PMF should be carefully advised about the hazards of further dust exposures.

Workers presenting with respiratory symptoms should undergo careful evaluation. The initial history and examination should be supplemented by chest radiograph, spirometry with bronchodilators, diffusing capacity, electrocardiogram, and resting arterial blood gas measurement as indicated. A thorough initial data base allows accurate assessment of the worker's respiratory health and serves a starting point for observing the response to therapy or progression of disease.

Smoking cessation is important, regardless of symptoms of respiratory disease, chest radiograph abnormalities, or pulmonary function status. Physicians should not only encourage the patient to stop smoking but should provide psychological support, use of nicotine substitutes, and behavior modification techniques as well.

Coexisting symptomatic reversible airflow obstruction should be treated with inhaled bronchodilator therapy as indicated. Patients with severe obstruction who show inadequate improvement from the usual measures should be considered for a trial of glucocorticoids.

Hypoxemia can be a serious complication in those with PMF. As in other interstitial lung diseases, it first presents typically during exercise, but with advancing illness, it can occur at rest and during sleep. Chronic hypoxemia can lead to the complications of polycythemia, pulmonary hypertension, cor pulmonale, and cerebral dysfunction. Therapy with low flow oxygen is indicated when the arterial oxygen tension is less than 55 mmHg or when clinical evidence of cor pulmonale is present.

Workers with significant airflow obstruction or PMF should receive appropriate immunization with influenza and pneumococcal vaccines. Bacterial and viral episodes of bronchitis or pneumonia should be promptly recognized and appropriately treated. Similarly, miners with concomitant exposure to silica dust (most often roof bolters, drillers, and motormen) require special attention with regard to mycobacterial infection, as already noted for silicosis. Symptoms of weight loss, fever, sweats, a change in sputum production, or malaise

should be promptly investigated with a chest radiograph and examination of respiratory secretions through stain and culture for AFB. Active tuberculosis in this population can be usually successfully treated with the usual drug regimens, provided rifampin is one of the drugs used.[224,225] In coal miners with a significant history of concurrent silica exposure, the treatment for tuberculosis may need to be more aggressive, and long-term follow-up is essential in view of reports of recurrent pulmonary tuberculosis in patients with PMF after completion of apparently adequate therapy.[85]

Pneumothoraces can be particularly troublesome events in miners with pneumoconiosis. Those with bullous disease in the presence of advanced complicated pneumoconiosis appear to be at the greatest risk. Typically, once the lung collapses, it is difficult to expand it, a feature attributable to the decreased compliance associated with interstitial lung disease. Despite this problem, therapy with one or several chest tubes is often therapeutic. Recurrent pneumothoraces, or a pneumothorax which cannot be expanded, may require an open procedure and pleurodesis.

Respiratory failure may complicate advanced PMF, as it does in other chronic respiratory diseases. Ventilatory support measures are indicated when the failure is precipitated by a treatable complication. The application of ventilatory support measures should be discussed with the patient before the need arises. In general, miners with advanced pneumoconiosis are poor candidates for long-term mechanical ventilation.

Prevention strategies to decrease incidence of CWP in miners include education, exposure control, medical surveillance, and research. A series of primary and secondary preventive measures should include the following:

1. Education about the respiratory health hazards from uncontrolled exposures to coal mine dust must be widely available to workers, employers, production managers, government representatives, and health care providers. This information provides the basis of implementing any programs addressing worker health. This is primary prevention.
2. Major efforts must be directed to improving work methods or work practices, including engineering controls, to progressively reduce dust exposures to acceptable levels.
3. Environmental dust surveillance programs should be implemented. Data generated from these programs allow for the critical feedback needed to justify improvement of the ambient air quality and modify work methods if exposures exceed acceptable levels. This is also primary prevention.
4. Medical screening and surveillance programs should be designed to benefit the individual worker and future workers, and include feedback to environmental surveillance and work practice evaluations. The recognition of disease provides a strong impetus for changes in environmental surveillance. More important than the identification of a single case is the collection of information which addresses the cumulative burden of disease, or prevalence, in a population. This allows the educators to monitor trends over time and the effectiveness of primary preventive measures. Since case identification represents failures in primary prevention, this is secondary prevention.
5. Research should be encouraged to improve therapy, to improve diagnostic capabilities, and to better understand the pathogenesis of CWP. Critical to the issue of research is the relationship between dust exposures and the development and progression of disease. These research efforts should not displace efforts at achieving effective dust control.

REFERENCES

1. Corn J. Historical aspects of industrial hygiene-silicosis. Am Ind Hyg Assoc J 1980;41:125-132.
2. Holt P. Silicosis. In: Holt P, ed. Inhaled dust and disease. New York: John Wiley and Sons, 1987:46-85.
3. Lapp N. Lung disease secondary to inhalation of nonfibrous minerals. Clin Chest Med 1981;2:219-233.
4. Morgan WKC. Silicates and lung disease. In: Morgan WKC, Seaton A, eds. Occupational lung diseases. 3rd Ed. Philadelphia: WB Saunders, 1995:268-307.
5. American Thoracic Society. Adverse effects of crystalline silica exposure. Am J Respir Crit Care Med 1997;155:761-765.
6. Banks D, Bauer M, Castellan R, Lapp N. Silicosis in surface coalmine drillers. Thorax 1983;38:275-278.
7. Seaton A. Silicosis. In: Morgan WKC, Seaton A, eds. Occupational lung diseases. 3rd Ed. Philadelphia: WB Saunders, 1995:222-267.
8. NIOSH. Request for assistance in preventing silicosis and deaths from sandblasting. Publication No. 92-102. 1992.
9. Bailey W, Brown M, Buechner H, et al. Silicomycobacterial disease in sandblasters. Am Rev Respir Dis 1974;110:115-125.
10. Glindmeyer HW, Hammad YY. Contributing factors to sandblasters' silicosis: inadequate respiratory protection equipment and standards. J Occup Med 1988;30:917-921.
11. Wagner GR. Editorial: the inexcusable persistence of silicosis. Am J Public Health 1995;85:1346-1347.
12. Banks D, Morring K, Boehlecke B, et al. Silicosis in silica flour workers. Am Rev Respir Dis 1981;124:445-450.
13. Norboo T, Angchuk PT, Yahya M, et al. Silicosis in a Himalayan village population: role of environmental dust. Thorax 1991;46:341-343.
14. Silicosis and Silicate Disease Committee. Diseases associated with exposure to silica and nonfibrous silicate minerals. Arch Pathol Lab Med 1988;112:673-720.
15. Allison A, Harrington J, Birbeck M. An examination of the cytotoxic effects of silica on macrophages. J Exp Med 1966;124:141-154.
16. Bowden D, Adamson L. The role of cell injury and the continuing inflammatory response in the generation of silicotic pulmonary fibrosis. J Pathol 1981;144:149-161.
17. Iyer R, Hamilton RF, Li L, Holian A. Silica-induced apoptosis mediated via scavenger receptor in human alveolar macrophages. Toxicol Appl Pharmacol 1996;141:84-92.
18. Vanhee D, Gosset P, Boitelle A, et al. Cytokines and cytokine network in silicosis and coal workers' pneumoconiosis. Eur Respir J 1995;8:834-842.
19. Vallyathan V, Xianglin S, Dalal N, et al. Generation of free radicals from freshly fractured silica dust. Am Rev Respir Dis 1988;138:1213-1219.

20. Ghio AJ, Kennedy TP, Schapira RM, et al. Hypothesis: is lung disease after silicate inhalation caused by oxidant genetation? Lancet 1990;336:967-969.
21. Chen J, Armstrong LC, Liu S, et al. Silica increases cytosolic free calcium ion concentration of alveolar macrophages in vitro. Toxicol Appl Pharmacol 1991;111:211-220.
22. Rojanasakul Y, Wang L, Malanga CJ, et al. Altered calcium homeostasis and cell injury in silica-exposed alveolar macrophages. J Cell Physiol 1993;154:310-316.
23. Schmidt J, Oliver C, Lepe-Zuniga J, Gery I. Silica-stimulated monocytes release fibroblast proliferation factors identical to interleukin 1. A potential role for interleukin 1 in the pathogenesis of silicosis. J Clin Invest 1984;73:1462-1472.
24. Oghiso Y, Kubota Y. Enhanced interleukin 1 production by alveolar macrophages in Ia-positive lung cells in silica-exposed rats. Microbiol Immunol 1986;30:1189-1198.
25. Piquet P, Collart MA, Grau J, et al. Requirement of tumour necrosis factor for development of silica-induced pulmonary fibrosis. Nature 1990;344:245-247.
26. Mohr C, Gemsa D, Graebner C, et al. Systemic macrophage stimulation in rats with silicosis: enhanced release of tumor necrosis factor-alpha from alveolar and peritoneal macrophages. Am J Respir Cell Mol Biol 1991;5:395-402.
27. Williams AO, Flanders KC, Saffiotti U. Immunohistochemical localization of transforming growth factor-beta 1 in rats with experimental silicosis, alveolar type II hyperplasia, and lung cancer. Am J Pathol 1993;142:1831-1840.
28. Rom WN, Bitterman PB, Rennard SI, et al. Characterization of the lower respiratory tract inflammation of nonsmoking individuals with interstitial lung disease associated with chronic inhalation of inorganic dust. Am Rev Respir Dis 1987;136:1429-1434.
29. Lukacs NW, Kunkel SL, Allen R, et al. Stimulus and cell-specific expression of C-X-C and C-C chemokines by pulmonary stromal cell populations. Am J Physiol 1995;268:L856-L861.
30. Driscoll KE, Howard BW, Carter JM, et al. Alpha-quartz induced chemokine expression by rat lung epithelial cells: effects of in vivo and in vitro particle exposure. Am J Pathol 1996; 149:1627-1637.
31. Piquet P, Vesin C. Treatment by human recombinant soluble TNF receptor of pulmonary fibrosis induced by bleomycin or silica in mice. Eur Respir J 1994;7:515-518.
32. Davis G, Hill-Eubanks L, Pfeiffer L, et al. Reduced silicosis in C3H/HeJ-LPS^d mice: an implied role for cytokine production deficiency. Am Rev Respir Dis 1992;145:A325.
33. Jagirdar J, Begin R, Dufresne A, et al. Transforming growth factor-β in silicosis. Am J Respir Crit Care Med 1996;154:1076-1081.
34. Heppleston A, Fletcher K, Wyatt I. Changes in the composition of lung lipids and the turnover of dipalmitoyl lecithin in experimental alveolar lipoproteinosis induced by inhaled quartz. Br J Exp Pathol 1974;55:384-395.
35. Gabor S, Zugravu E, Kovats A, et al. Effects of quartz on lung surfactant. Environ Res 1978;16:443-448.
36. Dethloff L, Gilmore L, Brody A, Hook G. Induction of intra- and extracellular phospholipids in the lungs of rats exposed to silica. Biochem J 1986;233:111-118.
37. Kawada H, Horiuchi T, Shannon J, et al. Alveolar type II cells, surfactant protein A (SP-A), and the phospholipid components of surfactant in acute silicosis in the rat. Am Rev Respir Dis 1989;140:460-470.
38. Miller B, Dethloff L, Hook G. Silica-induced hypertrophy of type II cells in the lungs of rats. Lab Invest 1986;55:153-163.
39. Miller B, Dethloff L, Gladen B, Hook G. Progression of type II cell hypertrophy and hyperplasia during silica-induced pulmonary inflammation. Lab Invest 1987;57:546-554.
40. Miller B, Bakewell W, Katyal S, et al. Induction of surfactant protein A (SP-A) biosynthesis and SP-A mRNA in activated type II cells during acute silicosis in rats. Am J Respir Cell Mol Biol 1990;3:217-226.
41. Hughes JM. Radiographic evidence of silicosis in relation to silica exposures. Appl Occup Environ Hyg 1995;10:1064-1069.
42. Honda K, Kimura A, Dong R-P, et al. Immunogenetic analysis of silicosis in Japan. Am J Respir Cell Mol Biol 1993;8:106-111.
43. Rihs HP, Lipps P, May-Taube K, et al. Immunogenetic studies on HLA-DR in German coal miners with and without coal workers' pneumoconiosis. Lung 1994;172:347-354.
44. Eden K, Seebach HV. Atypical dust-induced pneumoconiosis in SPF rats. Virchows Arch 1976;372:1-9.
45. Kreiss K, Greenberg L, Kogut S, et al. Hard-rock mining exposures affect smokers and nonsmokers differently. Am Rev Respir Dis 1989;139:1487-1493.
46. Buechner H, Ansari A. Acute silicosis. Dis Chest 1969;55:274-284.
47. Hoffman EO, Lamberty J, Pizzolato P, Coover J. The ultrastructure of acute silicosis. Arch Pathol 1973;96:104-107.
48. Steenland K, Brown D. Silicosis among gold miners: exposure-response analyses and risk assessment. Am J Public Health 1995;85:1372-1377.
49. Trasko V. Some facts on the prevalence of silicosis in the United States. Arch Ind Health 1956;14:379-387.
50. Green F, Althouse R, Weber K. Prevalence of silicosis at death in underground coal miners. Am J Ind Med 1989;16:605-615.
51. Banks D, Morring K. Silicosis in the 1980's. Am Ind Hyg Assoc J 1981;42:77-89.
52. NIOSH. Work-related lung diseases surveillance report. DHHS(NIOSH) publication 91-113. 1991.
53. Banks D, Balaan M, Wang M. Silicosis in the 1990s, revisited. Chest 1997;111:837-838.
54. Rosenman K, Reilly M, Kalinowsky D. Silicosis in the 1990s. Chest 1997;111:779-786.
55. Russell AE, Britten RH, Thomson RL, Bloomfield JJ. The health of workers in dusty trades. II. Exposure to siliceous dust. Washington, D.C.: Public Health Bulletin 187, 1929.
56. Russell AE. The health of workers in dusty trades. VII. Restudy of a group of granite workers. Washington, D.C.: Public Health Bulletin 269, 1941.
57. Hosey AD, Trasko VM, Ashe HB. Control of silicosis in the Vermont granite industry: progress report. Washington, D.C.: Publication 557, 1957.
58. Ashe HB, Bergstrom DE. Twenty-six years experience with dust control in the Vermont granite industry. Ind Med Surg 1964;33:73-78.
59. Graham WGB, Ashikaga T, Hemenway D, et al. Radiographic abnormalities in Vermont granite workers exposed to low levels of granite dust. Chest 1991;100:1507-1514.
60. Kreiss K, Zhen B. Risk of silicosis in a Colorado mining community. Am J Ind Med 1996;30:529-539.
61. McDonald C. Silica, silicosis, and lung cancer: an epidemiological update. Appl Occup Environ Hyg 1995;10:1056-1063.
62. Caplan A. Certain unusual radiographic appearances in the chest of coalminers suffering from rheumatoid arthritis. Thorax 1953;8:29-30.
63. Ziskind M, Jones RM, Weill H. Silicosis. Am Rev Respir Dis 1976;113:643-665.
64. Nugent K, Dodson R, Idell S, Devillier J. The utility of bronchoalveolar lavage and transbronchial lung biopsy combined with energy-dispersive x-ray analysis in the diagnosis of silicosis. Am Rev Respir Dis 1989;140:1438-1441.
65. Dee P, Suratt P, Winn W. The radiographic findings in acute silicosis. Radiology 1978;126:359-363.
66. Sampson HL. The roentgenogram in so-called "acute" silicosis. Am J Public Health 1933;23:1237-1239.
67. Chapman E. Acute silicosis. JAMA 1932;98:1439-1441.
68. Anderson WH, Hamilton GL, Dorsett BE Jr. A comparison of coal miners exposed to coal dust and those exposed to silica dust. Arch Environ Health 1960;1:540-547.
69. Teculescu D, Stanescu D, Pilat L. Pulmonary mechanics in silicosis. Arch Environ Health 1967;14:461-468.
70. Jones R, Weill H, Ziskind M. Pulmonary function in sandblasters' silicosis. Bull Physiopathol Respir 1975;11:589-595.

71. Kinsella M, Muller N, Vedal S, Staples C. Emphysema in silicosis. A comparison of smokers with nonsmokers using pulmonary function and computed tomography. Am Rev Respir Dis 1990;141:1497-1500.
72. Hodous TK, Attfield MD. Progressive massive fibrosis developing on a background of minimal simple pneumoconiosis. VIIth International Pneumoconiosis Conference. Pittsburgh, PA: DHHS (NIOSH), 1988;122-126.
73. Suratt P, Winn W, Brody A, et al. Acute silicosis in tombstone sandblasters. Am Rev Respir Dis 1977;115:521-529.
74. Gardner LU. Pathology of so-called silicosis. Am J Public Health 1933;23:1240-1249.
75. Morgan WKC. Epidemiology and occupational lung disease. In: Morgan WKC, Seaton A, eds. Occupational lung diseases. 3rd Ed. Philadelphia: WB Saunders, 1995.
76. Guidelines for the Use of ILO International Classification of Radiographs of Pneumoconioses. Revised Edition. Geneva: International Labour Office, 1980.
77. Gross B, Schneider H, Proto A. Eggshell calcification of lymph nodes: an update. AJR 1980;135:1265-1268.
78. Begin R, Bergeron D, Samson L, et al. CT assessment of silicosis in exposed workers. AJR 1987;148:509-514.
79. Bergin C, Muller N, Vedal S, Chan-Yeung M. CT in silicosis: correlation of plain films and pulmonary function tests. AJR 1986;146:477-483.
80. Sherson D, Lander F. Morbidity of pulmonary tuberculosis among silicotic and nonsilicotic foundry workers in Denmark. J Occup Med 1990;32:110-113.
81. Cowie R. The epidemiology of tuberculosis in gold miners with silicosis. Am J Respir Crit Care Med 1994;150:1460-1462.
82. Sherson D, Svane O, Lynge E. Cancer incidence among foundry workers in Denmark. Arch Environ Health 1991;46:75-81.
83. American Thoracic Society. Treatment of tuberculosis and tuberculous infection in adults and children. Am J Respir Crit Care Med 1994;149:1359-1374.
84. Cowie R. Short course chemoprophylaxis with rifampicin, isoniazid and pyrazinamide for tuberculosis evaluated in gold miners with chronic silicosis: a double-blind placebo controlled trial. Tuberc Lung Dis 1996;77:239-243.
85. Morgan E. Silicosis and tuberculosis. Chest 1979;75:202-203.
86. Lin T-P, Suo J, Lee C-N, Yang S. Short course chemotherapy for pulmonary tuberculosis in pneumoconiotic patients. Am Rev Respir Dis 1987;136:808-810.
87. Cowie R. Silicotuberculosis: long term outcome after short-course chemotherapy. Tuberc Lung Dis 1995;76:39-42.
88. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A controlled clinical comparison of 6 and 8 months of antituberculosis chemotherapy in the treatment of patients with silicotuberculosis in Hong Kong. Am Rev Respir Dis 1991;143:262-267.
89. Davis GS. Pathogenesis of silicosis: current concepts and hypotheses. Lung 1986;164:139-154.
90. Doll N, Stankus R, Hughes J. Immune complexes and autoantibodies in silicosis. J Allergy Clin Immunol 1981;68:281-285.
91. Idel H, Seemayer NH, Prugger F. Autoimmunity phenomena and alterations of humoral immunological responses in silicotic patients. VIIth International Pneumoconiosis Conference. Pittsburgh, PA: DHHS (NIOSH), 1988:1455-1458.
92. Karnik AB, Saiyed HN, Nigam SK. Humoral immunologic dysfunction in silicosis. Indian J Med Res 1990;B92:440-442.
93. Nigam SK, Saiyed HN, Malaviya R, et al. Role of circulating immune complexes in the immunopathogenesis of silicosis. Toxicol Lett 1990;51:315-320.
94. Nagaoka T, Tabata M, Kobayashi K, Okada A. Studies on production of anticollagen antibodies in silicosis. Environ Res 1993;60:12-29.
95. Bramwell B. Diffuse scleroderma: its frequency; its occurrence in stone-masons; its treatment by fibrinolysin: elevations of temperature due to fibrinolysin injections. Edinb Med J 1914;12:387-401.
96. Erasmus LD. Scleroderma in gold-miners on the Witwatersrand with particular reference to pulmonary manifestations. S Afr J Lab Clin Med 1957;3:209-231.
97. Rodnan G, Benedek R, Medsger T, Cammarata R. The association between progressive systemic sclerosis (scleroderma) with coal miners' pneumoconiosis and other forms of silicosis. Ann Intern Med 1967;66:323-334.
98. Cowie RL. Silica-dust-exposed mine workers with scleroderma (systemic sclerosis). Chest 1987;92:260-262.
99. Sluis-Cremer GK, Hessel PA, Hnizdo EH, et al. Silica, silicosis and progressive systemic sclerosis. Br J Ind Med 1985;42:838-843.
100. Pelmear PL, Roos JO, Maehle WM. Occupationally-induced scleroderma. J Occup Med 1992;34:20-25.
101. Klockars M, Koskela RS, Jarvinen E, et al. Silica exposure and rheumatoid arthritis: a follow up study of granite workers 1940-81. BMJ 1987;294:997-1000.
102. Sluis-Cremer G, Hessel P, Hnizdo E, Churchill A. The relationship between silicosis and rheumatoid arthritis. Thorax 1986;41:596-600.
103. Jones R, Turner-Warwick M, Ziskind M, Weill H. High prevalence of antinuclear antibodies in sandblasters' silicosis. Am Rev Respir Dis 1976;113:393-395.
104. Sanchez-Roman J, Wichmann I, Salaberri J, et al. Multiple clinical and biological autoimmune manifestations in 50 workers after occupational exposure to silica. Ann Rheumatol Dis 1993;52:534-538.
105. IARC. Silica and some silicates. IARC Monogr Eval Carcinog Risks Hum 1987;42:39-143.
106. Wagner M, Wagner J. Lymphomas in the Wistar rat after intrapleural inoculation of silica. J Natl Cancer Inst 1972;49:89-91.
107. Wagner M, Wagner J, Davies R, et al. Silica-induced malignant histiocytic lymphoma: incidence linked with strain of rat and type of silica. Br J Cancer 1980;41:908-917.
108. Muhle H, Takenaka S, Mohr U, et al. Lung tumor induction upon long-term low-level inhalation of crystalline silica. Am J Ind Med 1989;15:343-346.
109. McDonald JC. Silica, silicosis, and lung cancer. Br J Ind Med 1989;46:289-291.
110. Forastiere F, Lagorio S, Michelozzi P, et al. Silica, silicosis and lung cancer among ceramic workers: a case-referent study. Am J Ind Med 1986;10:363-370.
111. Mehnert WH, Staneczek W, Mohner M, et al. A mortality study of a cohort of slate quarry workers in the German Democratic Republic. IARC Sci Publ 1990;97:55-64.
112. McLaughlin J, Jing-Qiong C, Dosameci M, et al. A nested case-control study of lung cancer among silica exposed workers in China. Am J Ind Med 1992;49:167-171.
113. Mastrangelo G, Zambon P, Simonato L, Rizzi P. A case-referent study investigating the relationship between exposure to silica dust and lung cancer. Int Arch Occup Environ Health 1988;60:299-302.
114. Amandus H, Costello J. Silicosis and lung cancer in U.S. metal miners. Arch Environ Health 1991;46:82-89.
115. Amandus HE, Castellan RM, Shy C, et al. Reevaluation of silicosis and lung cancer in North Carolina dusty trades workers. Am J Ind Med 1992;22:147-153.
116. Weill H, McDonald J. Exposure to crystalline silica and risk of lung cancer: the epidemiological evidence. Thorax 1996;51:97-102.
117. Oxman AD, Muir DCF, Shannon HS, et al. Occupational dust exposure and chronic pulmonary disease: a systematic overview of the evidence. Am Rev Respir Dis 1993;148:38-48.
118. Churg A. Small airways disease associated with mineral dust exposure. Semin Respir Med 1992;13:140-148.
119. Cowie RL, Hay M, Thomas RG. Association of silicosis, lung dysfunction, and emphysema in gold miners. Thorax 1993;48:429-435.
120. Wang ML, Banks DE. Airways obstruction and occupational inorganic dust exposure. In: Banks DE, Parker JE, eds. Occu-

pational lung disease: an international perspective. London: Chapman and Hall, 1998. (in press).
121. Collis EL, Yule GU. The mortality experience of an occupational group exposed to silica dust, compared with that of the general population and an occupational group exposed to dust not containing silica. J Ind Hyg 1933;15:395-417.
122. Steenland NK, Thun MJ, Ferguson CW, Port FK. Occupational and other exposures associated with male end-stage renal disease: a case/control study. Am J Public Health 1990;80: 153-159.
123. Giles RD, Sturgill BC, Suratt PM, Bolton WK. Massive proteinuria and acute renal failure in a patient with acute silicoproteinosis. Am J Med 1978;64:336-342.
124. Banks D, Multinovic J, Desnick R, et al. Silicon nephropathy mimicking Fabry's disease. Am J Nephrol 1983;3:279-284.
125. Sharma S, Pande J, Verma K. Effect of prednisolone treatment in chronic silicosis. Am Rev Respir Dis 1991;143:814-821.
126. Lapp N, Goodman G, Castranova V, et al. Acute silicosis responding to corticosteroid therapy. Chest 1990;98:67S.
127. Mason G, Abraham J, Hoffman L, et al. Treatment of mixed-dust pneumoconiosis with whole lung lavage. Am Rev Respir Dis 1982;126:1102-1107.
128. Liang Y, Sun U, Chen C, et al. Clinical evaluation of massive whole lung lavage for treatment of coal workers' pneumoconiosis. He Bei Liano Yang (J Hebei Convalescence) 1992;1: 1-9.
129. Wilt J, Banks D, Weissman D, et al. Reduction of lung dust burden in penumoconiosis by whole lung lavage. J Occup Environ Med 1996;38:619-624.
130. Kennedy M. Aluminum poweder inhalation in the treatment of silicosis. Br J Ind Med 1956;13:85-101.
131. Jinduo Z, Jingde L, Guizhi L. Long-term follow-up observations of the therapeutic effects of PVNO. Zbl Bkt Hyg Abt Orig 1983;B178:259-262.
132. Dubois F, Begin R, Cantin A, et al. Aluminum inhalation reduces silicosis in a sheep model. Am Rev Respir Dis 1988;137: 1172-1179.
133. Begin R, Masse S, Dufresne A. Further information on aluminum inhalation in silicosis. Occup Environ Med 1995;52:788-780.
134. Yu X, Zou C, Lin M. Observation of the effect of tetrandrine on experimental silicosis in rats. Exotoxicol Environ Safety 1983;7:306-312.
135. Li Q, Xu Y, Zhon Z, et al. The therapeutic effect of tetrandrine on silicosis. Chin J Tuberc Respir Dis 1981;4:321-324.
136. Seow W, Ferrante A, Li S-Y, Thong Y. Antiphagocytic and antioxidant properties of plant alkaloid tetrandrine. Int Arch Allergy Appl Immunol 1988;85:404-409.
137. Seow W, Li S-Y, Thong Y. Inhibitory effects of tetrandrine on human neutrophil and monocyte adherence. Immunol Lett 1986;13:83-88.
138. Castranova V, Kang J, Ma J, et al. Effects of bisbenzylisoquinoline alkaloids on alveolar macrophages: correlation between binding affinity, inhibitory potency, and antifibrotic potential. Toxicol Appl Pharmacol 1991;108:242-252.
139. Vermeire P, Tasson JF, Lamont EA. Respiratory function after lung homotransplantation with a 10 month survival in man. Am Rev Respir Dis 1972;106:515-527.
140. 29 CFR (United States Code of Federal Regulations) 1910.1000. Washington, D.C., 1994.
141. NIOSH. Criteria for a recommended standard: occupational exposure to crystalline silica. HEW Publication Np (NIOSH), 1974:75-120.
142. NIOSH. Request for assistance in preventing silicosis and deaths in rock drillers. Publication No. 92-107. 1992.
143. NIOSH. Request for assistance in preventing silicosis and deaths in construction workers. Publication No. 96-112. 1996.
144. Stahl R. Coal and derivatives. Encyclopedia of occupational health and safety. Geneva: International Labour Organisation, 1989.
145. Thomas L. Handbook of practical geology. New York, NY: John Wiley & Sons, 1992.
146. Hilt C. Die Beiziehungen zwischen der Zusammensetzung und der technischen Eigenschaften der Steinkohle. Bezirksvereinigung Ver. Deutsch. Ing Z 1873;17(4):157-169.
147. Haught OL. Coal and coal mining in West Virginia. Morgantown, WV: West Virginia Geological and Economic Survey, 1955.
148. NIOSH. Criteria for a recommended standard: occupational exposure to respirable coal mine dust. Cincinnati, OH: DHHS (NIOSH) publication No. 95-106, 1995.
149. Coates DR. Energy and fossil fuels. Environmental geology. New York, NY: John Wiley and Sons, 1981.
150. Coleman LL. Coal data. Washington, D.C.: The National Coal Association, 1992.
151. Taylor LD, Thakur PC. Recent developments in coal mining technology and their impact on miners' health. Occupational medicine: state of the art reviews. Philadelphia: Hanley & Belfus, 1993;109-126.
152. Stout KS. Mining methods and equipment. New York, NY: McGraw-Hill, 1980.
153. Euler WJ. Surface mining of coal. In: Meyers RA, ed. Coal handbook. New York: Marcel Dekker, 1981;75-114.
154. Meiklejohn A. History of lung disease of coalminers in Great Britain, Part I, 1800-1875. Br J Ind Med 1951;8:127-137.
155. Meiklejohn A. History of lung diseases of coal miners in Great Britain, Part II, 1875-1920. Br J Ind Med 1952;9:93-98.
156. Meiklejohn A. History of lung diseases of coal miners in Great Britain, Part III, 1920-1952. Br J Ind Med 1952;9:208-220.
157. Gregory JC. Case of peculiar black infiltration of the lungs resembling melanosis. Edinb Med Surg J 1831;36:389-392.
158. Marshall W. Cases of spurious melanosis of the lungs or phthisis melanotica. Lancet 1833-1834;ii:271-274.
159. Ogle W. Supplement of the 45th annual report of the Registrar General for England and Wales. : Her Majesty's Stationary Office, 1885.
160. Collis EL. Industrial pneumoconiosis (Milroy Lectures, 1915). London: His Majesty's Stationary Office, 1919.
161. Collis EL, Gilchrist JC. Effects of dust upon coal trimmers. J Ind Hyg Toxicol 1928;10:101-109.
162. Gough J. Pneumoconiosis of coal trimmers. J Pathol Bacteriol 1940;51:277-285.
163. Hepplestone AG. The essential lesson of pneumoconiosis in Welch coal workers. J Pathol Bacteriol 1947;59:453-460.
164. King EJ, Maguire BA, Nagelschmidt G. Further studies of the dust in the lungs of coal-miners. Br J Ind Med 1956;13:9-13.
165. Amandus HE, Petersen MR, Richards TB. Health status of anthracite surface coal miners. Arch Environ Health 1989;44:75-81.
166. Lainhart WS, Doyle HM, Enterline PE, et al. Pneumoconiosis in Appalachian bituminous coal miners. Washington, D.C.: U.S. Government Printing Office, 1969.
167. McBride WW, Pendergrass E, Lieben J. Pneumoconiosis study of Pennsylvania anthracite miners. J Occup Med 1963;5: 376-388.
168. McBride WW, Pendergrass E, Lieben J. Pneumoconiosis study of Pennsylvania anthracite miners. J Occup Med 1966;8:365-367.
169. USA. Coal Mine Health and Safety Act. U.S. Public Law No. 91-173, Statute 2917. 1969.
170. Attfield MD, Castellan RM. Epidemiological data on US coal miners' pneumoconiosis, 1960-1968. Am J Public Health 1992;82:964-970.
171. Attfield MD, Althouse RB. Surveillance data on US coal miners' pneumoconiosis, 1970-1986. Am J Public Health 1992;82: 971-977.
172. Attfield MD. British data on coal miners' pneumoconiosis and relevance to US conditions. Am J Public Health 1992;82:978-983.
173. McLintock J, Rae S, Jacobsen M. The attack rate of progressive massive fibrosis in British coal miners. In: Walton WH, ed. Inhaled particles III. Woking: Unwin Brothers, 1971:933-950.
174. Davies I, Mann KJ. 9th International Congress on Industrial Medicine. Bristol, 1949:768.
175. Enterline PE. A review of mortality data for American coal miners. Ann N Y Acad Sci 1972;200:260-272.

176. Enterline PE. Mortality rates among coal miners. Am J Public Health 1964;54:758-768.
177. 1967 Occupational study. Chicago, IL: Society of Actuaries, 1967.
178. Editorial. Coal mining and mortality. BMJ 1979;2:1168-1169.
179. Cochrane AL, Haley TJL, Moore F, Hole D. The mortality of men in the Rhondda Foch, 1950-1970. Br J Ind Med 1978;36:15-22.
180. Atuhaire LK, Campbell MJ, Cochrane AL, et al. Mortality of men in the Rhondda Fach 1950-1980. Br J Ind Med 1985;42:741-745.
181. Ortmeyer CE, Baier EJ, Crawford GMJ. Life expectancy of Pennsylvania coal miners compensated for disability. Arch Environ Health 1973;27:227-230.
182. Stocks P. On the death rates from cancer of the stomach and respiratory diseases in 1949-1953 among coal miners and other male residents in counties of England and Wales. Br J Cancer 1962;16:592-598.
183. Matolo NM, Klauber MR, Gorishek WM, Dixon JA. High incidence of gastric carcinoma in a coal mining region. Cancer 1972;29:733-737.
184. Rockette HE. Cause specific mortality of coal miners. J Occup Med 1977;19:795-801.
185. Ortmeyer CE, Costello J, Morgan WKC, et al. The mortality of Appalachian coal miners. Arch Environ Health 1974;29:67-72.
186. Meijers JMM, Swaen GMH, Slangen JJM, et al. Long-term mortality in miners with coal workers' pneumoconiosis in the Netherlands: a pilot study. Am J Ind Med 1991;19:43-50.
187. Jacobsen M, Rae S, Walton WH, Rogan JM. The relation between pneumoconiosis and dust-exposure in British coal mines. In: Walton WH, ed. Inhaled particles III. Woking: Unwin Brothers, 1971;903-917.
188. Kuempel ED, Stayner LT, Attfield MD, Buncher CR. Exposure-response analysis of mortality among coal miners in the United States. Am J Ind Med 1995;28:167-184.
189. Vallyathan V, Green FHY, Rodman NF, et al. Lung carcinoma by histologic type in coal miners. Arch Pathol Lab Med 1985;109:419-423.
190. Morgan WKC. Industrial bronchitis. Br J Ind Med 1978;35: 285-291.
191. Douglas AN, Lamb D, Ruckley VA. Bronchial gland dimensions in coalminers: influence of smoking and dust exposure. Thorax 1982;37:760-764.
192. Kibelstis JA, Morgan EJ, Reger R, et al. Prevalence of bronchitis and airway obstruction in American bituminous coal miners. Am Rev Respir Dis 1973;108:886-893.
193. Marine WM, Gurr D, Jacobsen M. Clinically important respiratory effects of dust exposure and smoking in British coal miners. Am Rev Respir Dis 1988;137:106-112.
194. Seixas NS, Robins TG, Attfield MD, Moulton LH. Exposure-response relationships for coal mine dust and obstructive lung disease following enactment of the Federal Coal Mine Health and Safety Act of 1969. Am J Ind Med 1992;21:715-734.
195. Heppleston AG. The pathogenesis of simple pneumoconiosis in coal workers. J Pathol Bacteriol 1954;67:51-63.
196. Kleinerman J, Green F, Lacquer W, et al. Pathology standards for coal workers' pneumoconiosis. Arch Pathol Lab Med 1979;103:374-432.
197. Morgan WKC, Burgess DB, Lapp NL, et al. Hyperinflation of the lungs in coal miners. Thorax 1971;26:585-590.
198. Shennan DH, Washington JS, Thomas DJ, et al. Factors predisposing to the development of progressive massive fibrosis in British coal miners. Br J Ind Med 1981;38:321-326.
199. Wagner JC. Etiologic factors in complicated coal workers' pneumoconiosis. Ann N Y Acad Sci 1972;200:401-404.
200. Caplan A, Payne RB, Withey JL. A broader concept of Caplan's syndrome related to rheumatoid factors. Thorax 1962;17: 205-212.
201. Lapp NL, Castranova V. How silicosis and coal workers' pneumoconiosis develops — a cellular assessment. Occupational medicine: state of the art reviews. Philadelphia: Hanley and Belfus, 1993:35-65.
202. Adamis Z, Timlar T. Studies on the effect of quartz, bentonite, and coal dust mixtures on macrophages in vitro. Br J Exp Pathol 1978;59:411-419.
203. Dalal NS, Suryan MM, Vallyathan V, et al. Detection of reactive free radicals in fresh coal mine dusts and their implication for pulmonary injury. Ann Occup Hyg 1989;33:79-84.
204. Castranova V, Bowman L, Reasor M, et al. The response of rat alveolar macrophages to chronic inhalation of coal dust and/or diesel inhalation. Environ Res 1985;36:405-419.
205. Adamson IYR, Bowden DH. Adaptive responses of the pulmonary macrophagic system to carbon: II. morphologic studies. Lab Invest 1978;38:430-438.
206. Borm PJA, Henderson PT. Symposium on the health effects of occupational exposures to inorganic dusts. Exp Lung Res 1990;16:1-3.
207. Ray SC, King EJ, Harrison CV. The action of small amounts of quartz and large amounts of coal and graphite on the lungs of rats. Br J Ind Med 1951;8:68-73.
208. Lapp NL, Lewis D, Schwegler-Berry D, et al. Bronchoalveolar lavage in asymptomatic underground coal miners. In: Ramani RV, ed. Proceedings of respiratory dusts in the mineral industry. Society of Mining Engineering, 1991:159-169.
209. Wagner JC, Burns J, Munday DE, McGee JD. Presence of fibronectin in pneumoconiotic lesions. Thorax 1982;37:54-56.
210. Wallaert B, Lassalle P, Fortin F, et al. Superoxide anion generation by alveolar inflammatory cells in simple pneumoconiosis and in progressive massive fibrosis of non-smoking coal miners. Am Rev Respir Dis 1990;141:129-133.
211. Rivers D, Wise M, King E, Nagelschmidt G. Dust content, radiology, and pathololgy in simple pneumoconiosis of coal-workers. Br J Ind Med 1960;17:87-108.
212. Watson AJ, Black J, Doig AT, et al. Pneumoconiosis in carbon electrode workers. Br J Ind Med 1959;16:274-285.
213. Heise ER, Mentnech MS, Olenchock SA, et al. HLA-A1 and coalworkers' pneumoconiosis. Am Rev Respir Dis 1979;119: 903-908.
214. Soutar CA, Turner-Warwick M, Parkes WR. Circulating antinuclear antibody and rheumatoid factor in coal pneumoconiosis. BMJ 1974;3:145-147.
215. Lippmann M, Eckert HL, Hahon N, Morgan WKC. Circulating antinuclear and rheumatoid factors in United States coal miners. Ann Intern Med 1973;79:807-811.
216. Wagner JC, McCormick JN. Immunological investigations of coalworkers' disease. JR Coll Physicians Lond 1967;2:49-56.
217. Benedek TG, Zwadzki ZA, Medsger TAJ. Serum immunoglobulins, rheumatoid factor, and pneumoconiosis in coal miners. Arthritis Rheum 1976;19:731-736.
218. Hahon N, Morgan WKC, Petersen M. Serum immunoglobulin levels in coal workers' pneumoconiosis. Ann Occup Hyg 1980;23:165-174.
219. Burrell R. Immunological aspects of coal workers' pneumoconiosis. Ann N Y Acad Sci 1972;200:94-105.
220. Balaan MR, Weber SL, Banks DE. Clinical aspects of coal workers' pneumoconiosis and silicosis. Occup Med 1993;8:19-34.
221. Lapp NL, Seaton A, Kaplan KC, et al. Pulmonary haemodynamics in coal workers' pneumoconiosis. In: Walton WH, ed. Inhaled particles III. Woking: Unwin Brothers, 1971:645-657.
222. Lyons JP, Clarke WG, Hall AM, Cotes JE. Transfer factor (diffusing capacity) for the lung in simple pneumoconiosis of coal workers. BMJ 1967;4:349-359.
223. Fernie JM, Douglas AN, Lamb D, Ruckley VA. Right ventricular hypertrophy in a group of coalworkers. Thorax 1983;38:436-442.
224. Ball JD, Berry G, Clarke WG, et al. A controlled trial of antituberculosis chemotherapy in early complicated pneumoconiosis of coal workers. Thorax 1969;24:399-406.
225. Dubois P, Gyselen A, Prignot J. Rifampicin-combined chemotherapy in coal-workers' pneumoconio-tuberculosis. Am Rev Respir Dis 1977;115:221-228.

Title:	Interstitial Lung Disease
Pub Date:	02/1998
Edition #:	3
Publisher:	Decker, B. C. Incorporated
Contributor:	Marvin I. Schwarz
Contributor:	Talmadge E. King
Contrib. Suppl:	Jr.
ISBN LEVEL FIELDS-	
Binding Code:	Trade Cloth
ISBN:	1-55009-060-7
Avail:	Ingram, JA Majors
Pages:	760
ISBN status:	Active
PRICE FIELDS-	
Currency Code:	$
Price:	145.00
Price Type:	Distributor
Price Source:	Publisher
PRICE FIELDS-	
Currency Code:	$
Price:	179.95
Price Type:	Ingram
Price Source:	Ingram
SUBJECTS-	
Subject Type:	Bowker:
Subject:	LUNGS - DISEASES
Subject Type:	BISAC:
Subject:	MEDICAL / Diseases / Cardiopulmonary