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Rare Pneumoconioses: Metalloconioses

Victor L. Roggli

A variety of inorganic particulates in the ambient air may be inhaled and deposited in the respiratory tract, with the potential to interact with the cells of the lung and subsequently produce disease. Some dusts, such as coal dust (see Chap. 34), silica and certain nonfibrous silicates (see Chap. 35), and asbestos (see Chap. 36), are known to be fibrogenic when sufficient amounts accumulate within the lungs. Other dusts may incite an immunologic response with consequent interstitial pneumonitis and fibrosis. Still other dusts are relatively inert even at high burdens. Some of the rarer forms of pneumoconiosis, including their histologic features, diagnostic criteria, and possible pathogenetic mechanisms, are discussed in this chapter (Display 37-1).

BERYLLIOSIS

Beryllium is a lightweight metal with many properties that make it an industrially useful material. These properties include an unusually high melting point, exceptionally low density, high modulus of elasticity, low coefficient of thermal expansion, good thermal and electrical conductivity, relative transparency to x-rays, and low neutron absorption.[1] The main source of beryllium is the mineral beryl ($3BeO \cdot Al_2O_3 \cdot 6SiO_2$), deposits of which are located in Colorado, New Mexico, Utah, Brazil, and China.

Once an important component of fluorescent lights, beryllium is now used primarily in the aerospace industry for the manufacture of structural materials, guidance systems, optical devices, rocket motor parts, and heat shields. It is also used in ceramic parts, in the manufacture of thermal couplings and crucibles, and as a controller in atomic reactors. Exposures also occur during mining and extraction of beryllium ores.

The first cases of respiratory disease related to the inhalation of beryllium were reported from Europe in 1936. Severe forms of acute chemical pneumonitis related to beryllium exposure were first reported in the United States in 1943[2]; in 1950, Vorwald reported on 40 patients with chronic beryllium disease.[3] The association of beryllium exposure with respiratory disease led to the first ambient air quality standard ever in this country. This standard, established in 1949, allowed an 8-hour time-weighted average maximum permissible level of 2.0 $\mu g/m^3$, with a peak level of 25 $\mu g/m^3$, and a concentration in air around factories not to exceed 0.01 $\mu g/m^3$. This air quality standard, which is still in effect, preceded all others by about 25 years.[2]

Berylliosis is the term used for pulmonary disease occurring as a consequence of exposure to beryllium. As noted above, both acute and chronic forms are recognized. Acute berylliosis is a form of chemical pneumonitis that rapidly develops following short-term, high-level exposure (>25 $\mu g/m^3$) to soluble beryllium salts. Patients present with dyspnea, cough, chest pain, tachycardia, rales, and cyanosis. The lungs in fatal cases are wet, heavy, and congested. Diffuse alveolar damage is observed microscopically, with pulmonary edema, congestion, swollen epithelial cells, and scattered inflammatory cells within the alveolar spaces and the pulmonary interstitium. These changes are nonspecific and resemble any other acute chemical pneumonitis. This form of berylliosis has largely disappeared because of improved industrial hygiene.

Chronic berylliosis is a more insidious form of disease related to beryllium exposure, especially to insoluble compounds such as the oxide or silicate. Chronic berylliosis may develop in as many as 17% of patients with acute berylliosis, often a decade or more postexposure. The chronic form also occurs in individuals with no history of acute disease. Only about 0.4% to 2.0% of workers at risk develop berylliosis, and some cases occur after exposures consistently below the permissible exposure limit of 2.0 $\mu g/m^3$.

The criteria for diagnosis of chronic beryllium disease include at least four of the following six features:

DISPLAY 37-1. RARE FORMS OF PNEUMOCONIOSIS

Berylliosis
Hard metal lung disease
Aluminosis
Siderosis
Stannosis
Baritosis
Zirconium lung disease
Antimony lung disease
Man-made mineral fibers (see Table 37-1)
Vinyl chloride
Thesaurosis
Oil mists

1. History of significant beryllium exposure
2. Presence of beryllium in lung tissue, lymph nodes, or urine
3. Evidence of lower respiratory tract disease and a clinical course consistent with beryllium disease
4. Radiographically detected interstitial disease consistent with a fibronodular process
5. Pulmonary function tests showing a restrictive or obstructive defect or diminished diffusing capacity of the lung for carbon dioxide (DLCO)
6. Pathologic changes consistent with beryllium disease.[1]

A Beryllium Case Registry has been established in the United States at the Massachusetts General Hospital, in Boston, for the study of this disease, and new patients should be reported to this registry.

The gross pathologic features of chronic berylliosis include small, fibrotic lungs that may show honeycomb changes. Bilateral hilar lymphadenopathy may be present, raising the clinical suspicion of sarcoidosis. Microscopically, there is an interstitial lymphocytic infiltrate and non-necrotizing granulomatous inflammation (Fig. 37-1), which may progress to diffuse interstitial fibrosis. Giant cells often contain inclusions, such as Schaumann bodies (Fig. 37-2) or asteroid bodies (Fig. 37-3). The histologic appearance may be reminiscent of either sarcoidosis or hypersensitivity pneumonitis but should not be confused with either of these.[3]

Beryllium has classically been identified in lung tissue by wet chemical spectrographic techniques. More recently, electron energy loss spectrometry and laser microprobe or ion microprobe mass spectrometry have been employed to identify individual particles of beryllium in tissue sections.[4]

The occurrence of berylliosis in only a small fraction of individuals at risk and at relatively low exposure levels[5] suggests that beryllium toxicity is a hypersensitivity phenomenon.[6] Beryllium may function as a hapten, binding to some large carrier molecule to form an antigen. Interactions between macrophages, which phagocytize particulate beryllium, and sensitized T cells could initiate and perpetuate a chronic inflammatory and granulomatous response that ultimately leads to fibrosis.[1] There is also some evidence that exposure to beryllium results in an increased risk of lung cancer.[7,8]

HARD METAL LUNG DISEASE

Tungsten carbide is a metal that is useful in the manufacture of cutting tools, drilling equipment, armaments, alloys, and ceramics. It has properties of extreme strength, rigidity, and heat resistance.[9] Production of tungsten carbide involves a process of powdered metallurgy in which tungsten and carbon are heated and fused in the presence of a binder, which is cobalt. The finished product contains 5% to 25% cobalt by weight. The manufacturing process generates particles with an aerodynamic equivalent diameter of 2.0 μm or less, which are thus in the respirable size range.

Workers exposed to tungsten carbide are at risk for the development of interstitial lung disease, which appears to be due to the presence of cobalt in the respirable dust. Interstitial lung disease usually follows exposure to peak air concentrations of cobalt exceeding 500 $\mu g/m^3$, although some cases have occurred among individuals exposed to less than 50 $\mu g/m^3$.[9,10] Fewer than 1% of

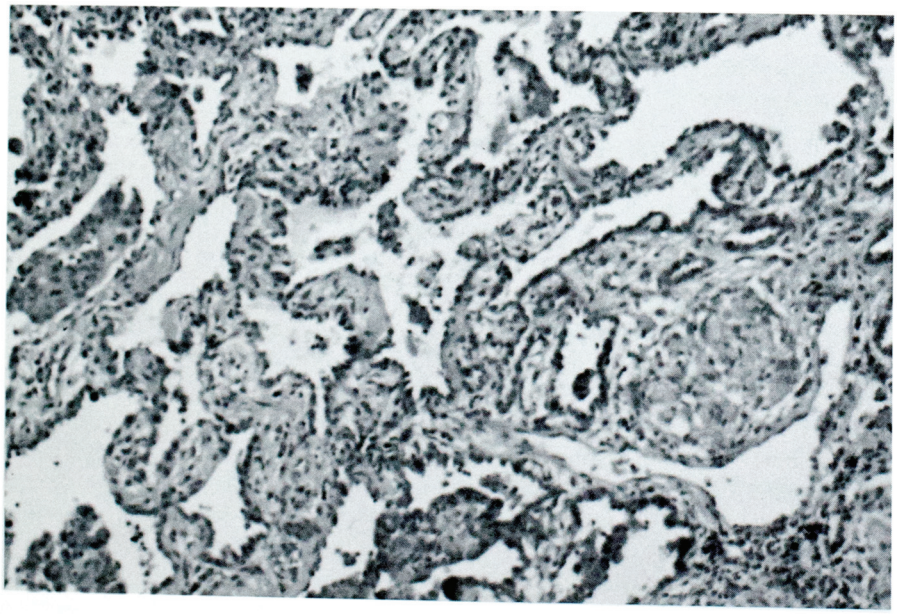

FIGURE 37-1. An open lung biopsy specimen from a patient with berylliosis shows chronic interstitial inflammation with focal granuloma formation. (H & E stain; intermediate magnification; courtesy of F.B. Askin, M.D., Baltimore, MD.)

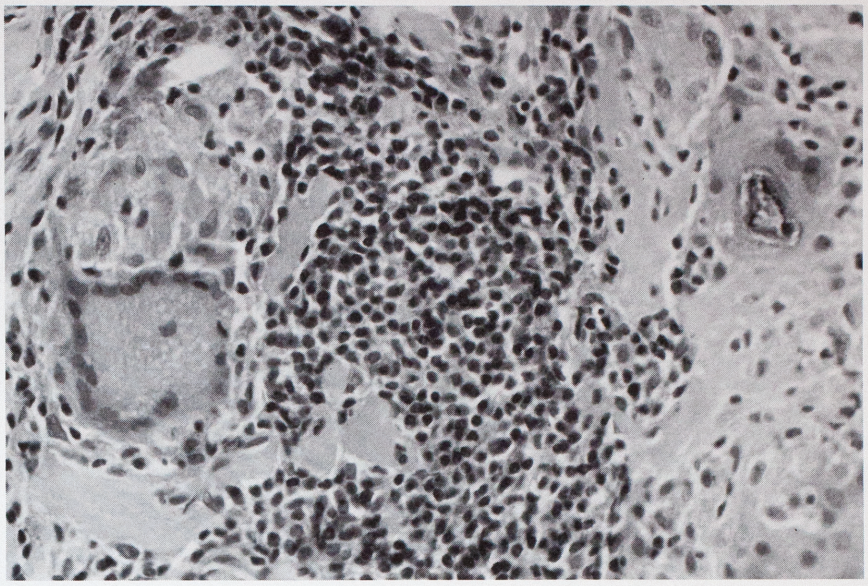

FIGURE 37-2. Another specimen from the patient in Figure 37-1 shows chronic inflammation (*center*) and granuloma formation with giant cells (*left, right*). The giant cell on the right contains a basophilic Schaumann body. (H & E stain; intermediate magnification.)

individuals at risk in cross-sectional studies of current workers actually develop interstitial lung disease, suggesting that, like beryllium, cobalt toxicity is a hypersensitivity phenomenon.

Exposed workers present with insidious onset of dyspnea, small lung volumes and restrictive changes on pulmonary function testing, diminished DLCO, and increased interstitial markings on chest x-ray films. Some workers develop an asthmalike condition associated with obstructive changes and wheezing, and these symptoms may precede the development of interstitial lung disease by several years.[11] The obstructive airways syndrome in tungsten carbide workers is also associated with cobalt exposure, and workers exposed to more than 50 $\mu g/m^3$ of cobalt are at greater risk than those exposed to lesser concentrations.[10] In cross-sectional studies, the obstructive airways syndrome occurs in about 10% of workers at risk.

Hard metal lung disease is a term used for interstitial pneumonitis and fibrosis occurring in tungsten carbide workers. In fatal cases, the lungs are small and fibrotic. Histologically, the characteristic picture is that of giant cell interstitial pneumonitis.[12] Multinucleated giant cells may be observed within the alveolar spaces or lining the thickened, chronically inflamed alveolar septa (Fig. 37-4). Ultrastructurally, the intraalveolar multinucleated giant cells have histiocytic features, whereas those lining the alveolar septa resemble type II cells. The multinucleate cells may also be observed in bronchoalveolar lavage samples, and their occurrence may be a clue to the correct diagnosis (Color Fig. 37-1).[11] Other histologic patterns that may be observed in some cases include desquamative interstitial pneumonitis (Fig. 37-5) and usual interstitial pneumonitis (see Chaps. 31 and 32).

The finding of giant cell interstitial pneumonitis is almost pathognomonic of hard metal lung disease and should provoke an investigation of occupational exposure history.[12] The diagnosis may be confirmed by the detection of substantial numbers of tungsten, titanium, and tantalum particles by means of energy-

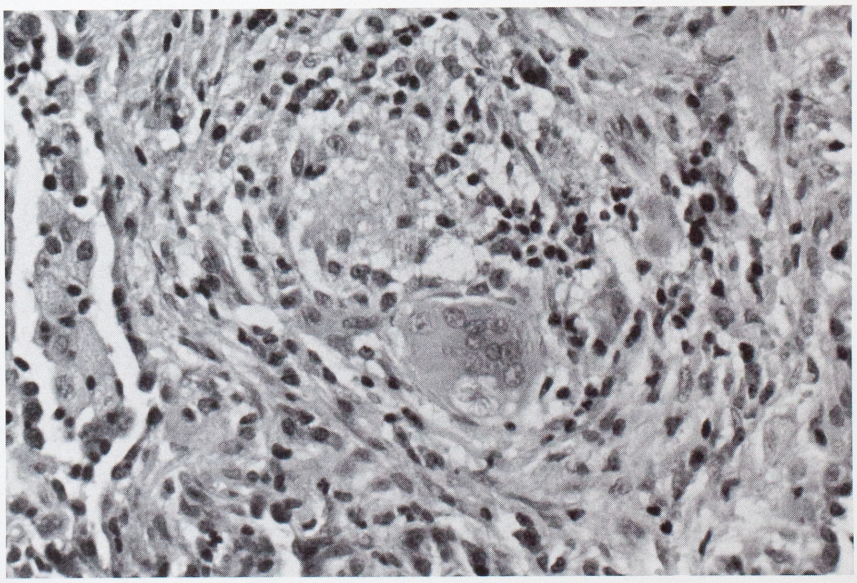

FIGURE 37-3. Granulomatous inflammation is also present in this microscopic field from the patient in Figures 37-1 and 37-2 with berylliosis. A giant cell with an asteroid body (*center*) is seen. (H & E stain; intermediate magnification.)

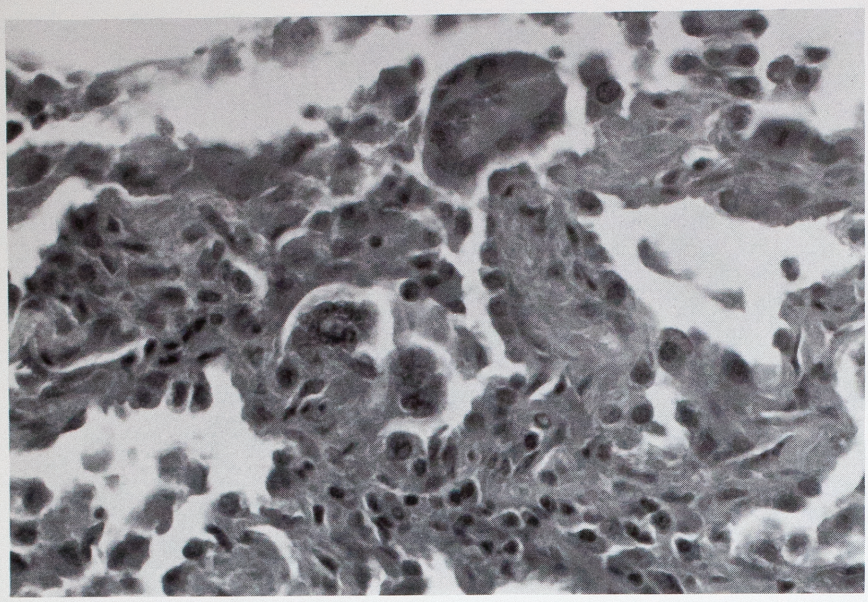

FIGURE 37-4. A biopsy specimen from a patient with hard-metal lung disease shows interstitial pneumonitis and fibrosis with prominent multinucleate giant cells. The pattern is typical for giant-cell interstitial pneumonitis. (H & E stain; intermediate magnification.)

dispersive x-ray analysis (EDXA),[13] or by detection of increased concentrations of these elements in lung tissue by means of neutron activation analysis[14] in a patient with interstitial pneumonitis. Cobalt may be variably present because its water solubility makes it susceptible to removal by aqueous fixatives.[11] Some investigators have also reported the identification of tungsten and titanium particles in giant cells or macrophages recovered from the lungs of tungsten carbide workers by bronchoalveolar lavage.[15]

The occurrence of hard metal lung disease in a small fraction of individuals at risk and at relatively low exposure levels suggests that this disease is a hypersensitivity phenomenon. As is suspected to be the case for beryllium, cobalt may function as a hapten, binding to some larger carrier molecule to form an antigen. Support for the role of cobalt in this disease derives from the finding of a similar interstitial pneumonitis among diamond polishers, who are exposed to cobalt but not tungsten carbide.[16] Further support comes from animal studies, which have shown that intratracheal instillation of tungsten carbide is innocuous, whereas mixtures of tungsten carbide and cobalt produce a chemical pneumonitis.[17]

ALUMINOSIS

Aluminum is a lightweight metal that is used extensively in industrial and manufacturing processes. Substantial exposure to aluminum may occur during aluminum smelting, manufacture of aluminum-oxide abrasives, aluminum polishing, and aluminum arc-welding.[18,19] It has been estimated that some 1,800,000 workers are exposed to aluminum oxide alone.[19] Aluminum abrasives, referred to as corundum, are made by finely grinding bauxite, iron, and coke and fusing the mixture in an electric furnace. The resulting fumes contain particles less than 1 μm in diameter with a composition of aluminum oxide (50%), amorphous silica (36%), ferric oxide (3%–4%), and traces of titanium oxide and

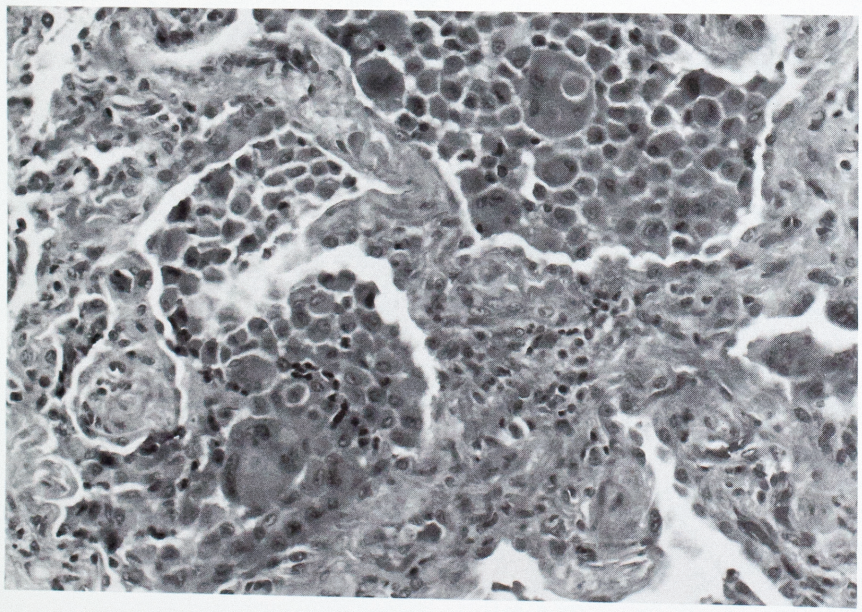

FIGURE 37-5. Hard-metal lung disease with alveoli packed with macrophages in a pattern resembling desquamative interstitial pneumonitis is seen in the same patient as in Figure 37-4 and Color Figure 37-1. (H & E stain; intermediate magnification.)

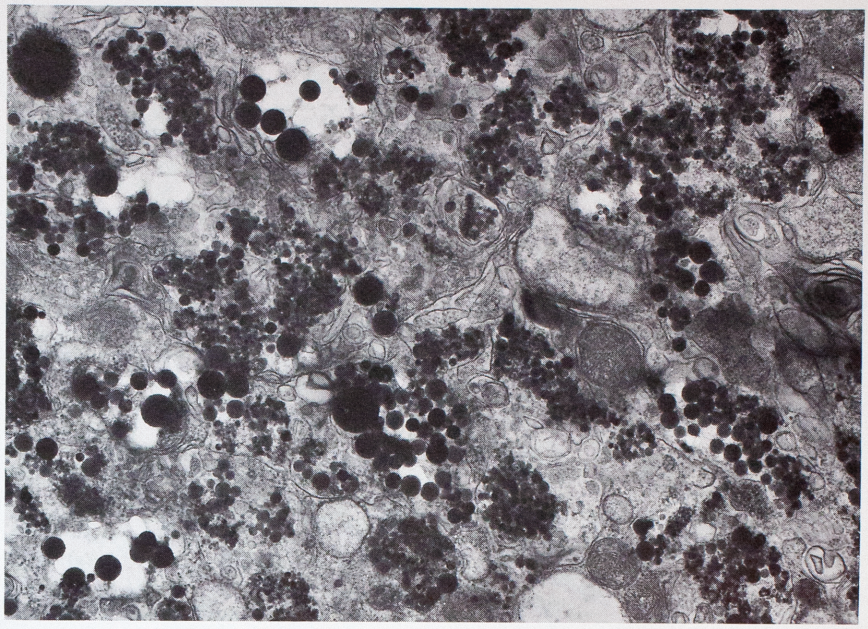

FIGURE 37-6. Transmission electron micrograph of cytoplasm of a macrophage from the lungs of an aluminum arc-welder shows aggregates of numerous spherical particles ranging in size from 0.1 to 1.0 μm. (Original magnification × 15,000.) See Color Figure 37-2.

other constituents. Numerous respirable-size particles are also produced during aluminum smelting and aluminum arc-welding.

Pulmonary disease related to exposure to aluminum is uncommon, and the clinical and pathologic presentations are quite variable. Initially, bauxite lung or Shaver disease was described in workers exposed to fumes generated during the manufacture of aluminum abrasives. Individuals exposed to these fumes developed dyspnea and radiographic changes as early as 3 months after exposure.

Asthma and chronic obstructive lung disease have been described in aluminum potroom workers involved with aluminum smelting, and interstitial fibrosis has been described in five potroom workers with 10 to 37 years of exposure to alumina dust.[18] Pulmonary fibrosis has also been described in aluminum arc-welders[20] and aluminum polishers.[18] Other patients have been described with a desquamative interstitial pneumonitis pattern[21] or with a granulomatous response resembling sarcoidosis.[22]

In fatal cases of Shaver disease (*i.e.*, bauxite lung), the lungs are heavy and grayish black and have dense fibrotic areas scattered throughout. Dense pleural adhesions and large subpleural emphysematous bullae may also be present, and the latter may predispose to spontaneous pneumothorax. A metallic sheen resembling tarnished aluminum has been described in the lungs of aluminum arc-welders.

Microscopically, there is diffuse alveolar septal fibrosis associated with aggregates of black dust particles, which may progress to obliteration of alveolar spaces. The pattern of fibrosis resembles that of usual interstitial fibrosis in many of the published cases.[19,23] Macrophages may be numerous and contain fine, gray to brown cytoplasmic dust (Color Fig. 37-2).[20,21]

Ultrastructurally, the dust consists of electron-dense spheres 0.1 μm to 1.0 μm in diameter (Fig. 37-6). Analysis of these particles by means of EDXA yields a peak for aluminum only (Fig. 37-7). Analysis of lung tissue in a few patients has yielded hundreds of millions to tens of billions of aluminum-containing particles per gram of dry lung.[19,23]

The rarity of aluminum-induced pulmonary disease and the occasional report of a granulomatous reaction to aluminum have raised the question of a hypersensitivity reaction, similar to that described for beryllium and cobalt exposures. Indeed, a helper T-cell lymphocytosis in bronchoalveolar lavage fluid and a blastogenic response of peripheral blood lymphocytes to soluble aluminum compounds *in vitro* have been described in a patient with sarcoidlike lung granulomatosis.[22] In another patient, large numbers of aluminum fibers, averaging 1 μm in length and 0.06 μm in diameter, were recovered from lung digests of a potroom worker with diffuse interstitial fibrosis. This study raised the question of whether the fibrous form of the particles may be important in the fibrogenicity of aluminum.[23] More information is needed to understand the rarity of aluminum-induced pulmonary disease and the mechanism or mechanisms of tissue injury by aluminum particles.

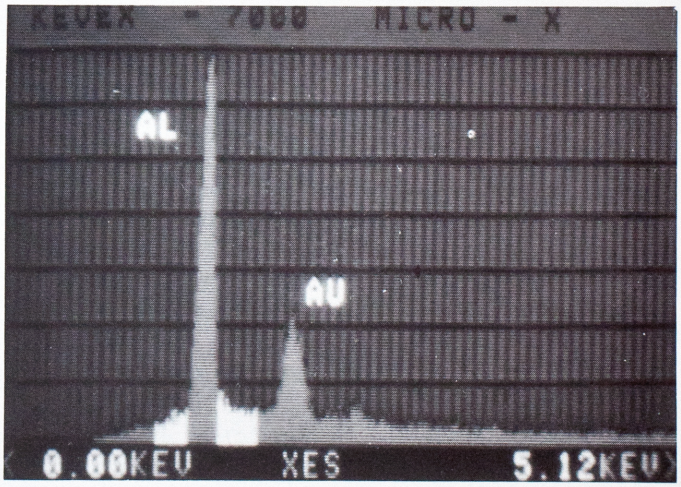

FIGURE 37-7. Energy-dispersive spectrum of a particle recovered from the lung of an aluminum arc-welder (i.e., same patient as in Fig. 37-6 and Color Fig. 37-2) shows a prominent peak for aluminum. The smaller peak for gold is derived from sputter-coating the specimen.

SIDEROSIS

Exposure to substantial amounts of oxides of iron, especially iron sesquioxide (Fe_2O_3) occurs in several occupational settings. Welders are exposed to metal fumes made up of particles less than 1 μm in aerodynamic diameter.[24] Miners of hematite ore, deposits of which are located in Belgium, Sweden, England, and the western end of Lake Superior in the United States, are exposed to iron oxides along with varying amounts of silica and silicates. Finally, gray iron foundry workers are exposed to iron oxides as well as silica, coke oven emissions, and other particulates and fumes found in iron smelting operations.

The accumulation of iron oxides within the lung results in the condition known as siderosis. Chest radiographs in these patients may show prominent interstitial markings as a result of extensive deposits of iron oxides within alveolar macrophages and the pulmonary interstitium. This radiopacity may be misinterpreted as fibrosis, but iron oxides are relatively inert particles with a minimal fibrotic response. Histologically, iron oxides appear as dark aggregates of spherical particles, often in a perivascular or peribronchiolar distribution. A characteristic feature of some of these particulates is the presence of dark brown to black centers with a golden brown outer layer or rim (Color Fig. 37-3). This most likely represents *in situ* conversion of iron oxide to iron hydroxide, commonly referred to as hemosiderin.[25]

The pathologic response of the lung in siderosis is somewhat dependent on the other constituents of the inhaled dust, especially alpha quartz. The lungs of hematite miners can be classified macroscopically into one of three patterns: diffuse, nodular, or massively fibrotic. In the diffuse variety, the lung has a brick-red appearance, with minimal, diffuse fibrosis. Focal emphysema may be present, as in coal worker's pneumoconiosis (see Chap. 34). The nodular form is characterized by the presence of firm, reddish black nodules up to 2 cm in maximum diameter. These tend to be more numerous in the upper lung zones. Pleural adhesions are frequently noted.

The massive fibrotic form is similar to progressive massive fibrosis in coal worker's pneumoconiosis. The irregular, sharply circumscribed masses of fibrotic tissue occur primarily in the upper lung zones and have a brownish red color. Both the nodular and the massively fibrotic forms may undergo central cavitation. Hilar lymph nodes are enlarged and fibrotic, with a mottled brick-red to black appearance.

Microscopically, iron oxide deposits are abundant, and birefringent dust particles, mostly silicates, are observed with polarizing microscopy. When silicotic nodules are also present (see Chap. 35), this process is sometimes referred to as siderosilicosis.[25]

Welder's pneumoconiosis is characterized by perivascular and peribronchiolar deposits of iron oxides with little if any accompanying fibrosis. Various sheet silicates may also be found in the lungs, often lying free or associated with macrophages in alveolar spaces. These may be partially coated with iron to form pseudoasbestos bodies, also known as nonasbestos ferruginous bodies. Because welders are frequently exposed to substantial amounts of asbestos in the workplace environment, especially shipyard welders, true asbestos bodies and appreciable amounts of peribronchiolar and alveolar septal fibrosis may also be observed (see Chap. 36). The occurrence of parietal pleural plaques in some welders is a further indication of concomitant asbestos exposure.

Foundry workers are often exposed to silica, and silicotic nodules may be present within their lungs. However, some foundry workers have been described in whom diffuse alveolar septal fibrosis is associated with ferruginous bodies with cores composed of iron oxides.[26] I have observed two additional foundry workers with diffuse fibrosis in whom lung tissue digests yielded numerous ferruginous bodies with brown-to-black central cores (Color Fig. 37-4). Electron microscopic analysis with energy-dispersive spectrometry demonstrated the presence of numerous coated and uncoated iron oxide fibers in these patients. The fibrous nature of these particles may be responsible for the fibrogenic reaction that has been observed.

Some studies have suggested that there is an increased risk of lung cancer among hematite miners and welders, raising the question of carcinogenicity of iron oxides. However, the high prevalence of lung cancer in underground hematite miners in West Cumberland, United Kingdom, has been traced to contamination of the mines with radon gas.[25] The increased risk of lung cancer in welders can be explained by a combination of cigarette smoking, asbestos exposure, and exposure to hexavalent chromium derived from welding of stainless steel.[27] There is no convincing evidence for an independent carcinogenic effect of iron oxides.

STANNOSIS

Tin is a silver-white metal that is important industrially because of its malleability and capacity to readily form alloys with other metals. It is mined primarily as tin dioxide ore, also known as cassiterite. Like most ores, deposits of tin dioxide are often associated with quartz-bearing rock. In the past, miners of tin ore often developed silicosis (see Chap. 35). However, this risk has been greatly decreased with the advent of wet drilling processes. The greatest exposures to tin occur during the bagging process or during the smelting of tin ore.[25] Exposures also occur as a result of tin-plating or soldering and in the manufacture of fungicides and pesticides.[28,29]

Pneumoconiosis resulting from the inhalation of tin-containing dusts is referred to as stannosis. Abnormal chest films were described in 121 of 215 tin refinery workers in one series.[28] Radiographic changes are often rather striking because of the high atomic number of tin ($Z = 50$). However, tin oxide is a rather inert dust with little if any fibrogenic capacity.

The lungs of workers with stannosis show gray-to-black, 2- to 5-mm macules distributed fairly uniformly throughout the lung parenchyma. Massive fibrosis does not occur; as much as 3 g of tin dioxide has been recovered from the lungs of some of these workers.[30] Microscopically, perivascular and peribronchiolar accumulations of macrophages containing brightly birefringent dust particles are observed. Prominent dust deposits also may occur subpleurally, within secondary lobular septa, and within hilar lymph nodes.[25] Exposure to tin does not appear to carry an excess risk of carcinoma of the lung.

BARITOSIS

Barium sulfate, or barytes, is a relatively insoluble salt of barium that is mined in several locations in the United States, including Georgia, Mississippi, and Nevada.[31] Deposits of barium ore are often associated with other minerals, such as calcite, fluorite, and

quartz. Barium sulfate is used in the manufacture of glass and vulcanized rubber; as a filler for paints, papers, and textiles; as a substitute abrasive for sandblasting; and in radiographic contrast media.[29] Exposure to barium may occur during mining or refining of the raw ore or during any of the industrial applications noted above. In addition, barium sulfate used in upper gastrointestinal radiographic contrast studies may be aspirated into the lungs.[25,32]

Pneumoconiosis resulting from the inhalation of barium-containing dusts is referred to as baritosis. Radiographic evidence of pneumoconiosis was found in the majority of workers in one study of a small factory that processed barium ores.[33] Radiographic changes were rather striking because of the high atomic number of barium (Z = 56). However, as is the case for tin dioxide, barium sulfate is a rather inert dust with little if any capacity for fibrogenesis. The lungs of workers with baritosis show nonpalpable white foci in sites where the barium has accumulated. These are analogous to the soft, black foci of carbon pigment seen in virtually all adult lungs.

Microscopically, most of the particles appear in alveolar spaces, and many are phagocytized by alveolar macrophages. Barium sulfate particles are refractile and brightly birefringent when viewed with polarizing microscopy. They often have a greenish tinge in hematoxylin and eosin–stained sections.[29] Little if any fibrotic response occurs; its presence should prompt a search for other inciting agents, such as quartz. Exposure to barium does not appear to result in an excess risk of carcinoma of the lung.

ZIRCONIUM LUNG DISEASE

Zirconium is a grayish metal used in the production of steel, in the manufacture of refractory ceramics, as a polishing and abrasive agent, in enamels and glasses, and as a substitute for sand in foundries.[29] Exposure to zirconium occurs during mining and refining of zirconium ore, or in any of the industrial applications noted above. The National Institute for Occupational Safety and Health has estimated that as many as 1,300,000 workers are exposed to zirconium in the United States alone.[28]

Zirconium is considered to be an inert substance, and exposure leads to accumulation of dust particles in a peribronchiolar and perivascular distribution with little if any fibrotic response. A granulomatous reaction has rarely been described.[34] Miners and refiners may also be exposed to quartz, which can result in silicosis. Exposure to substantial amounts of soluble zirconium chloride can produce a chemical pneumonitis with diffuse alveolar damage.[35] Exposure to zirconium does not lead to an increased risk of carcinoma of the lung.

ANTIMONY LUNG DISEASE

Antimony is a brittle, lustrous, white metallic element used in the production of certain metal alloys, in paints and glass, and in linotype setting.[29] Exposure to antimony occurs during the mining and refining of antimony-containing ores, or in any of the industrial applications noted above. The National Institute for Occupational Safety and Health has estimated that as many as 1,400,000 workers are exposed to antimony in the United States alone.[28]

Like zirconium, antimony is considered to be an inert substance, and exposure leads to an accumulation of dust particles in a peribronchiolar and perivascular distribution. There is little if any fibrotic response to antimony-containing dust. Exposure to substantial amounts of soluble antimony trichloride or pentachloride can produce a chemical pneumonitis with diffuse alveolar damage.[35] Exposure to antimony does not result in an increased risk of carcinoma of the lung.

MAN-MADE MINERAL FIBERS

Mineral fibers by definition are particles with an aspect (*i.e.*, length-to-diameter) ratio of 3:1 or more and roughly parallel sides. Man-made mineral fibers are amorphous, glassy silicates made from a liquid melt at high temperatures (1000–1500°C). Fibers are produced by drawing the melt out or by a blowing or spinning process. Man-made mineral fibers have the properties of high tensile strength and resistance to heat, cold, and chemicals. As a result of these properties, synthetic fibers have a wide range of industrial applications (Table 37-1).[36,37]

Dimensional considerations are critical to any analysis of the biologic effects of mineral fibers. Because of the tendency of fibers to align their long axes along the direction of laminar airflow, the aerodynamic behavior of fibers is more dependent on fiber diame-

TABLE 37-1
Man-Made Mineral Fibers

Type	Source	Uses	Diameter
Fibrous glass	Borosilicate and low-alkaline silicate glasses	Textiles; reinforcement for plastics; filter products	>8 μm
Rock wool	Volcanic rock	Thermal insulation	0.2–6 μm
Slag wool	Industrial slag	Thermal insulation	0.2–6 μm
Refractory ceramic fibers	Refractory materials from ceramics industry	Materials requiring high thermal or chemical resistance	0.2–11 μ
Glass microfibers	Borosilicate and low-alkaline silicate glasses	Scientific filter papers; aircraft and spacecraft industry	0.05–1.0 μm

From Lockey JE. Nonasbestos fibrous minerals. Clin Chest Med 1981;2:203; Wagner JC, Gibbs AR. Diseases due to synthetic mineral fibers. In: Churg A, Green FHY, eds. Pathology of occupational lung disease. New York: Igaku-Shoin, 1988:327.

ter than fiber length. Fibers with a diameter of 3.5 μm or less may penetrate to the lung periphery, whereas those with a larger diameter impact primarily in the upper airways. Fibers with lengths well over 200 μm can penetrate into respiratory bronchioles and alveolar ducts, provided they have an appropriately thin diameter. Experimental studies have shown that long (>8 μm) and thin (<0.25 μm) fibers are the most carcinogenic in an animal model of pleural mesothelioma.[38] Thus, long and thin fibers are particularly dangerous because of their access to distal airways and their biologic activity.

Fibrous Glass

Fibrous glass is manufactured from borosilicate and low-alkaline silicate glasses mixed with various amounts of silica, soda, lime, aluminum, and titanium.[36] Depending on the particular industrial application, these fibers vary in diameter from 0.05 μm for some special-application microfibers to 254 μm for some coarse glass fibers. The lengths of individual fibers range from less than a micron to many hundreds of microns.

As noted above, long and thin fibers are the most biologically active. Other properties of glass fibers that affect their disease-producing potential are their brittleness, with a tendency to break transversely, and their *in vivo* solubility. Experimental animal studies have shown that long glass fibers tend to break up into shorter ones, which are then transported to regional lymph nodes.[39] Glass fibers also will dissolve in tissues, especially in an alkaline environment.[40]

Experimental studies in which animals were exposed to aerosolized fine and coarse vitreous fibers found no evidence of significant fibrosis or excess neoplasia.[41,42] Other studies reported a greater fibrogenic response to long glass fibers as compared with short glass fibers, but much less fibrosis than occurred with exposure to asbestos fibers.[39] Intrapleural or intraperitoneal implantation of fine glass fibers results in the production of mesotheliomas in experimental animals,[43,44] but these do not occur with coarser fibers.[45] An excess of nonmalignant respiratory disease was noted in one study of a group of fibrous glass workers,[46] although most studies have not found an excess of chronic respiratory disease in exposed workers.[36,47,48]

A slightly increased risk of malignant mesothelioma in fibrous glass workers reported in one epidemiologic study[49] has not yet been confirmed. Finally, examination of the fiber content of lung tissue found no significant difference between individuals who had worked as long as 30 years in the fiberglass industry and nonexposed controls.[50]

Refractory Ceramic Fibers

Refractory ceramic fibers are made from refractory materials from the ceramics industry and are used in materials requiring high thermal or chemical resistance.[36] These fibers are less soluble *in vivo* than fibrous glass, and many have dimensions within the respirable size range (see Table 37-1). Therefore, there is considerable concern regarding the disease-producing potential of these fibers.[51]

One experimental animal study found that the inhalation of refractory ceramic fibers resulted in the development of mesothelioma in more than 40% of animals exposed.[52] Data are not yet available regarding the lung cancer risk among refractory ceramic fiber workers.[51] Further monitoring of the industry is also necessary to determine if there is a mesothelioma risk in humans exposed to refractory ceramic fibers.

I have examined lung tissue from three refractory ceramic fiber workers, including one with adenocarcinoma of the lung and parietal pleural plaques.[53] Substantial numbers of aluminum silicate fibers were identified in each patient that were consistent with refractory ceramic fibers. In one patient, a few ferruginous bodies with refractory ceramic fiber cores were observed (Fig. 37-8). A few fibers were observed with a granular, moth-eaten appearance, suggesting that they were undergoing disintegration. Energy-dispersive spectrometry of these latter fibers showed a reduced ratio of silicon to aluminum (Fig. 37-9).

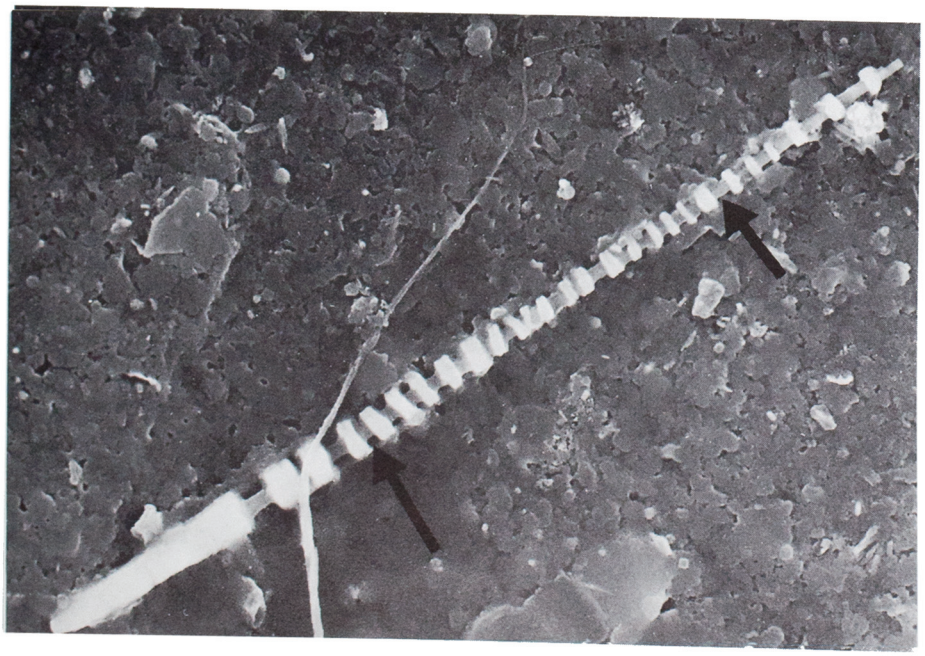

FIGURE 37-8. Scanning electron micrograph of a ferruginous body (*arrows*) isolated from the lung of a worker in the refractory ceramic fiber industry. The central core fiber was composed of aluminum and silicon. (Original magnification ×1500.)

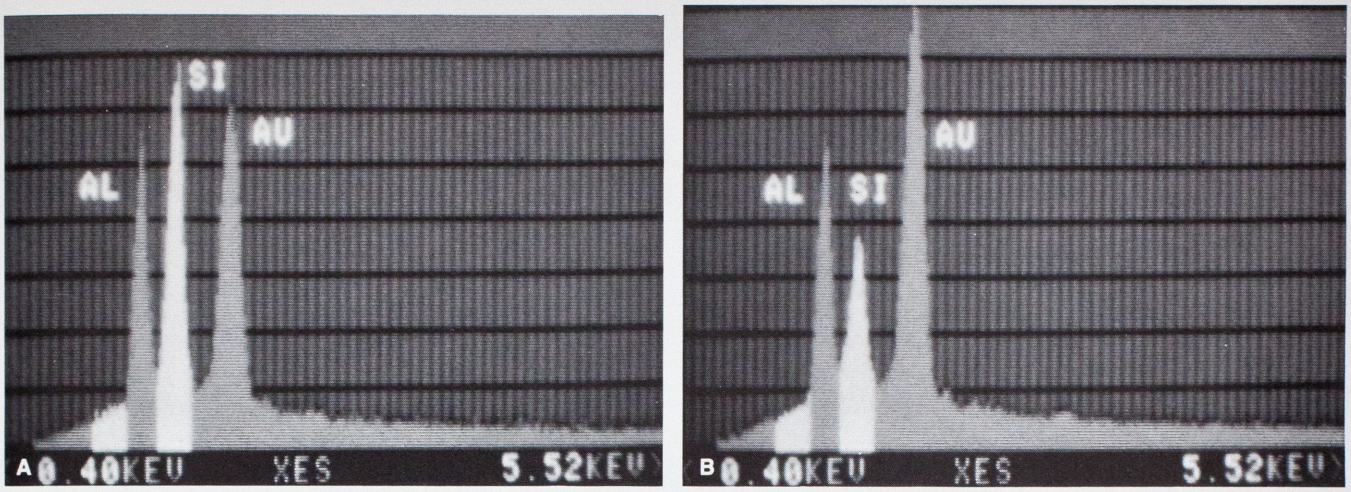

FIGURE 37-9. Energy-dispersive spectrum from (**A**) an intact refractory ceramic fiber and (**B**) a fiber that appeared to be undergoing disintegration. Note the relative reduction of the silicon peak as compared with the aluminum peak. The peak for gold is derived from sputter-coating the sample.

Mineral Wool Fibers

Mineral wool fibers include rock wool, made from volcanic rock, and slag wool, made from industrial slag. These fibers are used for thermal insulation and have diameters ranging from 0.2 to 6 μm. Many fibers are therefore in the respirable size range.

One study of workers exposed to mineral wool fibers with a mean diameter of 2.1 μm demonstrated no significant mortality from nonmalignant respiratory disease.[54] However, small but significantly increased standard mortality ratios for lung cancer have been reported among mineral wool production workers in both the large European and U.S. cohort studies.[55–57] Cancer rates appeared to be linked to the early technology phase of fiber production, with no excess in lung cancer associated with lower fiber exposures in later industry phases.[51,55]

VINYL CHLORIDE

Vinyl chloride occurs in both monomeric and polymeric forms. As the monomer, vinyl chloride is a flammable gas with a pleasant odor. The polymeric form, polyvinyl chloride (PVC), is a white powder consisting of particles less than 5 μm in diameter. PVC is an important base material for the manufacture of plastics, whereas vinyl chloride monomer (VCM) is used to produce other resins, as a chemical intermediate, and as a solvent. Exposure to both PVC and VCM is common in facilities where PVC is produced. In addition, exposure to VCM occurs in industries that are associated with the manufacture of organic chemicals and rubber.[58] In the 1960s and early 1970s, an exposure limit of 500 ppm vinyl chloride was in effect in the workplace. However, following the demonstration of human carcinogenesis from exposure to vinyl chloride in the workplace, the Department of Labor adopted a standard of 1 ppm.[59]

The carcinogenic potential of VCM was reported in animals and humans in the early 1970s. In animals, the neoplastic effect occurred at concentrations below 10 ppm. In humans, angiosarcomas of the liver were reported, and malignancies of the brain, lung, and hematopoietic system were noted as well. PVC also appears to be associated with hepatic angiosarcomas and pulmonary carcinomas. Workers exposed to vinyl chloride are also at risk for several non-neoplastic conditions, including hepatitis, dermatitis, Raynaud phenomenon, thrombocytopenia, and acroosteolysis.[58,60]

Pneumoconiosis appears to be associated with exposure to PVC rather than VCM. Radiographic abnormalities in the form of small irregular opacities in the mid and lower lung zones occur in 3% to 23% of vinyl chloride polymerization workers.[61–63] A dose-response relationship was demonstrated in one study.[61] Pathologic reports have been scanty, but the findings include diffuse infiltration of interstitial macrophages and multinucleated giant cells with finely vacuolated cytoplasm.[64,65] Electron microscopy revealed numerous 0.3- to 0.4-μm granules within secondary lysosomes with an appearance identical to that of a powdered sample of PVC.[64]

THESAUROSIS

Hair spray consists of a base of polyvinylpyrrolidone, polyvinyl acetate, or shellac, mixed with alcohol, perfumes, aromatic oils, and a fluorochlorohydrocarbon propellant.[66] Despite widespread use of hair sprays and probable moderate to heavy exposures in some occupational groups, few well-documented cases of lung disease associated with hair spray exposures have been reported in the literature.[58] Lung disease secondary to hair spray inhalation has been referred to as thesaurosis, and patients may present with symptoms of chest tightness, nonproductive cough, or dyspnea. Radiographic findings include diffuse reticulonodular infiltrates and hilar lymphadenopathy.

Histologically, the predominant features are giant cell granulomas in the lungs and hilar lymph nodes with or without diffuse pulmonary fibrosis. Accumulations of foamy macrophages are observed with periodic acid-Schiff–positive cytoplasmic inclusions.[66–69] Ultrastructurally, these macrophages contain lamellar material attached to cell membranes and within secondary lysosomes. Although the agents responsible for the disease are unknown, the histopathologic findings are consistent with

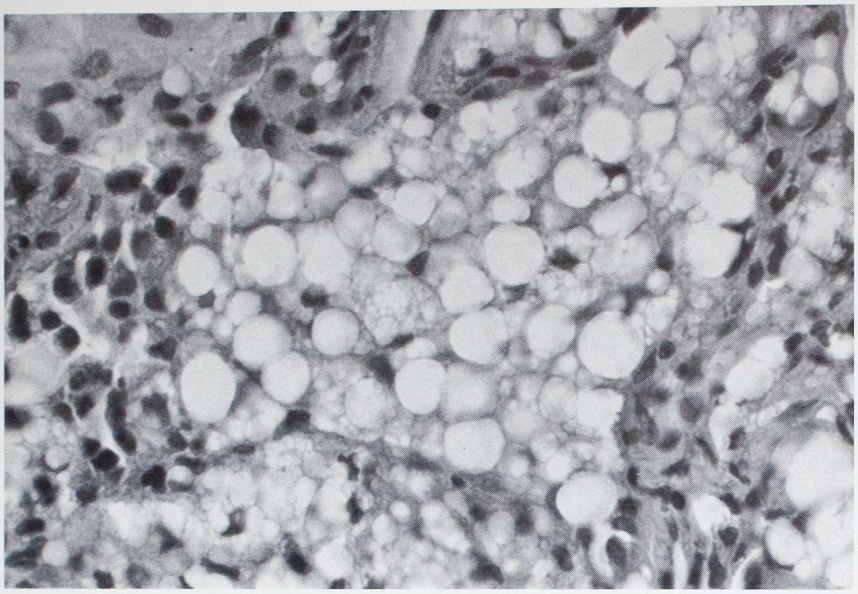

FIGURE 37-10. A transbronchial biopsy specimen from a patient with exogenous lipoid pneumonia shows numerous large lipid vacuoles, mostly within macrophages. (H & E stain; intermediate magnification.)

a foreign-body histiocytic reaction to the oils and other high-molecular-weight components of hair spray.[58]

OIL MISTS

Mineral oils may be natural or synthetic and often contain a number of additives, including emulsifiers, antifoaming agents, colorants, germicides, extreme pressure additives, and corrosion inhibitors. Exposure to mineral oil mists occurs in mechanical engineering, mining, printing, construction, and textile industries. The major hazard associated with exposure to oil mists is exogenous lipoid pneumonia.[58] Most cases have occurred following extremely high acute exposures. The histopathologic features are identical to those related to chronic aspiration of mineral oils.[70] These include large clear vacuoles within macrophages or surrounded by giant cells, organizing pneumonia, and fibrosis (Fig. 37-10).

Mineral oils can be demonstrated in frozen sections stained with oil red O or Sudan black. Postfixation with osmium tetroxide followed by routine embedding and sectioning usually reveals far more lipid than is detected with those stains. It has been reported that the occurrence in cytologic specimens of multinucleated giant cells with large lipid vacuoles in their cytoplasm can be a clue to the correct diagnosis (Color Fig. 37-5).[71]

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