Silicosis: A Review

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Introduction

Silicosis is a potentially fatal, irreversible, fibrotic pulmonary disease that may develop subsequent to the inhalation of large amounts of silica dust over time. In most circumstances, silicosis only develops subsequent to substantial occupational exposures. The disease has a long latency period and may clinically present as an acute, accelerated, or chronic disease.

The pathophysiology of chronic silicosis involves chronic inflammation arising as a result of the accumulation of various inflammatory mediators and fibrogenic factors. Under the influence of these factors, pulmonary silicoproteinosis develops as eosinophilic proteinaceous material accumulates in the pulmonary alveolar spaces. The rate of disease progression appears to depend upon the rate of silica deposition in the lungs, as well as the total amount of crystalline silica that is actually retained in the lung.

In some cases, silicosis may be associated with the concomitant development of other diseases, including tuberculosis, cancer, or autoimmune disease. Currently, no cure or effective treatment is available for silicosis.

Due to the association between occupational exposure to silica and the subsequent development of silicosis, a variety of federal and state agencies have initiated strict regulations aimed at preventing the development of silicosis in certain workers. These regulations generally emphasize adequate ventilation on job sites and limiting the amount of time workers may spend in potentially exposing environments.[1-3]

Historical Perspective

Respiratory disease associated with occupational exposure to crystalline silica has been described throughout history. Hippocrates described a condition of "breathlessness" in miners, and in 1690, Lohneiss noted that when "the dust and stones fall upon the lungs, the men have lung disease, breathe with difficulty."[1] Bernardo Ramazzini studied so-called "miners' phthisis," and other trades of the day wherein workers inhaled substantial

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amounts of dusts. These dust-related afflictions have been known by various names, including "miners' phthisis," "dust consumption," "mason's disease," "grinders' asthma," "potters' rot," and "stonecutters' disease."[1] These problems are now collectively referred to as silicosis. Peacock and Greenhow reported finding silica dust in the lungs of miners in the 1860s, and 10 years later, Visconti used the term "silicosis" to describe the disease caused by inhalational exposure to silex.[1,4]

Statistical and epidemiological analyses have contributed important information towards understanding silicosis. At the turn of the 20th century, the Metropolitan Life Insurance Company reported that workers from foundries, quarries, and machine shops were absent from work substantially more frequently than other workers. This constituted the first modern suggestion of the clinical importance of silica exposure. However, it was not until the so-called Hawk's Nest Tunnel disaster of the early 1930s that silicosis was clearly defined as an important public health concern.

The Hawk's Nest Tunnel was a hydroelectric power project constructed by blasting into massive natural rock formations in the area of Gauley Bridge, West Virginia. The construction techniques used in this project did not employ so-called wet-drilling techniques to reduce drilling and blasting-related dust. Consequently, enormous amounts of construction-related dusts were generated during the course of this project.[5] During the project, it was noted that a number of workers became ill and many died from what appeared to be a nondescript, yet severe, form of respiratory disease. Pneumonia was noted as the cause of death in many of the workers and company doctors for the project dubbed the respiratory problems plaguing these workers "tunnelitis."[1,6]

When the drilling and blasting phase of the Hawks Nest project was complete, an epidemic of silicosis was identified among men who had worked at the Gauley Bridge site. Four hundred drillers died, and lung-related disabilities were reported in the majority of surviving workers.[6] Investigations eventually revealed that blasting for the Hawks Nest project actually involved the disruption of rock formations composed largely of pure silica. Eventually it was shown that the exposures at Gauley Bridge involved prolonged and unprotected exposure times in conjunction with extremely high levels of pure silica liberated into the immediate breathing space of workers.

Investigators working with the U.S. Public Health Service first classified silicosis by state, industry, and job description. Since then, a variety of occupations have been identified as having the potential to be associated with silica exposure. These occupations are listed in Table 1. The Occupa-

TABLE 1. Industrial processes and activities associated with silica exposure[7]

Type of Exposure	Exposure	
	Crystalline Silica	**Amorphous Silica**
Industrial	Abrasive blasting	Diatomaceous earth removal
	Cleaning fossil fuel furnaces, flues	Refractory brick production
	Metal preparation, pouring	Electrometallurgical processes
	Mining	Agricultural work (burning/incineration of rice, sugar cane harvesting, etc)
	Molding, core making	Ferro-alloy production
	Petroleum refining	Silicon, ferrosilicon, and chromium manufacture
	Smelting copper or lead	Occupational exposure to pumice dust
	Steel production	Animal feed industry
Other (hobbyists, artisans)	Glassblowing	
	Sculptoring stone containing granite and other sources of crystalline silica	

tional Safety and Health Administration (OSHA) has reported that as many as two million American workers may be chronically exposed to crystalline silica.[7] Of these workers, roughly 100,000 are employed in what may be considered potentially "high-risk" settings, such as sandblasting, rock drilling, roof bolting, and foundry-related industries.[7] In 2002, the National Institute for Occupational Safety and Health (NIOSH) published an updated report entitled "Work-Related Lung Disease Surveillance Report."[8] This report indicated that approximately one-third of all decedents who had silicosis from 1990 through 1999 had been employed in the construction and mining industries (Table 2).

Chemical Properties of Silica

Silica refers to the chemical compound SiO_2 (silicon dioxide) that occurs in two specific and distinct forms: amorphous and crystalline (Tables 3 and 4). The word "crystalline" implies that the silicon and oxygen atoms are oriented and related to each other in a fixed pattern as opposed to the random fashion that predominates in the amorphous form of silica. Crystalline silica naturally exists in a polymerized tetrahedral framework producing several polymorphs. These polymorphs are a function of the temperature and pressure: alpha quartz (or quartz), the most common polymorph found on the earth's surface, is stable over most temperatures and pressures found in the earth's crust. In contrast, beta quartz is stable at high temperatures, whereas tridymite and cristobalite

TABLE 2. Most frequently recorded industries on death certificates, US residents aged 15 years and over: selected states and years (1990-1999)[8]

Industry	Deaths (n)	Percent of All Industries
Construction	118	13.4
Metal mining	86	9.8
Coal mining	69	7.8
Blast furnaces, steelworkers, rolling/finishing mills	51	5.8
Nonmetallic mining/quarrying (except fuel)	48	5.5
Iron and steel foundries	48	5.5
Nonmetallic mineral and stone products, miscellaneous	44	5.0
Manufacturing industries (not specified)	33	3.8
Machinery (except electrical; not elsewhere classified)	23	2.6
Structural clay products	20	2.3
All other industries	317	36.0
Industry not reported	23	2.6
Total	880	100.0

TABLE 3. Synonyms for crystalline silica[7]

Name/Formulation	Alternative or Trade Names
α Quartz	CSQZ
	DQ 12
	Min-U-Sil
	Sil-Co-Sil
	Snowit
	Sykron F300
	Sykron F600
Keatite	
Silica W	
Porosils	Zeosils
	Clathrasils
Tridymite	
Cristabolite	

are stable only at high temperatures and low pressures. Other silica polymorphs include coesite and stishovite. These may be encountered at a wide range of temperatures but only in a high-pressure environment and therefore they may be created during a variety of industrial processes including ceramic manufacturing, foundry processes, and any other industrial operation wherein quartz may become heated to high temperatures at elevated pressures. The most common crystalline forms of silica involved in workplace exposures include quartz, tridymite, and cristobalite. Silica may also occur naturally and at varying concentrations in rocks such as sandstone (67% silica) and granite (25 to 40% silica).

TABLE 4. Synonyms for amorphous silica[7]

Aerosil (130, 200, 255, 300, 380)	Pyrogenic silica
B-6C	Ronasphere
Biogenic silica	Silica, anhydrous 31
Cab-O-Sil (EH-5, LM-130, MS55, M-5)	Silica gel
CI 7811	Sipernat
Diatomaceous earth	Sorbosil (AC33, AC 35, AC 37, AC 39, AC 77, BFG50, TC15)
Diatomite	Sorbso BF G10
EP 10TP	Spherica
Fossil flour MBK	Speriglass
Fumed silica	Spheron (L-1500, N-2000, P-1000, P-1500, PL-700)
Fused silica	Tripolite
Greensil K	Vitreous silica
Kieselguhr	Wacker HDK (P 100H, N 20P, N 25P, T 30, V 15, V15P)
LUDOX HS 40	Wessalon
Neosil (CBT50, CBT60, CBT70, CBT60S, CL2000, CT11, PC10, PC50S)	Zelec sil
Opal	
Pigment white 27	
Precipitated silica	

Silicates are structures composed of silicon dioxide bound to cations such as magnesium, aluminum, or iron. Examples of silicates include mica, soapstone, talc tremolite, Portland Cement, and others.

Opal, diatomaceous earth (tripolite), silica-rich fiberglass, fume silica, mineral wool, and silica glass (vitreous silica) are common amorphous forms of silica. Other forms of amorphous silica are listed in Table 3. Dusts composed of amorphous silica, with the exception of fiberglass, are not generally considered to be harmful to humans.[9]

Quartz, cristobalite, and some forms of tridymite are inherently piezoelectric. Piezoelectricity is a property that produces opposite electric charges on opposite sides of the physical structure when pressure is applied directly to the crystal. This phenomenon occurs in crystalline silica because the chemical structure does not have a center, reflecting an inversion symmetry. In addition, the opposite sides of these crystals have dissimilar surfaces and carry opposite electrical charges. It is theorized that these piezoelectric characteristics may play a role in the pathophysiology of silica-related illness by the generation of oxygen free radicals produced on the cleaved surfaces of silica molecules and as a result of silica-damaged alveolar macrophages.[10,11] Silanol (SiOH) groups present on the surface of silica particles are capable of forming hydrogen bonds with oxygen and nitrogen groups found in biologic cell

TABLE 5. Secondary disorders common in silicosis[7]

Bronchitis
Emphysema
Chronic obstructive pulmonary disease
Scleroderma
Rheumatoid arthritis
Systemic lupus erythematosus
Renal disease

membranes, which then may lead to a loss of membrane structure, lysosomal leakage, and tissue damage. These processes may all contribute to the development of lung scarring.[11] Experimental data suggest that there is a distinct fibrogenic order of potency for these materials as follows: tridymite > cristobalite > quartz (Table 5).[12-14]

Occupational Exposure to Silica

Workers engaged in specific occupations, such as abrasive blasting, may have the potential for medically important exposures to crystalline silica. The American College of Occupational and Environmental Medicine (ACOEM) considers that silica exposure today is still widespread and the estimated death rate due to silicosis in the United States may be in the range of 200 to 300 individuals per year.[15] It has been noted that some workers may have the potential for silica exposure even despite efforts to limit and control occupationally based exposures.[7]

Abrasive blasting operations use a variety of abrasive compounds to clean and/or add texture to various industrial materials for a variety of purposes. For example, the shipbuilding and automotive industries utilize abrasive blasting in a variety of applications.[16] Sand has historically been used as the primary abrasive material in sandblasting, and these techniques may, at times, result in elevated concentrations of crystalline silica suspended in the air surrounding blasting operations. Recently, new techniques have attempted to utilize substitute abrasives and agents in blasting operations. These alternative abrasive compounds contain reduced concentrations of silica and may include varying amounts of coal slag, hematite, smelter slag, minerals, metals, or synthetic abrasives. Nonetheless, these methods may still generate silica-containing dust especially in circumstances where the surfaces to be abraded contain silica.[17]

Silicosis and Construction Work

Approximately one million American workers are employed in heavy construction jobs, with 39% of these individuals engaged in road and

street construction work.[3] According to a 2002 NIOSH report derived from death certificate information, 13.4% of decedents who succumbed to silicosis from 1990 to 1999 were employed in the construction industry[8] (Table 2).

Rehabilitation of the U.S. national highway infrastructure has gained recent focus and legislation has accelerated spending for this purpose. Increased highway construction may lead to increased potential for exposure to crystalline silica dust in some settings.[3] Unfortunately, to date, few extensive or long-term surveillance projects have been completed to monitor highway repair processes as possible sources of silica exposure. This is due in part to the fact that these jobs do not typically generate the large amounts of respirable silica associated with other occupational activities such as abrasive blasting or sandblasting.[3] A so-called "cut-and-repair" technique for road maintenance, utilizing quick-setting concrete, has become popular since the mid 1980s. This method reportedly may produce varying quantities of silica-containing dust during the cutting, break-up, and removal process of concrete road surfaces. Depending upon the nature and extent of exposure, this process may thus pose a potential risk for silica exposure for some workers involved in highway repair and construction.

Pathologic Mechanisms in Silicosis

A number of clinical and pathologic varieties of silicosis have been identified including simple, or nodular, silicoisis, silicoproteinosis (acute silicosis), complicated silicosis (progressive massive fibrosis), and interstitial fibrosis.

The postmortem examination of silicotic lungs (simple silicosis) reveals dark pulmonary tissue in conjunction with associated enlarged and fibrotic hilar and peribronchial lymph nodes. Pulmonary nodules in the lung parenchyma are usually present and are typically located in the upper lobes. The characteristic lesions may have variable degrees of calcification and may range from only a few millimeters to more than a centimeter in diameter. The condition, known as progressive massive fibrosis (PMF) or complicated silicosis, is said to develop when the above described pulmonary lesions coalesce forming pulmonary masses 2 cm or larger. PMF may progress to a stage of central necrosis with cavitation. Secondary infections with a variety of mycobacterial organisms including *Mycobacterium tuberculosis, Mycobacterium kansasii,* and *Mycobacterium intracellulare* may also develop. Microscopic sections may reveal silica-containing macrophages and reticulin fibers. These areas may organize, forming the classic silicotic lung nodules that represent the classic X-ray findings consistent with chronic silicosis. These nodules

have been described as "histologic tornadoes" with a "quiet" center of hyaline and collagen fibers concentrically arranged around the center.[1,18] The periphery of these "tornadoes" contain a variety of inflammatory cells (macrophages, lymphocytes) progressing away from the center. This outward configuration induces a fibrous reaction in normal vessel, airway, and pleural structures.[4,19]

Polarized light microscopy usually reveals the presence of crystalline silica particles as areas of weak birefringence in the center of silicotic nodules. The birefringence sometimes observed inside nodules are the result of inhaled silicate particles, which are mixed with silica dust. The microscopic findings reveal periodic acid–Schiff stained positive alveolar exudate and cellular infiltrates in the walls of the alveoli, histologically known as silicoproteinosis.

Acute Silicosis

Acute silicosis may involve a variety of different mechanisms of injury when compared with chronic silicosis. In lungs affected by acute silicosis, electron microscopy reveals hypertrophic type II pneumocytes lining the alveoli. These hypertrophic pneumocytes may produce excessive amounts of proteinaceous material and surfactant protein and the alveoli may then become filled with protein-containing material.[20] Excessive free-radical formation may also contribute to the development of silicotic lung disease in the acute setting. Freshly fractured silica may contain higher proportions of free radicals than intact silica and thus may generate a stronger inflammatory response.[21,22] Freshly fractured silica, by definition, contains abundant cleaved particle surfaces, where surface reactive oxygen species such as peroxides and hydroperoxides tend to form.[23] The presence of excessive free radicals thus produced may result in altered activation of transcription factors leading to cell and/or DNA damage.[24] Occupations such as sandblasting and rock drilling have been documented to produce freshly fractured silica particles and acute silicosis has been historically associated with those occupations specifically.[6,25]

Chronic Silicosis

Chronic silicosis is associated with chronic inflammatory changes within the alveoli. This condition of chronic alveolitis may ultimately result in the development of pulmonary fibrosis. The exact mechanism for this has not yet been fully elucidated, but it is believed that it is initiated when alveolar macrophages phagocytize silica particles in an attempt to clear them from the lung. Freshly fractured silica appears to be more reactive within alveolar macrophages than aged silica (eg, sand). When

silica particles are not efficiently cleared from the lung by alveolar macrophages, these alveolar macrophages may become damaged. Macrophages damaged in this way are thought to become stimulated and release reactive oxygen species, reactive nitrogen species (RNS), and excess free radicals.[19] Transcription factors (NFkB and activator protein-1) may then be released triggering the production and release of inflammatory cytokines (TNF-α, IL-1β, and IL-6), proteases, and arachidonic acid metabolites (leukotriene-B4, prostaglandin E2). When alveolar macrophages containing silica die, they release silica particles that are then re-engulfed by other alveolar macrophages, thus inducing a cycle of injury.[23] This cycle is accompanied by the movement of neutrophils and lymphocytes to the areas of injury resulting in further inflammatory changes. Inflammatory cytokines including interleukin 1 (IL-1), tumor necrosis factor-α, arachidonic acid metabolites (eg, leukotrienes), and chemokines such as IL-8, macrophage inflammatory protein (MIP)-2, MIP-1α, MIP-1β, and monocyte chemoattractant proteins all appear to be involved in this inflammatory process.[4,19,26-28] In addition, macrophage-derived fibrogenic factors such as platelet-derived growth factors, transforming growth factors (TGF)-α and -β, epidermal growth factor, and insulin-like growth factor-1 are released as the body initiates reparative measures. A constant production of fibrotic factors appears to contribute to the evolution of silicotic lesions by recruiting type II pneumocytes and fibroblasts that produce large amounts of fibronectin and collagen.[18,29] Scar tissue results, and the pulmonary architecture then becomes permanently altered. Laboratory treatment of mice with an antibody to TNF-α has been shown to decrease the production of MIP-2, inflammation, and the subsequent pulmonary fibrosis.[11]

Former miners with severe silicosis-related lung disease have been found to have a higher incidence of single nucleotide polymorphisms of TNF-α, as well as greater gene–gene and gene—gene environment interactions.[30] It has been proposed that alveolar macrophages may be activated, but not killed, when silica particles are engulfed. This phenomenon is implied by the finding that bronchoalveolar-lavage fluid from silica-exposed humans shows morphologic signs of activation within local macrophages.[31] This macrophage activation may then lead to collagenase production and resultant lung parenchymal lung destruction.[32,33]

Particle Burden in Silicosis

A number of studies have investigated the relationship that may exist between pulmonary silica burden and the subsequent development of silicosis. Nagelschmidt summarized the historical data regarding silica

toxicity and describes a possible association between increasing cumulative weight of retained silica in the lung and increasing severity of silicosis.[9,34] However, there may also an association between the presence or absence of other minerals and the development of silicosis. Exposure to 4 to 10 grams of total dust and/or 1 to 3 grams of pure quartz is associated with silicosis. The percentage of quartz contained in the dust may be as high as 18% or more. In rapidly developing silicosis the dust quartz content usually exceeds 30% but may be even higher in some instances. Exposures of this magnitude may be found in some gold mining and some foundry work. If there is concomitant exposure to other, nonfibrogenic dusts, then the same weight of silica may produce only minor silicotic lung changes. Varied dust exposure is typical for hematite or coal miners. This "interactive dust phenomenon" may demonstrate the absorption of other dust types onto the surface of silica particles, consequently decreasing the toxicity of inhaled silica in humans.

Because there are different mineralogic types of silica particles, research has been conducted to investigate the different pathogenic potentials of those particles. The exact relationship between fibrotic potential and the specific silica subtype has not yet been fully elucidated. However data have consistently shown that tridymite, cristobalite, and quartz are generally more fibrogenic than amorphous silica.[9,12,13,35]

Clinical Presentation of Chronic Silicosis

Chronic or classical silicosis is the most common clinical form of silicosis. This form of silicosis develops only after decades of repeated exposure to high concentrations of silica dust. Since symptoms may not develop for as long as 45 years following exposure, the diagnosis in asymptomatic patients requires radiographic confirmation.[1,36] In these cases, the physical examination may reveal stigmata of associated disease, including emphysema and/or cor pulmonale. Nodular lesions predominantly located in the upper lobes may be present on chest radiograph. Table 5 lists secondary disorders common in silicosis.

Chronic silicosis not usually associated with mycobacterial infections and tends to be mild and not disabling. However, chronic silicosis may develop into PMF, a serious and debilitating subset of the disease. Chronic silicosis can be radiographically distinguished from acute disease presentations by virtue of large upper lobe opacities in conjunction with small, diffuse nodular lesions. Basilar emphysematous changes may also be apparent on chest X-ray. Patients with PMF are often noted to be hypoxic at rest and are prone to mycobacterial infections and spontaneous pneumothoraces and may ultimately develop fatal respiratory failure.

Patients may also present with a condition known as accelerated silicosis. This condition is associated with profound silica exposures occurring over a relatively shorter time course when compared with chronic silicosis. Accelerated silicosis is typically related to an exposure history in the range of 5 to 15 years.[37] In many cases of accelerated silicosis, disease progression is evident even though the patient may have been promptly removed from continuing silica exposure. Accelerated silicosis has been associated with a variety of autoimmune disorders.

Clinical Presentation of Acute Silicosis

Acute silicosis differs both histologically and pathologically from chronic silicosis. Accurate diagnosis of acute silicosis is essential as there are significant implications for the patients who present with this form of disease. Acute silicosis has a low rate of occurrence and the Hawk's Nest disaster described above represents the most extensive recorded epidemic of acute silicosis.[6,38]

Patients diagnosed with acute silicosis may report substantial occupational exposures to silica which occurred, in some cases, over a relatively short amount of time. Specific occupations have been associated with the development of acute silicosis, including silica flour processing, tombstone sandblasting, and surface drilling.[25,39,40] These jobs result in exposure to mechanically broken, cleaved, or fractured silica particles from the grinding and cutting processes.[24] Presenting symptoms may include dyspnea, fatigue, weight loss, fever, and pleuritic pain. Pathologic changes consistent with acute silicosis include the filling of alveolar spaces with eosinophilic-granular material, similar to that observed in accelerated silicosis.[41] The clinical course for acute silicosis is often dramatic as there may be rapid progression to respiratory failure from a loss of pulmonary function and impaired gas exchange.[24]

Diagnosis of Silicosis

The diagnosis of silicosis is based on a clearly documented history of substantial silica exposure, usually in the occupational setting. Casual exposures are generally not considered to be important causes for the development of silicosis. In conjunction with a history consistent with medically important exposures to silica, chest radiographs confirming the presence of nodular opacities are important. It is important to remember that the differential diagnosis for silicosis is extensive and includes diseases that have a similar presenting profile, including fungal infections, miliary tuberculosis, sarcoidosis, and idiopathic pulmonary fibrosis.

For both chronic and accelerated silicosis, chest radiography usually reveals nodular opacities in the upper lung field. Thoracic lymph nodes calcify in a characteristic pattern, often referred to as "eggshell" calcification. However, this eggshell pattern of lymph node calcification is not specific and may also be seen with sarcoidosis, radiation-treated Hodgkin's disease, blastomycosis, scleroderma, amyloidosis, and histoplasmosis.[42] Progressive massive fibrosis is often characterized by large fibrotic masses in conjunction with a distortion of the lung architecture often involving an upward displacement of the mediastinal and hilar structures attributable to volume loss. In addition, lower areas of the lung may appear hyperventilated and emphysematous, often in conjunction with multiple bullae.

Acute silicosis may be differentiated from chronic silicosis on chest X-ray based on the phenomenon of acute alveolar filling, causing a ground-glass appearance of the lung fields. Linear opacities in the lower lobes may foretell the initiation of fibrosis and enlargement of the hilar nodes may also be prominent.

Pathologic findings and chest radiographs may not always correspond.[43] Chest X-rays may demonstrate only minimal changes even in the face of extensive fibrosis. High-resolution computed tomography of the chest is the imaging study of choice to evaluate nodules, as well for the detection of emphysematous pulmonary changes. High-resolution computed tomography may also help differentiate confluent lesions from simple silicosis.[44] Other pulmonary imaging modalities such as magnetic resonance imaging and digitized radiography may be useful adjuncts in the diagnosis and monitoring of silicosis.

Pulmonary function tests may be normal early in the course of simple silicosis. However, with disease progression, a restrictive and/or obstructive pattern may emerge. A reduction in the volume of exhaled air over 1 second, as well as reduced forced vital capacity, decreased diffusing capacity, total lung capacity, and lung compliance, may be manifest in severe cases and in cases of progressive disease.[45,46] Flow parameters may be altered due to airway obstruction resulting from fibrosis and consequent abnormalities of the underlying lung-architecture. It is important to remember the importance of noting coexisting factors (eg, tobacco smoking and pulmonary infections) when evaluating pulmonary function tests. It is also important to remember that bronchoalveolar lavage is not generally helpful in diagnosing silicosis as patients exposed to silica may have silica and increased protein levels in lung washings, regardless of the stage of the disease or the specific disease state.[39]

Classification of Silicosis

The International Labor Office (ILO) has standardized the radiographic classification by providing guidelines for grading silicosis.[47,48] A variety of factors are taken into consideration when grading cases of silicosis, including the degree of pleural involvement as well as the size, shape, and profusion of opacities.[36] The quality of the X-ray image is also a critical factor in that poor-quality X-rays may be confounding and interfere with accurate radiological classification.

Based on ILO standards, round pulmonary nodules measuring 1.5 to 3 mm are designated as "*p*," and those measuring 3 to 10 mm are designated "*r*." Irregularly shaped nodules are termed "*s*," "*t*," and "*u*." Large nodules are designated "*A*" if each is larger than 1 cm and the aggregate diameters are less than 5 cm; "*B*" nodules are larger than 5 cm and have an aggregate diameter less than that of the right upper lobes, and "*C*" nodules have a combined area larger than the right upper lobe. Concomitant pleural involvement is characterized with regard to the presence and degree of calcification, thickening, or effusion.

Treatment of Silicosis

A variety of treatment modalities aimed at decreasing the pulmonary inflammatory response to silica are available. However, no consistently effective treatment regimen has yet been developed. The use of whole-lung lavage techniques may improve symptoms in some patients. However, these patients usually do not demonstrate sustained improvement in pulmonary function parameters.[49] Corticosteroids and aluminum citrate have been used in pharmacologic treatment protocols with varying success for silicosis. One limited, controlled study did demonstrate an improvement in both inflammatory bronchoalveolar lavage and pulmonary function tests when corticosteroids were administered.[50] Another report indicated acute silicosis was reversed by corticosteroid therapy.[51] However, most authorities believe that corticosteroids have, at best, limited efficacy in the treatment of silicosis. The administration of inhaled aluminum citrate powder theoretically coats silica particles retained within the lung, thus reducing the solubility of these particles. Some controlled studies have shown a degree of symptomatic improvement using inhaled aluminum citrate; however, no change in either the objective disease parameters or overall mortality was demonstrated.[52] Adverse effects may be associated with the administration of aluminum citrate and these may outweigh any positive treatment outcome. Based on serial chest radiographs, pulmonary function tests, and pulmonary lavage,

aluminum lactate aerosols did not favorably influence the course of the disease in silicotic sheep.[53]

Polyvinylpyridine-*N*-oxide (PVPNO) has been shown to concentrate silica particles inside of cells and consequently has improved the functional capabilities of some patients by slowing the course of disease.[54] PVPNO, acting as a hydrogen acceptor, has been shown to coat the surface of silica particles and thereby decrease the potential for silica toxicity in both in vitro and in vivo models.[11] PVPNO decreases the generation of reactive oxygen species and possibly reduces silica-induced DNA damage by selectively blunting the active sites at the particle surface.[20] However, animal studies suggest that the efficacy of PVPNO may be limited by its potential for kidney and liver toxicity. Other therapies that are currently being evaluated include the use of alveolar macrophage inhibitors and monoclonal antibodies directed against IL-1.[41]

Unfortunately, none of the currently proposed therapies have clearly reduced the mortality associated with silicosis. Consequently it is critically important that comorbid problems, such as mycobacterial infections, tuberculosis, and other pulmonary infections, be identified and treated promptly in all silicosis patients. Symptomatic patients with chest X-rays suggestive of silicosis should have a purified protein derivative placed intradermally as soon as possible and a positive purified protein derivative should prompt consideration of antituberculous therapy. Steroid therapy should not commence until it is clear that any coexisting mycobacterial infection has resolved. Some authorities have suggested that patients should be treated empirically with isoniazid during steroid therapy to prevent activation of undiagnosed mycobacterial disease.[50,53-55] Individuals diagnosed with silicosis should be promptly removed from any further exposure to silica and treated with bronchodilators and supplemental oxygen as required.

Illnesses Associated with Silicosis

A variety of illnesses have been identified as being associated with the different forms of silicosis as follows.

Tuberculosis

Early observers noted that silicosis and tuberculosis frequently coexisted. The clinical introduction of radiography, as well as the introduction of tuberculin tests and sputum staining, allowed physicians to distinguish silicosis from other respiratory diseases, including tuberculosis. Today, the risk of developing tuberculosis has been substantially reduced by

improved respiratory dust protection as well as the development of antibiotics active against mycobacteria. Nevertheless, mycobacterial infections continue as common complications associated with all forms of silicosis.[56] Silicotic patients are often diagnosed with atypical mycobacteria, including *Mycobacterium avium intracellulare* and *M. kansasii*. The standard of care for all patients suffering from silicosis requires a thorough search for the presence of mycobacterial species, especially if there are any documented functional or clinical declines in the patients' condition.

Neoplastic Disease

Currently, much controversy exists with regard to the potential carcinogenicity of inhaled silica.[57,58] In 1987, the International Agency for Research on Cancer (IARC) stated that despite "sufficient evidence" that silica poses a carcinogenic threat to laboratory animals, there was only "limited evidence" to link silica to human carcinogenicity. At that time, silica was classified by IARC as a Group 2B carcinogen ("probably carcinogenic" to humans).[59] An IARC subgroup subsequently reclassified crystalline silica as a Group 1 carcinogen ("carcinogenic to humans") based on an exhaustive reevaluation of the literature published through 1997.[60]

A review of the literature was undertaken in 2000 by another group of researchers using different inclusion and exclusion criteria from the ones employed for the 1997 IARC investigation. This more recent review did not find any evidence for a causal association between silicosis and lung cancer.[61] This assessment included studies that were not confounded by smoking or known exposure to specific occupational carcinogens. The assessment also looked at studies that were essentially free of bias, that used appropriate reference groups, and that did not involve compensation agreements. However, studies that could have included confounding exposures to chemicals such as radon, arsenic, or polycyclic aromatic hydrocarbons were not excluded as long as there was no demonstrated association with silicosis. According to a recently promulgated evidence-based statement from the ACOEM, the risk for cancer in silicotic persons "appears to be greatest in workers with silicosis who smoke." The ACOEM document goes on to state "the cancer risk to silica-exposed workers without silicosis (especially if they are not smokers) is less clear despite continuing research, some of which has yielded disparate results."[15]

One study was unable to demonstrate an increase in the risk for lung cancer among silicosis patients who had a history of chronic bronchitis or

asthma.[62] The same study reported that the risk for lung cancer was increased in those patients who did not have either chronic bronchitis or asthma.[62] These investigators theorized that the presence of obstructive pulmonary disease may cause silica to be deposited in the more proximal regions of the lung preferentially, thereby potentially decreasing the risk of silicosis and lung cancer.[62] With regard to the question of a causal association between silicosis and lung cancer, the main scientific uncertainty involves whether the lung cancer rates reported in descriptive studies are confounded by smoking history, socioeconomic status differences, and inappropriate comparison populations. It is also possible that some exposure-response studies may have failed to identify a real relationship between silica exposure and lung cancer (if one exists). It is important to note that significant cancer risks in subjects listed on silicosis registries in the past may have been the result of selection and diagnostic bias. Consideration of the possible relationship between silica exposure and lung cancer conferring the same increased risk to subjects without silicosis and whether it is justifiable to assume that quartz and cristobalite have similar health effects are all important issues.[63]

Autoimmune Disease

It has been suggested that silicosis may be associated with rheumatoid arthritis, scleroderma, lupus, and progressive systemic sclerosis.[20,64-66] Some silicosis patients may have serum antinuclear antibodies, rheumatoid factor, and elevated serum concentrations of various immunoglobulins and immune complexes.[65] In addition, renal disease without pulmonary changes has been associated with silica exposure and may manifest as nephritic syndrome or renal failure. Specifically, some workers who are involved in the production of industrial sand, as well as ceramic and granite workers, reportedly have an increased incidence of end-stage renal disease.[67,68] An increased incidence of renal disease, including nephritic syndrome and glomerulonephritis, has been reported in Bedouin tribes people who are exposed to frequent dust storms, as well as individuals who may have consumed water contaminated with silica.[69] In such cases, immune complexes located in the glomerulus may be responsible for the renal damage.[70]

Preventative Measures Against Silicosis

Ever since the first century A.D. when Pliny the Elder recommended that miners “envelop their faces with loose bladders, which enable them to see without inhaling the fatal dust,”[71] virtually all occupational

regulatory bodies have advocated the use of respiratory protection against exposure to potentially hazardous industrial dusts.

Today, a variety of engineering controls and personal protective measures have been developed for sandblasters. Fully enclosed and ventilated blasting chambers may be utilized to minimize human exposure to the dust generated during these operations. These chambers contain a series of baffles designed to selectively extract dust from the chamber environment. The venting system maintains a slight negative pressure within the chamber to pull the exhausted air away from the workers' zone of inhalation.

Personal protective equipment is recommended for sandblasters and others working in similar environments. This equipment includes coveralls, boots, and properly fitted helmets supplied with filtered air. Blasting chambers and ventilation-filtration systems should be inspected and tested for integrity and functionality on a regular basis and workers should not spend extended periods of time inside a blasting chamber. A designated observer should oversee the process from a vantage point outside the chamber.

Open-air sandblasting may not be as well monitored or controlled as closed sandblasting chambers. This type of sandblasting optimally should occur a safe distance away from other workers, and adequate ventilation should be provided. Workers employing open air sandblasting techniques should wear adequate respiratory protection. If the abrasive being used contains silica, the respirator should be a type "CE," pressure-demand, abrasive-blast-supplied air respirator having an assigned protection factor rating of 2000.

Federal guidelines have been established to minimize worker exposure to silica particles. The current permissible exposure limit for occupational exposure to respirable crystalline silica, as promulgated by OSHA, is an 8-hour, time-weighted average of 10 mg per cubic millimeter of air. This is two hundred times the recommended exposure limit currently promulgated by NIOSH.[59,72,73] In 2001, the American Conference of Industrial Hygienists adopted a threshold limit value of 0.05 mg/m^3 for respirable crystalline silica.[2,3] This parallels the recommended exposure limit proposed by NIOSH in 1974.[3,74] Internationally, standards may differ. In the U.S., sandblasting abrasive should contain less than 1% free silica, whereas in Great Britain, industrial abrasives containing silica were banned in 1950.

Silicosis-associated mortality has decreased over the last several decades. In the 1920s and 1930s, there were roughly 1000 deaths annually attributed to silicosis.[75] However, during the most recent several decades,

silicosis mortality has declined to less than 200 deaths per year in the late 1990s.[8] Despite this improvement in statistics, regulatory compliance is often difficult to monitor, and violations may occur. A 1983 report revealed that a substantial number of U.S. foundries reportedly did not practice control of silica inhalation, and approximately one-third of the workers at these sites may have been exposed to airborne silica particles.[72] NIOSH's 2002 *Work-Related Lung Disease Surveillance Report* indicates that, from 1993 to 1999, a total of 16 states had geometric mean respirable quartz exposure levels in non-mining industries exceeding the recommended exposure limit of 0.05 mg/m^3, as determined by samples obtained by OSHA.[8] NIOSH research further reported that silicosis cases tend to be associated with worksites using silica-based abrasives, as well as worksites with poor ventilation and poorly controlled work practices.[76] In addition, worksites with inadequate respiratory protection and worksites that have not established medical surveillance programs are reported to be at higher risk for silicosis.[73] Samples collected during inspections of the construction and fabricated metal product industries revealed that over one-third of samples exceeded the permissible exposure limit.[75] Consequently, it is clear that continued efforts are needed to train and supervise workers to promote worker safety with regard to silica exposure.

The 1987 NIOSH Sentinel Event Notification System for Occupational Risks program advocated case-based surveillance and follow-up measures for occupational injury and disease associated with silicosis, as well as a variety of other occupational health conditions. With a seven-state network, silicosis and silica exposure are monitored via physician/hospital reporting, death certificates, and worker's compensation claims.[76] In 1996, OSHA began a so-called "Special Emphasis Program" to reduce or eliminate the occupational incidence of silicosis arising from exposure to crystalline silica. This program focused on workplace inspections where silica exposure was expected.[77] Consequent to IARC's reclassification of crystalline silica as a human carcinogenic agent, there has been considerable controversy regarding the need to lower permissible exposure limits.[78]

Conclusion

Silicosis has been a historically important occupational disease and continues to be a concern. Workers who may be exposed to high concentrations of free crystalline silica in unprotected settings may be at risk for developing pulmonary fibrosis, mycobacterial infection including tuberculosis, autoimmune disease, and lung cancer.

To reduce the incidence of industrial silica exposure, it is important to evaluate the degree of exposure, type, and source of exposure. Optimally, silica-containing materials should be replaced; work processes should be isolated and enclosed; adequate ventilation should be provided, and personal protective equipment used at all times of possible silica exposure. Even with such measures, some settings may witness rates of exposure that exceed OSHA guidelines.[79] Silicosis is expected to be an occupational medical concern for the foreseeable future on a worldwide scale since many countries do not maintain or enforce appropriate regulations controlling silica exposure for workers.

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