Section I
Chapter 5

PATHOLOGIC RESPONSES TO INHALED SILICA

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CONTENTS

I. INTRODUCTION

Silicosis is defined as pulmonary disease resulting from the inhalation of crystalline silica. In the human, silicosis manifests as four pathologically distinct entities: acute silicosis (silicolipoproteinosis), accelerated silicosis, chronic simple silicosis, and complicated silicosis. Complicated silicosis develops to progressive massive fibrosis by the conglomeration of nodular lesions. Rheumatoid pneumoconiosis, silicotuberculosis, and scleroderma are also associated with silica exposure.

The components of the silicotic response have strong temporal and exposure associations. Acute silicosis and accelerated silicosis have short latency periods (several months to several years) and are associated with intense, brief exposures. Chronic simple silicosis and complicated silicosis, by contrast, are more likely to occur a decade or more after first exposure and are associated with lower levels of

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exposure over long periods of time. However, overall cumulative exposure (exposure level × duration) may be similar in patients presenting with different types of disease.

Although this classification and the general principles enumerated concerning latency and exposure apply to most cases of silicosis, certain qualifications apply. First, this disease classification describes a spectrum of changes that may exist in transitional forms (e.g., accelerated silicosis has features in common with both acute silicosis and chronic simple silicosis). Second, the various distinctive lesions may co-exist in the same lung (e.g., pulmonary alveolar proteinosis may be seen in patients with silicotic massive fibrosis).[1] Third, the features of silicosis may be modified by the presence of other minerals in the dust (see Chapter 4, Section II).

The number of workers at risk for developing silicosis remains high. The National Institute for Occupational Safety and Health (NIOSH) estimated in 1986 that 2.3 million workers were exposed to quartz dust.[2] Every year, approximately, 1,500 cases of silicosis are diagnosed in the U.S.[3] It is likely that many more cases remain undiagnosed.

However, silicosis is now rare in populations of workers exposed to quartz levels averaging less than the current permissible limit of 100 $\mu g/m^3$.[3] Most cases today occur in poorly regulated or unregulated industrial settings or in situations where the exposure was not recognized. Unusual sources of exposure resulting in silicosis include inhalation of crack cocaine,[4] scouring powder,[5] exposure in the electronics industry,[6] grinding maize,[7] farming,[8] living in desert-like terrain,[9,10] and the cutting of gemstones.[11,12] Exposure to silica-containing dust can also result in cryptic pulmonary disease that is not detected radiologically. Craighead and Vallyathan described small fibrotic lesions associated with deposits of crystalline silica in post mortem specimens of 15 granite workers who lacked radiological evidence of pneumoconiosis.[13]

It is important to bear in mind that silica is not a single entity. Free silica (silicon dioxide) occurs in crystalline and amorphous forms. The major crystalline phases are quartz, cristobalite, tridymite, stishovite, and coesite. In general, the toxicity of the crystalline forms of silica is directly related to the temperature and pressure at which the minerals have formed. Thus, tridymite is more toxic than quartz, and cristobalite is more toxic than tridymite.[14,15] Free silica may also exist in cryptocrystalline forms in which minute grains of quartz are cemented together with amorphous silica. Flint, chert, and chalcedony are examples of cryptocrystalline forms of silica. Diatomite and vitreous silica are examples of amorphous silica. In and of itself, amorphous silica is relatively nontoxic; however, in the industrial setting, heating and processing may convert the amorphous silicon dioxide into microcrystalline particles of tridymite and cristobalite. In a critical review, Parkes concluded that studies showing a toxic effect of amorphous silica can largely be accounted for by the presence of contaminating crystalline forms (see Chapter 1, Section II).

Amorphous silica can also exist in biogenic form and may have a fibrous morphology. It occurs in many food crops and in dry plant matter. SiO_2 concentrations have been measured at up to 12% by weight in rice, 3.4 to 5% in wheat and up to 16.4% in corn.[16] A major source of release of this biogenic silica is the burning of wheat, stubble, grass, and sugarcane leaf. Airborne amorphous fibers generated during sugarcane leaf burning were found to measure between 3.5 and 65 microns in length with a mean length of 12 microns and an average diameter of 0.6 microns. The biologic significance of these fibers is uncertain; however, epidemiologic studies have associated biogenic silica with increased risk for cancers of the upper digestive tract and of the lungs and pleural cavities.[16]

II. PATHOGENESIS AND MORPHOGENESIS

Crystalline silica is one of the most toxic minerals known. It is ubiquitous in the environment, and exposure to fine particulates of crystalline silica are common in the industrial and environmental setting. The pathogenesis of silicosis has been extensively researched (see Chapter 1, Section III). Crystalline silica is toxic to a wide range of animal species, including man. Individual susceptibility does not appear to be an important factor in the development of silicosis. Cumulative exposure, intensity of exposure, and latency are the most important factors in determining the type and progression of silicosis in humans.[17]

Examination of human lungs and lungs from experimental animals at various stages and severity of disease indicates that the classic silicotic nodule evolves through a series of immature forms. The evolution of these lesions can be interpreted as an attempt by the body to sequester the silica particles from sensitive tissues and cells. The earliest lesions consist of aggregates of macrophages and histiocytes, which assume a granulomatous arrangement. Lymphocytes are seen within the lesion at this stage. With

further maturation, the histiocytic cells assume the characteristics of fibroblasts and the amount of collagen increases. Gradually over a period of several months to several years, the connective tissue fibers become circularly orientated to the center of the lesion. At this stage, the lesion can be confidently diagnosed as a silicotic nodule. Over a period of several years to decades the nodules become more acellular, histiocytic cells and lymphocytes disappear from the body of the lesion, and the collagen fibers become more hyalinized. Finally, central necrosis, calcification, or secondary infection with mycobacteria may occur.

Radiographic studies have shown that silicosis tends to progress even in the absence of continuing exposure.[11,17] It is not possible to determine from autopsy material whether this growth occurs as a result of a chronic stimulus for collagen deposition from silica dust already present within the nodule, or results from the accretion of newly deposited or redistributed dust to its surface.

The mechanism(s) of silica toxicity has remained elusive. Investigations into the pathogenesis of silicosis have focused on four broad areas of research:

A. PHYSICAL AND CHEMICAL PROPERTIES OF PARTICULATE SILICA

On an equivalent weight or surface area basis, the toxicity of silica is much greater than other nonfibrous mineral dusts found in the occupational setting. Theories based on the reaction of silanol (hydroxyl) groups on the particle surface, or hydrogen donation by polymeric silicic acid to form complexes with phospholipids in cell membranes, do not adequately explain the toxicity of silica.[18,19] The formation of silica free radicals on the particle surface may be a factor in the cytotoxicity of the silica.[20–22] The greatest production of free radicals occurs when the mineral is freshly fractured.[21] As the dust ages, free radical formation is reduced. This factor may account for differences in toxicity seen in animal and epidemiologic studies. Other surface properties such as charge, shape (edge effects), and surface area may also play a role in the toxicity of silica but have not been extensively investigated. The toxicity of silica can be markedly reduced by coating of the particle surface or chemical modification. Surface modification experiments include such compounds as organosilane,[23] surfactant,[24,25] polyvinylpyridine-N-oxide (PNO),[26] and aluminum compounds.[27]

B. DEPOSITION, CLEARANCE, AND RETENTION OF SILICA PARTICLES

Several observations indicate that lymphatic injury and obstruction to the lymphatic clearance pathways may be important factors in the pathogenesis of silicosis. Morphologic studies indicate that silica is more likely to be retained in the lung than an "inert" dust or amorphous silica[28–30] and that silica particles become concentrated at convergence points for clearance pathways.[31] At low exposure concentrations, when alveolar clearance mechanisms are presumably intact, the lung parenchyma of silica dust-exposed workers are usually free of disease, and silicotic nodules are only seen in the tracheo-bronchial and intrapulmonary lymph nodes.[32] Once a certain exposure threshold has been breached, it is likely that silica injures lymphatic vessels, impeding clearance of the particles.[33] This would explain the characteristic distribution of parenchymal silicotic nodules along the lymphatic routes in the pleura, interlobular septa and bronchopulmonary rays. At even greater exposure levels, lesions are seen throughout the pulmonary interstitium, and the alveoli become flooded with lipoproteinaceous material (silicolipoproteinosis). These features would indicate that lung liquid clearance is inhibited. Thus lymphatic obstruction could also be a factor in the progressive accumulation of lipoproteinosis material in acute and accelerated silicosis.

C. INTERACTION OF SILICA PARTICLES WITH CELL MEMBRANES, CELLS, TISSUES, AND ORGANS

Regardless of the mechanism, there is extensive evidence that quartz particles are membranolytic and cytotoxic to macrophages and other cells. For further discussion of the many interactions between silica particles and cellular components, see Chapter 1, Section III.

D. CELLULAR AND HUMORAL RESPONSES ASSOCIATED WITH DISEASE AND DISEASE PROGRESSION

Exposure to quartz results in the release of inflammatory cytokines, such as tumor necrosis factor (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and platelet-derived growth factor (PDGF) from macrophages and possibly from other cells. These cytokines modulate the inflammatory and fibroblastic

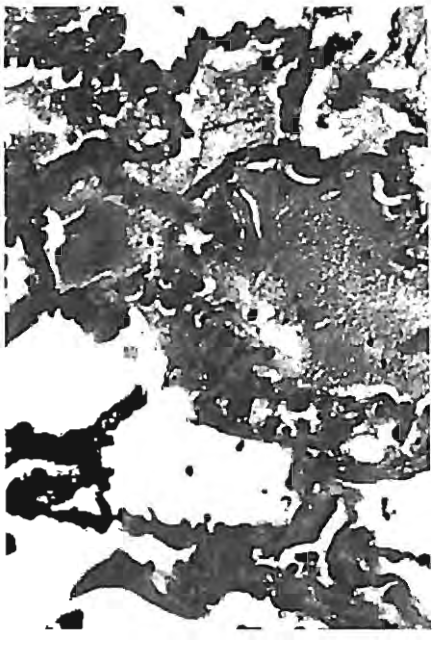


FIGURE 1 Acute silicolipoproteinosis in a 33 year surface coal miner (rock driller). Open lung biopsy section showing granular material within the alveoli.

response and interact, in ways that are currently not understood, to produce the classic nodular and other pathologic features of silicosis. In addition, release of proteolytic enzymes following membrane damage may also play a role in promoting leakage of fluid from blood vessels and lymphatics and in the development of emphysema (see section M.). Activation of T-lymphocytes by inflammatory cytokines may also play an important role in disease progression and systemic effects.[34] A detailed discussion of these factors is beyond the scope of this chapter (see Section III).

III. PATHOLOGICAL FEATURES

A. SILICOLIPOPROTEINOSIS (ACUTE SILICOSIS)

Acute silicolipoproteinosis is a rapidly progressive form of silicosis with a high mortality rate. It follows intense exposure to crystalline silicon dioxide, usually in the form of quartz, but also to the more fibrogenic polymorphs, cristobalite and tridymite. It may develop after only six months of such exposure. It has been described in workers involved in tunneling,[35] sandblasting,[36] silica flour mill operations,[37] rock drilling, and in the ceramic industry.[38,39] These activities produce fine particles of quartz (<1 μm) with cleaved or sheared surfaces rich in relatively short-lived free radicals of Si and SiO.[20,21] Small particle size and "freshness" of the particle surface are important factors in silica particle toxicity.

The lungs from fatal cases at autopsy are heavy and firm, and their cut surfaces exude glistening fluid. The lungs may have a slightly nodular texture. The gross appearances of the lungs are similar to those observed in other forms of alveolar lipoproteinosis.[40] The gross appearances should be distinguished from acute pulmonary edema. In this condition, the lungs are softer and exude frothy blood-tinged fluid, which is maximal in the dependent zones.

Microscopically, the fluid within the alveoli in alveolar lipoproteinosis bears a superficial resemblance to classic alveolar edema. However, it is a deeper pink on hematoxylin and eosin (H&E) stained sections and at high magnification it has a finely granular appearance (Figure 1) and may contain cholesterol clefts. The material stains magenta with periodic acid-Schiff method (PAS) and is resistant to diastase digestion. It is nonreactive with traditional mucin stains.[39,40] It contains abundant lipid which is best seen on frozen sections stained by Oil Red O or Sudan Black. There is usually an associated chronic interstitial pneumonitis. Granulomatous inflammation and early silicotic nodules may also be seen. These inflammatory and fibrotic changes, when present, help to differentiate silicolipoproteinosis from other forms of

alveolar lipoproteinosis which do not have an interstitial or inflammatory component. Birefringent particles may be seen within the alveoli on polarizing microscopy; however, in most cases the particles are below the limits of resolution of the light microscope (<0.5 μm). The alveoli are lined by prominent type II cells which have been shown to be both hypertrophic and hyperplastic.[41] Surfactant apoprotein has been demonstrated immunohistochemically in human lungs showing alveolar lipoproteinosis.[42] This is associated with increases in surfactant phospholipids and surfactant proteins.[41] Electron microscopy of the alveolar material shows that it largely consists of multilaminated structures, membranous vesicles, granules, and other electron opaque materials. Abnormal tubular myelin-like multilaminated structures account for 30 to 60% of the total particulate volume.[43]

Silica is one of many agents that can increase phospholipid levels in the lung. These include oxidant gases, particulates, soluble agents, and therapeutic agents with amphiphilic cationic properties (see Chapter 8, Section III). A history of exposure to dust or fumes has been elicited in about half the reported cases of alveolar lipoproteinosis,[40] including exposure to wood dust, kaolin, aluminium, cement, welding fumes, and cadmium, in addition to silica. Backscatter electron microscopy in combination with X-ray microanalysis of the alveolar material has been used to demonstrate particulates in 78% of cases of lipoproteinosis.[44] These particles are usually very small and below the resolution of the light microscope.

Experimental studies have shown that silica induces hyperplasia and hypertrophy of alveolar type II cells associated with massive accumulation of intracellular and extracellular phospholipids in the lung. The number of lamellar bodies is also greatly increased in the hypertrophic cells, indicating increased biosynthesis of phospholipid and surfactant protein-A.[45–47] Enhanced secretion alone cannot account for the progressive accumulation of the surfactant materials. Recent experimental evidence indicates that imbalances between biosynthesis, secretion, and clearance are also important.[48] Because of the many morphological and biochemical similarities between human and experimental silicosis, it is likely that similar mechanisms are involved in the pathogenesis of human disease. Silica may be a particularly potent inducer of alveolar-lipoproteinosis in view of its cytotoxic effects on the alveolar capillary membrane,[49] leading to alveolar flooding. Analysis of fluid from patients with alveolar lipoproteinosis reveals large amounts of protein in addition to phospholipid.[41] Serum proteins and, in particular, fibrinogen are potent inhibitors of surfactant activity,[50,51] and they may, in part, account for the loss of normal surface active properties of material extracted from lung specimens.[52]

B. ACCELERATED SILICOSIS

This form of the disease is associated with high to moderately intense exposure and has a latency of 1 to 14 years. It has been described in men exposed to dust in silica flour mill operations,[37] during the manufacture of slate pencils, and in shipyard sandblasters[53] and stonemasons.[36]

In this condition, the exudative alveolar response of acute silicosis[54] may progress to a predominantly interstitial process characterized by chronic inflammation and the formation of cellular fibrotic nodules. The latter contain histiocytic cells enmeshed in a variable amount of mature and immature collagen and reticulin. Some of the lesions have the appearance of granulomas (Figure 2); others show a greater number of fibroblasts with circular orientation of the collagen fibers. The latter are the immature form of the hyalinized classic nodule of chronic simple silicosis described below. From the description it can be seen that accelerated silicosis occupies an intermediate position, showing some of the features of acute silicosis at one extreme and of chronic nodular silicosis at the other.

C. CHRONIC SIMPLE SILICOSIS

This is the most common form of lung disease associated with the inhalation of crystalline silica. The disease may take several decades of low intensity exposure to become apparent on the chest radiograph. Thereafter the disease may progress slowly over many years. Epidemiologic studies based on chest radiography have shown that the overall density and size of the silicotic nodules are primarily determined by cumulative exposure and latency.

The characteristic pathologic lesion is the silicotic nodule. Macroscopically, the nodules appear as rounded, firm to hard regions of fibrosis that are sharply demarcated from the surrounding lung parenchyma (Figure 3). They range in size from a few millimeters to several centimeters in diameter. The nodules are more common in the upper and posterior regions of the lung and frequently involve the visceral pleura. They are seen in greatest density in regions of the lung rich in lymphatic channels. These sites include pleura, interlobular septa, and peribronchial connective tissues. They are not confined to

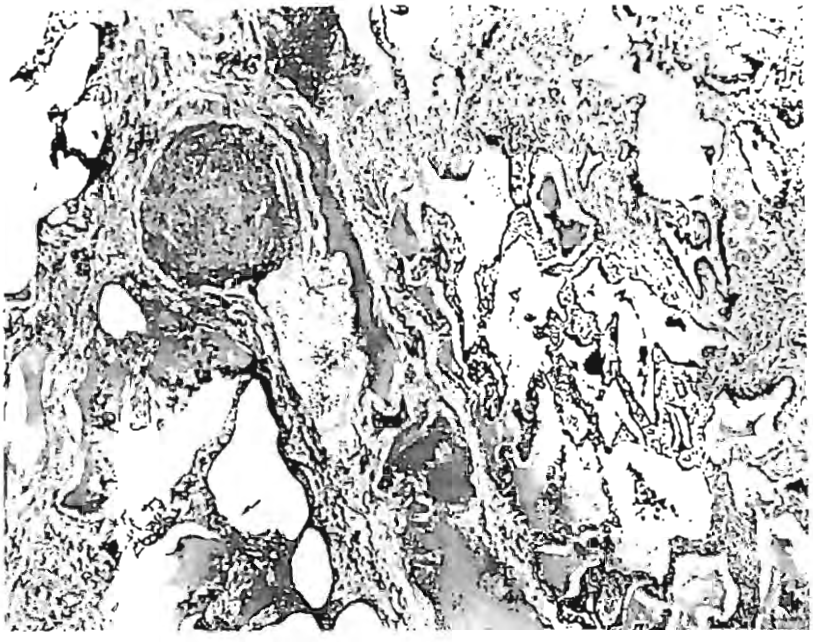


FIGURE 2 Accelerated silicosis. Low magnification view showing thickened alveolar septa lined by hyperplastic type II cells and enclosing lipoproteinaceous material. An evolving silicotic nodule is seen at bottom left.

FIGURE 3 Chronic simple silicosis in a coal miner. Whole lung section showing round silicotic nodules predominantly in the upper zone of the lung. Many of the nodules have pale centers, and there is a tendency of the nodules to coalesce.

these sites, however, and may originate in any part of the lung parenchyma, including the peripheral interstitium and even within the alveoli.[55] The center of the cut surface of the classic lesion is pale but may become pigmented due to concomitant exposure to carbonaceous dust. They frequently show calcification.

The microscopic appearance of the simple silicotic nodule is characteristic and unlikely to be confused with other pathologies. In its mature form, the nodule is composed of concentrically arranged, whorled bundles of hyalinized collagen showing variable calcification within the center (Figure 4). The nodule itself may be relatively free of pigmentation but is usually surrounded by a more cellular periphery consisting of dust-containing macrophages, fibroblasts, reticulin, and occasional lymphocytes. Polarizing microscopy reveals dull, birefringent particles, consistent with quartz, primarily within the center of the hyalinized nodule. Brightly birefringent particles with acicular and needle-shaped profiles, indicative of silicates, are also commonly present and tend to be concentrated at the periphery of a lesion. Identification of the chemical nature of the particles can be performed *in situ* on 5 μm paraffin sections using backscatter electron imaging and X-ray microanalysis (Figure 5).[56]

Parenchymal silicosis is almost invariably associated with the development of silicotic nodules within the lymph nodes. However, the reverse is not true, and many individuals develop nodules in the lymph nodes without having parenchymal silicosis.[32,33] It is therefore important not to make the diagnosis of silicosis based on examination of lymph nodes alone.

D. SILICA CONTENT OF HUMAN LUNGS

The mean number of exogenous mineral particles in the lungs of urban dwellers without specific occupational exposures has been shown to be approximately 508 (±417 SD) × 10^6 per gram of dry lung.[57] Approximately 18% of these mineral dust particles had a chemistry consistent with silica. The other major mineral species were aluminum silicates (38%), rutile (10%), iron oxide (6%), and magnesium (3%). This burden of mineral dust was not associated with the development of disease. By contrast, the lungs of patients with silicosis may contain up to 16,000 × 10^6 exogenous mineral particles per gram of dry lung of which up to 50% may be silica.[57] Gravimetric analyses of silica content of normal lungs have shown that approximately 0.1 to 0.2% of dry tissue is comprised of silica dust and pulmonary lymph nodes may contain from 0.23 to 0.6% silica.[14] The silica content of silicotic lungs may be as high as 20% of the dry weight[35] but more commonly is in the range of 2 to 5%.[58,59]

E. PROGRESSIVE MASSIVE FIBROSIS

Silicotic progressive massive fibrosis (PMF) is a large fibrotic lesion that is somewhat arbitrarily distinguished from the classic nodule on the basis of size. The Silicosis and Silicate Disease Committee of NIOSH recommended that PMF be defined as a lesion greater than 2 cm in diameter.[39] However, the radiologic definition of PMF, established by the International Labor Office (ILO), defines PMF as an opacity on the chest X-ray that is 1 cm in diameter or greater.[60] The situation is further complicated by the fact that radiologic size, assessed on the chest film, may not be identical to pathologic size due to the divergence of the X-ray beam from its source to the film. A radio-dense nodule with an actual size of 1 cm situated in the anterior thorax will appear approximately the same size on a standard postero-anterior film; whereas the same nodule in the posterior thorax would appear approximately 15% larger.[133] For this reason, and because there are important legal implications in making a diagnosis of PMF, we recommend that pathologists document the exact size of the larger nodular lesions in the lungs of a patient with silicosis.

PMF is formed by the coalescence and agglomeration of smaller nodules. It is usually symmetrically bilateral and may undergo cavitation. It is associated with destruction of the lung parenchyma and broncho-vascular structures. Marked distortion of the adjacent lung is seen due to contraction of the fibrosis (Plate 1*). Mycobacterial infection should be suspected in cases showing cavitation and appropriate attempts made to isolate and identify the organisms.

Histologically, PMF shows discrete and coalescing silicotic nodules enclosing areas of cavitation and necrosis (Figure 6). Silicotic alveolar proteinosis may be present adjacent to the areas of fibrosis.[1] Elastic stains are useful in these advanced lesions to demonstrate widespread destruction of blood vessels and airways.

F. PLEURAL AND LYMPH NODE LESIONS

Subpleural silicotic nodules are a common feature of silicosis. They appear as pale elevated domes above the pleural surface surrounded by a zone of black pigmentation. They have been termed candle wax

* Plate 1 follows page 50.

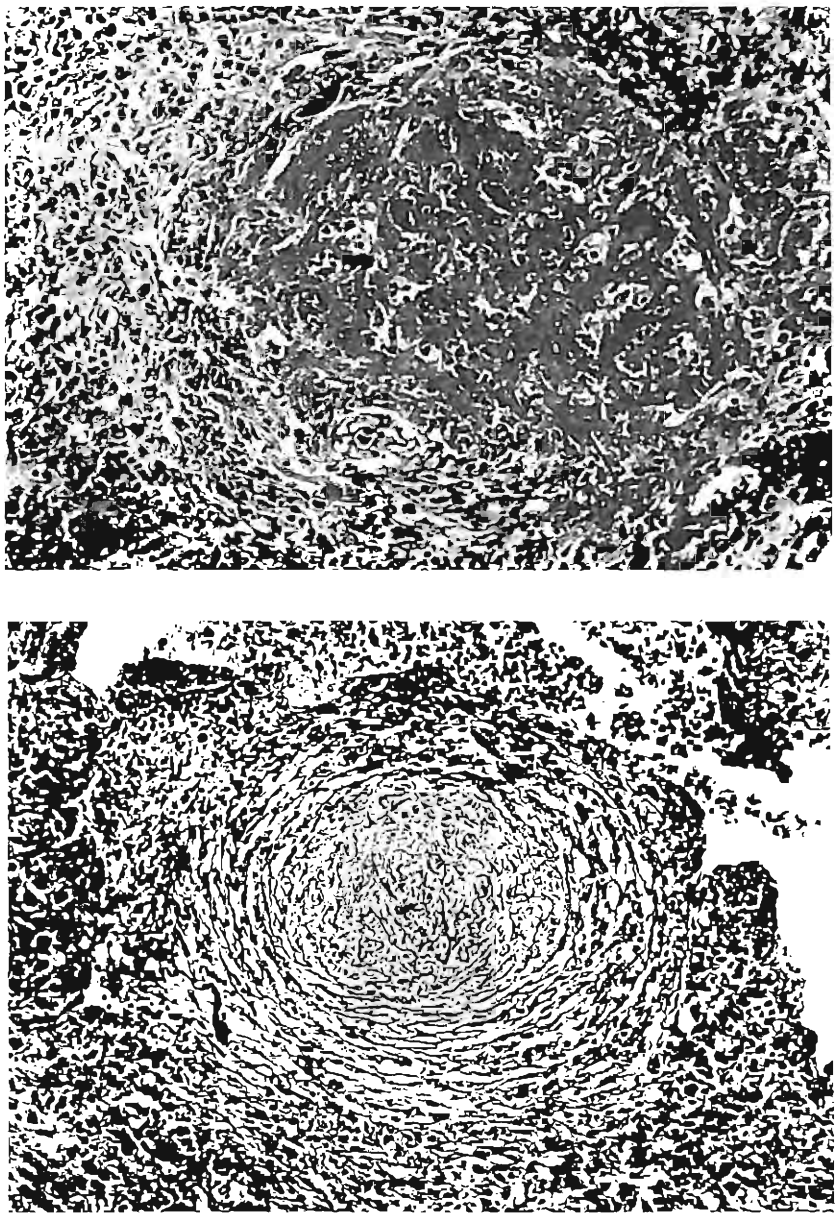


FIGURE 4 Chronic simple silicosis. The four photomicrographs show the classic silicotic nodule at varying stages of evolution. A. Silicotic nodule in granulomatous phase. The lesion is composed predominantly of histiocytic cells, collagen fibers, and lymphocytes. The orientation of the collagen fibers is not apparent at this stage. B. Cellular fibrotic nodule containing irregularly arranged collagen at center with circularly arranged collagen at the periphery. Histiocytes and lymphocytes are prominent in this lesion. C. More mature nodule: the center of the lesion is acellular and avascular. Small amounts of dust are trapped within the circularly orientated collagen fibers. A cellular mantle of macrophages and pigment is seen at the periphery. D. Mature nodule in late stages. The outline of the nodual is circular, apart from a small mantle of dust and macrophages. The nodual is composed entirely of dust and collagen, and the center has become calcified.

lesions because of these characteristic features.[39] Histologically, the nodules have a hyalinized core with the concentric arrangement of collagen fibers seen in the classic silicotic nodule (Figure 7A). The overlying pleura is fibrotic. Adjacent lesions may coalesce to form a network of lesions. Pleural pearls have been described in association with these lesions and may represent sequestration of subpleural nodules into the pleural cavity[134] (Figure 7B). Silicotic pleural lesions should not be confused with asbestos pleural plaques which form on the parietal aspect of the pleural surface.

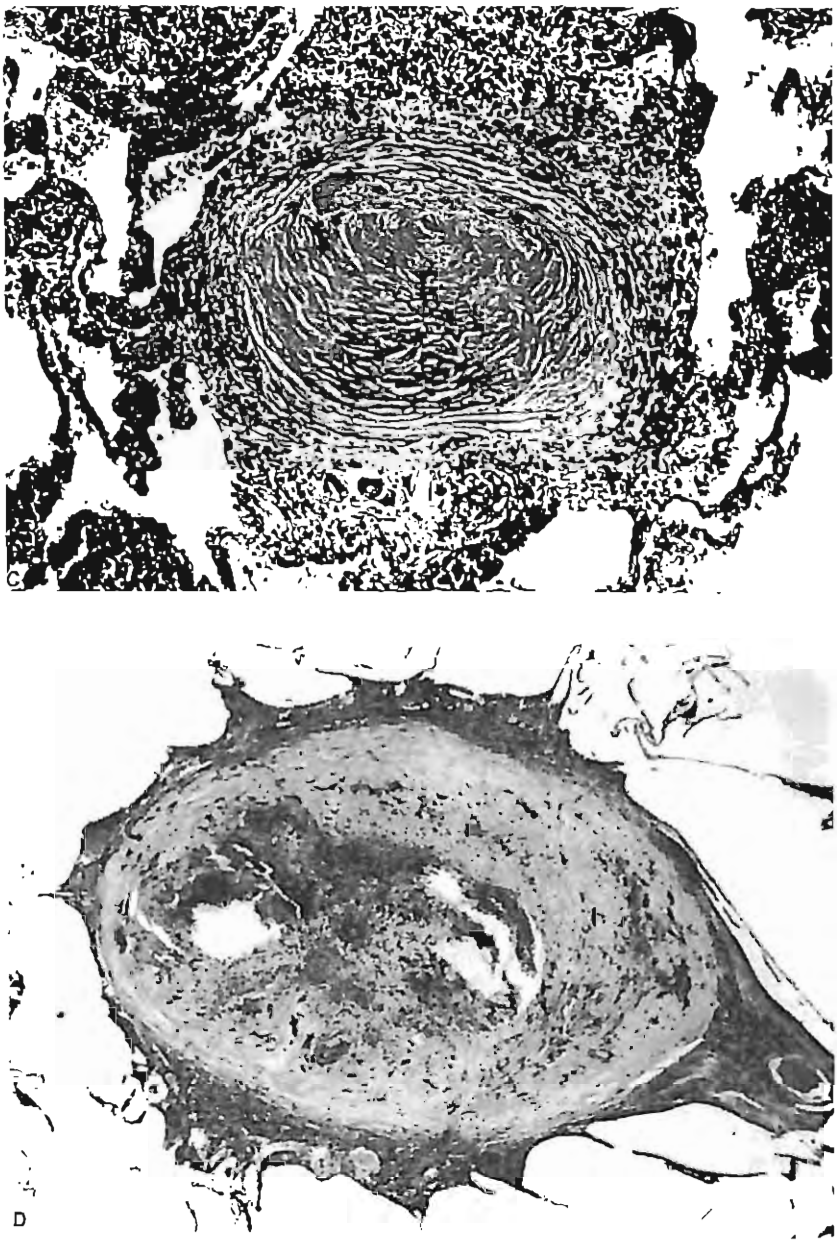


FIGURE 4 (continued)

Exposure to silica is also associated with the development of fibrotic nodules in the hilar lymph nodes (Figure 8),[32,33] and at distant sites (see section P.). It has been suggested that the development of fibrotic nodules in the lymph nodes may predispose to the subsequent development of parenchymal silicosis[33] due to the obstruction of the lymphatic drainage of the lung with resultant increase in lung dust burden.

G. MIXED DUST PNEUMOCONIOSIS

This term was originally applied by Uehlinger in 1946 to a form of nodular fibrosis caused by free silica in combination with less fibrogenic dusts such as iron oxide, silicates and coal.[61] The term is only applied to those situations where the silica is inhaled at the same time as the other dusts.[14] Mixed dust fibrosis has been described in workers in the following industries: hematite mining (free silica and iron oxide), slate quarrying (quartz, muscovite),[62] iron and steel foundries (quartz, tridymite, or cristobalite

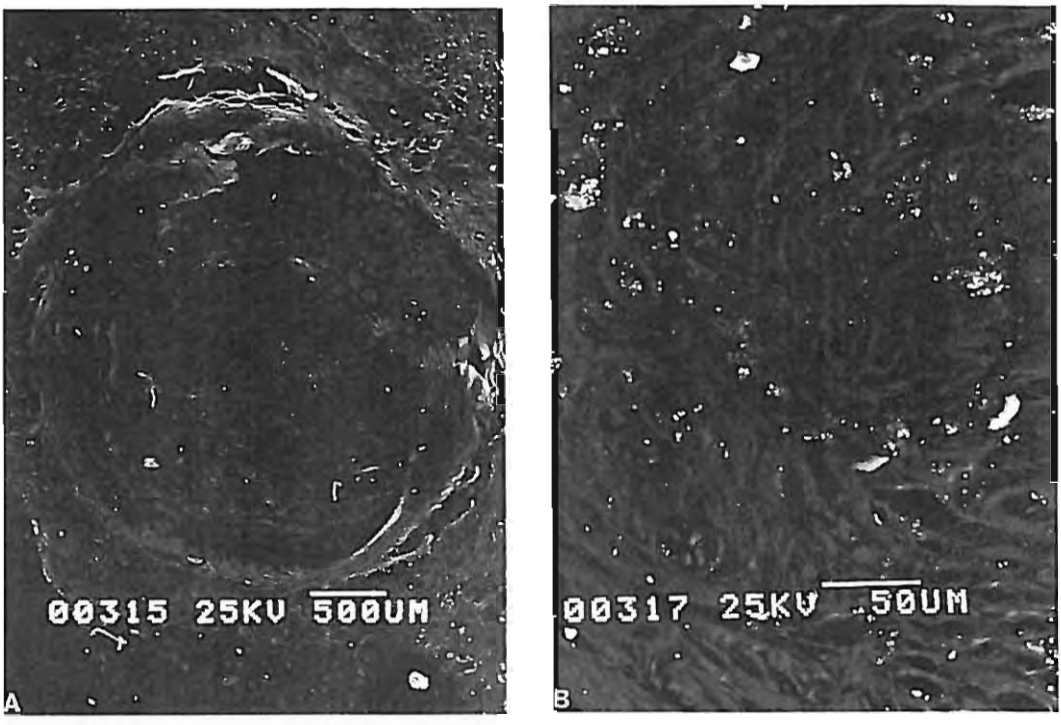


FIGURE 5 Scanning electron micrographs of a 5 micron, deparaffinized section of silicotic nodule mounted on a carbon stub. A. The orientation of the collagen fibers is apparent when viewed in secondary electron mode. B. Backscattered electron image from center of lesion showing large numbers of high atomic number particles embedded in the collagenous stroma. X-ray microprobe analysis of these particles (data not shown) revealed that the majority had a chemistry consistent with silicon dioxide.

and iron oxide), welding (quartz and iron oxide fumes), oil shale mining (quartz, mica, and kaolin), ceramic and china clay industry (quartz, kaolinite, and mica), coal mining (quartz, aluminosilicates, carbonates, and feldspars), and manufacture of silicon carbide abrasives[63,64] and other dusts.[14,65]

The amount of quartz in the dust varies but is usually less than 20%; above this level, the pathology more closely resembles classic nodular silicosis.[15] A variety of experimental and human evidence indicates that quartz is less fibrogenic in the presence of these other minerals. The ability of coal dust to reduce quartz fibrogenesis is considerable. In one experiment, Rhesus monkeys exposed to coal dust containing 40% quartz failed to produce classic silicotic lesions.[66] This mitigating effect has also been studied in rats where it was thought that it resulted from non-quartz silicates and other minerals in the coal.[67] Iron oxide is potent at mitigating fibrogenesis in experimental situations.[68] Studies of deceased miners also indicate that iron hydroxide may be effective in preventing quartz fibrogenesis.[69] Metallic aluminum dust and aluminum lactate have also been used to inhibit silicosis in experimental animals.[27,70,71] Based on the results of the early studies, aluminum inhalation was employed in an attempt to prevent the development of silicosis in gold miners during the early 1940s to the mid 1950s.[14] The results of these trials were not successful.[14,72]

The distribution of the nodules of mixed dust fibrosis is similar to that seen for silicosis and coal workers' pneumoconiosis (CWP).[39,73] The nodules range in size from 2 mm to 1 cm or more and may show varying degrees of pigmentation depending on the composition of the dust. The mixed dust nodule has a more irregular border than the classic silicotic nodule, and the fibrosis tends to extend out into the surrounding lung parenchyma.

Microscopically, the nodules show irregularly arranged, interlacing bundles of collagen and reticulin fibers interspersed with dust. The concentric arrangement of fibers typical of the classic silicotic nodule is not seen. The dust is uniformly distributed throughout the nodule, and polarizing microscopy commonly reveals brightly birefringent silicates in addition to occasional particles of the less birefringent quartz. A distinctive feature of the mixed dust nodule is an irregular or serpiginous border, with

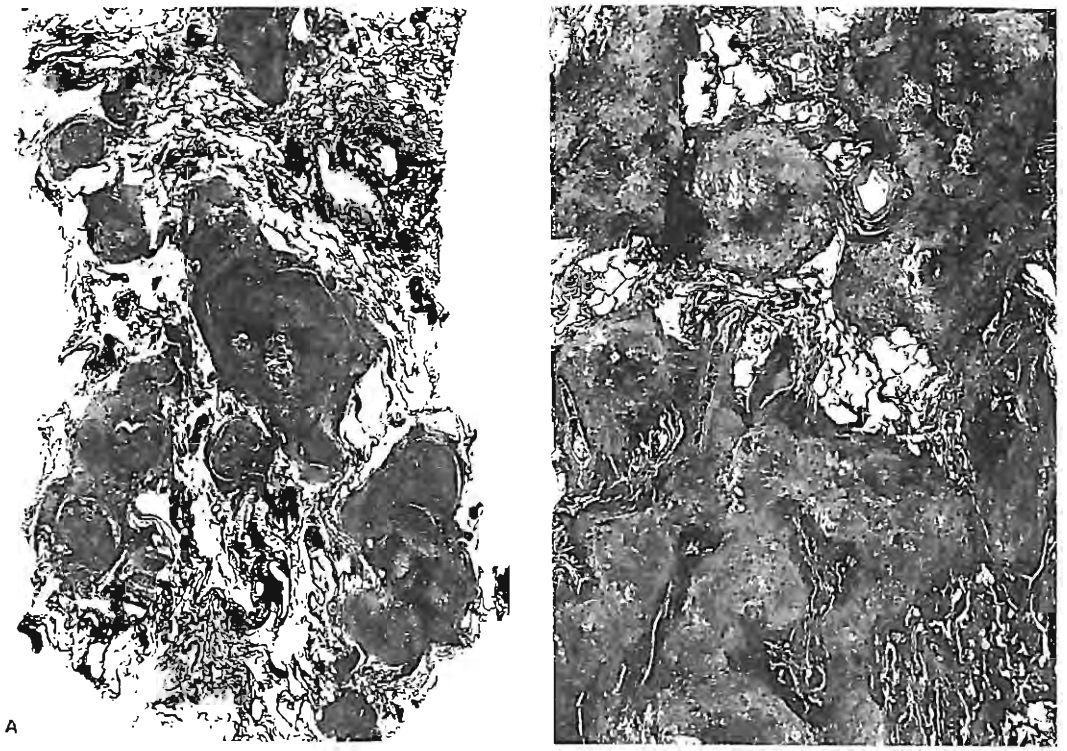


FIGURE 6 Silicotic progressive massive fibrosis. A. Section of lung from miner with advanced simple silicosis showing fusion of discrete silicotic nodules to form massive lesions. B. More advanced stage of silicotic progressive massive fibrosis showing fusion of multiple nodules to form large conglomerate areas of fibrosis in which the outlines of individual nodules can still be discerned. Several areas within the fibrosis show cavitation, a feature characteristic of massive fibrosis.

finger-like extensions into the adjacent interstitium (Figure 9). Although calcification and necrosis can occur, these features are uncommon. Massive fibrosis and tuberculous pneumoconiosis may arise in association with mixed dust fibrosis. Macules, interstitial fibrosis, and ferruginous bodies may also be associated with mixed dust pneumoconiosis.[39]

H. SILICOSIS IN COAL WORKERS

Exposure to quartz at underground and surface coal mines depends on a number of factors including the thickness of the seam, the composition of the adjacent rock strata, faults and undulations, method of mining, and specific job of the miner. Miners employed in transportation, roof bolting, and tunnel drilling are at much greater risk of developing silicosis than miners employed in other job categories.[32,75–77] Marked regional differences in the prevalence of silicosis have been found. In an autopsy study of U.S. underground coal miners, a very high prevalence of silicosis (35%) was noted in miners previously employed in the eastern anthracite coal fields of Pennsylvania. This finding is in keeping with epidemiologic studies documenting a high prevalence of pneumoconiosis in anthracite miners.[78] By state, Pennsylvania had the highest overall prevalence of silicosis (15%) followed by Wyoming and Utah (14.2%), West Virginia (13.7%), Colorado (9.5%), Virginia (6.5%), Illinois (5.2%), Kentucky (4.5%), and Ohio (4.1%).[32]

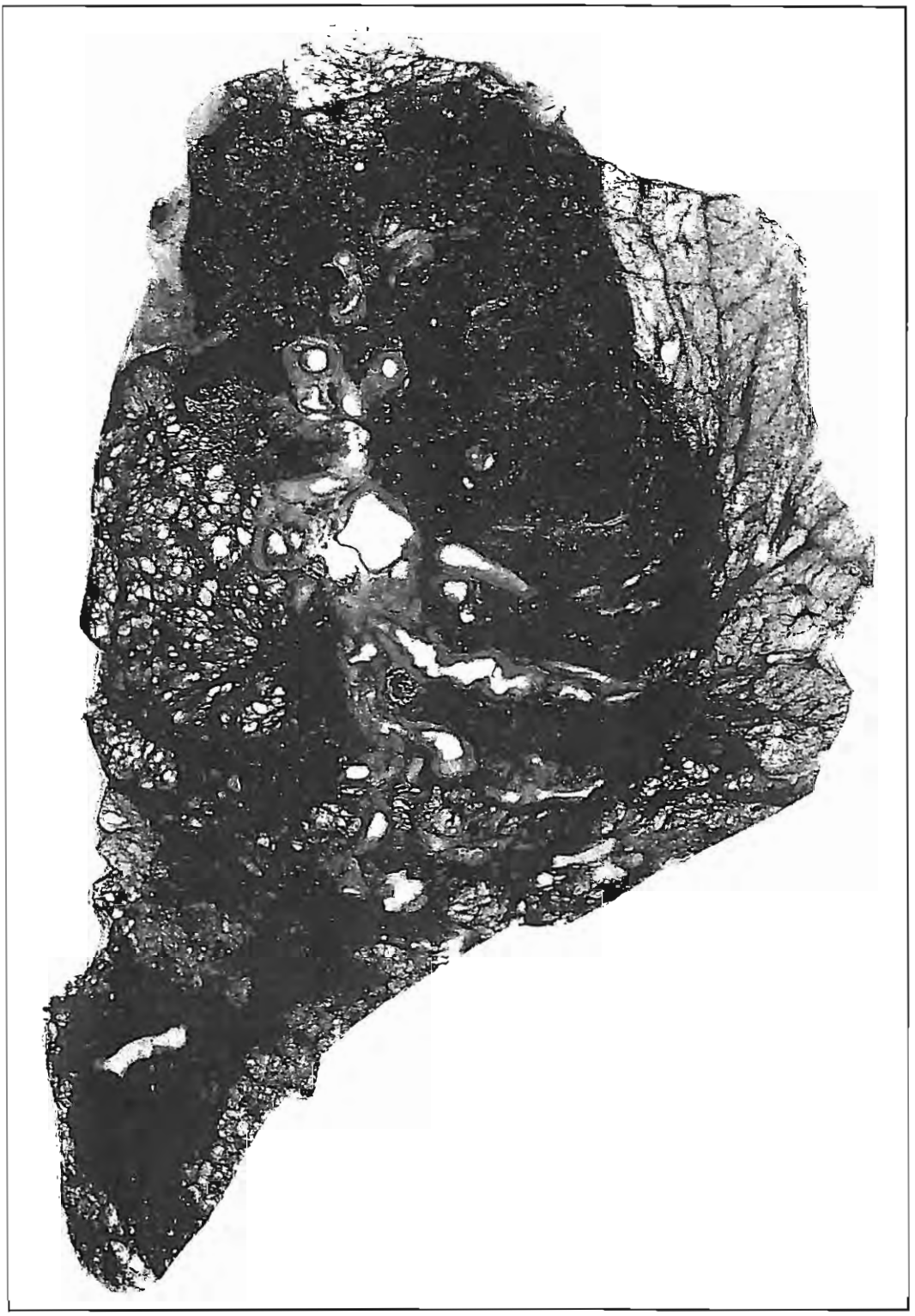
Although the majority of nodular lesions in coal workers can be considered to be of the mixed dust variety, classic silicotic nodules are also seen in the lungs of coal workers. Many of these contain a central hyalinized and concentrically arranged core of collagen surrounded by a heavily pigmented border of irregularly arranged collagen and reticulin (Figure 10). A study of autopsy specimens from U.S. underground coal workers submitted to the National Coal Workers Autopsy program revealed that 12.5% of the population showed classic silicotic nodules in the lung parenchyma. A much larger proportion (53%) showed silicotic nodules in the tracheobronchial lymph nodes (Table 1).[32] Furthermore, an exposure-response relationship was noted for both extent and severity of silicotic lesions in the lung parenchyma.

FIGURE 7 Pleural lesions: A. Subpleural silicotic nodule:[23] This section shows two fused nodules with characteristic concentric arrangement of the collagen fibers. The surface of the nodule projects from the pleural surface and compresses the adjacent underlying lung. B. Pleural Pearl: the silicotic nodule projects from the pleural surface. Other lesions were detached from the pleural surface.

A reliable diagnosis of silicosis in coal workers can only be made at autopsy or lung biopsy,[39,73] as it is impossible on routine chest radiography to distinguish the nodules of CWP from those of silicosis.[60] It is also possible by pathologic examination to distinguish silicotic nodules from those associated with infections (for example, tuberculosis and histoplasmosis) and from nonspecific scars in the lung. A radiographic feature that does appear to correlate with the presence of silicosis pathologically is the presence of r-type opacities.[79,80] However, this is a statistical association and is of limited usefulness in the diagnosis of an individual case. A radiographic sign that is thought to be indicative of silicosis is egg-shell calcification of the tracheo-bronchial and hilar lymph nodes.[14] Calcification is a nonspecific response to injury and may be seen in inflammatory and infectious conditions as well as chronic fibrosing conditions such as silicosis. Moreover, the high prevalence of silicotic nodules in tracheo-bronchial lymph nodes in U.S. coal miners in the absence of parenchymal lesions would indicate that the sign has little diagnostic usefulness for predicting the presence of parenchymal silicosis.[32]

I. RHEUMATOID PNEUMOCONIOSIS

Rheumatoid pneumoconiosis is a rare condition characterized by rapidly evolving large radiologic opacities, particularly in the peripheral areas of the lung in patients with rheumatoid disease or with sera positive for rheumatoid factor.[14] Macroscopically, the lesions exhibit alternate laminations of light and dark areas due to zones of dust deposited within areas of necrosis. They range in size from 0.5 to 5 cm, tend to be located in the periphery of the lung, and, unlike PMF, occur against a background of mild pneumoconiosis. They have a similar appearance to those seen in coal workers.[39,55] Microscopically they consist of a central zone of fibrinoid necrosis surrounded by pallisaded histiocytes and variable numbers of polymorphous neutrophils, lymphocytes, and fibroblasts. They can only be reliably distinguished from mycotic and mycobacterial infectious nodules through culture and appropriate histologic stains.



SECTION I, CHAPTER 5, PLATE 1

Whole lung section of silicotic progressive massive fibrosis.

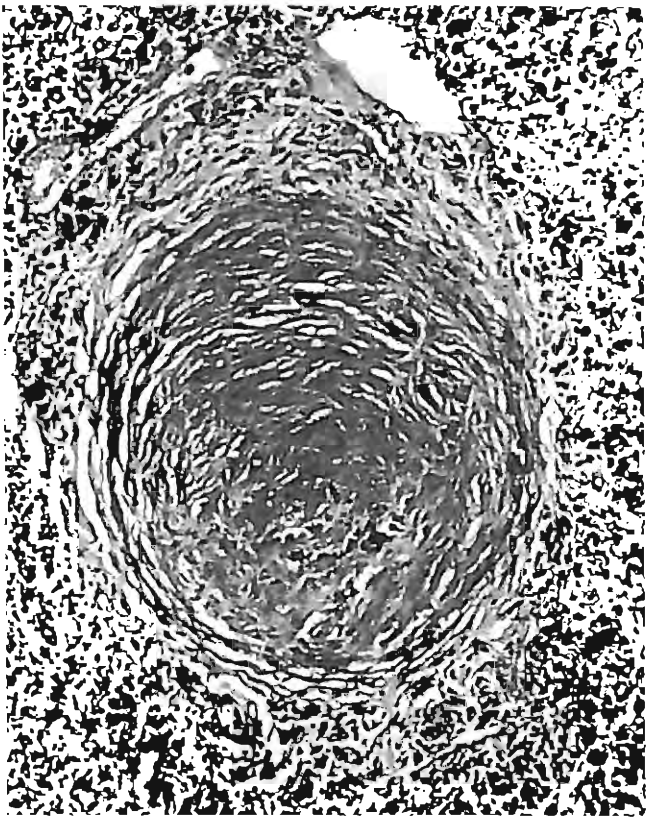


FIGURE 8 Silicotic nodule in a lymph node. The nodule is morphologically identical to those found in the pulmonary parenchyma. The periphery consists of lymphoid tissue.

J. SILICO-TUBERCULOSIS

Tuberculosis is a common complication of silicosis that may occur at any stage in the evolution of the disease but is more likely to occur in older workers with severe grades of silicosis.[14,81] Historically, death from tuberculosis among miners has been of epidemic proportions.[82,83] In the early 20th century, the average working life of a black South African gold miner was 5 years,[84] and pulmonary tuberculosis was a major contributor to death in virtually every instance.[85] Indeed, the association of mining with tuberculosis has been so strong that a clear distinction between silicosis alone and silicosis with tuberculosis was not made until 1935.[86] Since that time the incidence of tuberculosis has progressively decreased with the initial enforcement of dust control measures in 1912, the development of drug regimens that could cure tuberculosis in 1950, and the institution of short-course chemotherapy in 1977.[82] Despite these advances the incidence of tuberculosis remains high in black South African gold miners. A group of 1,153 gold miners without evidence of tuberculosis at entry in 1984 was followed for 7 years by a routine mine surveillance program for detection of tuberculosis.[81] The incidence of tuberculosis increased from 1% per annum for 335 men without silicosis to 2.2% in miners with Category I silicosis, to 2.9% for those with Category 2, and to 6.3% for those with Category 3. An increased risk for pulmonary tuberculosis with higher grades of silicosis has also been reported in a recent study of Danish foundry workers.[87]

The clinical features vary, but rapid radiologic progression, cavitation (unilateral), and hemoptysis are all highly suspicious of tuberculous infection in a person with pre-existing silicosis. Tuberculosis in a person exposed to silica dust may be difficult to distinguish from PMF and rheumatoid pneumoconiosis, both clinically and pathologically; hence, a high degree of suspicion combined with appropriate bacteriologic study is required to establish the diagnosis.

The predilection of mycobacteria to colonize and proliferate in silicotic lung tissue is not confined to *M. tuberculosis*. Other pathogenic mycobacteria: *M. avium-intracellulare*, *M. scrofulaceum,* and *M.*

FIGURE 9 Characteristic mixed dust nodule in a coal worker. Note that the nodule is composed of interlacing bundles of collagen mixed with pigment and that there is no central orientation of the collagen fibers. The irregular serpiginous borders are characteristic of the mixed dust nodule.

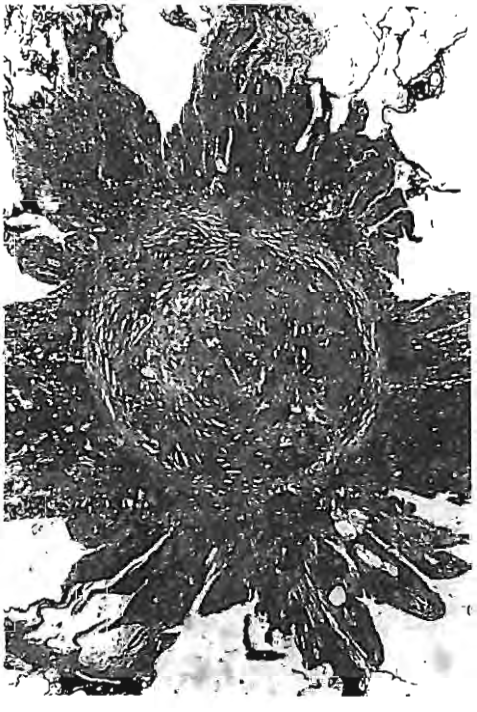


FIGURE 10 Silicotic nodule in a coal miner. The lesion is composed of a central silicotic nodule with characteristic circular arrangement of the collagen fibers surmounted by an irregular mantle of pigment, collagen, and reticulin extending out into the adjacent interstitum. These lesions have the appearance of classic silicotic nodules at the center and mixed dust nodules at the periphery, sometimes referred to as *anthracosilicosis* in the literature. (From Churg, A. and Green, F.H.Y., *Pathology of Occupational Lung Diseases*, Igaku-Shoin Medical Publishers, New York, 1988, 138.)

TABLE 1
Silicotic Nodules, Coal Dust Nodules, and Coal Macules in U.S. Coal Miners at Autopsy

Pathologic Type	Percent Positive
Silicotic nodule (parenchyma)	12.6
Silicotic nodule (lymph node)	52.9
Mixed dust nodules (parenchyma)	18.9
Coal dust macules	45.6

Data from U.S. National Coal Workers Autopsy Study.

kansasii have also been implicated, and nonpathogenic mycobacteria such as photochromogenic and nonphotochromogenic mycobacteria may colonize the lung and be isolated in the sputum.[88] The potentiating effect of silica dust on tuberculosis infection has been confirmed in other species[89] for both pathogenic and nonpathogenic strains of mycobacteria.[90] The mechanism that accounts for the enhancement of mycobacterial infection is not known with certainty. Most theories implicate the pulmonary macrophage. *In vitro* experimental studies have shown that macrophages dusted with silica are unable to kill mycobacterium tuberculosis[91,92] or even usually nonpathogenic mycobacteria.[93] However, the relevance of these studies to human disease is uncertain, as macrophages obtained from men with silicosis have been shown to have normal viability and function.[94]

It is of interest that tuberculosis and silicosis both favor the apices of the lung. It has been proposed that this is not fortuitous but results from impaired clearance mechanisms in this region.[95] Although this concept would provide a unifying hypothesis for the synergism between the two diseases, it would not account for the finding of increased extrapulmonary tuberculosis in men with silicosis.[81] The latter would implicate a systemic abnormality of immune function.

K. INTERSTITIAL FIBROSIS

Diffuse or focal interstitial fibrosis may be seen in association with the nodular lesions of chronic silicosis (Figure 2). This form of pulmonary fibrosis is more common in workers exposed to a combination of silica and silicates[96] and workers exposed to diatomaceous earth which contains a high concentration of cristobalite.[97,98] The interstitial fibrosis is usually of mild severity but may be sufficiently severe to result in honeycombing and respiratory failure.

L. VASCULAR LESIONS AND COR PULMONALE

Chronic cor pulmonale is defined as right ventricular hypertrophy due to structural or functional abnormalities of the lungs.[99] Advanced silicosis is associated with the development of pulmonary hypertension and cor pulmonale.[100,101] A recent case-control study of 732 South African gold miners showed that the risk for cor pulmonale increased with severity of silicosis.[102] Both chronic hypoxia and vascular obliterative changes probably contribute to the development of the cor pulmonale. The latter are common in silicosis due to the encroachment of silicotic nodules and lesions of massive fibrosis on the pulmonary vessels. Elastin stains are useful for the demonstration of obliterated and partially obliterated blood vessels in, and adjacent to, the lesions of silicosis.

M. EMPHYSEMA AND CHRONIC AIRFLOW OBSTRUCTION

Mortality studies of white South African gold miners have shown an association between cumulative dust exposure and death from chronic respiratory diseases (bronchitis, emphysema, and pneumoconiosis).[103-106] In these studies, both smoking and silica dust exposure were demonstrated to be major risk factors. Post-mortem examination of 1,553 lungs from autopsied white South African gold miners showed a positive association between cumulative dust exposure and both centriacinar and panacinar emphysema.[107] Centriacinar, but not panacinar emphysema, was also associated with the presence of silicosis in the lung. Animal experimental studies have also linked silica dust exposure with the subsequent development of small airway lesions and emphysema.[108] The emerging findings, with respect to the association between emphysema and silica dust exposure, are similar to those found for coal miners.[55]

N. AIRWAY LESIONS

Direct extension of silicotic lesions into the airway walls is a rare complication of silicosis[6] and is the only noninfectious cause of broncholithiasis.[109] Patients present with cough, hemoptysis, lithoptysis, pneumonia, fistula formation, and varying degrees of airway obstruction. Biopsy of the lesion may reveal florid granulation tissue and/or secondary infection overlying the calcified silicotic nodule.[6]

O. SILICOSIS AND LUNG CANCER

The relationship between silica exposure, silicosis, and lung cancer is controversial and has yet to be adequately resolved. Human epidemiologic and case registry studies have on balance shown that workers in industries exposed to silica, or individuals with silicosis, have a higher mortality from lung cancer than control populations[110–112] (see Chapter 2, Section V). Unfortunately most of these studies have not been adequately controlled for possible effects of confounding factors such as exposure to cigarette smoke, asbestos, polycyclic hydrocarbons, and radon gas. Furthermore, no clear dose-response relationship has been demonstrated in the positive studies. Animal studies have in general shown increased lung tumors in animal inhalation studies,[113] and, based on these data, the International Agency for Research on Cancer (IARC) classified silica as probable human carcinogen in 1987.[114] The relevance of the animal studies can be questioned as the studies show species and gender differences and little evidence for a dose-response relationship.[111] Moreover, recent evidence implicates particle loading rather than a specific agent as the trigger for development of lung tumors in rodents[115] (see also Chapter 1, Section V).

Unfortunately, very few pathologic studies have been conducted on appropriate populations. Well controlled pathologic studies could be used to determine whether silica influences the distribution of cell types (histogenesis), and microanalytical procedures could be used to determine the amount of silica and the presence of other mineral types, such as asbestos, and metals, such as arsenic. An autopsy study of South African gold miners found an increased prevalence of lung cancer in miners with silicotic nodules in the lymph node but not of the lung parenchyma.[116] The author speculated that reduced lymphatic clearance as a result of silica exposure may impede clearance of inhaled carcinogens.

P. SYSTEMIC EFFECTS OF SILICA EXPOSURE

Silica exposure is associated with local and systemic alterations in immune function.[3,38,103,117] These latter effects may account for the association of silicosis with scleroderma,[93,118] renal abnormalities,[119,120] hepatic abnormalities,[121] rheumatoid pneumoconiosis,[14,122] and susceptibility to infection with mycobacterium *tuberculosis* and *mycobacterium* avium *intracellulare*.

Scleroderma in association with silica exposure may be atypical in that the skin disease is often localized[123] and that other features of scleroderma, such as Raynaud's phenomena, microstoma, and systemic involvement, may be absent.[14] A recent survey of male patients with scleroderma in East Germany revealed that 93 of 120 (78%) had evidence of long term exposure to silica dust.[118] Antinuclear antibodies, antibodies against double stranded DNA, and anticentromere antibodies together with abnormalities of collagen metabolism were found in some, but not all, patients. The investigators proposed that crystalline particles of silica activate macrophages to release lymphokines and monokines, which in turn activate fibroblasts to synthesize collagen and glycosaminoglycans. They also proposed that silica may act as an adjuvant to increase immuno-reactivity. A more direct local effect of silica particles on the skin cannot be ruled out in view of a recent finding of silica particles within the skin of patients with systemic sclerosis.[124]

The renal lesions associated with silica exposure are varied. They include: segmental necrotizing glomerulonephritis and arteriolitis,[120] focal mesangial proliferation,[119] degenerative changes of the proximal tubular cells,[119] and acute glomerulonephritis associated with the deposition of IgM and C3 component of complement.[125] Increased silicon content in the kidney has been demonstrated in some cases.[14]

Q. SILICOSIS IN ANIMALS

Animals exposed to free silica in the natural environment show pathologic lesions remarkably similar to those seen in humans. Environmental silicosis has been described in birds,[126] horses,[127] New Zealand kiwis,[128] and camels.[129] Animals exposed to silica dust under controlled experimental conditions also show many of the same features of human silicosis including acute silicosis (silicotic lipoproteinosis) and the formation of granulomatous and collagenous nodules. Species demonstrating these effects include rats, hamsters, guinea pigs, monkeys, and mice.[49,130–132] Features of acute silicosis and granulomatous

reactions are the most frequently described histopathologic lesions. Classic silicotic nodules and massive fibrotic reactions occur but are less common. These differences probably reflect the time scales involved rather than intrinsic differences in species response to silica.

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