Pneumoconioses

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Objectives:

1. To review the pathology, pathophysiology, and radiographic similarities and differences between coal worker's pneumoconiosis and silicosis.
2. To explain asbestos-induced lung and pleural diseases, with emphasis on the functional abnormalities and the ILO system for classifying the pneumoconioses.
3. To discuss malignancies related to asbestos. The associations previously reported between asbestos and malignancies other than mesothelioma and lung cancer will be placed in perspective.
4. To review briefly a variety of other nonorganic pneumoconioses.

Key words: asbestos; berylliosis; coal worker's pneumoconiosis; hard metal lung disease; occupational neoplasms; pneumoconiosis; silicosis; talcosis

This chapter will deal with dust-related lung diseases. The term *pneumoconiosis* was coined in 1866 by Zenker; the word is derived from Greek and simply means "dusty lung." In modern parlance, pneumoconiosis should be reserved for the permanent alteration of the structure of the lungs due to the inhalation of a mineral dust and the reaction of the lung tissues to the presence of this dust, not including emphysema and bronchitis. Some dusts (*eg*, iron, tin, and barium) do not incite a fibrogenic reaction in the lungs. Others (*eg*, silica, coal dust, and asbestos) may cause an extensive fibrotic reaction. Still others (*eg*, beryllium) cause a systemic illness and induce a granulomatous reaction within the lungs. The pneumoconioses may produce significant disability or premature death, and they must be considered in the differential diagnosis of patients who present with respiratory complaints or abnormal chest radiographs. The diseases that will be considered in this presentation are the more important dust-related diseases:

- Silicosis
- Coal worker's pneumoconiosis
- Asbestos-related diseases
- Talcosis
- Berylliosis
- Hard metal lung disease

Other less common dust-related diseases will be discussed only briefly.

Silicosis

Occupational Exposure

Exposure can occur during the mining, quarrying, and tunneling of siliceous rocks. Stone cutting, restoring or cleaning sandstone buildings, abrasive blasting, glass manufacture, fillers in the rubber industry, foundry work, ceramics, boiler scaling, vitreous enameling, and the manufacture of cultured quartz crystals are all occupations that place workers at risk of inhaling a sufficient silica dust burden to develop silicosis. Until World War II, silicosis was the most important pneumoconiosis. It has declined in frequency since then, primarily due to substitution by other materials and hygienic measures.

Pathology

The fundamental lesion is the silicotic nodule. The dust particles attract macrophages, and the developing nodule has a distinct architecture centered around cells and dust. Fibroblasts and collagen tissue begin to surround the central zone, with subsequent organization into a nodular form, and are located around vessels. Eventually, there are concentrically arranged zones of a cellular hyaline substance enclosed in a collagenous capsule. The nodules tend to occur in clusters and may subsequently fuse into conglomerations.

Pathogenesis

Inhaled silica dust particles are initially deposited in the bronchoalveolar space, where they are ingested by alveolar macrophages within 48 h. Intracellular lysosomal rupture occurs, causing damage to surrounding structures, with cytotoxicity, release of oxidants, enhanced fibroblast growth factors, an influence on lymphocytes, excessive accumulation of neutrophils, and hyperplasia and activation of type II pneumocytes. Although their pathophysiol-

Figure 1. *(A)* Chest radiograph from a patient with simple (uncomplicated) silicosis. Note the presence of multiple rounded opacities, more pronounced in the upper than the lower lung zones. *(B)* Chest radiograph from a patient with conglomerate masses from silicosis. Note the relative symmetry of these masses, which usually helps to distinguish silicosis from lung cancer.

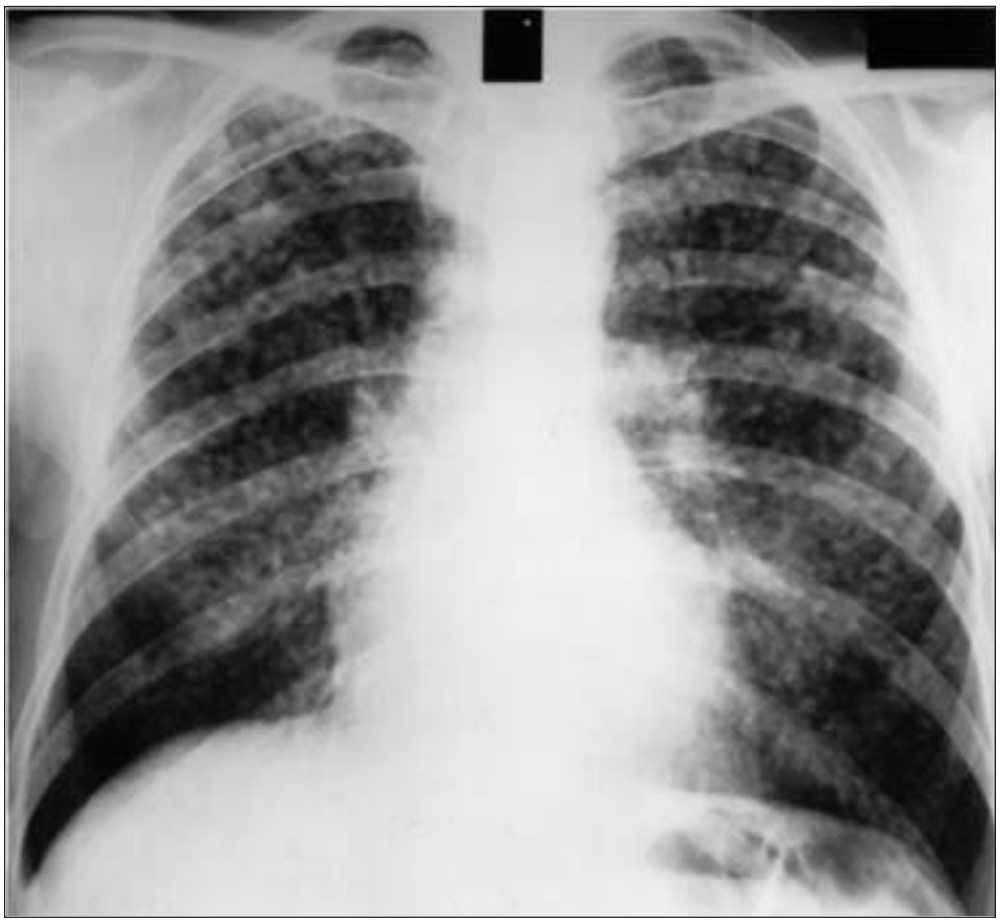


Figure 1 *A*

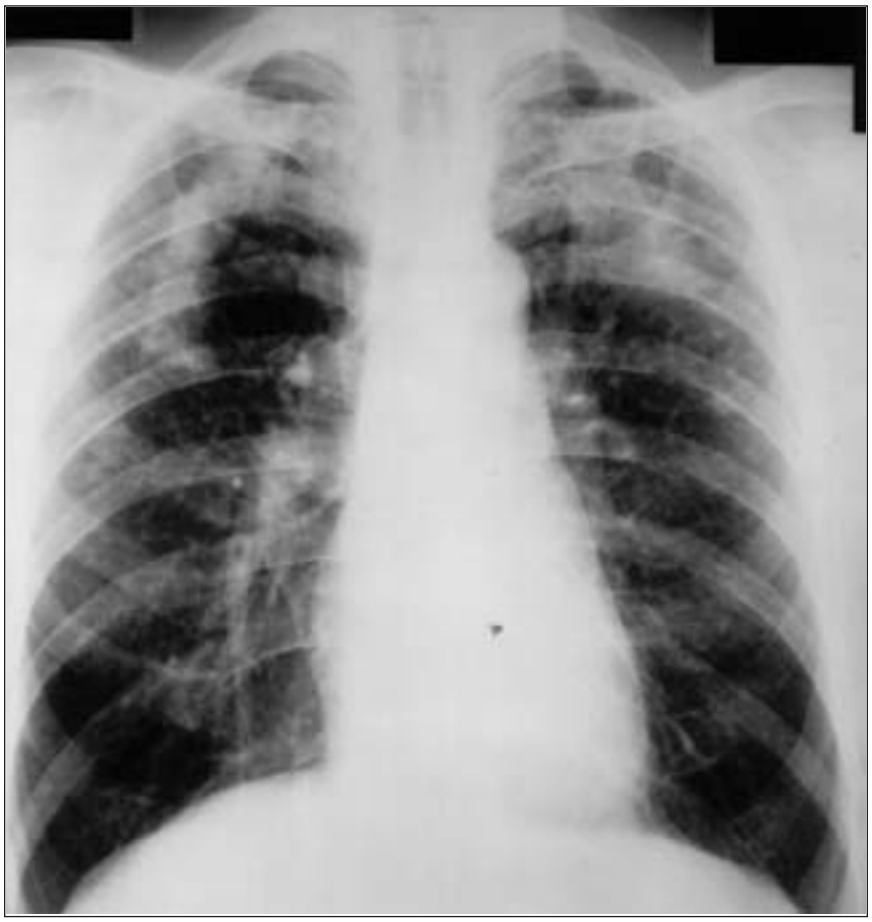


Figure 1 *B*

ogy remains incompletely understood, several lines of evidence suggest the participation of cytokines produced by alveolar macrophages, at least in the initiation of the alveolitis. *In vitro* exposure of alveolar macrophages (obtained from healthy subjects) to coal dust particles triggered a significant release of tumor necrosis factor and interleukin 6 compared with a biologically inert control dust. Moreover, it appeared that coal mine dust was more aggressive than similar concentrations of pure silica, suggesting that cytokine secretion induced by coal mine dust was not exclusively related to the presence of silica but resulted from a complex interaction between the different components. BAL showed a large influx of mononuclear phagocytes, with an increased spontaneous production of oxidants, fibronectin, neutrophil chemotactic factor, and also of interleukin 6 and tumor necrosis factor alpha.

Clinical Features

Even when the chest radiographic abnormalities are fairly pronounced, some patients may be asymptomatic. When present, symptoms associated with silicosis include cough (usually not productive) and dyspnea, which can progress with the disease. Chest pain is not a feature of silicosis. If present, hemoptysis or weight loss should alert the clinician to suspect coexistent tuberculosis; the predisposition of patients with silicosis to activation of latent tuberculous infection has been known since the beginning of the century. Silicosis is the only pneumoconiosis that predisposes a person to the development of pulmonary tuberculosis.

Physical findings range from normal to findings characteristic of severe cor pulmonale and right-sided congestive heart failure in the most advanced cases. Cyanosis is typically absent except in advanced disease, and finger clubbing is not usually seen. Distortion of the chest or tracheal deviation may accompany fibrosis. Breath sounds are typically normal, unless another process (*eg*, emphysema or asthma) is also present.

The risk of lung cancer from asbestosis has been appreciated and accepted for several decades. That silicosis is also associated with an increased risk for the development of lung cancer is still debated, although the weight of recent evidence does suggest a significant association, albeit less than that for asbestosis.

Pulmonary Function Studies: With simple, uncomplicated silicosis, lung function is usually normal. In more advanced disease, there may be a slight reduction in the vital capacity and hypoxemia with exercise and finally at rest. Impairment of lung function is not usually as great as the chest radiographic abnormalities might suggest. A restrictive ventilatory defect may be seen, and with massive conglomeration of silicotic nodules there may be an impairment of gas transfer (a reduced D_{LCO}). Airflow obstruction is not typical; when present, it is usually the result of a second disorder.

Radiographic Findings: The earliest radiographic findings are small discrete opacities that are usually found in the upper lung zones and vary in size from 1 to 3 mm. More often than not, these abnormalities are round (Fig 1, *A*). There appears to be a clear relationship between the total dust burden and the extent of radiographic abnormalities; use of a standard set of ILO reference films (see "Asbestos-Related Diseases" for more details) helps to quantify the extent of disease.

As the disease progresses, the discrete opacities increase in number and size and occupy the lower lung zones as well. Eventually, the nodules coalesce to form conglomerate masses (Fig 1, *B*). Such masses are usually located in the upper lung zones, and they tend to be bilateral and symmetrical. When they are unilateral, there may be difficulty in distinguishing them from lung cancer.

As the nodules coalesce into conglomerate masses, there is often formation of bullae in the adjacent vicinity, with distortion of the trachea. Cavity formation is unusual, unless tuberculosis is also present. Lymph nodes may become calcified, sometimes with a ring shadow that resembles an eggshell. Diffuse bilateral pleural fibrosis may occur in advanced disease. Very large masses, which can cavitate, are seen with silicosis and rheumatoid arthritis; this unusual situation is referred to as Caplan's syndrome.

Diagnosis

If a satisfactory occupational history accompanies high-quality chest radiographs, the diagnosis of silicosis should be relatively straightforward. It is rare that a biopsy will be needed to establish a diagnosis of silicosis. Occasionally, biopsy is indicated to distinguish a lung cancer from a conglomerate silicotic mass.

Prognosis, Treatment, and Prevention

Simple, uncomplicated silicosis does not usually shorten life or lead to severe disability. Progressive disease (especially with conglomerate silicosis or when tuberculosis complicates silicosis) may produce severe disability and lead to premature death. The course of the disease can occasionally be complicated by spontaneous pneumothorax, paralysis of the recurrent laryngeal nerve, or esophageal compression with dysphagia. There is no specific treatment to halt the progression or cause resolution of silicosis. Corticosteroids do not help and are potentially dangerous if coexistent tuberculosis is not recognized. A high standard of dust control and use of efficient respirator masks when exposure might occur are the mainstays in preventing silicosis.

Mixed-Dust Pneumoconiosis and Diatomite Pneumoconiosis

When a given occupation gives rise to the inhalation of crystalline silica (quartz) and other dusts such as carbon, iron, kaolinite, and feldspars, the term *mixed-dust pneumoconiosis* is applied. If the proportion of free silica to the other dusts is low, the lesions are more often irregular fibrotic rather than typical silicotic nodules. Diatomaceous earth is a siliceous sedimentary rock that consists mainly of the fossilized skeletons of a unicellular aquatic plant. It is used primarily for filtration purposes. Pneumoconiosis due to diatomaceous earth is unusual, since the number of persons exposed in their occupations is relatively small. Both types of pneumoconioses resemble ordinary silicosis, but progressive abnormalities and severe lung dysfunction are rare.

Figure 2 *A*

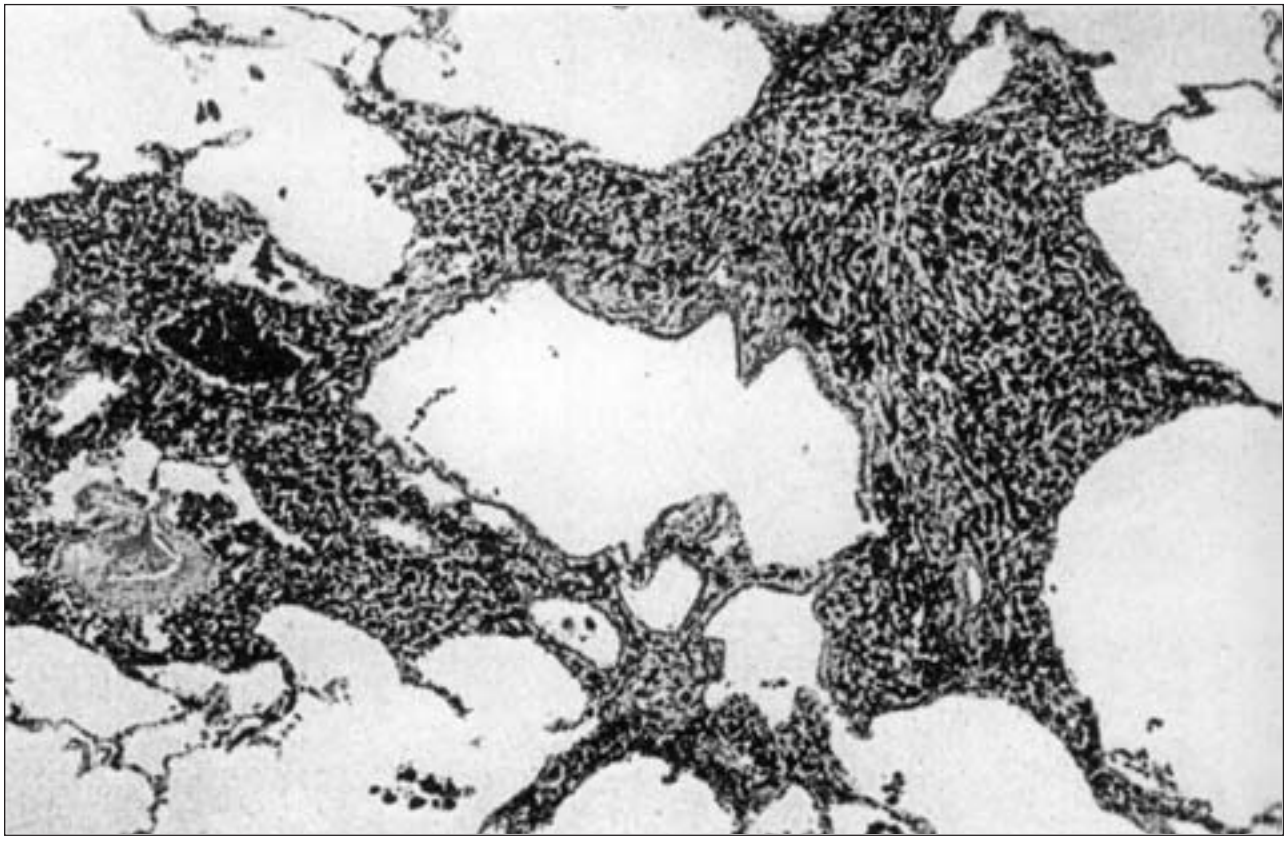


Figure 2. *(A)* Photomicrograph of a coal worker's pneumoconiosis. Note the black color, absence of collagen deposition, and random direction of the nodules. *(B)* Photomicrograph of a silicotic nodule. Note the concentrically arranged zones of cellular hyaline substance enclosed in a collagenous capsule.

Coal Worker's Pneumoconiosis

Background

Coal worker's pneumoconiosis (CWP) occurs among coal workers, graphite workers, and persons who work with other types of carbon. It is distinguished from silicosis because:

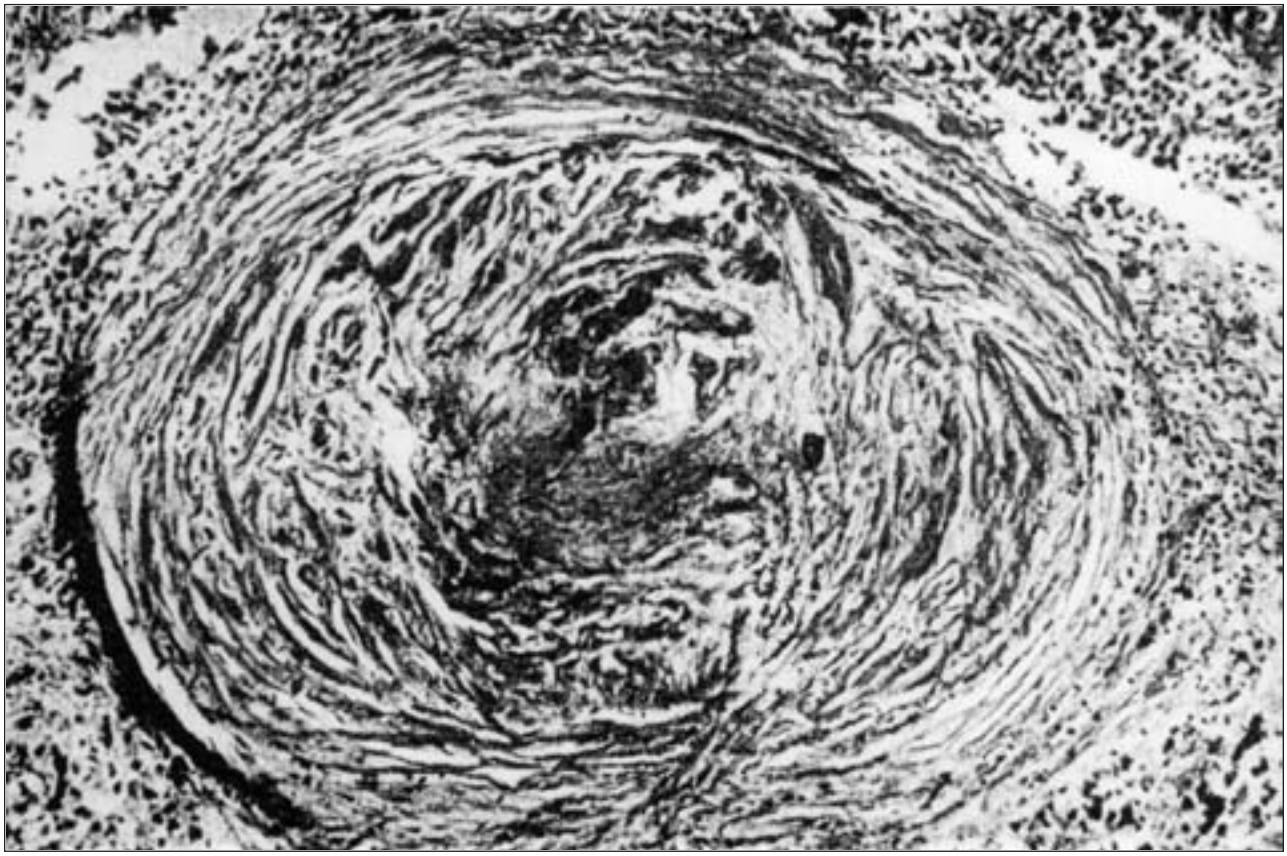
- The pathology is different from nodular silicosis.
- The role of quartz in the pathogenesis is not clear.
- It has been more extensively investigated than silicosis.

Synonyms for this disorder include anthracosilicosis and black lung disease; however, CWP is the preferred term. The pathology and clinical features are not different, whether the exposure is to coal, graphite, or synthetic carbons. The rank of coal does not influence the features of CWP, but higher-rank coals (especially anthracite) are associated with a greater prevalence of CWP. Pure carbon black and graphite may produce simple pneumoconiosis and progressive massive fibrosis, but fibrogenesis in CWP appears to be determined chiefly by the amount of total dust lung burden. Activation of macrophages with oxidation and fibronectin excess production have been documented.

Occupational Exposure

The highest concentrations of dust exposure occur in underground workers, especially those who work at the face of the mine. A lack of adequate dust control measures in coal mines through the late 1940s made CWP a very common problem for miners. Improvement in dust control through the mid-1960s has reduced the incidence of this disease, together with mechanization of the mining process at the mine face.

Figure 2 *B*



Pathology

Black lines may be found, running parallel to the ribs, on the parietal pleura. The lung parenchyma is marbled blue-black by subpleural dust deposits, but pleural thickening is uncommon. The lymph nodes in the hila and mediastinum are densely black and sometimes enlarged. Black dust nodules commonly in the upper half of the lungs are found on the cut surface. Progressive massive fibrosis (PMF) may occur. The black color of the nodules distinguishes them from typical silicotic nodules. In many cases, centrilobular emphysema is present, but it is irregularly distributed and mild in degree.

The microscopic picture includes intra- and extracellular dust concentrated around respiratory bronchioles and their vessels. Fibrosis with collagen deposition is not present. Dust-containing macrophages are abundant in some of the alveolar spaces; capillaries are often obliterated. The nodular lesions run in random directions, in contrast to the concentric collagen arrangement of silicotic nodules (Fig 2). Diffuse interstitial pulmonary fibrosis is sometimes found in association with CWP.

Pathogenesis

The quartz content of coal dust may be very low or very high. In general, however, it tends to be low. The total amount of dust in the lungs with CWP is much greater than with silicosis. The quantity and rate of accumulation of coal dust in the lungs appears to be the most important factor in the pathogenesis of CWP—probably more so than the chemical composition of the dust. Coal and carbon are not cytotoxic, behaving as inert dusts. Coal and quartz are cytotoxic to macrophages, and the presence of the quartz influences the pathogenesis of CWP. The coal dust, however, tends to mute the effects of the quartz. Immunologic factors may influence the susceptibility and development of PMF (or Caplan's syndrome) in a person with CWP.

Clinical Features

Simple CWP is not associated with any symptoms. Cough, sputum production, and dyspnea, if present, are due to other coexistent disease, typically bronchitis and / or emphysema from cigarette smoking. More advanced cases with conglomeration may also be asymptomatic, but dyspnea and disability may occur. Caplan's syndrome is the association of PMF with rheumatoid arthritis, although either disorder may antedate the other, and some patients with PMF may never develop active arthritis and have only a positive serologic test for rheumatoid factor. Sputum production does not accompany PMF in nonsmokers and its volume is typically small in smokers unless infection accompanies or complicates PMF. If hemoptysis is present, tuberculosis should be suspected, as is the case for silicosis. Small amounts of hemoptysis occasionally may be seen with PMF, however.

There are no special physical findings in patients with CWP. Finger clubbing is not a feature. Wheezing and rhonchi, if present, should suggest the presence of coexistent bronchitis. The clinical features of rheumatoid arthritis should be sought. Signs of cor pulmonale and congestive heart failure may occur in the most advanced forms of CWP.

Pulmonary Function Tests: These are not helpful in establishing a diagnosis of CWP. So long as CWP remains simple and uncomplicated (*ie*, no conglomerate masses or PMF), more advanced radiographic changes are not associated with declining lung function. More advanced PMF may be, but is not always, associated with a reduction in FVC and an obstructive ventilatory defect.

Radiographic Features: These are essentially the same as those described for silicosis.

Prognosis, Treatment, and Prevention

Simple CWP is not likely to shorten a patient's life or lead to any disability. Occasionally, PMF may progress suddenly and unexpectedly at any age. Advanced PMF affects mortality only in a minority of cases. Development of tuberculosis or infection by opportunistic mycobacteria may lead to more symptoms and premature death. Carcinoma of the lung is not caused by CWP. There is no treatment for CWP itself; the complications (bronchitis, heart failure, tuberculosis) are managed in standard fashion. Dust control measures and use of personal respirator masks have been very effective in reducing the incidence of CWP among miners.

Asbestos-Related Diseases

Background

The commercial production of asbestos increased from the latter part of the 19th century through the 1970s. The industrial revolution con-

tributed to this 80,000-fold increase in worldwide production and utilization of asbestos because of the fire-resistant qualities of asbestos and its usefulness as an insulating agent.

Asbestos was discovered in 1870, and since then, the world's production of asbestos has increased from 500 tons until about 5,000,000 tons per year were being produced. From the peak years of production, the health effects have been understood better, and production has dramatically decreased. Asbestos mining is typically an open pit operation where mechanical shovels and bulldozers mine and then load trucks or train cars for transport of the ore to a mill. Fracturing, sorting, and screening to separate the asbestos from undesired ores further process the raw material. Milling further concentrates the fibers by eliminating contaminants and sorting fibers by types and quality.

In the past, the major end-users have been the construction industry, the shipbuilding industry, and the automobile and railroad equipment industries. Today, many insulation and friction materials are made of nonasbestos replacement fiber materials. Potential worker exposures still occur during mining, milling, handling, manufacturing processes, and particularly during the destruction of previously manufactured material (asbestos abatement). Asbestos is virtually indestructible and remains in the environment indefinitely. Once the fibers are incorporated into a manufactured item, such as flooring tile, there is little health risk unless the item is disrupted.

The adverse health effects of asbestos exposure were first observed in the early 1900s and were first reported in 1907.

Physical Characteristics and Fiber Types

Chrysotile: The mineral is white, and the fibers are usually long and silky. Chrysotile penetrates the lung less efficiently than the amphiboles. Fragmentation in the lung after a period of storage is typical, and then the short fragments may behave more like the amphiboles. Chrysotile is useful for the manufacture of textiles because of its long pliable fibers, which split progressively into finer fibrils.

Amphiboles: There are three different types:

- Crocidolite (a harsher blue fiber).
- Amosite (brown and harsh).
- Anthophyllite (mined and used in Finland).

Amphiboles are rectilinear and penetrate the lung more efficiently. The thinner fibers (crocidolite) will penetrate the lung more deeply than do the broader fibers (anthophyllite). The amphiboles are more acid-resistant and are valuable for marine insulation. Many asbestos cement products are made from blends of chrysotile, amosite, and crocidolite fibers. Asbestos fibers are also used for paper products, friction materials, and in the chemical and plastics industries. Once incorporated into other manufactured items, the asbestos fibers pose less of a health hazard unless the product is cut or destroyed.

Occupational Exposure

The majority of clinically significant exposures occur in the workplace. Few people are exposed in the United States in the mining process. Most workers are exposed in occupations where asbestos is used, particularly the construction industry. The greatest risk occurs among individuals who handle asbestos before it is bonded into the final product or who cut, saw, file, sand, or demolish finished products that contain asbestos. The shipping industry has been an important historical place where workers are exposed, primarily because of the closed environment and the installation or removal of old insulation.

Nonoccupational exposure may occur in family members of individuals who work with asbestos. This is especially true for female patients, particularly if asbestos-laden clothing is cleaned at home. Residence near an asbestos factory or mine is another way patients may have significant nonoccupational exposure to asbestos.

Control of asbestos dust in the workplace is the most effective way to prevent disease. The current allowable US limit is 0.1 fibers/cc of air. In the past, although peak asbestos fiber counts in the workplace air sometimes exceeded 100 fibers/cc (in the manufacturing or installation of asbestos containing products), more typical exposures ranged from 5 – 20 fibers/cc.

Dose-Response Relationships and Biologic Effects

Epidemiologic studies have shown a clear relationship between the amount of exposure to asbestos (dose) and the biologic response in the exposed individual. The length of exposure is an important variable. Other variables of importance are:

- Intensity of exposure (number of respirable particles per cubic meter of air).
- Circumstances of exposure (closed vs open environment).
- Dust control measures (use of a respirator mask capable of filtering asbestos fibers from the respired air).

Time Since Initial Exposure

This is especially important because of the latency since first exposure to the development of most asbestos-related diseases. The intensity of exposure was greatest during the 1930s through 1950s because control measures had not been introduced or were not enforced. The clinician, when confronted with a patient with known or suspected asbestos-related disorders, can estimate the intensity of exposure by asking about visible dust particles in the work environment. Visible dust particles are generally too large to be respirable, but there is a rough correlation between the visible dust levels and the concentration of invisible respirable particles. Although there is a general concept of a dose-response curve for various asbestos-related diseases based on population surveys and the intensity and time of exposure, there is a varying susceptibility among individuals. This variation in susceptibility may be due to one or more of the following:

- The innate immunologic characteristics of the individual and his or her method of handling inhaled asbestos fibers.
- The efficiency of clearance mechanisms from the lungs.
- The anatomic characteristics of the lungs/airways system.
- The physical fitness of the person (unfit persons ventilate more for a given workload).
- The type of asbestos fiber. Crocidolite is the most dangerous carcinogen. The amphiboles are more fibrogenic than chrysotile, and crocidolite is the most fibrogenic among the amphiboles.

Evidence of Exposure to Asbestos

Ferruginous bodies (iron-coated fibers) are structures 20 to 200 μm in length and 2 to 6 μm in width. They are yellow-brown under ordinary light microscopy and have clubbed ends with a segmented appearance. They were originally thought to be specific for asbestos exposure, and a coated asbestos fiber was called an "asbestos body." However, it has been demonstrated that other fibers may also be transformed into ferruginous bodies. Ferruginous bodies are developed by the ingestion of fibers by macrophages, which coat the fibers with mucopolysaccharides. Iron, in the form of hemosiderin, is incorporated by the macrophage into its phagosomes and then concentrated around the fiber.

Ferruginous bodies are found in the lungs of all urban dwellers. There is no excess of asbestos-related diseases in the general public as a result of urban asbestos air or water pollution. The finding of ferruginous bodies in sputum, BAL fluid, lung tissue, or other tissue is suggestive of asbestos-related disorders. However, the history of exposure to asbestos must also be included in the interpretation, as other fibers (glass and cotton fibers, diatomaceous earth, talc, graphite, and Carborundum particles) may be transformed into ferruginous bodies. The ratio of coated fibers (ferruginous bodies) to uncoated fibers within the lung appears to be fairly constant at 10% to 30%.

Pleural Disorders Related to Asbestos Exposure

Pleural Plaques: Generally speaking, the identification of a pleural plaque by plain chest radiograph, CT assessment, or at thoracotomy or autopsy indicates a significant occupational exposure to asbestos (greater than casual exposure from residence in an urban area). By itself, however, the presence of a pleural plaque has little other significance.

Pleural plaques are discrete, raised, gray or white lesions on the inner surface of the thoracic cavity or diaphragm. They tend to be more frequent over the lower ribs, and are often at the posterolateral or anterolateral part of the rib cage. The diaphragm is typically involved, especially over the central tendon.

The microscopic appearance is that of a rather monotonous dense collagenous material, with little cellularity.

Calcium deposition tends to occur with more time lapse after they initially form. Pleural plaques can be seen after exposure to any type of asbestos fiber. However, it is extremely difficult to find ferruginous bodies in the plaques with ordinary light microscopy. Using the electron microscope,

very small uncoated fibers can be found in most plaques, particularly in the calcified zones of the plaques. Pleural plaques are more likely to be seen after longer time lapses since initial exposure. They are typically identified 20 or more years from initial exposure to asbestos.

The pathogenesis of pleural plaques is unknown. It is generally thought that the inhaled asbestos fiber traverses the visceral pleura, becoming impaled in the parietal pleura. The typical lower lung zone location may relate to the better ventilation in these areas than the upper lung zone. An alternative theory is that asbestos fibers are cleared by the parenchymal lymphatic plexus and accumulate in the mediastinal lymph nodes, and then microfibrils reach the parietal pleura through retrograde lymphatic drainage involving flow from the mediastinal nodes to the retrosternal and intercostal lymphatics.

The clinical significance of a pleural plaque is typically nil, except that they usually indicate prior asbestos exposure. Pleural plaques are an incidental radiographic finding, rather like a tattoo, in that the presence of a pleural plaque usually indicates exposure to asbestos. Plaques do not produce symptoms. Any decrements in lung function that might be attributed to pleural plaques can only be identified in population surveys. They do not transform into malignant mesotheliomas (a single case report). Of 13 investigations of the possible relationship between asbestos-related pleural plaques and lung cancer, only three supported the hypothesis that lung cancer risk is elevated among persons with pleural plaques over the risk in unexposed people. These three studies had the most defects in design. The other 10 studies failed to confirm the hypothesis. Thus, the weight of evidence favors the conclusion that persons with asbestos-related pleural plaques do not have an increased risk of lung cancer in the absence of parenchymal asbestosis.

Diffuse Pleural Thickening: Clinically, the radiographic and pathologic picture is very similar to that of pleural plaques, except the process is more widespread. Diffuse pleural thickening may be unilateral or bilateral. Mild reductions in lung volume may be seen but are rarely clinically significant to the extent that they create pulmonary disability.

Benign Asbestos Pleural Effusions: These should be considered in the differential diagnosis of "idiopathic" pleural effusions. The key to considering a benign asbestos-related pleural effusion is usually a detailed occupational (sometimes environmental) history.

The clinical features may be those of an acute presentation with pleuritic chest pain. An acute onset may be accompanied by fever, leukocytosis, elevated erythrocyte sedimentation rate, and generalized systemic symptoms. Benign asbestos pleural effusions may also have a chronic or insidious onset. They may be discovered incidentally at the time of a chest radiograph for some other reason. Benign asbestos pleural effusions are occasionally accompanied by positive serologic tests for rheumatoid arthritis, which makes the differential diagnosis difficult. The antinuclear antibody test is usually negative.

Fluid analysis typically reveals exudative characteristics. The fluid may be blood-tinged. Malignancy must be excluded. Cytology often shows atypical macrophages. Pleuroscopy or limited thoracotomy may be needed to exclude a malignant mesothelioma. Asbestos fibers are difficult to find.

Benign asbestos pleural effusions may recur several times over months to a few years; typically, they spontaneously resolve in several weeks to a few months. The pleural surfaces are hypervascular and exudative, with adhesions between parietal and visceral pleura. The underlying lung tissue shows interstitial changes that may be low-grade inflammation to organized subpleural fibrosis in which asbestos fibers or ferruginous bodies may be found. Diffuse pleural thickening may be a sequela, but complete resolution often occurs.

Malignant Mesothelioma: The first reports indicating a possible association with asbestos exposure were published in 1960.

- Epidemiology: The annual incidence is 1: 1,000,000/year in the general population. Malignant mesothelioma is associated with all fiber types except anthophyllite. Crocidolite is the most dangerous. Chrysotile probably does not cause mesothelioma, except as contaminated by a small percentage of amphiboles. Even low levels of exposure for brief periods in the remote past may cause mesothelioma. There is no synergistic effect with cigarette smoking. The lag time from initial exposure to development of mesothelioma is 20 to 40 years. Inadequate dust control measures until the late 1960s and 1970s mean that the incidence of malignant mesotheliomas will rise until shortly after the year 2000.

- Pathogenesis: Short straight fibers (1 to 2.5 μm wide, approximately 10 μm long) are deposited into the more peripheral airways. This is related to the aerodynamic properties of the fibers. The fibers penetrate the pleura and incite mesothelial growth, or they get to the parietal pleura via lymphatics (as described above as an alternative pathogenetic mechanism).
- Pathology: Malignant mesothelioma spreads along serosal surfaces. Grossly, the tumor is a thick yellowish-gray mass involving the parietal and visceral pleura, making decortication extremely difficult. Local invasion of adjacent structures is characteristic. Penetration through the diaphragm to involve the upper abdomen by the time of death is common for tumors arising in the pleura. Distant (blood-borne) metastases may be seen in up to 50% of patients by the time of death, particularly for the sarcomatous variety.
- The ratio of pleural to peritoneal origin has variably been reported as 2:1 to 54:1. There is a higher ratio for largely male populations, reflecting the difficulty in distinguishing ovarian carcinoma from peritoneal mesothelioma in females.
- Microscopic features include the following: (1) Epithelial mesothelioma has a tubulopapillary configuration with branching acini containing cuboidal or columnar cells that often contain mucin. This type may be confused with or difficult to distinguish from adenocarcinoma, as it is from a peripheral lung primary. (2) Mesenchymal mesothelioma has a sarcomatous appearance with variable amounts of collagen. (3) Undifferentiated mesothelioma shows solid sheets of polygonal cells with abundant eosinophilic cytoplasm. (4) Mixed mesothelioma contains all the features of the other types. This is the most common variety. Immunohistochemical staining techniques are helpful to the pathologist to state with a higher level of certainty that the tumor in question is truly a mesothelioma, and especially to distinguish this tumor from a primary adenocarcinoma of the lung, which seeds the adjacent pleura and may mimic mesothelioma clinically and radiographically.
- Clinical features include an insidious onset, which is typical, with gradual weight loss and dyspnea. Pain is the dominant presenting complaint and becomes the overriding clinical problem. The typical age at onset is 55 years or older, reflecting the long lag time from initial exposure. Other symptoms and signs usually reflect invasion to adjacent structures, *eg*, constrictive pericarditis/tamponade, Horner's syndrome, brachial plexopathy, and superior vena caval obstruction. Abdominal distention and ascites are more common with peritoneal origin, but may also be seen when the tumor arises from pleura and grows through the diaphragm to involve the abdomen. Clubbing and hypertrophic pulmonary osteoarthropathy may also be seen but are unusual.
- Diagnosis: A strong clinical suspicion based on presenting symptoms, history of exposure to asbestos, and radiographic features is needed. Mesothelioma may be very subtle initially. Radiographs may show a slowly enlarging pleural effusion, but encasement of the lung with mass-like pleural densities is more characteristic. The CT features are often helpful.
- Pleural fluid analysis for definitive diagnosis is extremely difficult. Closed needle biopsy is only slightly better. The tumor may grow into needle tracks after thoracentesis or biopsy. Open biopsy (perhaps via thoracoscopy) is usually needed. Even then, the diagnosis is not always established. Fibrous tumors may not have easily recognized malignant features. Other primary sites of origin (lung, ovary) may create confusion.
- Treatment: Surgery is rarely curative. Combination programs are advocated by some (surgical debulking, external radiation, and chemotherapy—usually Adriamycin based). Symptom relief and palliation is the most common goal, especially pain control. Neurosurgical techniques may become necessary. Thoracic involvement makes cordotomy less often effective and more likely to cause further compromise of respiratory function.

Pulmonary Disorders Related to Asbestos Exposure

Pulmonary Fibrosis (Asbestosis): The mere presence of pulmonary fibrosis in an asbestos worker does not prove a cause-and-effect relationship. Other causes must be considered, *eg*, sarcoidosis, rheumatoid arthritis, and drug reaction.

- Criteria recommended as necessary for a clinical diagnosis of asbestosis include (1) a history of exposure to asbestos, (2) dyspnea, (3) persistent basilar crackles in two or more locations, (4)

reduced lung volumes in pulmonary function tests, and (5) radiographic abnormalities 1/1 or greater on the ILO scale. The clinical diagnosis of asbestosis in the absence of radiographic abnormalities of this degree is highly suspect.

- Pathology at an early stage reveals minimal changes of basilar fibrosis that may be difficult to see. When more fully developed, widespread fibrosis is present, the lungs are small, and the cut surface shows that subpleural locations are affected first; lower lobes more than middle lobes more than upper lobes. Honeycombing is evident in advanced cases, and the pleural surfaces invariably are involved. Conglomerate lesions are rare, unless exposure is to a mixture of dusts (*eg*, talc and silica).

  The microscopic picture shows an early reaction: desquamation in the alveoli with an influx of macrophages. The basic lesion is widespread peribronchiolar fibrosis. More diffuse deposition of collagen and interstitial fibrosis ensues, with distortion of the parenchymal architecture.
- Pathogenesis: Some fibers are more fibrogenic than others (especially crocidolite and amosite). Macrophages are attracted to the asbestos fibers, ingest them, and release substances that stimulate fibroblast influx/deposition of collagen. Immunologic factors, such as certain HLA types, may predispose some subjects to greater fibrotic reactions than others for a given inhaled asbestos burden.
- Clinical features: The dominant symptom is dyspnea, but a dry cough is common (occasionally, small amounts of mucoid sputum). Crackles are best heard at the posterolateral bases; wheezing and rhonchi are unusual. Clubbing may or may not be present; if present, it is not related to the severity of the fibrosis. Cyanosis and pedal edema, related to cor pulmonale, are late findings.
- Pulmonary function: The typical finding in well-established asbestosis is a restrictive ventilatory defect. This is manifest as a reduction in the FVC with preservation or an increase in FEV_1/FVC ratio, unless there is coexistent obstructive lung disease due to other causes (asthma, chronic bronchitis, emphysema, etc). The diagnosis is more confident if the TLC is also reduced. In patients with coexistent emphysema, the TLC may be increased initially but fall into a normal range as fibrosis progresses. Most of the time serial data are missing to demonstrate this phenomenon. The diffusing capacity also may be reduced, but D_{CO} measurements are subject to greater variability of the testing methodology than simple spirometry.
- Airflow obstruction: Peribronchiolar fibrosis is thought by some to lead to a reduction in parameters that reflect small airways dysfunction. However, the variability of normal values makes this relationship less clear. In a recent large population survey of asbestos-exposed construction and shipyard workers 20 years after initial asbestos exposure, people who had never smoked were found to have decreased expiratory flows and increased total lung capacities compared with unexposed people who had never smoked.
- Radiographic changes: A high-quality posteroanterior chest radiograph remains the most widely used method. Under- or overpenetrated films lead to variability in interpretation. Other technical and clinical features may confound the interpretation (depth of inspiration, overlying pleural changes, coexisting congestive heart failure, etc). Application of the ILO system, using standard radiographs for comparison, helps to systematically identify abnormalities. The ILO system has been demonstrated to be reproducible in epidemiologic surveys for experienced and qualified readers. Generally, a 1/1 profusion "cut point" is used as the lower threshold of abnormality to confidently state that the chest radiograph shows sufficient abnormality of the lung parenchyma to support a diagnosis of asbestosis. There is interreader variability, with some tendencies to underread or overread plain chest radiographs, even when the ILO system is used.

CT assessment, particularly with high-resolution or thin-section technique, is advocated by some. The increased sensitivity is offset by a potential reduction in specificity. Imaging should be done in the prone as well as supine positions to overcome the problem of gravity-dependent pooling of blood, which could be mistaken for pulmonary fibrosis. When present, asbestosis produces non-position-dependent subpleural short lines as a fairly consistent finding. The cost of chest CT examinations precludes widespread application, particularly in epidemiologic studies.

Rounded Atelectasis: This unusual entity is a combined pleuroparenchymal process, in which the subpleural lung becomes entrapped by the adjacent pleural fibrotic process. Patients present

with a mass-like density on chest radiographs; rounded atelectasis is usually slowly progressive, and it is most commonly confused with primary bronchogenic carcinoma. CT assessment, showing its contiguous relationship with the adjacent pleura and a "comet-tail" appearance, is often helpful in the differential diagnosis. Invasive biopsy, especially percutaneous needle aspiration with negative results, increases the confidence level that this process is benign when CT radiographic features are also considered.

Lung Cancer: The initial association with asbestosis was suggested in individual case reports in the 1930s. Epidemiologic data supporting their relationship were more persuasive in the 1940s and 1950s and fairly firmly established by 1955.

- Relative risk and association with cigarette smoking: Epidemiologic data implicate asbestos as a carcinogen by itself. The effects of cigarette smoking as a carcinogen are far more important than asbestos. Carcinoma of the lung develops only rarely in nonsmoking asbestos-exposed persons (but approximately 1.5 to 3 times more frequently than in non-asbestos-exposed persons). The risk of lung cancer associated with exposure to asbestos and cigarette smoking is considerably more than additive; it is probably the product of the two risks (multiplicative phenomenon) or somewhere in between additive and multiplicative.
- Type of asbestos fiber in relationship to lung cancer: All major fiber types have been implicated. The relative risk data are not completely worked out, but it appears that crocidolite and amosite are more carcinogenic than anthophyllite and chrysotile.
- The lag time between first exposure and development of lung cancer is usually long (rarely <10 years, and usually >20 years). The increased use of asbestos in World War II (ship building) and through the early 1970s may be partly responsible for the surge in lung cancer from 1960 through the present.
- Intensity and duration of exposure to asbestos and its relationship to lung cancer: There is more risk with greater intensity and duration of exposure to asbestos. The excess of lung cancer is most notable when the dust exposure index is >200 million particles per cubic foot-years.
- Cell type and location of lung cancer in relation to asbestos: Many earlier studies suggested that there is a higher incidence of adenocarcinoma and a higher incidence in the lower lobes among asbestos-exposed persons who develop lung cancer. However, recent studies have not shown such relationships.
- Relationship of lung cancer and pulmonary fibrosis: Lung cancer is twice as common in asbestos workers with moderate or severe pulmonary fibrosis than in asbestos-exposed persons who do not have pulmonary fibrosis. The proportion of adenocarcinoma increases with moderate or severe pulmonary fibrosis. Asbestos-related bronchogenic carcinoma occurs on a background of alveolitis with thickening of the alveolar walls and peribronchiolar regions of the lung. It is probably not possible to separate the process of carcinogenesis of the lung from inflammation and fibrosis in the asbestos worker with more than 20 years of exposure.

Other Asbestos-Related Cancers: In the early cohort studies of mortality in asbestos workers, the risk of all cancers appeared to be greater than expected. The relative risks of mesothelioma and lung cancer are the greatest and best established. GI cancers were thought to be more common. However, a recent review (Gastroenterology 1990; 99:876) of all studies on the most common GI malignancy (colorectal carcinoma) carefully analyzed the bias in those studies that indicate such a relationship, and the author concluded that the observed vs expected numbers of cases for all 21 reported cohorts is 0.97 (P>0.05). Similarly, early cohort studies reported that laryngeal cancer is more common in asbestos workers. Cigarette smoking and ethanol intake, well-recognized risk factors for laryngeal carcinoma, were not well controlled in these early cohort studies. More recent cohort studies do not indicate a major excess mortality from laryngeal cancer.

A relationship with other cancers (ovary, kidney, brain, breast, leukemia, and lymphoma) has been suggested, but the data associating them with asbestos exposure are even less secure.

Talcosis

Background

Talc pneumoconiosis was first described in 1896. The radiographic appearance may be similar to nodular silicosis, CWP, or sarcoidosis. Diffuse interstitial pulmonary fibrosis may also be seen.

Talc is a hydrated magnesium silicate occurring in sheets that readily cleave and break down to form flat flaky plates. Low-grade talcs may contain in excess of 50% impurities and significant amounts of quartz. The value of talc relates to its softness, whiteness (when pure), high lubricating power because of slippage of the flakes over one another, and oil adsorption properties. It is used primarily in the paint, pharmaceutical, rubber, and cosmetics industries.

Types of Pulmonary Disease Associated With Talc

Talcosilicosis: This is caused by talc mined with a high silica content. The findings in this disorder are essentially identical to silicosis.

Talcoasbestosis: Crystalline talc, contaminated by asbestos fibers, is the cause of this disorder. It resembles asbestosis, including the potential for pleural plaque formation and the development of malignant tumors.

Talcosis: Inhalation of pure talc leads to acute or chronic bronchitis as well as interstitial inflammation. Small airway obstruction and radiographic features of small irregular nodules may be found.

IV Injection of Talc: Oral medications that are melted down and injected or the "cutting" of heroin or other illicit street drugs for injection leads to the formation of vascular granulomas in the lungs. The radiographic lesions may be small or large, and pulmonary hypertension due to occlusion of a sufficient portion of the pulmonary vascular bed has been reported.

Berylliosis

Background

Beryllium was discovered in France in 1798, but it was not produced commercially in the United States until the 1930s. Berylliosis has been recognized as a distinct disease entity for only the past 60 years; in all respects, it resembles and is indistinguishable from sarcoidosis except for the history of beryllium exposure. The first major use of beryllium was in fluorescent lights; more recently, it was used in the development of nuclear weapons and nuclear power. As berylliosis was recognized, the Atomic Energy Commission developed strict air standards that are essentially unchanged today; the incidence of the disease is now very low. Most workers are exposed in industries that fabricate and machine beryllium-containing alloys, used in the aerospace and nuclear industries.

Acute Disease

The skin, mucous membranes, and respiratory tract may be affected. Beryllium is a direct irritant, and it can cause tracheobronchitis and pneumonitis as well as inflammation of the eyes, nose, and pharynx. The pneumonitis is similar to any other chemical pneumonitis, with cough, sputum, dyspnea, chest pain, crackles, and cyanosis. Infiltrates, either localized or diffuse, are seen on the chest radiograph. A restrictive ventilatory defect and hypoxemia are seen. Treatment is by removal from exposure, supplemental oxygen, supportive measures, and steroids in the more advanced forms. Recovery is usual, but chronic changes may be seen in up to 17% of cases.

Chronic Disease

Chronic berylliosis is a systemic disease with primary pulmonary manifestations, identical to sarcoid. Granulomas are the typical pathologic feature. Dyspnea is the most common presenting symptom, but cough, weight loss, chest pain, arthralgias, and fatigue are also seen. Physical findings include crackles, skin lesions, enlargement of liver or spleen, and lymphadenopathy. Rarely, cor pulmonale and right heart failure may develop.

- Pulmonary function tests may show reduced lung volumes and diffusing capacity. An obstructive ventilatory defect may also be seen.
- Chest radiographs typically show enlarged hilar lymph nodes and diffuse infiltrates.
- Pathology of involved tissue shows noncaseating granulomata. In addition to a history of beryllium exposure, proof of beryllium disease requires the presence of beryllium in lung tissue, lymph nodes, or urine.
- Pathogenesis: Although beryllium is a primary irritant, which accounts for the acute disease, it is now evident that beryllium can trigger a cell-mediated immune reaction in addition to being directly cytotoxic. Alveolar macrophages ingest beryllium, then release lysosomes, stimulate T-lymphocytes, and lead to granuloma formation.

Hard Metal Lung Disease

Background

Hard metal or cemented tungsten carbide (WC) is found in tools for high-speed cutting, drilling, grinding, or polishing of other metals or hard materials. The consensus is that WC is not the agent responsible for the disease, which is seen in a minority of persons who work with it. The more probable cause is cobalt, which is used as a catalyst to promote the binding of tungsten to carbon.

Asthma

It is probable that an acquired hypersensitivity plays a role in the development of a hypersensitivity bronchitis or asthma-like picture in a small percentage of hard metal workers.

Pulmonary Fibrosis

The pneumonitis is initially of the desquamative type. In its subacute form, multinucleated giant cells are seen. It has been proposed that giant cell interstitial pneumonitis is pathognomonic for hard metal exposure. With prolonged or very intense exposure, as with accidental spills of cobalt powder, a more advanced form of pulmonary fibrosis that can lead to disability and premature death has been reported.

Occupations at Risk

Workers in industries that manufacture cutting tools, drills, and the like are at highest risk. However, users of such tools may also be exposed, particularly in small shops where the ventilation is poor and protective measures are not used, *eg*, dental laboratories, sharpening of saws, and diamond polishers.

Miscellaneous

Metal Fume Fever

Exposure to high concentrations of metal fumes, especially (but not exclusively) zinc oxide, leads to metal fume fever. This is characterized by an influenzalike or malarialike illness with fever, chills, and malaise with relatively mild respiratory symptoms, and classically little or no radiographic or functional abnormalities. The symptoms may be accompanied by a sweet metallic taste, and they usually begin at home a few hours after a heavy exposure to metal oxides. Leukocytosis is present during the acute illness. A strange feature of this syndrome is that tolerance develops: symptoms only occur when exposure takes place over a period of days, and they do not appear on subsequent days.

Siderosis

Small nodular densities that are uniformly distributed on the chest radiograph are characteristic of this disorder, which does not produce symptoms. It is caused by inhalation of iron compounds and is found in iron miners, welders, and during the refining or manufacture of iron or steel.

Other Rare Pneumoconioses

These include those caused by tin, barium, antimony, and zirconium (benign, nonfibrogenic disorders), aluminum (a rare cause of interstitial fibrosis or asthma), and a few others.

Annotated Bibliography

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This review is the second of a two-part review of heavy metal toxicity. This part identifies the salient features of the toxiocopathophysiology, clinical presentation, and emergency department management of metal fume fever and lead toxicity.

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Challenges the concept that lung cancer cannot be ascribed to asbestos exposure without a diagnosis of asbestosis.

LaDou J, Landrigan P, Ballar JC III, et al. A call for an international ban on asbestos. CMAJ 2001; 164:489-490
The authors of this article recommend an immediate international ban on the mining and use of all asbestos, because of the epidemic of illnesses caused by asbestos. They assert that safer substitutes exist, and that the commercial tactics of the asbestos industry are very similar to those of the tobacco industry: marketing asbestos in developing countries is offsetting the ban on use of asbestos in developed countries. The Canadian Medical Association Journal solicited two additional articles, with an accompanying editorial (CMAJ 2001; 164: 453), in the same issue. Camus (CMAJ 2001; 164:491-494) cautions that the authors of the first article selected a non-representative risk assessment, discarding others that suggest the risk from chrysotile (the dominant type of asbestos currently used in new products) is much less than for amphiboles. Camus also suggests that there are reasons to doubt the safety of substitutes for chrysotile, noting that any fiber can carry chemical and biological contaminants such as cigarette tars deeply into the lung by adsorption. Siemiatycki (CMAJ 2001; 164:495-497) asks whether Canadian health care professionals should support the call for a worldwide ban on asbestos, noting that the debate has not been a purely scientific one. He draws the analogy to the worldwide ban on DDT, the elimination of which has led to a staggering increase in malaria in developing countries.

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These authors found that simple CWP was a contributor to significant decrements in pulmonary function, and to an increased risk of respiratory symptoms.

Weiss W. Asbestosis: a marker for the increased risk of lung cancer among workers exposed to asbestos. Chest 1999; 115:536-549

This review examines the hypothesis that excess lung cancer risk in worker cohorts exposed to asbestos occurs only among those with asbestosis. The evidence indicates that asbestosis is a much better predictor of excess lung cancer risk than measures of exposure and serves as a marker for attributable cases.

Weiss W. Asbestos and colorectal cancer. Gastroenterology 1990; 99:878-884

Critically assesses the literature as it pertains to the putative association of asbestos with GI malignancies (especially colorectal carcinoma), concluding that there is no firm relationship.

Notes

Notes