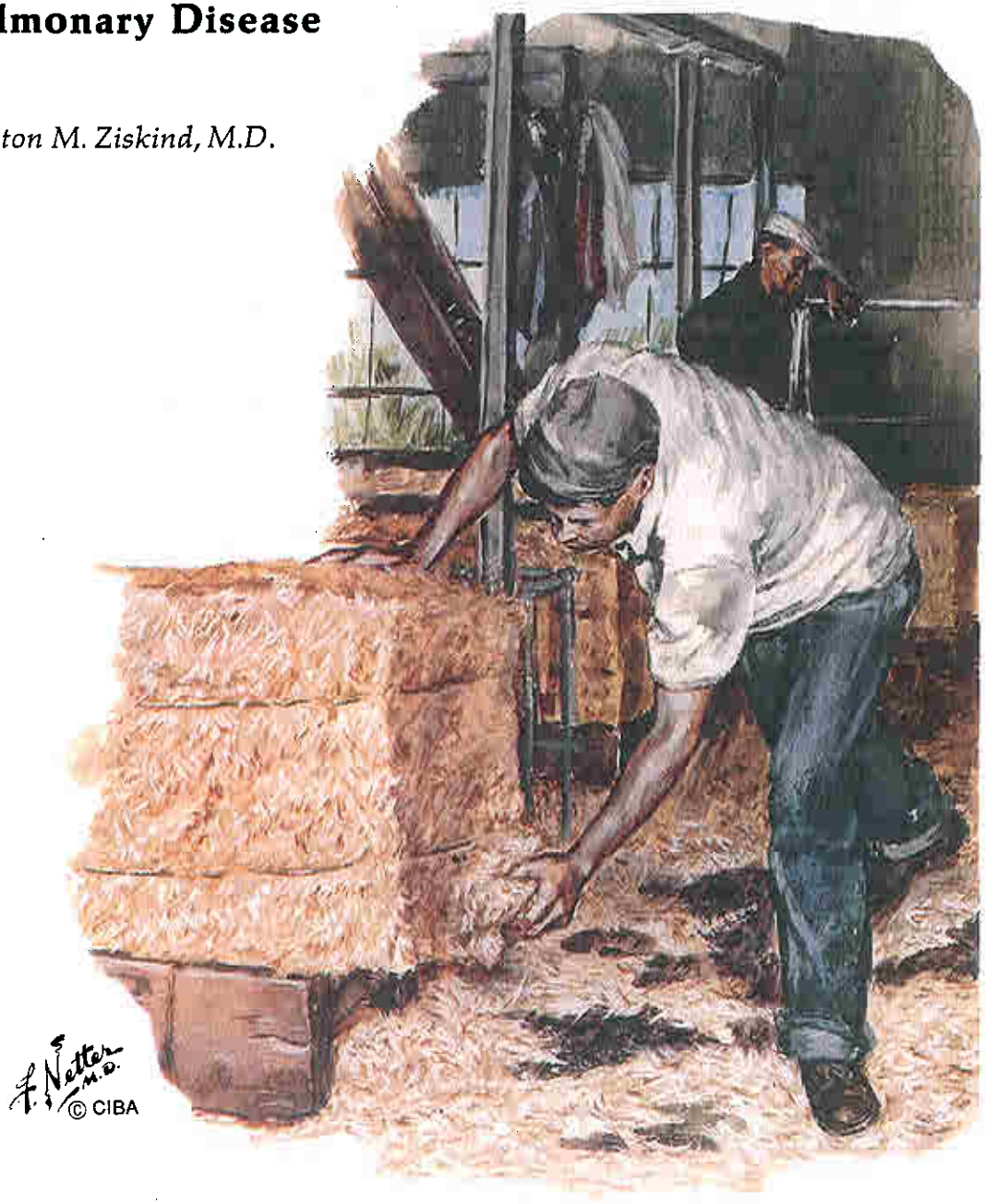
CLINICAL SYMPOSIA

CIBA

Volume 30 Number 4 1978 *Reprint*

Occupational Pulmonary Disease

Morton M. Ziskind, M.D.



CLINICAL SYMPOSIA

CIBA

VOLUME 30 NUMBER 4 1978

Occupational Pulmonary Disease

Morton M. Ziskind, M.D.
Illustrated by Frank H. Netter, M.D.
Edited by Kristine J. Bean

Inhaled Particles and Gases 2
Acute Reactions 3
Subacute Reactions 7
Chronic Disease 7
Diagnosis 20
History 20
Physical Signs 23
Roentgenography 23
Diagnostic Tests 27
Pulmonary Function Tests 28
Summary 30
Treatment 30
Prevention 32

Alister Brass, M.D., Directing Editor

CLINICAL SYMPOSIA *is published solely for the medical profession by CIBA Pharmaceutical Company, Division of CIBA-GEIGY Corporation, Summit, New Jersey 07901. Address all correspondence to Medical Education Division, CIBA Pharmaceutical Company, Summit, New Jersey 07901.*

Occupational Pulmonary Disease

MORTON M. ZISKIND, M.D.

Director of Pulmonary Diseases Section
Professor of Medicine
Associate Director of Specialized Center
of Research (SCOR) in Occupational Pulmonary Diseases
Department of Medicine, Tulane University School of Medicine
New Orleans, Louisiana

In 1556 Agricola's *Treatise on Mining* described all aspects of metal mining in the mountains of Silesia and Bohemia. Agricola's observation that men became sick and died from breathing dust led to the recognition of dust as an occupational hazard. Throughout the following centuries other observers recorded the relationship between occupations such as mining and quarrying and cough, dyspnea and wasting diseases. However, until the late nineteenth century few measures were taken to reduce the dangers of the workplace and protect workers.

Unfortunately, internal disorders resulting from prolonged exposure to occupational hazards are harder to detect than the more obvious injuries to skin or eyes. Many work-related diseases develop slowly over 20 or 30 years, and are asymptomatic in the early stages. The diagnosis of such diseases is difficult and requires a careful history and often the use of specialized instruments and techniques.

Most cases of occupational pulmonary disease are caused by the inhalation of noxious particles, gases or fumes by workers engaged in the extraction and manufacture of industrial substances. Workers are also exposed to respirable particles in mining, quarrying, milling, cleaning, mixing and shaping industrial materials. Others may work near stored materials or transport hazardous substances in trucks and trains. Also, workers who dispose of waste products or replenish spent stocks may be at risk.

However, the hazards of an industrial society involve not just workers but extend to the entire community. Families of workers have contact with clothing that is contaminated with industrial dusts. Local inhabitants may breathe air containing industrial gases or dusts produced by nearby industries. Accidental spills of toxic gases or chemicals during transportation endanger large numbers of people, and necessitate the evacuation of entire districts.

This monograph presents an overview of occupational pulmonary disease, including a discussion of the clinical findings in specific work-related lung disorders. A summary of pulmonary reactions to inhaled substances is offered in the table on page 31. As the site of reactions caused by exposure to industrial irritants depends largely on the physical properties of the inhaled material, a brief outline of these properties is presented as a prelude to descriptions of the acute, subacute and chronic effects of the inhalation of industrial dusts and gases.

INHALED PARTICLES AND GASES

Reactions to noxious substances occur chiefly at two levels: in the conducting airways and in the gas-exchanging alveoli, or both. Sometimes the pleura is also involved. The size of inhaled particles determines whether they will be deposited in the airways

Note: The illustrations by Frank H. Netter, M.D. appearing in this issue of CLINICAL SYMPOSIA will also appear in The Respiratory System, *Volume 7 of THE CIBA COLLECTION OF MEDICAL ILLUSTRATIONS, scheduled for publication in October 1978.*

or in the alveoli; the site of action of toxic gases is principally determined by their solubility. Other factors that play important roles in the development of occupational pulmonary disease are the concentration of particles or gases in the respired air, the length of exposure, the nature of the substance and, of course, the health and individual susceptibility of exposed individuals.

Inhaled particles larger than 10 microns in diameter are usually intercepted within the nose, or impact upon the walls of the airways by inertial force. Such particles are effectively removed from the tracheobronchial tree by ciliary action. Smaller particles, particularly those between 1 and 3 microns in diameter, remain suspended in the airflow and pass through the respiratory bronchioles into the alveoli, where they are often deposited.

Inhaled Gases. The solubility of *irritant gases* determines whether they act principally in the upper airways or in the more peripheral airspaces. Easily soluble gases, such as chlorine, ammonia and sulfur dioxide, are largely dissolved by the aqueous fraction of the tissues of the upper airways, where they produce either inflammatory or corrosive structural changes or cause reactions such as bronchospasm. Relatively insoluble gases like phosgene and the nitrogen oxides are less irritating to the upper airways and tend to be inhaled into the respiratory bronchioles and alveoli, thus injuring the more sensitive tissues and incapacitating gas exchange.

Nonirritating gases such as carbon monoxide may produce no reaction at all in the respiratory system although, because of their solubilities or chemical affinities, they are capable of entering the bloodstream and can produce damage in other body systems. They often show distinct tropisms, as illustrated by the affinity of carbon monoxide for hemoglobin, the solubility of aliphatic hydrocarbons in the lipids of the nervous system and the deposition of lead in bone marrow, gut and nerve. On the other hand, absorbable chemicals such as mercury and cadmium may damage the lower respiratory tract before entering the circulation to affect those organs susceptible to their action.

ACUTE REACTIONS

Acute reactions can be classified by the location of the reaction: those that occur chiefly in the airways (nasopharynx and tracheobronchial tree), and those that affect the fine airspaces (respiratory bronchioles, alveolar ducts and alveoli). Acute exposure usually causes acute bronchopulmonary disease, although the physician must always consider the concentration of the offending substance and the history of the patient in making such a diagnosis.

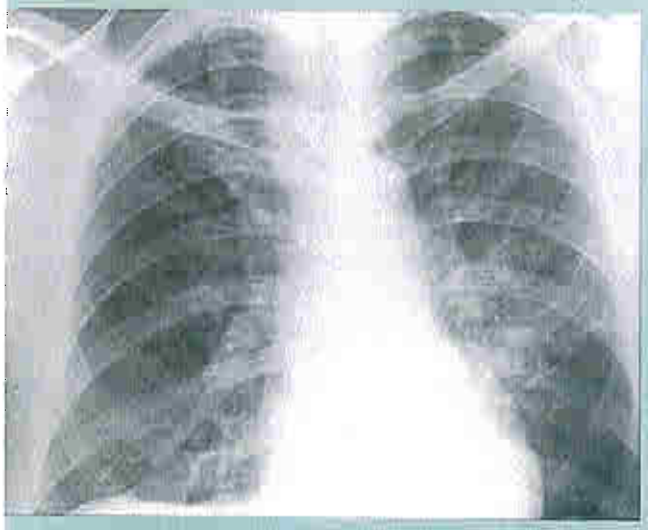
Acute Reactions in the Airways. The upper airways are particularly susceptible to the effects of soluble gases and to particles larger than 10 microns in diameter. *Soluble gases* such as chlorine, sulfur dioxide and ammonia quickly cause mucosal irritation in the conjunctivae and upper respiratory tract that is sufficiently uncomfortable to alert exposed workers to danger. If exposure to soluble gases is brief, only simple irritation of the eyes and of the nose and throat may result, leading to cough and expectoration. Severe and prolonged exposure to substances such as ammonia and sulfur dioxide may cause keratoconjunctivitis and bronchitis, and can lead to chronic suppurative bronchopneumonia, bronchiectasis and progressive respiratory insufficiency.

If the endangered worker is unable to escape, excessive concentrations of gas are inhaled into the lower airways and alveoli, damaging bronchial mucosa as well as the alveolo-capillary membranes. Symptoms of injury to the lower respiratory tissues include severe dyspnea, wheezing and orthopnea, usually followed by fever and purulent expectoration indicating secondary infection or acute pneumonia. Overwhelming exposure to toxic gas may lead to early death as a result of pulmonary congestion, edema and pneumonia, associated with diffuse damage to the mucous membranes (Plate 1).

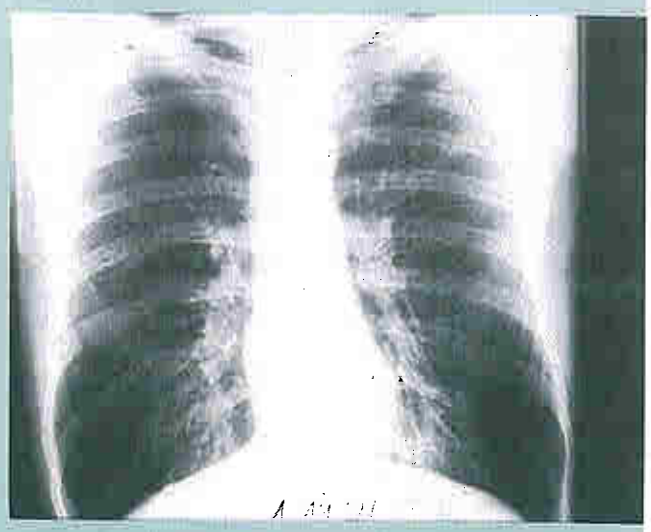
Acute reactions in the airways can also be a consequence of *hypersensitivity*. Hypersensitivity to specific industrial agents is an acquired condition. It is most likely to occur in allergic individuals, but does occur in individuals with no history of familial hypersensitivity. The symptoms may be *immediate* or *delayed* asthmatic reactions, including nocturnal wheezing, dyspnea and fever. Delayed reactions may occur hours after exposure or after the worker has left the workplace. Thus, the time lapse may obscure the relationship between the hypersensitivity reaction and the occupational exposure.

Substances known to cause hypersensitivity reactions include toluene diisocyanate,

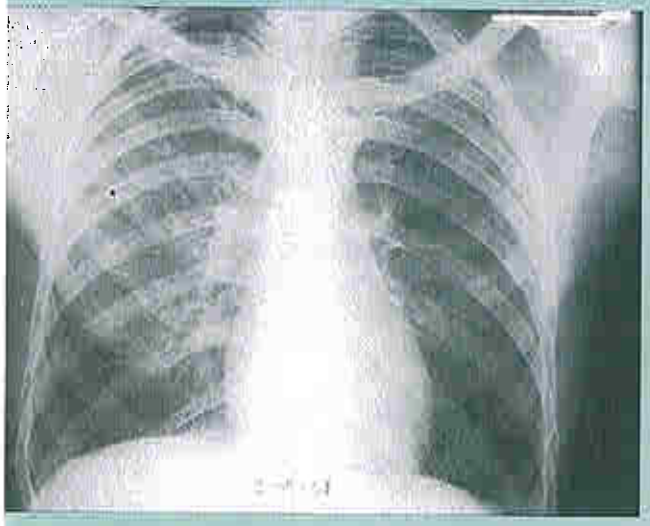
Effects of Exposure to Irritant Gases



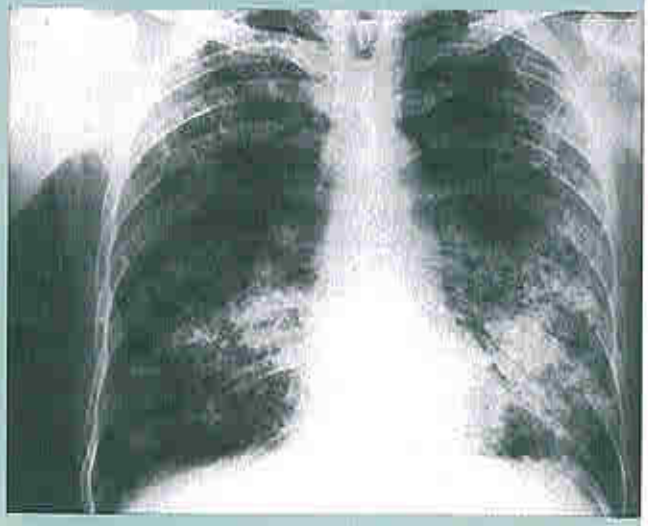
Ammonia fumes exposure: pulmonary edema apparent within a few hours of exposure



Ammonia fumes exposure: diffuse emphysematous changes, six months later



Chlorine gas exposure: acute, diffuse pulmonary edema



Nitrogen dioxide exposure: fine and coarse infiltrates, confluent in some areas

western red cedar dust, proteolytic enzymes, textile dusts and thermophilic actinomycetes (discussed under hypersensitivity pneumonia, page 7).

Toluene diisocyanate (TDI) is a substance used in the production of polyurethane foams, which are widely used as coating agents and insulation, and in upholstery. The threshhold limit value of TDI has been set at 0.02 parts per million for the average worker. However, some workers have become sensitized to concentrations of TDI well below this value. Asthmatic reactions to TDI in sensitized individuals are severe and may be prolonged. However, the biologic mechanism for TDI sensitization has not been established, and antibodies have not been demonstrated. In addition, TDI in excessive concentrations is a respiratory irritant that has caused chronic bronchitis in workers and firemen exposed to it in industrial accidents.

Western red cedar dust also causes hypersensitivity reactions in exposed workers, although the mechanism of the immune reaction remains uncertain. The reactions are delayed and may occur and recur at night after the worker has left the contaminated environment.

Proteolytic enzymes used in the manufacture of detergents also cause delayed

hypersensitivity reactions, which may be protracted. These enzymes are derived from *Bacillus subtilis*, and the finding of precipitins suggests that a type III (Arthus) hypersensitivity reaction is responsible for this form of industrial asthma—a type unrelated to familial asthma. Pulmonary infiltrations, which could indicate areas of pulmonary consolidation, are not found on roentgenograms of patients with this condition.

Cotton dust or *linters* may provoke acute bronchospasm in textile workers (especially those working in carding rooms) and cottonseed oil workers. The disease is known as byssinosis or "brown lung," and generally appears in workers who have been exposed to the dust for several years. The presenting symptoms are chest tightness (indicating bronchospasm) and a low-grade fever, which appear on the first day of work following a weekend or short layoff and, as a result, are known as "Monday fever." Later in the week the symptoms disappear. As the disease progresses, the symptoms extend beyond Monday to the rest of the week, and bronchitis with productive cough and dyspnea develops. If contact with the dust is not broken, byssinosis may lead to chronic obstructive pulmonary disease, even in workers who are not cigarette smokers.

It has been postulated that the cycle of symptoms in byssinosis is a pharmacologically mediated phenomenon. Cotton dust stimulation causes a discharge of naturally produced histamine leading to bronchospasm, which continues until the histamine stores are exhausted. This results in loss of reactivity, allowing the affected individual to work undisturbed for the remainder of the week.

Acute Reactions in the Fine Airspaces. Pulmonary edema and chemical pneumonia are the characteristic effects of exposure to insoluble gases and metal fumes. Toxic gases of low solubility produce less irritation to the airways than soluble gases, and since they may be inhaled for long periods of time with little or no discomfort, the exposed individual may not be prompted to an immediate escape. With prolonged exposure, damage to the fine airspaces is likely to occur. Insoluble gases, such as phosgene and nitrogen oxide and its polymers, if inhaled to an excessive degree, cause severe alveolar injury by chemical transformation to their corresponding acids. Acute pulmonary edema, which is often fatal, may result. Even in well treated cases of gas poisoning, the edema may be complicated by secondary bacterial pneumonia.

The use of phosgene and other insidious gases in chemical warfare is well known, but the risk of occupational exposure to such gases is not often appreciated. Today, workers may be exposed to phosgene in the production of chlorine and TDI.

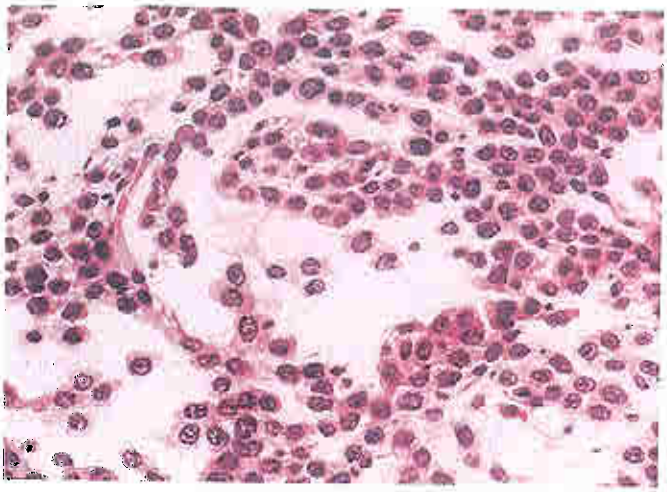
Exposure to high concentrations of nitrogen dioxide in filled silos (silo filler's disease), closed welding spaces and chemical laboratories first causes headache; and respiratory symptoms of chest tightness, cough, and shortness of breath appear later. The end result can be pulmonary edema or prolonged proliferative cellular reactions within the fine airspaces (Plate 1). The course of this disease is unusual. It is not uncommon for the early phase of pulmonary edema to be fatal. However, if the worker survives the early phase, apparent resolution occurs only to be succeeded in two to three weeks by bronchiolitis fibrosa obliterans, which may cause progressive and fatal dyspnea.

The inhalation of mercury, cadmium and beryllium fumes can also produce acute pulmonary edema and pneumonia, effects that are often fatal. Usually, the individual who recovers from the acute effects of exposure to mercury and cadmium will not develop chronic disease, although this has followed acute pneumonia resulting from beryllium exposure (page 19).

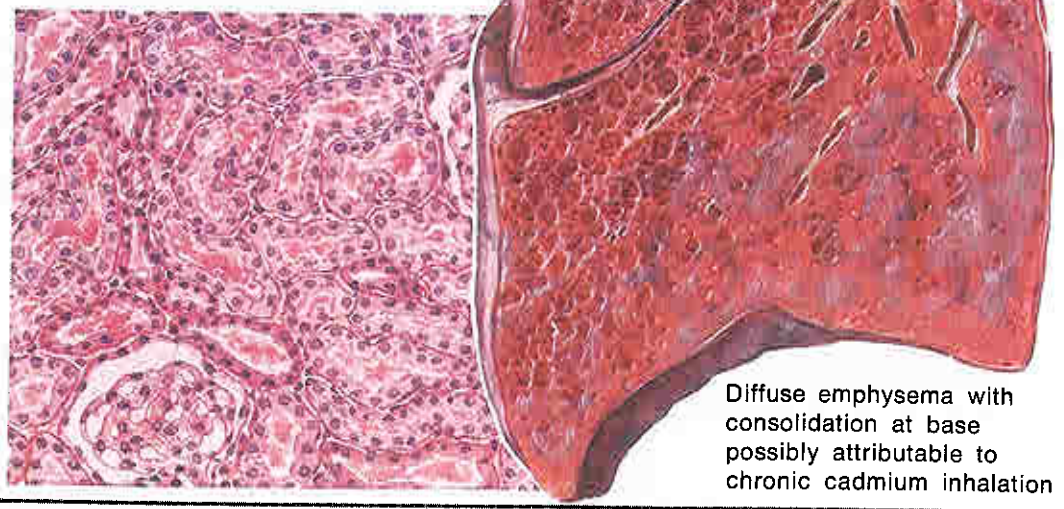
In fatal cases of cadmium exposure, the lungs show edema, congestion and hemorrhage (Plate 2), and necrotic lesions are found in the cortex of the kidneys. Degenerative changes in the testes have also been demonstrated. Acute, centrilobular emphysema occurs as a result of chronic exposure to cadmium fumes in animals, but the chronic effects of cadmium exposure on the human lung have not been adequately studied.

Systemic Effects. Inhaled *metal fumes*, notably those of copper and zinc, may cause a disease known as "metal fume fever." This reaction particularly occurs in welders employed in closed spaces, who refer to the disease as "galvanization." Other metals that cause this illness include magnesium, cadmium, iron, manganese, nickel, tin and antimony. The acute illness is characterized by fever, malaise, nausea and aching muscles. The symptoms last one or two days, after which complete recovery takes place. No chronic effects have been demonstrated.

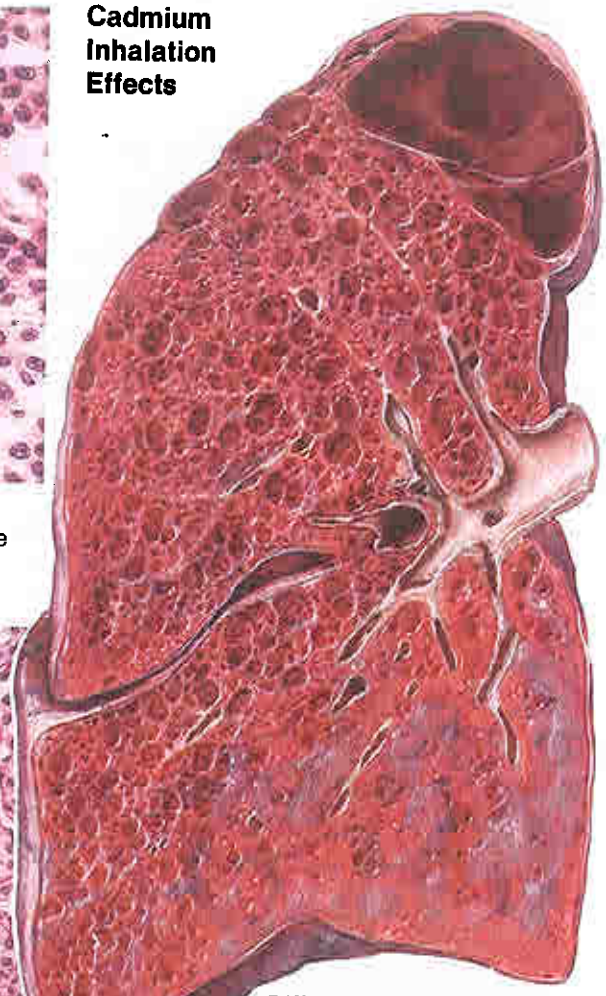
Cadmium Inhalation Effects



Acute reactions: metaplasia of alveolar epithelium may be accompanied by acute inflammation of the tracheobronchial tree and upper respiratory tract



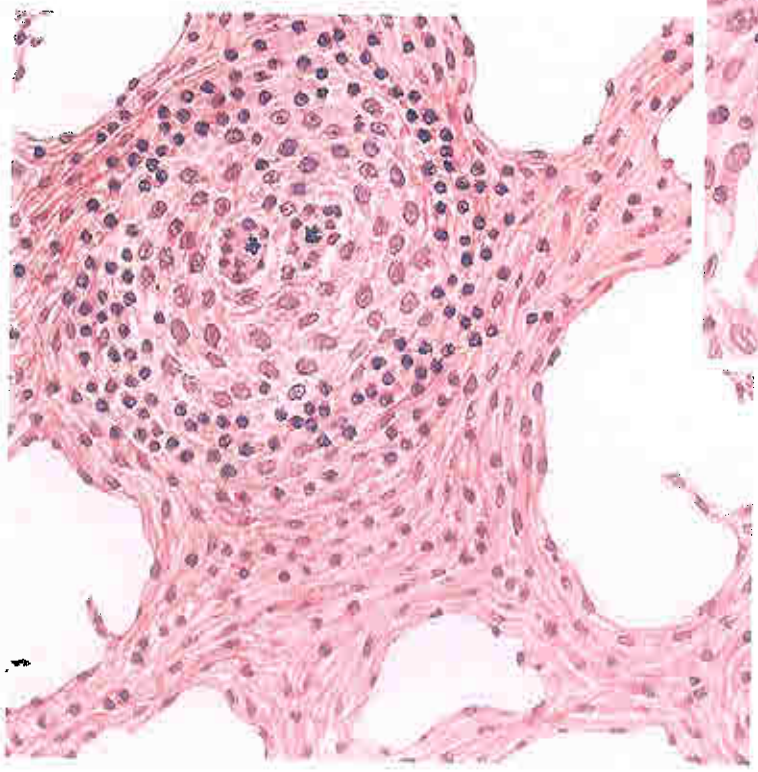
Chronic effects: PAS-positive cast material in renal tubules

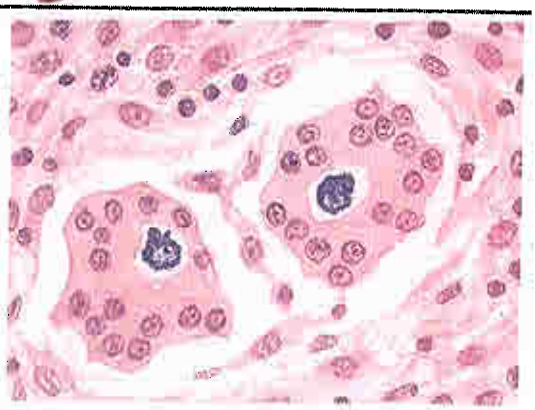


Diffuse emphysema with consolidation at base possibly attributable to chronic cadmium inhalation

F. Netter M.D. © CIBA

Chronic Beryllium Disease





High-power inset showing detail of giant cells containing Schaumann bodies

Granuloma with interstitial fibrosis resembling sarcoidosis: central deposition of endothelioid cells, some multinucleated, with surrounding cuff of lymphocytes and fibrous tissue. Skin and other tissues may show similar lesions

SUBACUTE REACTIONS

Hypersensitivity pneumonia refers to a group of pulmonary disorders that runs a more prolonged course than that of the episodic asthma or acute pneumonia previously discussed. It develops especially in workers sensitized to organic products.

Farmer's lung, the most common hypersensitivity disorder, affects individuals sensitive to moldy hay who inhale dust containing the spores of thermophilic actinomycetes (Plates 3 and 4). The disease affects farmers in the northern United States and in Great Britain, and causes recurrent episodes of pneumonia with fever, cough, shortness of breath and weight loss. If exposure continues, chronic effects such as pulmonary fibrosis will ensue.

Bagassosis, a similar illness, is commonly encountered in workers employed in the sugar cane industry of southern Louisiana (Plates 3 and 4). Bagasse, the dried fibrous residue of sugar cane, is used in the manufacture of paper, cardboard and building materials. In its fresh state it is innocuous; however, in processing, the bagasse is baled and stored in open fields where, exposed to moisture and high temperatures, it becomes the culture medium for the offending thermophilic organisms. Individuals who work with this dried bagasse are at risk of developing bagassosis. The organisms cause the disease not by tissue invasion but by precipitating an allergic reaction in the lung.

The symptoms and course of bagassosis strongly resemble those of farmer's lung. A chronic form can develop after repeated exposures, but this is uncommon.

Alveolar Filling and Accelerated Fibrosis. Although silicosis is the classic disease of chronic exposure to dust, a proliferative lung disease with diffuse fibrosis called "acute" silicosis or "silicoproteinosis" can result from a relatively short (as little as six months) but intense exposure to free silica. At risk are sandblasters working in enclosed places without an external air supply, even if they rely on respirators. A similar type of silicosis has been described in individuals engaged in the manufacture of scouring powder when high concentrations of finely divided free silica are inhaled.

When the rate of particle deposition is excessive, macrophages containing ingested silica accumulate and die in large numbers, producing a roentgenologic appearance resembling that of alveolar proteinosis. The principal symptom of acute silicosis is shortness of breath; fever caused by excessive cellular destruction in the alveoli can be present. In addition, acute silicosis can be complicated by tuberculosis, mycobacteriosis, and nocardiosis. The disease progresses rapidly, and disability and death occur early.

Treatment with corticosteroids can reduce the macrophage response in silicoproteinosis. However, this form of treatment may also predispose to complicating infection.

CHRONIC DISEASE

Chronic occupational pulmonary disease is usually the result of long-term exposure to toxic dusts. The histories of workers who develop the chronic pulmonary disorders commonly reveal exposure to dusts for 20 or more years before the disease becomes symptomatic. However, illness that is developing may be detected before symptoms appear if serial chest x-ray films are taken. Because of the insidious nature of these chronic diseases, measures must be taken to protect workers before the diseases develop. Such measures should include reduction of exposure to dust and periodic examination of the exposed workers.

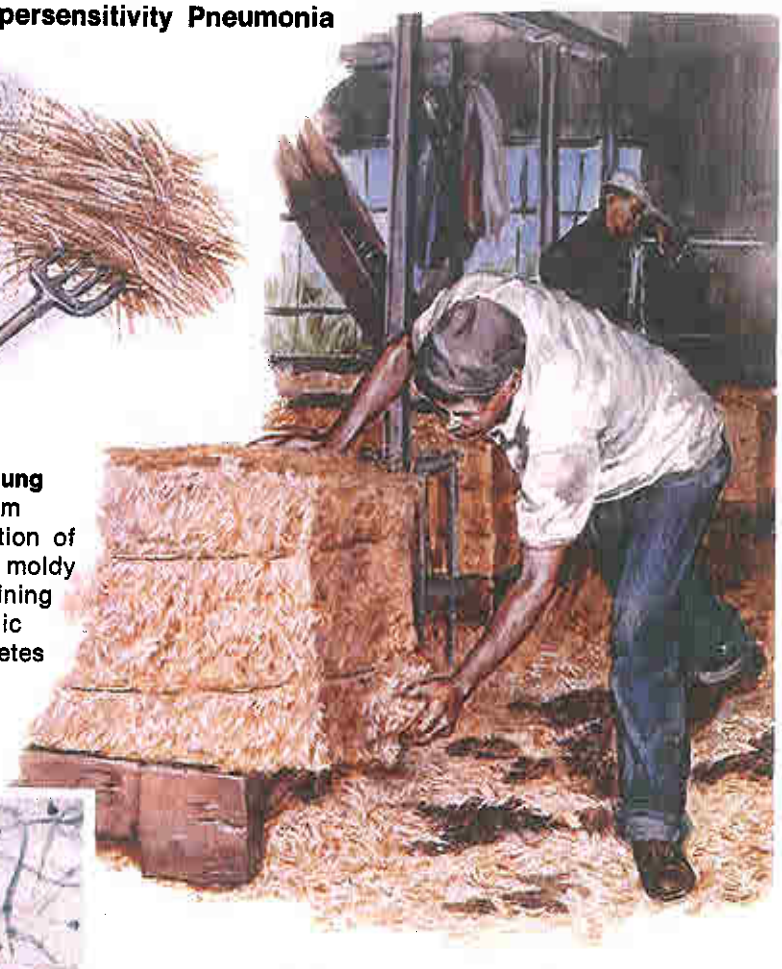
Chronic pulmonary diseases can be classified for convenience in terms of the predominant reactions or lesions: *pulmonary fibrosis* in silicosis, asbestosis and complicated coal worker's pneumoconiosis; *dust retention and fibrosis* in a variety of pneumoconioses; *granulomas* in chronic beryllium disease; *pleural fibrosis* and *carcinoma* in asbestosis; and *industrial bronchitis* and *mycobacterial infection*.

Pulmonary Fibrosis in Silicosis. Silicosis is the oldest recognized industrial disease of the lungs. The disease is widespread because free silica is useful in many industries: in construction, in ceramic manufacture and as an abrasive agent. In addition, many workers are exposed to silica in the mining of gold, copper, lead, zinc, iron and coal.

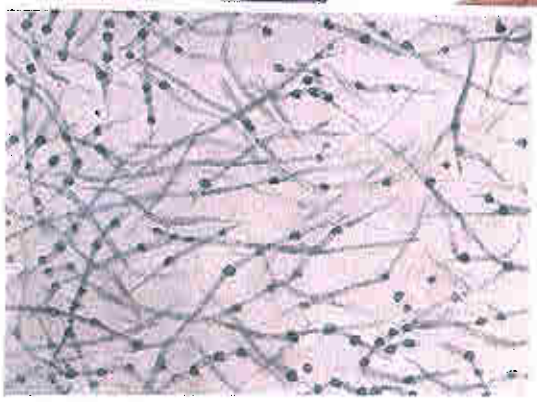
Silicosis can be classified according to the severity of the pulmonary reaction and its rapidity of onset and progression. Because it is a progressive disease, silicosis may develop from a *simple*, asymptomatic pneumoconiosis into *complicated* disease characterized by massive fibrosis and disability. Silicosis can be further classified into three types: *Acute* silicosis develops quickly, often after one to

Hypersensitivity Pneumonia

Farmer's lung results from the inhalation of dust from moldy hay containing thermophilic actinomycetes

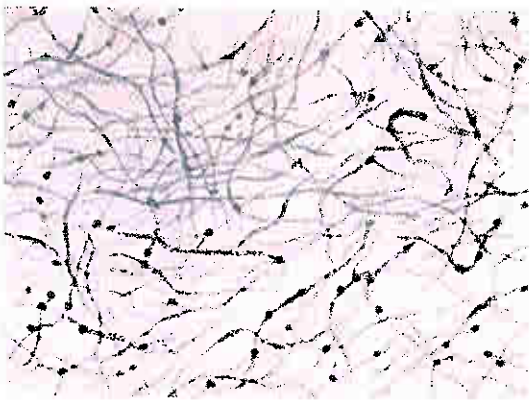


Bagassosis, a similar disease, results from the inhalation of dust from the dried residue of sugar cane, bagasse. When moldy, bagasse dust contains spores of thermophilic organisms that act as causative antigens

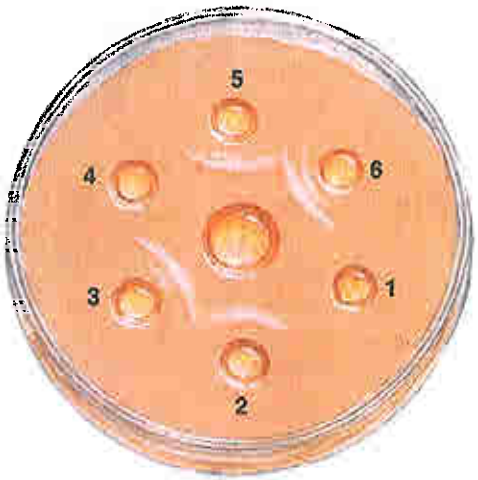


Farmer's lung: slide culture of *Micropolyspora faeni,* principal source of antigen. Also causes mushroom picker's disease and fog fever in cattle

F. Netter M.D. © CIBA

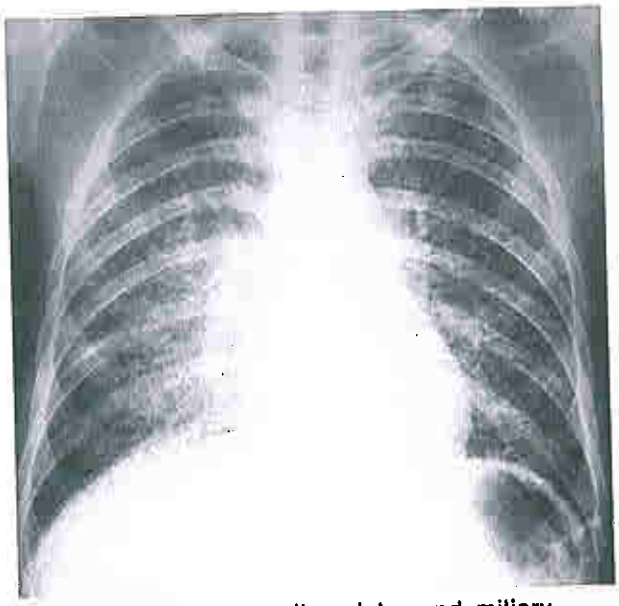


Bagassosis: slide culture of *Thermoactinomyces saccharii,* a thermophilic actinomycete that is principal source of antigen

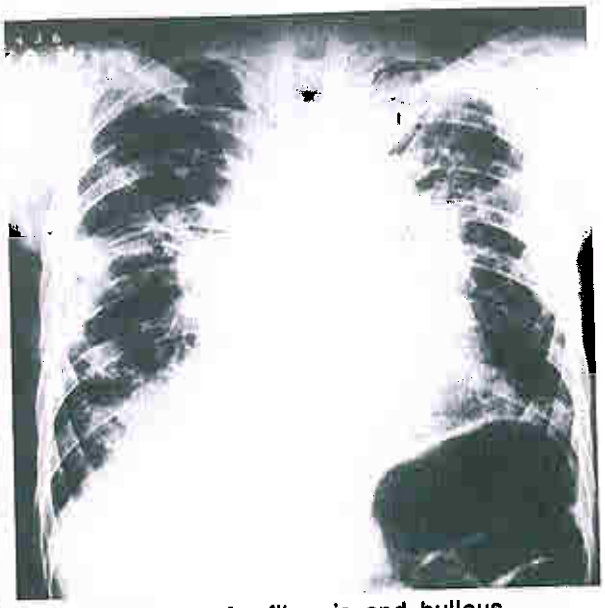


Precipitin reactions in bagassosis: patient's serum in central well and extracts of bagasse from various sources in peripheral wells. Specimens 1 and 4, from fresh bagasse, show no precipitin bands

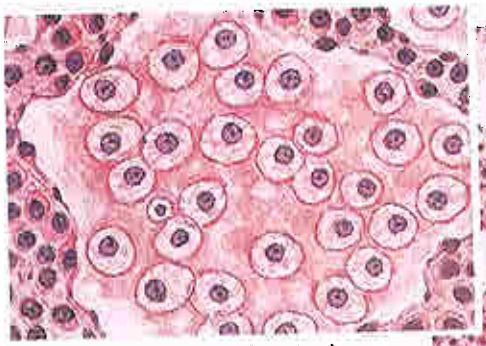
Hypersensitivity Pneumonia (continued)



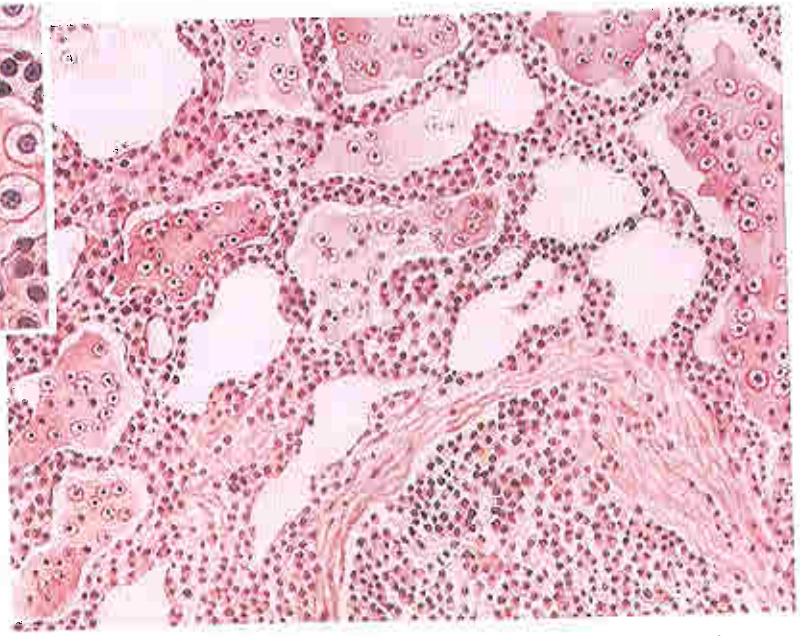
Acute bagassosis: small nodular and miliary densities in both lungs. Deposits may be hazier and more homogeneous in some cases



Chronic bagassosis: fibrosis and bullous emphysema after repeated episodes of respiratory illness during nine years of industrial exposure

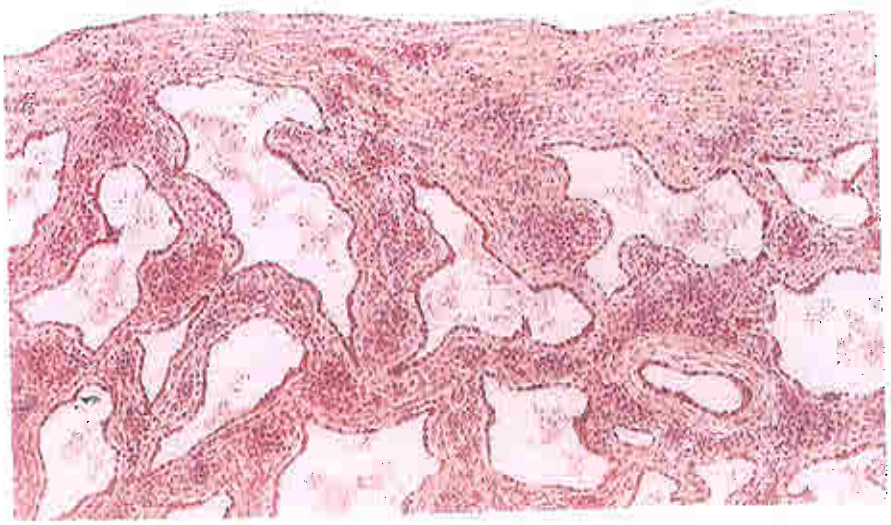


High-power section inset shows macrophages with vacuolated cytoplasm filling alveolar spaces



Tissue reaction in bagassosis: alveolar walls thickened with infiltrate of plasma cells and lymphocytes. Some alveolar spaces contain edematous fluid and desquamated histiocytes with vacuolated cytoplasm

F. Netter M.D. © CIBA



Tissue reaction in farmer's lung: extensive subpleural and interalveolar fibrosis with inflammatory cell infiltration characteristic of advanced stage of disease

three years; *accelerated* silicosis appears after an average of 10 years of exposure; and *chronic* silicosis develops late, after 20 or more years of exposure, generally to lower concentrations of free silica. The rate at which silicosis progresses and the severity of the lesions depend on the concentration of inhaled free silica and the presence of complicating factors such as infection and autoimmune disease.

The common denominator in all cases of silicosis is the inhalation of high concentrations of crystalline silica. Particles less than 10 microns in diameter are respirable, but the particles most likely to be deposited in the alveolar spaces, and which cause the disease, are 1 to 3 microns in diameter.

Pathology. The reaction in silicosis is directly related to the number of respirable free silica particles deposited in the lungs. In granite quarries and metal foundries where relatively low concentrations of silica dust are encountered, the workers may develop the classic nodular form of simple silicosis (Plate 5). The nodules result from a process in which alveolar macrophages ingest the silica particles. The macrophages are then killed by intracellular liberation of enzymes, producing in turn materials that attract other macrophages and subsequently fibroblasts to form a fibrous nodule (Plate 6). The center of the nodule is acellular, with cellular reaction at the periphery, giving an onionskin appearance on microscopy. The nodules are usually located near the bronchiolar entrance or the acinus. Usually, the fibrous nodular deposits alone do not produce any associated emphysema unless the simple silicosis is complicated by heavy cigarette smoking.

In complicated forms of silicosis the nodules form conglomerate masses (Plate 5). In slowly developing types of silicosis associated with lower concentrations of inspired silica, these masses are usually located within contracted upper lobes and are frequently accompanied by bullae in both upper and lower lobes. These changes, and the resulting distortion of the airways and reduction of pulmonary function, cause the typical symptoms of cough, expectoration and shortness of breath on exertion. In addition to the alterations in lung substance, enlargement and peripheral "eggshell" calcification of the lymph nodes and enlargement of pulmonary arteries are frequently seen in complicated silicosis. The latter is the result of pulmonary hypertension, leading to right ventricular hypertrophy and cor pulmonale.

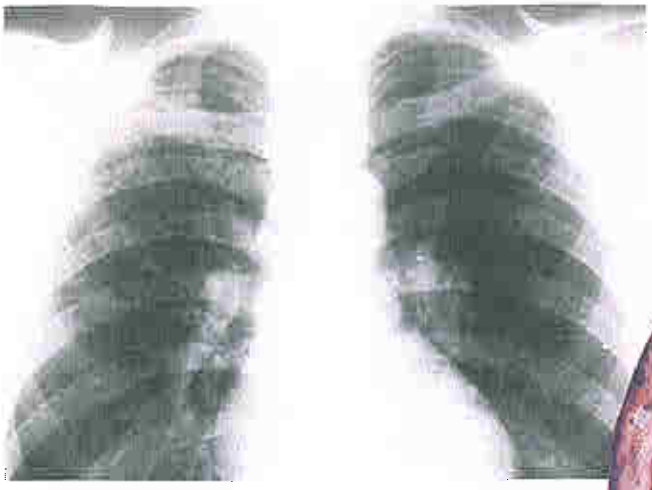
Complications of silicosis include infection with *Mycobacterium tuberculosis* or atypical mycobacteria and the presence of autoimmune disease. Silicotic patients have an increased predisposition to tuberculosis (Plate 7). Today, tuberculosis complicating chronic simple silicosis is less common than in the past, and bacteriologic proof of superinfection with tuberculosis may be difficult to obtain. However, the massive changes in complicated forms of silicosis are often related to mycobacterial disease. In patients with acute silicosis, bacteriologic proof of mycobacterial infection is almost always present.

In accelerated silicosis the incidence of mycobacterial infection is 25% and the distribution of lesions complicated by tuberculosis often varies from that typically found in silicosis, and predominantly lower lobe involvement is not unusual. The combination of massive changes associated with nodular deposits may make it difficult to distinguish silicotic from tuberculous nodules on the roentgenogram. The two forms are easier to distinguish after chemotherapy has been effective and the sputum has become negative for mycobacteria. At that time, uncomplicated tuberculous nodules will usually resolve, and remaining foci will represent either silicotic or larger silicotuberculous lesions, which often progress because of altered cellular immunity.

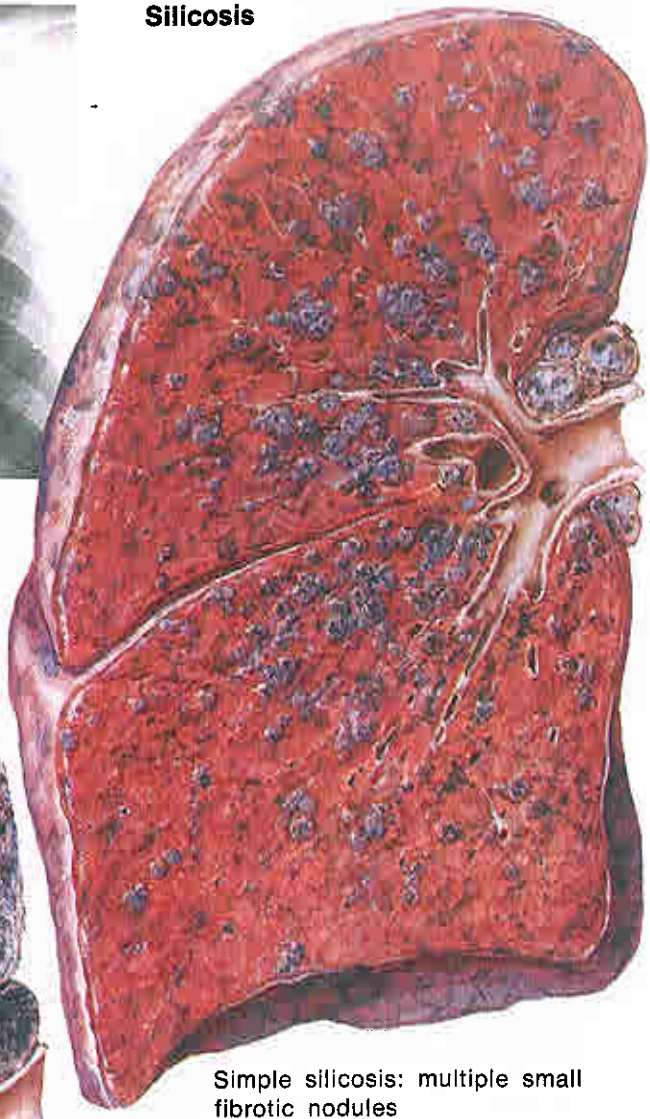
Autoimmunity, particularly in rheumatoid individuals, may also contribute to massive changes. Caplan noted that coal miners with rheumatoid arthritis or diathesis who are exposed to respirable free silica may develop nodular pulmonary lesions that form more rapidly than chronic silicotic foci and which resemble sites of metastatic cancer as seen on chest x-ray film. In patients with rheumatoid disease, disseminated simple silicotic foci may also be enlarged and transformed into "Caplan's nodules," which contain silica, and other dusts if exposure is mixed, and show characteristic rheumatoid reactions with palisading inflammatory cells surrounding a zone of central necrosis (Plate 7). The pulmonary changes are usually accompanied by general malaise and aggravation of the joint symptoms associated with rheumatoid arthritis. The diagnosis of rheumatoid pneumoconiosis is usually based upon these

10

Silicosis

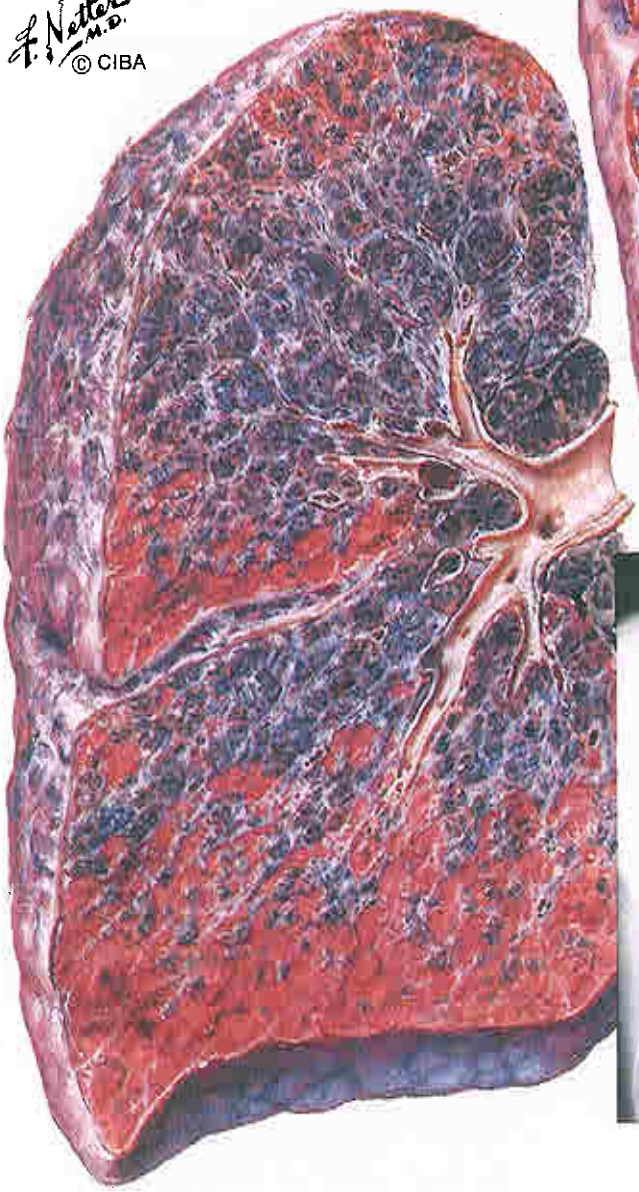


Simple silicosis: nodular fibrosis with calcification of hilar lymph nodes

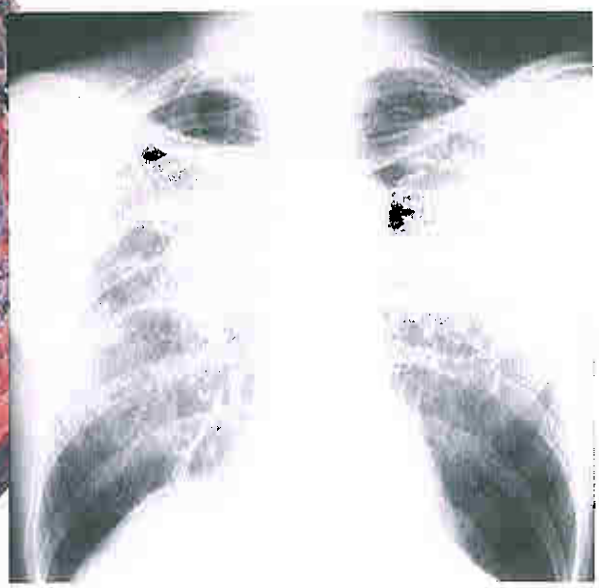


Simple silicosis: multiple small fibrotic nodules

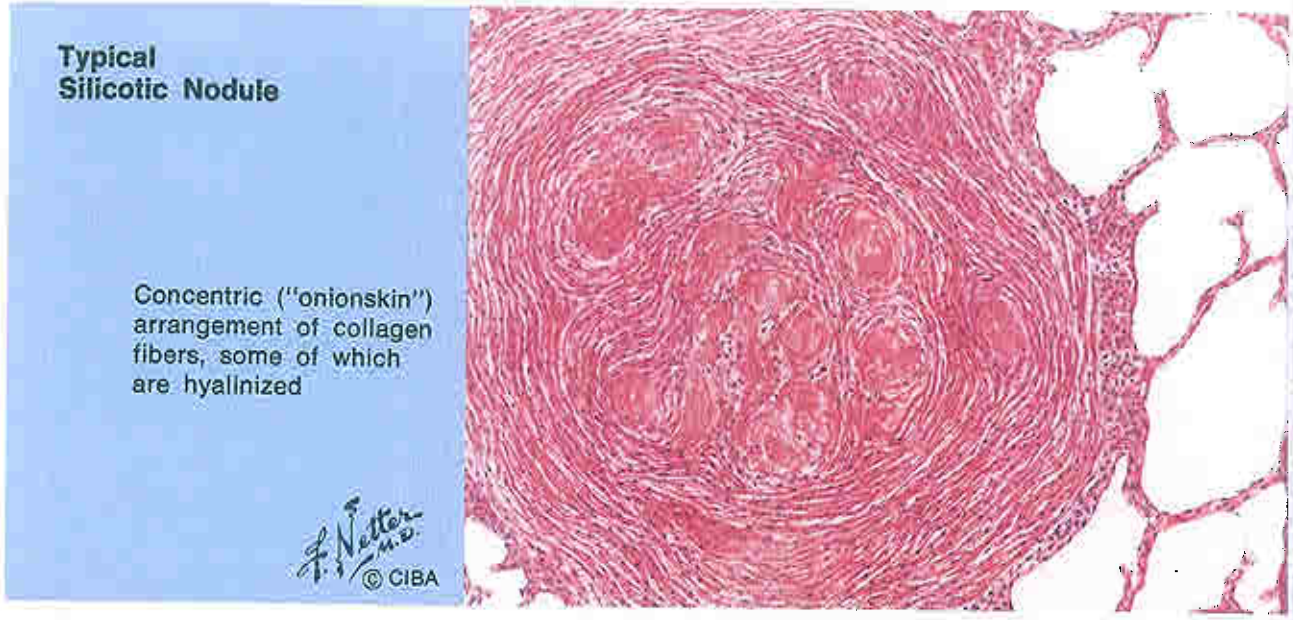
F. Netter M.D.
© CIBA



Complicated silicosis: massive fibrosis and conglomerate nodulation. Pleura thickened, nodulated, and adhesive



Complicated silicosis: extensive fibrotic opacification with hyperlucency at bases



clinical findings along with the rheumatoid serologic changes.

Miners exposed to silica appear more likely to develop progressive systemic sclerosis, an autoimmune connective tissue disease that is ordinarily far more common in females than in males. Sandblasters with accelerated silicosis have an increased incidence of antinuclear factor, and in this group of diseased workers the incidence of autoimmune connective tissue disease approaches 10%. In addition to rheumatoid arthritis and diffuse scleroderma, systemic lupus erythematosus and localized scleroderma complicating silicosis have been identified as well.

The clinical findings associated with silicotic lesions can be summarized briefly. Simple nodular silicosis is usually asymptomatic. Symptoms in patients with simple silicosis are usually caused by concurrent long-term cigarette smoking or by complications such as those produced by autoimmune disease, particularly rheumatoid arthritis. In complicated silicosis with massive changes and structural distortion, the patient suffers exertional dyspnea, obstructed breathing, cough and expectoration, and reduced exercise tolerance. In rapidly developing disease, chest pain, weight loss and hemoptysis are not uncommon.

The prognosis for silicotic patients depends largely on the rate at which the disease progresses to more serious stages. Although silicosis is progressive, chronic simple silicosis acquired in the mine or quarry is compatible with prolonged employment and with a life expectancy approaching that of a city dweller. In the so-called acute silicosis in individuals who develop diffuse fibrosis after heavy exposure without protection, the disease may run a rapid course. Death may occur within three years. In the less fulminating but accelerated disease in which disabling reactions occur after an average of 10 years of exposure, progression with rapid changes in course is common. For example, disease in a sandblaster will usually be visible on roentgenogram within 10 years of initial exposure. Once massive changes have developed pulmonary function deteriorates rapidly leading to early death.

In individuals who have been exposed to lower concentrations of free silica for long periods of time, chronic disease may develop and run a long course. Abnormalities on chest roentgenograms appear after 20 or more years of exposure, and symptoms and disability are delayed. Complications such as mycobacterial infection and pulmonary heart disease usually do not occur until the individual is elderly, appearing after an average of 40 years of exposure.

Pulmonary Fibrosis in Asbestosis. The term *asbestos* refers to a group of silicates whose unusual properties have been known since antiquity. Asbestos is durable and resistant to heat and has been used in many forms to protect people and property from fire. Because of its fibrous character, it is possible to impact it into sheeting that is used as insulation material. While asbestos can be credited with saving countless lives, it has

been increasingly implicated in the death and disability of many people. During the last 15 years, increased attention to asbestos exposure has shown that asbestos workers are liable to develop pulmonary fibrosis.

Exposure to asbestos is widespread in industries involved in the manufacture and handling of asbestos products. Families of asbestos workers and nearby communities may also be exposed to the fibrous dusts. In addition, there is concern that others may be endangered by asbestos dust that drifts through the air during manufacturing and installation activities. The presence of asbestos in ores such as taconite has also prompted discussion about the possible risk of disease from asbestos fibers in tailings deposited in large bodies of water from which nearby cities draw their water supply.

Exposure to asbestos varies in different occupations, and the concentration of the fibers per unit volume is dependent on the rate of production and whether the workplace is open or enclosed. Respirable particles of asbestos are usually quite long, and may extend beyond 50 microns. However, the most important factor in the deposition of inhaled asbestos is the diameter of the fiber. Fibers of small diameter (approximately 0.5 micron) remain suspended within the airways and drift with the airflow to deposit in the airspaces. Because of their length, these fibers impact within the bronchioles, and studies have shown that some of the earliest cellular and fibrotic lesions occur in this location.

The pathologic pattern of asbestosis is interstitial pulmonary fibrosis. The fibrosis involves the dependent portions of the lungs where asbestos bodies (asbestos fibers that have become coated with iron-rich proteinaceous materials in the lung) are usually found (Plate 8). Obliterative changes take place as the disease progresses: In late stages of the disease, great thickening and cellular fibrosis around the alveoli create the roentgenologic appearance of honeycomb lung. In addition, advanced asbestosis is often associated with peripheral lung carcinoma, and in individuals exposed to lower concentrations of asbestos, fibrous and calcified pleural plaques are commonly found.

The clinical manifestations of the structural changes in pulmonary asbestosis are clear cut. The principal symptom is shortness of breath on effort. Physical examination of individuals with asbestosis reveals rales at the lung bases and, frequently, clubbing of the fingers. Breathing is restricted, a finding consistent with the reduced lung volume.

These clinical signs and pulmonary function changes, which may be present before roentgenologic signs of the disease are detected, are diagnostic in asbestosis. Reduction in vital capacity is an important sign. (When the average vital capacity in a shift of workers is found to be significantly reduced, the presence of an adverse factor affecting the group is strongly suggested.) Spirometric tests showing reduced airflow in proportion to lung volume may indicate the obstruction of small airways by asbestos fibers. However, prolonged smoking may also contribute to reduced airflow rates.

Other specific functional disorders encountered in asbestosis are reduction of pulmonary diffusing capacity and impairment of gas exchange, resulting in hypoxia which is aggravated by exercise. Disturbance of diffusion with restricted lung volume is usually associated with hyperventilation and reduced carbon dioxide tension.

The respiratory disability of asbestosis is severe, progressive and irreversible. It is characterized by increasing exertional dyspnea, disability and progressive changes on chest roentgenograms. Changes on the chest roentgenograms may appear after 10 years of exposure to respirable asbestos fiber, but most commonly appear after 20 years. After that time, serial chest roentgenograms will demonstrate the progressive pulmonary reactions and pleural thickening. Increasing fibrosis of the lungs leads to pulmonary hypertension and cor pulmonale. Neoplastic complications usually occur after 20 years of continuous exposure or 20 years after the original exposure, as is the case in individuals who develop mesothelioma.

The prognosis is poor for the worker with established asbestosis because there is *no treatment* that will affect the progressive fibrosis. The decision to remove a worker from contact with asbestos depends on the degree of exposure and the rate at which the disease is developing. It is hoped that reducing industrial concentrations of asbestos fiber to levels as low as 2 fibers/mm^3 will result in a level where no disease results. However, this goal has not yet been achieved in the United States and, indeed, the biologic effects of even these very low concentrations of asbestos are still to be determined.

Pulmonary Fibrosis in Complicated Coal Worker's Pneumoconiosis. About 10% of coal workers develop simple pneumoconiosis without symptoms while a smaller number develop the complicated form, progressive massive pulmonary fibrosis (Plate 9). Symptoms of this complicated pneumoconiosis are the same as those previously noted for complicated silicosis. The disease is progressive, and length of life is definitely shortened.

Pathology. The damage in simple coal worker's pneumoconiosis develops as a result of the inhalation of respirable coal dust that first settles within the alveoli and later accumulates near the respiratory bronchioles. There, coal macules form with limited scarring, leading to disease of the respiratory bronchioles and focal emphysema. (If scarring is excessive, it may be related to concurrent exposure to silica in the mining process.) If exposure to coal dust continues, the disease may progress, but this is rare.

Complicated coal worker's pneumoconiosis is characterized by more serious pathologic changes. The lesions formed here are composed of black material bordered by fibrous capsules. They lie within scarred and contracted upper lobes in which the airways are obstructed and distorted, leading to demonstrable emphysema and reduced prominence of the simple nodular pattern of the disease. These changes are evident on the chest roentgenogram.

Complications of coal worker's pneumoconiosis deserve attention. The rheumatoid changes in the lungs in Caplan's syndrome have been discussed previously (Plate 7). Many patients with progressive massive fibrosis have rheumatoid factor in the serum and consistent joint disorders. Although tuberculosis was commonly associated with miner's pneumoconiosis in the past, the incidence of this complication is no longer excessive. However, coal workers are at risk of developing bronchitis; and the influence of occupation and environment in coal worker's bronchitis should be considered.

The clinical picture in the simple, nodular type of pneumoconiosis is reflected on chest x-ray films by the presence of nodular densities that vary in size from 1 to 10 millimeters in diameter. This pattern of the disease is rarely associated with exertional dyspnea. In nonsmokers, simple pneumoconiosis may be asymptomatic. Cigarette smoking is the usual cause of increased cough and expectoration in individuals with simple coal worker's pneumoconiosis; but in coal miners with many years of exposure, specific industrial bronchitis related to dust inhalation can contribute to the bronchial symptoms.

In complicated pneumoconiosis exertional dyspnea is an important symptom, and coughing and expectoration are increased. Expectoration of black sputum (melanoptysis) from excavated masses may also occur.

The functional changes in complicated disease, which usually appear after many years, are reduced vital capacity and increased functional residual volume leading to reduced airflow rates and pulmonary diffusing capacity. There is a disturbance of gas exchange, resulting in low oxygen tension at rest, a condition which is aggravated during exercise. Severe ventilatory failure and right heart failure secondary to pulmonary hypertension have been reported, but are far less common in coal worker's pneumoconiosis than in silicosis.

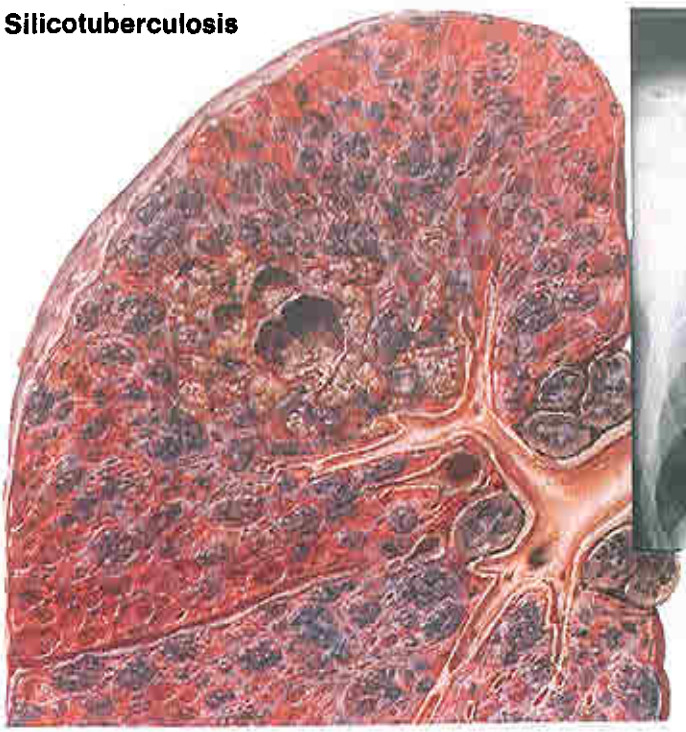
The outlook for patients with coal worker's pneumoconiosis is variable, although there is no specific treatment. However, complicating diseases such as bronchitis, rheumatoid arthritis, tuberculosis and secondary infections can be given specific or symptomatic treatment. In most instances, the simple asymptomatic disease is self-limiting, although progression to an advanced form is more likely to occur if the disease appears after a relatively short period of time.

Clearly, the complicated forms of coal worker's pneumoconiosis are disabling, and a decision must be made to remove workers from the mining environment when roentgenograms show excessive reaction to dust. Dust deposits visible on the chest x-ray film are, in general, proportional to the amount of dust inhaled, and thus provide an approximate basis for determining if a worker should be removed from the mine.

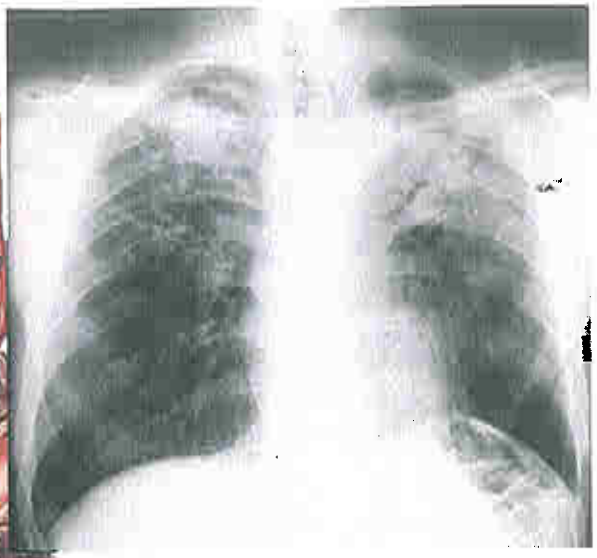
Dust Retention and Fibrosis. Besides crystalline free silica, asbestos and coal dusts, other materials can incite pulmonary tissue reactions, sometimes with serious clinical effects. Substances that can cause pulmonary reactions of varying severity include graphite, fuller's earth, kaolin, iron, mixed dusts and tungsten.

Not all dusts cause disabling pulmonary disease. Some dusts, when inhaled in high concentrations, are retained in the lungs but

Silicotuberculosis

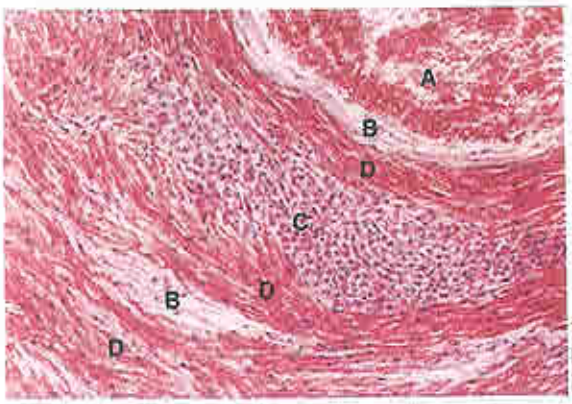


Tuberculosis with cavitation superimposed on silicosis

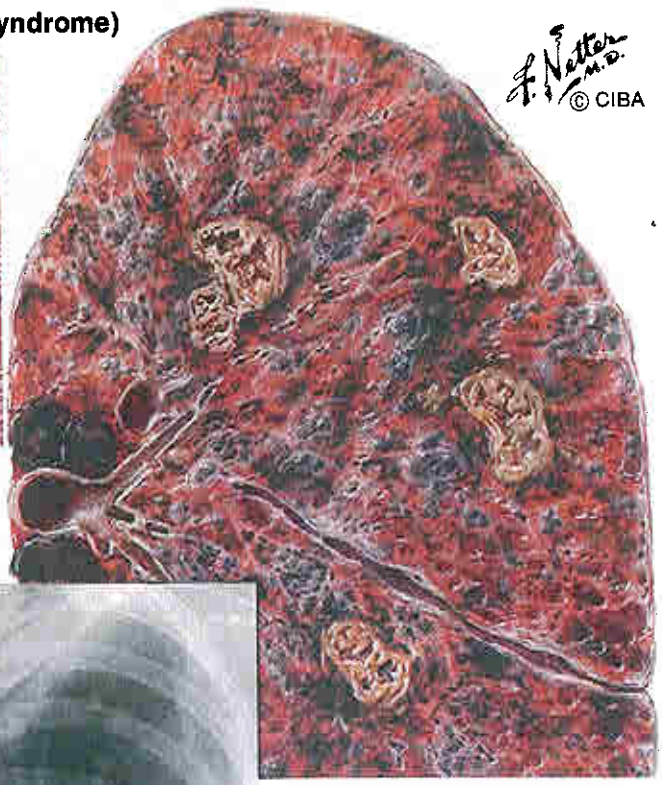


Supervention of tuberculosis on silicosis may be difficult or impossible to recognize on roentgenogram

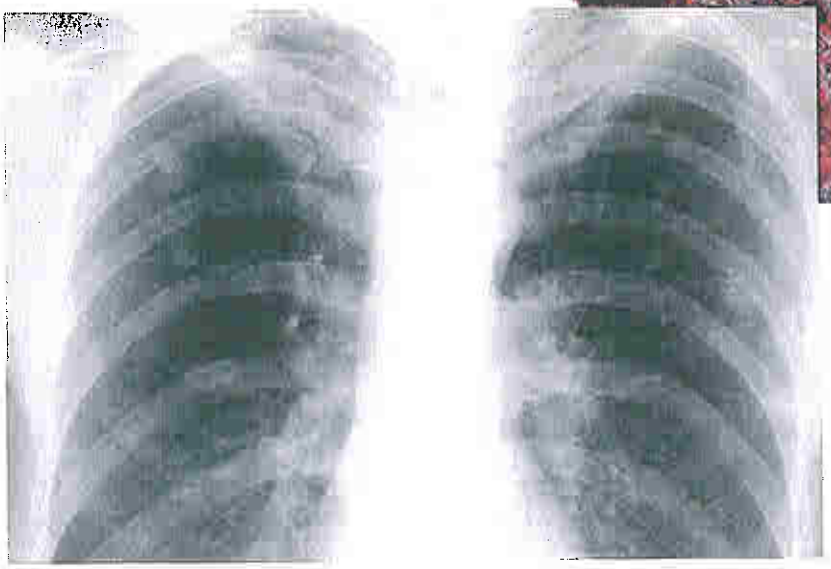
Rheumatoid Pneumoconiosis (Caplan's Syndrome)



Section through margin of Caplan's nodule: (A) necrotic central area, (B) clefts, (C) zone of fibroblasts and inflammatory cells, (D) collagen



Caplan's nodules of various sizes, silicotic nodules, and deposits of coal dust in lung



Caplan's nodules in both lungs, with some evidence of diffuse fibrosis

cause little or no tissue reaction. However, many industrial dusts are mixtures of various substances, and when silica is a part of the dust mixture, fibrosis is more likely to occur.

Graphite is carbon that contains variable amounts of quartz impurities. The silica content of graphite is usually low, however, and probably makes a minor contribution to the usual tissue reaction in this disease. Graphite is milled after mining and used in electrotyping, the manufacture of steel and the production of electrodes. It is also used as a lubricant and in school pencils.

The pathology, symptoms and prognosis of the disease are similar to those of coal worker's pneumoconiosis. The lesions of the simple form of the disease are carbon macules with surrounding fibrosis (Plate 10), which are situated next to the respiratory bronchioles and associated with emphysema of the center of the respiratory lobule. Complicated pneumoconiosis is less common, and may be complicated by right ventricular hypertrophy.

Fuller's earth, or calcium montmorillonite, is an aluminum silicate containing iron and magnesium that can produce diffuse pulmonary disease. This material is obtained by quarrying, and the dust is used as an absorbent clay. In the past it was used in "fulling," the extraction of grease from wool, but today it is an important agent in the refining of oils.

Marked dust retention has been seen in workers who have had long-term exposure to fuller's earth, but fibrosis has generally been limited (Plate 10). However, in several cases, progressive massive fibrosis has developed. Contamination of the fuller's earth dust with quartz is responsible for the excessive fibrogenic effect.

Kaolin, or china clay, is another nonfibrous silicate of importance. This hydrated aluminum silicate is obtained by quarrying, and the material containing the offending dust is extracted from the walls of the quarry by washing. Treatment of the substance involves drying, milling, bagging and loading. These are the dangerous phases of the operation in which the worker is exposed to excessive concentrations of respirable dust. Prolonged heavy dust exposure or excessive quartz admixture accounts for the rare appearance of pneumoconiosis (Plate 10).

Iron dust inhalation can lead to benign pneumoconiosis with little or no fibrosis (Plate 11). Arc welders are exposed to high concentrations of respirable particles of iron. Although the material has minimal fibrogenic effect, the dust clearance mechanisms are often overwhelmed with retained particles and accumulated dust-laden phagocytes.

Iron oxide gives a red coloration to the lung, when examined grossly, but histologic studies demonstrate little fibrosis. Nodular deposits that resemble the simple lesions of silicosis are often seen in the chest x-ray films of arc welders.

No associated clinical symptoms or defects in pulmonary function are noted in arc welder's pulmonary siderosis. Disability, therefore, is not great, and the incidence of lung cancer is not increased.

Mixed-dusts exposure is not uncommon because of their great variety in industrial processes (Plate 11). A common mixture, to which welders and foundry workers are exposed, is one containing iron oxide, carbon and free silica. Pneumoconiosis usually develops only after long-term exposure, often of more than 20 years.

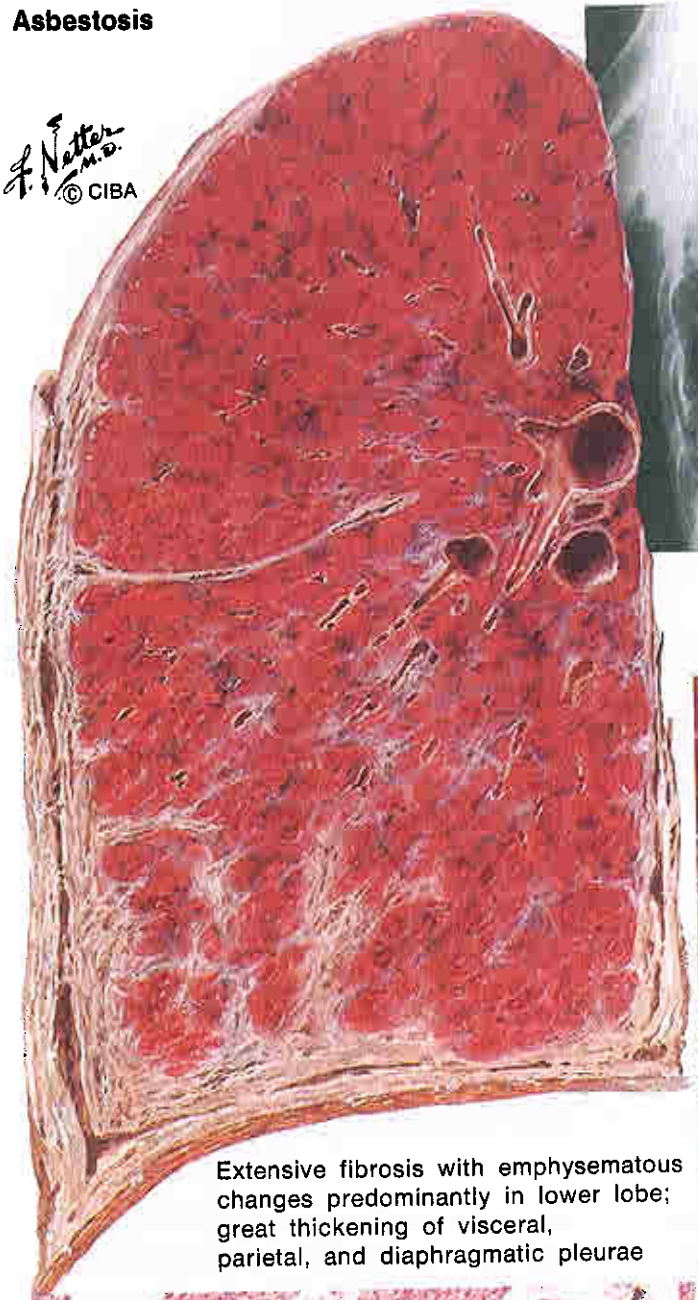
Chest roentgenograms in this condition are similar to those in cases of silicosis: Simple nodular or massive changes are characteristic. However, there are some variations from this pattern, and irregular and linear shadows are often seen as well. Pathologic examination of the lungs shows mixed-dust retention with black deposits, indicating retained carbon. The appearance is dominated by the red deposits of iron oxide in both diffuse and massive lesions (Plate 11).

Tuberculosis is believed to be a common complication of mixed-dust fibrosis. The prime symptom of the advanced disease is shortness of breath on exertion leading to disability and shortened life span.

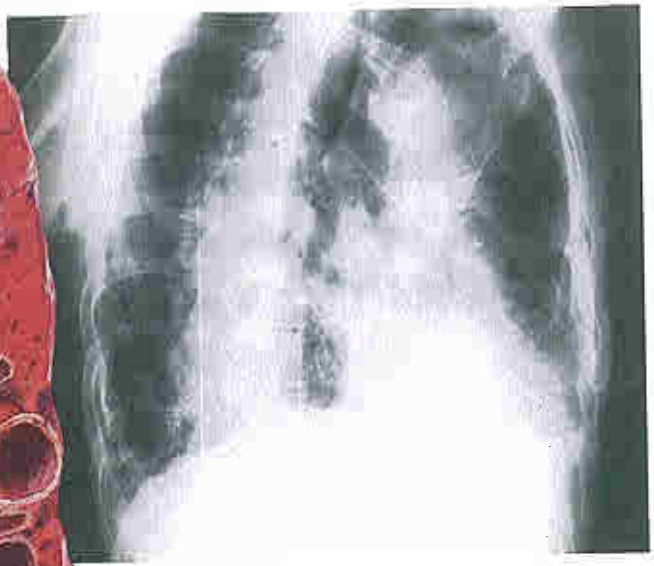
Tungsten workers are also subject to pulmonary fibrosis (Plate 11). These workers are exposed to very fine particles of tungsten, which is combined with carbon under the influence of cobalt to form the hard metal needed for the manufacture of industrial precision equipment.

The pathologic pattern resulting from tungsten inhalation is diffuse pulmonary fibrosis, which usually appears after 10 years of exposure. On the chest roentgenogram, a fine pattern of infiltration is seen in the upper lung zones. As the disease progresses, there is infiltration and thickening of the alveolar walls with metaplasia of the epithelium. Phagocytic and multinucleated cells are found

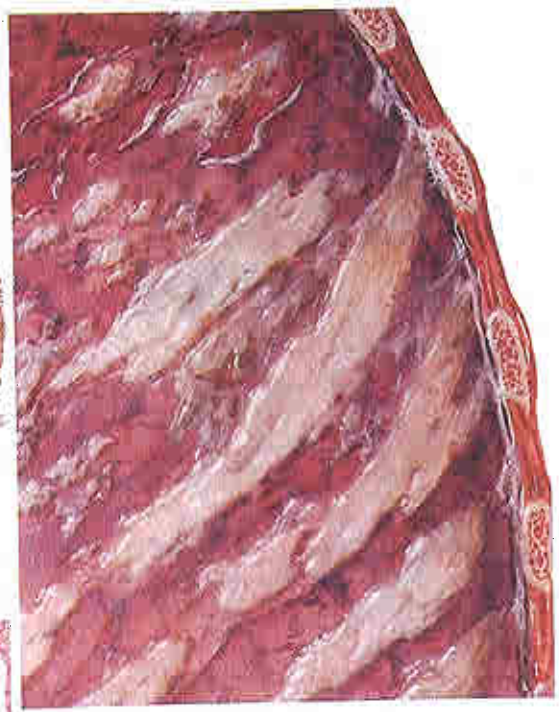
Asbestosis



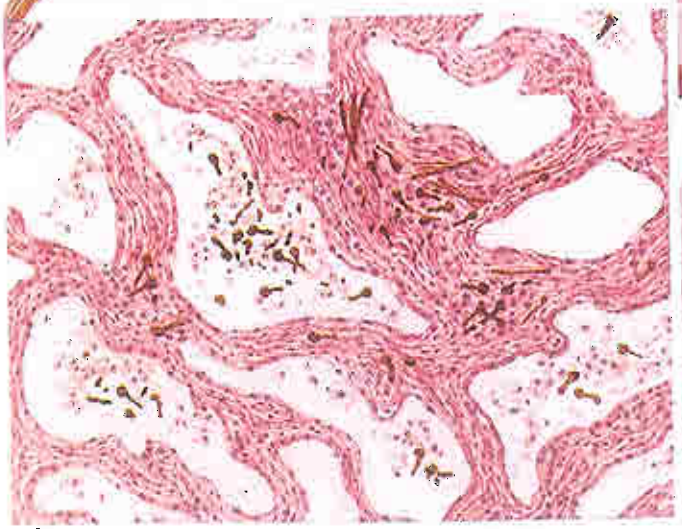
Extensive fibrosis with emphysematous changes predominantly in lower lobe; great thickening of visceral, parietal, and diaphragmatic pleurae



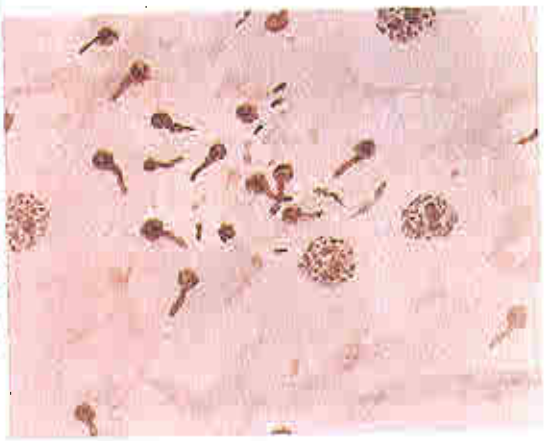
Calcified pleural plaques and irregular densities, chiefly in lower lobes, shown on oblique roentgenogram



Pleural plaques in pulmonary asbestosis



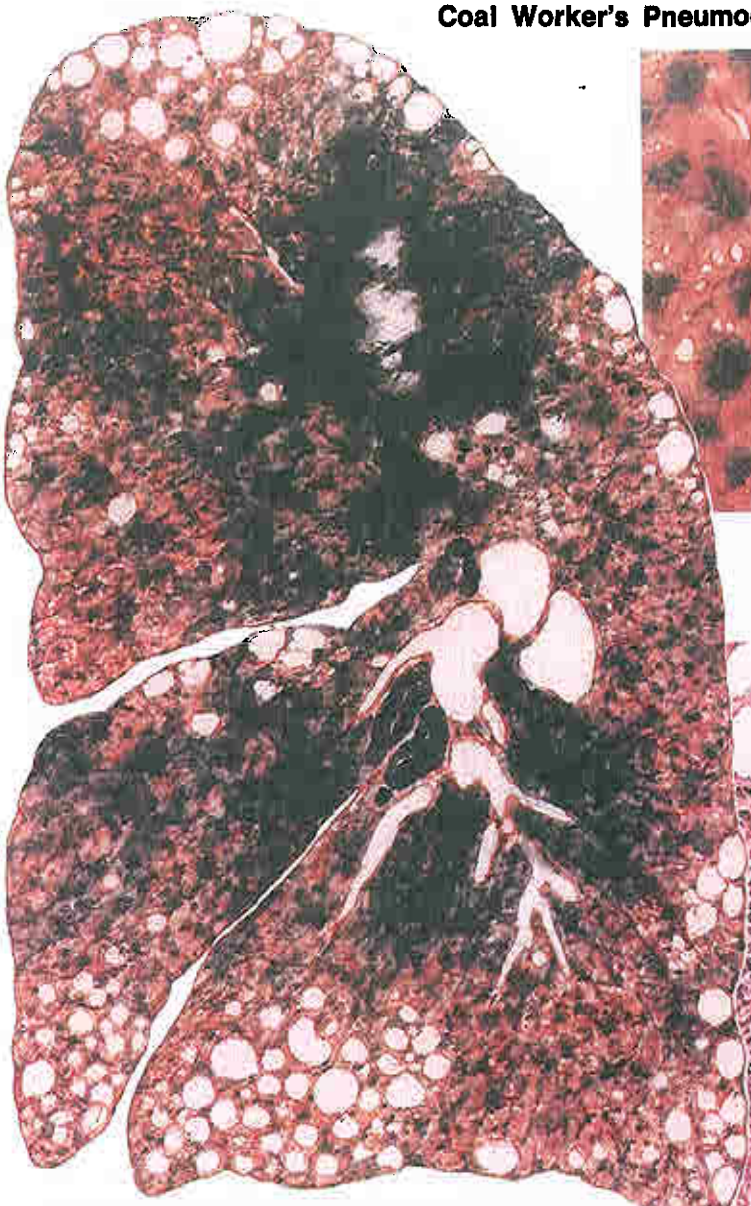
Moderately advanced asbestosis with extensive fibrosis and distorted alveoli. Asbestos bodies (some fragmented) and a few asbestos fibers in airspaces and interstitium



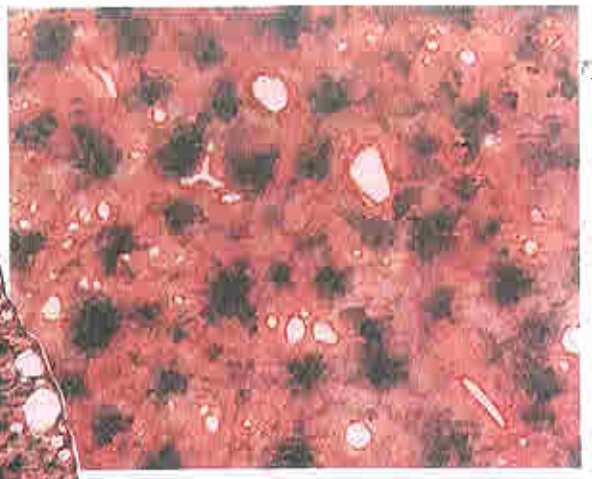
Asbestos bodies in sputum

Plate 9

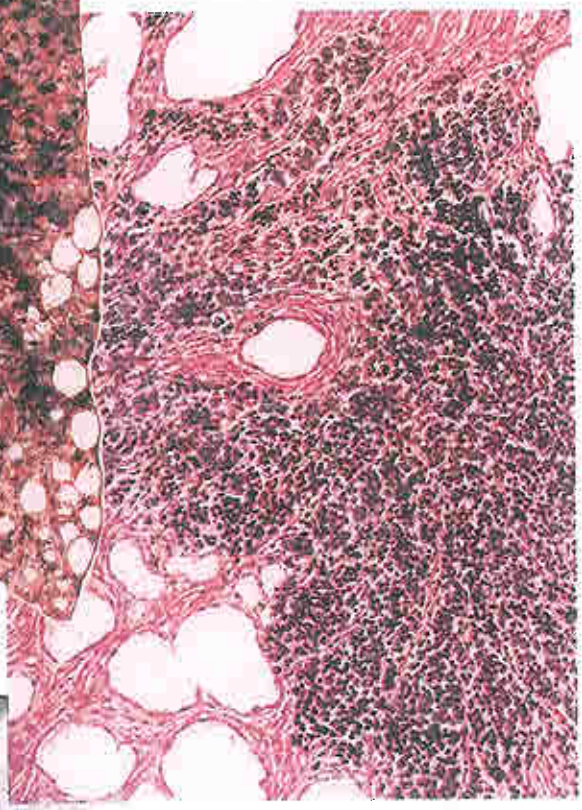
Coal Worker's Pneumoconiosis



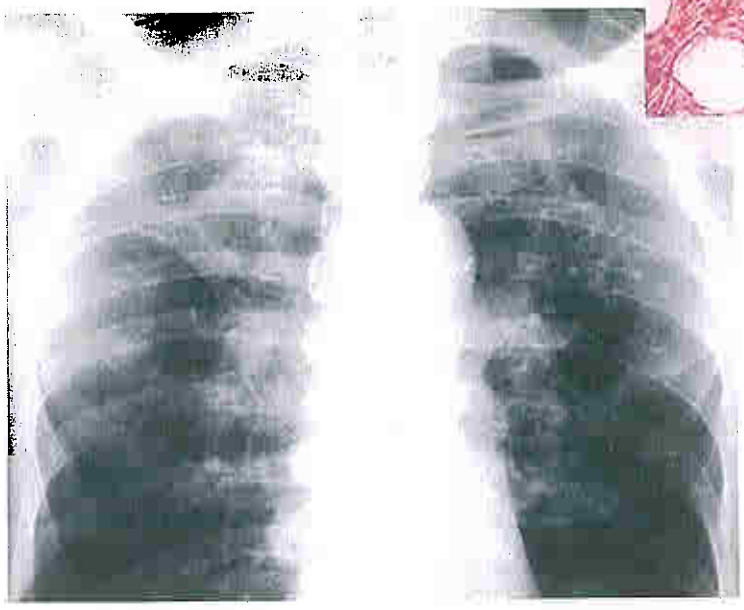
Thin section of whole lung showing massive black deposits, smaller nodules, necrotic areas, and emphysematous changes



Slightly magnified detail of lung showing indurated coal macules



Microscopic section through a coal macule demonstrating large amounts of coal dust, both intracellular and extracellular, with fibrosis near artery



Chest x-ray film of retired coal miner showing massive upper lobe lesions (sometimes called "angel wings") and nodular disease

F. Netter M.D. © CIBA

in the alveolar spaces with cellular infiltration of the alveolar walls (Plate 11). On electron microscopy, crystals thought to represent retained tungsten carbide have been observed. Experimental work has not shown that tungsten carbide can produce these lesions in the absence of cobalt, however, which suggests that cobalt is responsible for both the disease of the airways and the lesions within the fine airspaces.

The earliest symptom is a relatively unproductive cough. This is followed by shortness of breath on exertion, associated with tachypnea, rales and clubbing of the fingers. Ultimately, a severe restrictive disorder develops, leading to pulmonary hypertension and cor pulmonale.

As a result of exposure to metallic fumes, tungsten workers may also develop an obstructive chest syndrome, characterized by cough, expectoration and wheezing. In addition, there may be pruritus, the result of idiosyncrasy or hypersensitivity to the metal.

Granulomas can be caused by occupational exposure, particularly by exposure to beryllium (Plate 2). In the past, *beryllium disease* was generally contracted by individuals involved in the manufacture of fluorescent lamps, and because beryllium is no longer used in fluorescent lighting, the incidence of the disease has decreased. Today, beryllium is basically used in nuclear physics research.

As mentioned previously, exposure to beryllium fumes may cause acute pulmonary edema and pneumonia. While 90% of patients recover from this acute reaction, some develop chronic disease. Chronic granulomatous disease may also develop without a symptomatic acute phase, appearing years after the initial exposure and even long after exposure to beryllium is ended. Generally, chronic disease results from prolonged exposure to low concentrations of beryllium.

The principal symptoms of beryllium disease are dyspnea, dry cough, weakness, weight loss and associated skin lesions. Rales and rhonchi are heard during the physical examination. It is important to note that, on the roentgenogram, the epithelioid granulomas of beryllium disease cannot be distinguished from the hilar adenopathy and bilateral infiltration of sarcoidosis. The disease is slowly progressive, with dyspnea, hypoxemia and, occasionally, clubbing of the fingers. Complications include pneumothorax and cor pulmonale. Progressive and irreversible, chronic beryllium disease ultimately leads to fatal interstitial fibrosis and respiratory failure.

Pleural Fibrosis. Pleural changes are common in individuals exposed to asbestos (Plate 8). Pleural plaques are important indicators of asbestos-related disease and may occur in individuals who have had only a mild or brief exposure to asbestos, and who demonstrate no associated pulmonary changes. Hyaline or calcified pleural plaques develop in asbestos workers about 20 years after the first exposure to asbestos, and can even be seen on chest roentgenograms of asymptomatic individuals. They should be distinguished from muscular shadows accompanying lateral segments of ribs and from the residual effects of infection or trauma.

Pleural effusions can also occur in individuals exposed to asbestos for only a few years. In some cases, the pleural effusions have been later complicated by mesothelioma. However, follow-up of patients with pleural plaques has not been carried out for a sufficient period of time to establish the relationship of pleural fibrosis to mesothelioma.

Carcinoma. Cancers caused by occupational exposure are significant because, like many work-related diseases, many of them can be prevented. The forms of lung cancer linked to occupational exposure are bronchogenic tumors and mesothelioma. As in other occupational pulmonary diseases, the important etiologic factors are the nature of the inhaled substance and the duration or intensity of exposure. Researchers have identified many industrial agents as carcinogenic, and undoubtedly more will be identified. Interestingly, coal is one recognized industrial hazard that is not associated with an increased incidence of lung cancers.

Bronchogenic carcinoma may result from exposure to many industrial substances. In particular it is often associated with advanced asbestosis. In the majority of cases, the cancer arises in scarred tissue, is peripheral in location, and is a nodular adenocarcinoma (Plate 12), findings consistent with the fibrotic-scar cancer theory. Patients with asbestosis have developed multiple primary lung cancers of this type. In addition to the peripheral form, squamous cell carcinoma of the larger bronchi also occurs (Plate 13).

Combined exposure to asbestos fibers and cigarette smoking probably accounts for the variety of forms of lung cancer encountered

in patients with asbestosis. The combined influence of asbestos and smoking greatly increases the risk of developing lung cancer even if pulmonary fibrosis is not evident. Because these bronchogenic carcinomas usually develop in lungs already damaged by fibrosis, the chances of successful surgical treatment are slight, and the prognosis is poor.

The development of various histologic types of bronchogenic carcinoma has also been attributed to exposure to radioactive material, nickel (Plate 11), nickel carbonyl, chromates and bis(chloromethyl) ether.

Mesothelioma, normally a rare pleural or peritoneal tumor, is relatively common in individuals exposed to asbestos and has been diagnosed with increasing frequency since 1960 as the use of asbestos products has become more widespread (Plate 14). In the 1960s, it was noted that pleural and peritoneal mesotheliomas may develop after relatively short periods of exposure to asbestos. In some cases, although the actual exposure to the toxic substance is of short duration, the deposits of active material (asbestos fiber) maintain a low-grade reaction over the years, which ultimately leads to the development of mesothelioma. Workers exposed to asbestos for a brief period in the manufacture of torpedo tubes, and children who played in asbestos dumps, have developed the malignant pleural tumor 20 to 40 years after the original event. Current data indicate that most cases of mesothelioma are related to crocidolite (blue asbestos) exposure.

Symptoms of mesothelioma are chest pain, shortness of breath and weight loss. Chest roentgenograms show the presence of a large pleural effusion surrounded by a thick wall that is demonstrable after thoracocentesis. The pleural fluid is bloody; plugs of tissue may be present in the aspirating syringe and can be used to make a preliminary diagnosis. Mesothelioma is incurable, as attempts at surgical treatment have been unsatisfactory.

Industrial Bronchitis and Mycobacterial Infection. The problem of chronic bronchitis is of great interest in industrial medicine. It is characterized by persistent oversecretion of mucus from bronchial glands and goblet cells lining the conducting airways, and can be recognized by the presence of persistent cough and recurrent expectoration. However, the symptoms of bronchitis are widespread in the general population and, as they are most commonly associated with long-term cigarette smoking, it is often difficult to relate the development of chronic bronchitis to specific occupational exposures. Nevertheless, evidence has accumulated that strongly suggests that such reactions occur in individuals who work in dusty environments, particularly coal workers and grain trimmers. Current investigations are attempting to demonstrate the relationship of chronic bronchitis with other industrial inhalants.

All types of industrial dusts are associated with an increased incidence of infection with atypical mycobacteria. The evidence that these organisms colonize the lungs of workers who inhale industrial particles reinforces the need for regular examination of all who handle such materials.

DIAGNOSIS

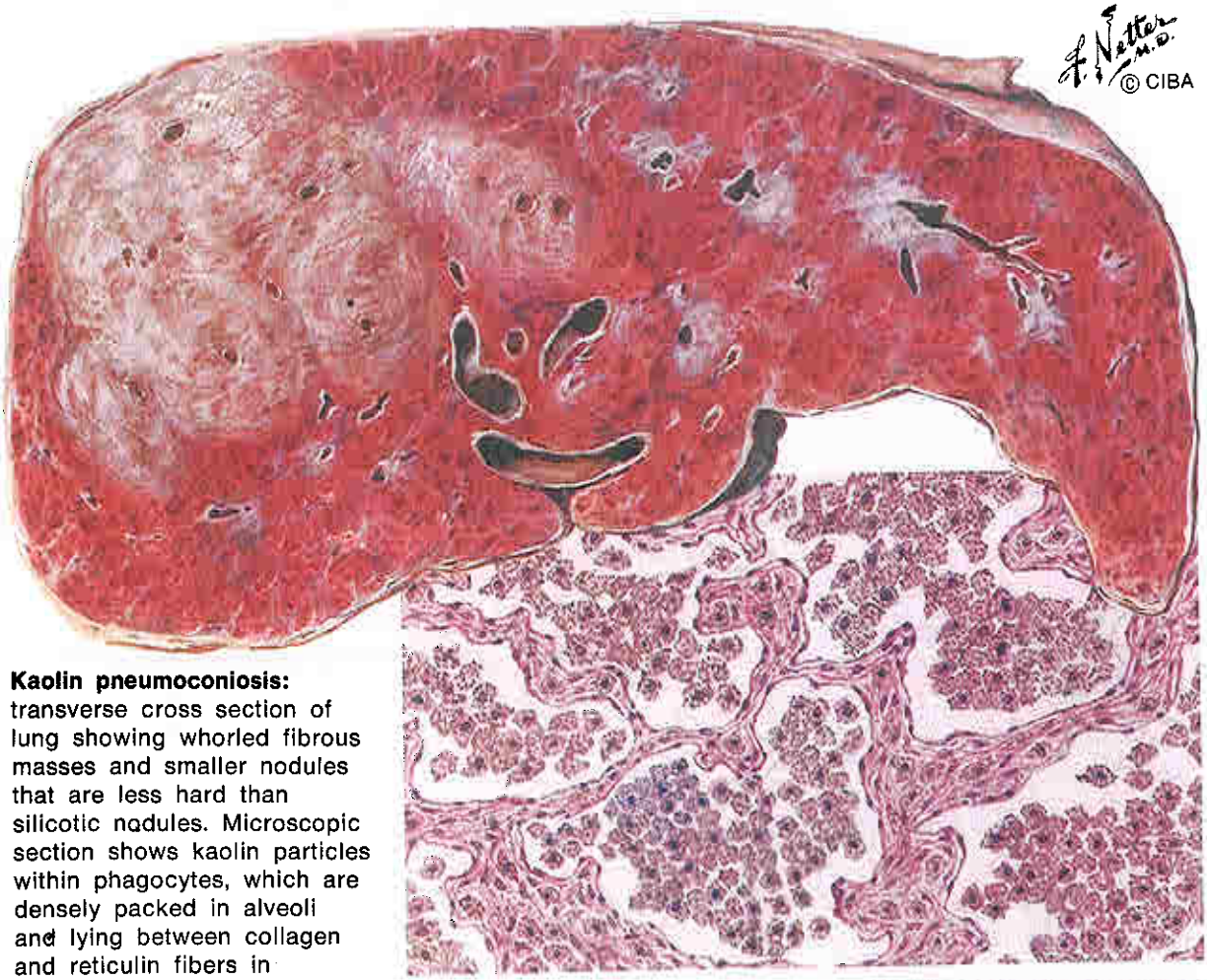
The diagnosis of occupational pulmonary disease requires a complete medical and occupational history to elicit any information concerning exposure to hazardous substances. A thorough physical and chest x-ray examination helps localize the site of pulmonary reactions, and specialized tests may also be required, including examination of tissue specimens for patterns of reaction or degeneration and mineral content, serologic and skin tests, provocative aerosol challenges and pulmonary function tests.

HISTORY

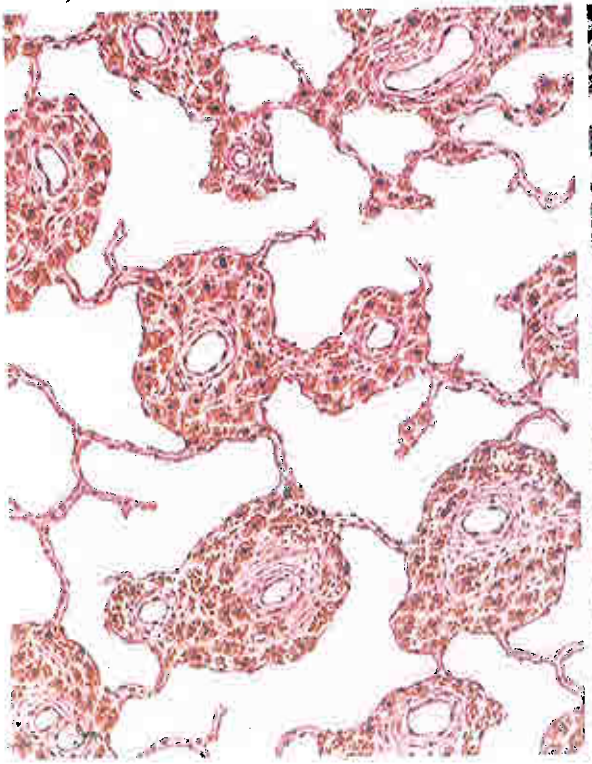
The recognition of occupational pulmonary disease begins with taking a careful history which includes occupational details. The history is often the most neglected portion of the initial patient evaluation, yet it may provide 50% of the diagnostic evidence in work-related disease.

A job description is particularly important. Details of the present and previous jobs should be recorded, including descriptions of the workplaces. Information concerning previous exposure is particularly significant in the diagnosis of diseases that develop years after a brief exposure to toxic materials such as beryllium and asbestos. Although a worker may not be directly involved in the extraction or production of a dangerous substance, he or she may be exposed to dusts from nearby operations. For example, welders employed in shipyards may also be exposed to respirable silica and asbestos if sandblasting or insulating activities are being carried on nearby.

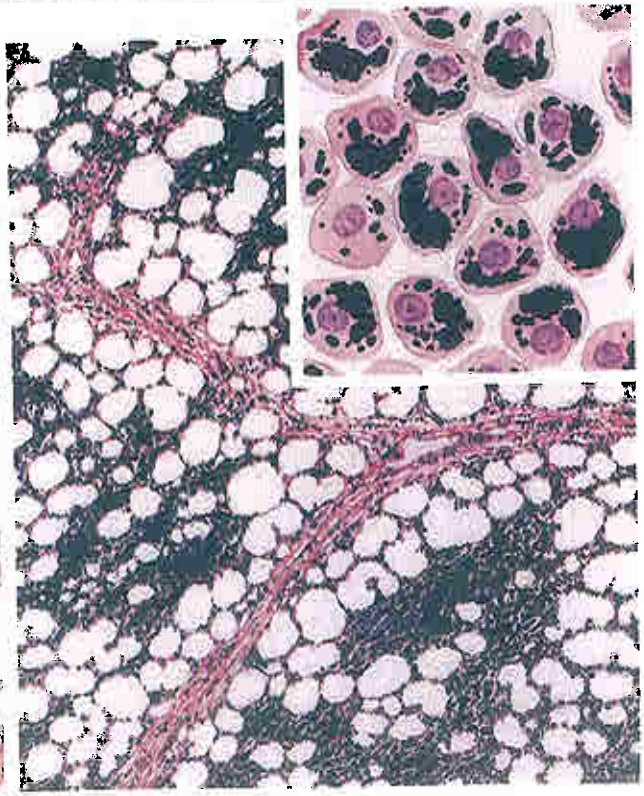
Other Mineral Pneumoconioses



Kaolin pneumoconiosis: transverse cross section of lung showing whorled fibrous masses and smaller nodules that are less hard than silicotic nodules. Microscopic section shows kaolin particles within phagocytes, which are densely packed in alveoli and lying between collagen and reticulin fibers in thickened stroma



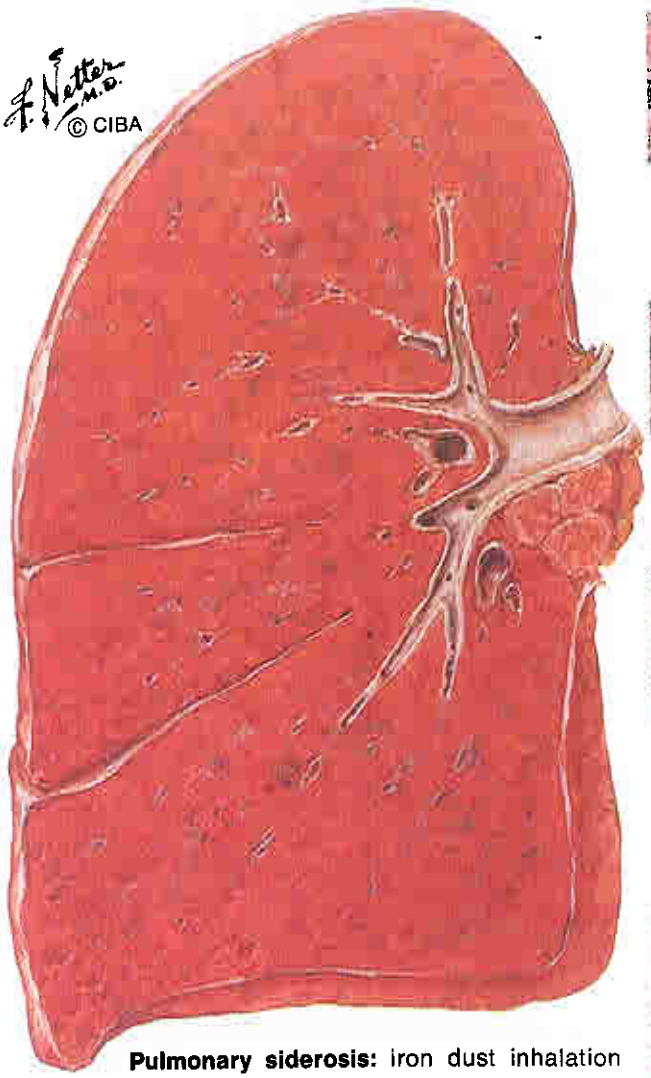
Fuller's earth pneumoconiosis: masses of brown pigment within macrophages, chiefly perivascular. Scant tissue reaction



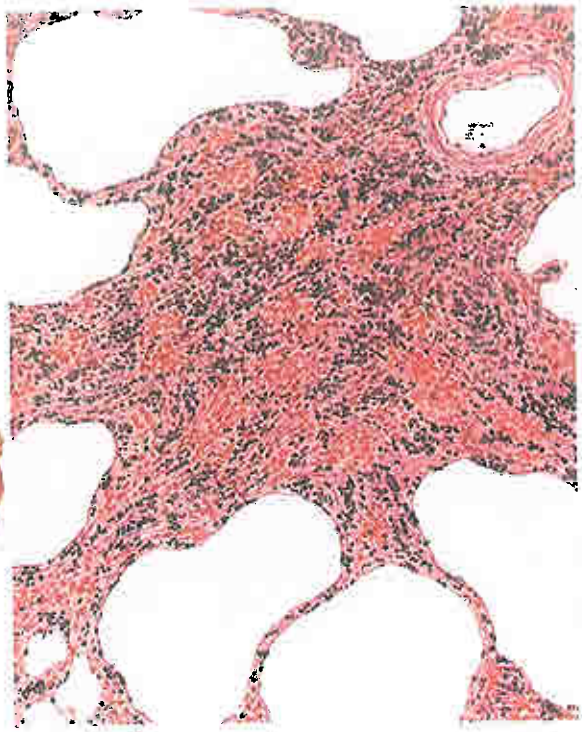
Graphite pneumoconiosis: black deposits and extensive fibrosis. High-power inset shows graphite in alveolar macrophages

Plate 11

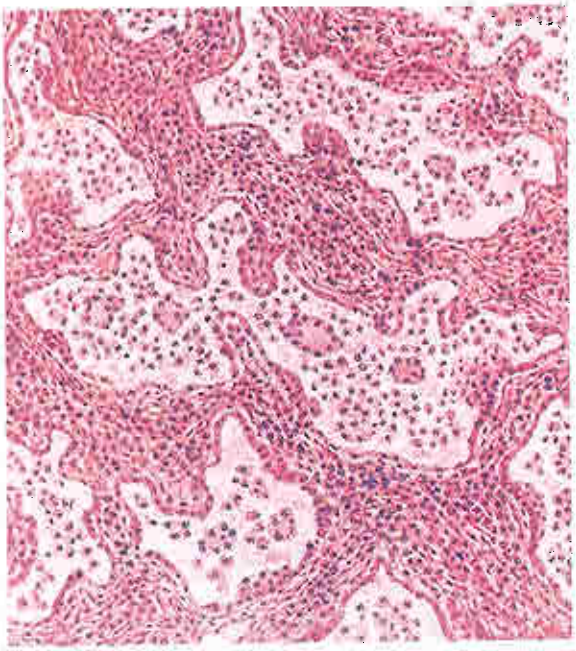
Reactions to Metals and Mixed Dusts



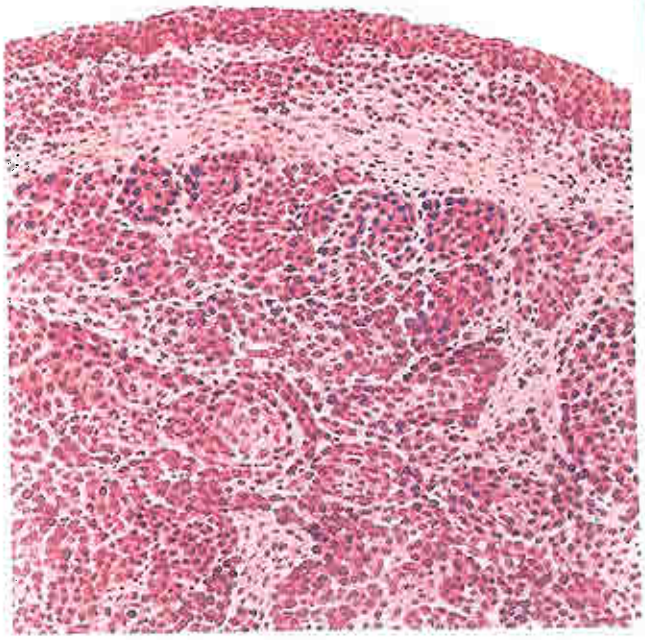
Pulmonary siderosis: iron dust inhalation produces little change in lungs other than brick-red coloration, unless iron is mixed with other dusts, chiefly silica, silicates, and/or carbon. The mild fibrosis, nodulation, and emphysema shown are probably caused by such admixture



Mixed-dust fibrosis: fibrosis surrounding deposits of iron oxide, carbon, and silica. Found in sandblasters, steel dressers, oxyacetylene cutters, and welders having long-term exposure to mixed dusts



Tungsten inhalation effects: cellular infiltration and increased collagen in lung interstitium. Alveoli show epithelial metaplasia and contain cellular exudate with some multinucleated cells



Nickel inhalation effects: squamous cell carcinoma with overlying metaplastic bronchial mucosa believed attributable to this metal

The history is of crucial importance in diagnosing acute reactions following the sudden release of high concentrations of irritants, such as chlorine, phosgene, sulfur dioxide and ammonia, into the atmosphere. Exposure to these substances is most often accidental, and may involve bystanders as well as the workers directly concerned with the industrial products.

A careful history is equally essential in discovering the cause of occupational asthma or hypersensitivity pneumonia. If the pulmonary reactions are delayed, the association with occupational exposure may be obscured. In the progressive fibrotic diseases such as silicosis and asbestosis, a history of exposure associated with consistent, abnormal x-ray films and symptoms is usually diagnostic.

PHYSICAL SIGNS

The presenting signs and symptoms of many occupational lung diseases are nonspecific and may not help localize the reaction in the lung. The most frequent general signs that cause a patient to consult a physician about a lung disorder are cough and dyspnea. Patients also often see a physician when abnormal findings are discovered on a routine roentgenogram, even though no symptoms of pulmonary disease have developed.

Cough is the most common sign of lung disease, and it is generally nonspecific. It is produced by irritation in the airways, and accompanies many industrial lung disorders, notably bronchitis, asthma, bronchogenic carcinoma and hypersensitivity reactions to organic dusts. *Dyspnea*, or shortness of breath, is also a presenting sign of many industrial disorders, and may indicate reactions either in the airways or in the airspaces. The complicated pneumoconioses are characterized by progressive dyspnea, which is often fatal.

Chest pain is also an important symptom of thoracic diseases. The nature of the pain, its duration, intensity and location, may suggest a diagnosis of associated diseases such as lobar pneumonia, pulmonary infarction, pleural effusion or trauma such as rib fractures. In occupational lung disease, persistent chest pain usually signals bronchogenic carcinoma or mesothelioma. Soreness of the chest, on the other hand, may result from episodes of severe coughing.

The presence of *fever* usually indicates infection complicating an underlying disorder, though this constitutional sign is also present in the hypersensitivity disorders and metal fume fever.

In addition to these generalized signs and symptoms, the patient may exhibit more specific signs, some of which are extrapulmonary. For example, the presence of tachypnea and cyanosis indicates that the disease is cardiorespiratory; and an unexplained association of clubbing of the fingers with pulmonary involvement has long been known. Nodular ulcerative skin lesions are nearly diagnostic of beryllium disease, and should lead to a thorough examination of the respiratory system. Perforation of the nasal septum occurs in chromate workers, who may also exhibit signs of major bronchial obstruction or pleural effusion, findings that are often related to bronchogenic carcinoma.

In the examination for occupational lung disease, the techniques of inspection, palpation and percussion can demonstrate gross changes. By using these methods, bronchial obstruction, pleural effusion and pneumothorax can be diagnosed. In industrial bronchitis, auscultation is useful in detecting inequalities of ventilation, and the presence of rhonchi, rales and prolonged expiration. Patients with pulmonary edema or acute pneumonia commonly exhibit inspiratory rales; crackling rales are characteristic of pulmonary fibrosis, and are most commonly demonstrated in patients with asbestosis.

ROENTGENOGRAPHY

Technique. Chest x-ray films provide the most sensitive and reliable means of localizing lung disease. Standard *posteroanterior (PA)* and *lateral* films are usually sufficient for this purpose, but special views can be useful. For example, *oblique* projections help define bronchial narrowing and irregularity, outline lobar disease and demonstrate pleural thickening. *Apical lordotic* views can demonstrate disease in the upper lung zones, which are often obscured by the bones of the thoracic inlet on routine PA roentgenograms. *Tomograms* are often used to demonstrate the presence of calcium, outline bronchi and cavities and distinguish between single nodules and the compound densities produced by multiple foci.

The chest x-ray film reveals the degree of lung involvement in the disease process. In examining the film for pulmonary disease, *diffuse or localized* patterns of disease can be

distinguished. In addition, chest roentgenography can also demonstrate extension of the disease to other components of the thorax. For example, neoplastic disease and mycobacterial infections of the lungs may involve neighboring bone and soft tissue. Cardiac abnormalities secondary to pulmonary disease may also be seen: Enlargement of the pulmonary arteries as a result of pulmonary hypertension is common, and although the heart may not appear enlarged on the erect PA view, an enlarged right ventricle can usually be demonstrated in the right oblique projection. The heart often appears small in the presence of emphysema, as may be seen in patients with longstanding obstructive disease of industrial origin.

The radiologic appearance of the lung fields may be altered by technical and anatomic factors, and these must always be considered to avoid overreading. For example, underexposed roentgenograms of obese, middle-aged individuals frequently show fine densities most prominently located in the pectoral areas. Increasing the exposure on subsequent films can eliminate these densities; they will not be present on oblique views. Although the quality of lateral films varies greatly, the presence of fine infiltrates may always be confirmed by using these views.

Diffuse Disease. The roentgenologic appearance of the lungs in diffuse disease shows widespread involvement of the air spaces, the interstitial structures, or both, and is often distorted by residues of previous disease. For example, in the presence of emphysema, best visualized in the upper lobes, the dilated airspaces are poorly ventilated and have a poor capillary bed, so that lobar pneumonia can lead to incomplete consolidation and the development of a coarse honeycomb pattern. By contrast, in younger individuals or individuals free from excessive obstructive pulmonary disease and emphysema, diffuse involvement of the airspaces by pneumonia or transudation produces fine areas of consolidation with a tendency to confluence. A striking example of diffuse involvement of the airspaces, similar to the pattern of alveolar proteinosis, is seen in acute silicosis. Very fine and discrete lesions that are widely distributed throughout the lungs are encountered in individuals who have worked with oil mists. More commonly, diffuse consolidation of the airspaces is coalescent, as in pulmonary edema resulting from exposure to insoluble gases or chemical pneumonia following inhalation of toxic fumes. Characteristic interstitial fibrosis and honeycombing, typically situated at the lung bases, are well demonstrated in advanced cases of asbestosis.

In early interstitial disease, *irregular nodules*, produced by obliteration of fine structural units of lung, are seen on the roentgenogram. As the scars become larger in well-developed interstitial disease, *linear* shadows are pronounced, and in the extreme and most widely recognized form, a *honeycomb pattern* is demonstrated. These changes are usually associated with reduction in the size of the lungs. Fine interstitial lesions involve the neighboring airspaces, and ultimately a mixed pattern is encountered in which the linear interstitial elements are associated with areas of consolidation and contraction.

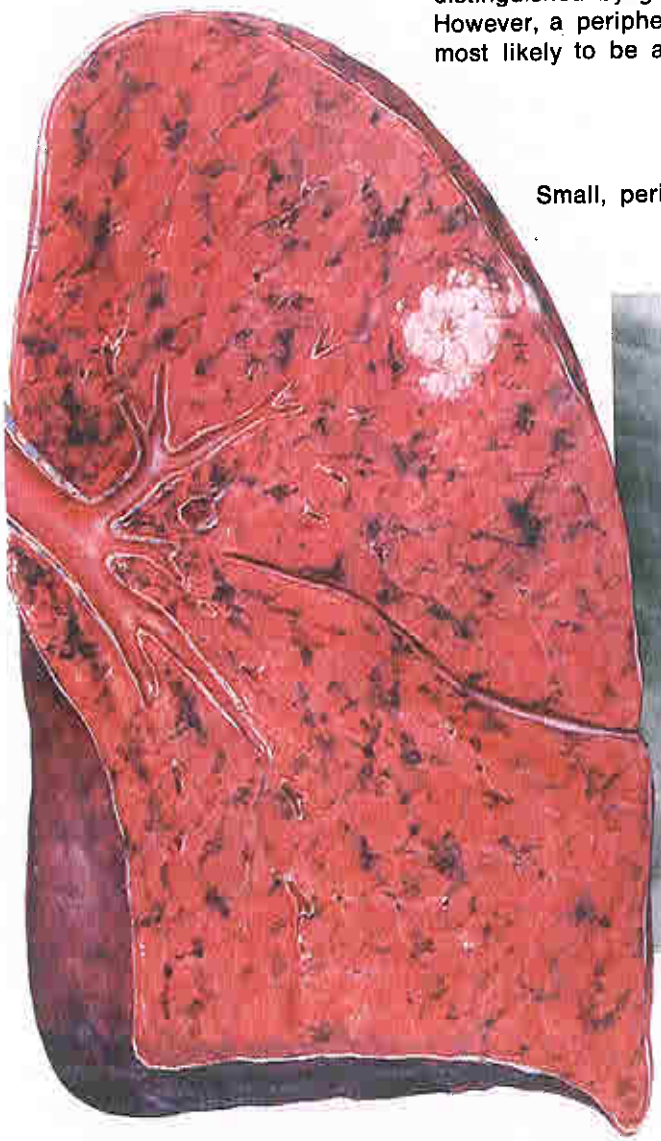
Diffuse changes, often of the butterfly pattern, are encountered in individuals with pulmonary edema, and pneumonia that develops following exposure to irritants usually follows the same distribution as pulmonary edema. Hypersensitivity pneumonia associated with exposure to organic dusts is usually widely distributed throughout the lungs, although in the chronic stage the reactions in the upper lobes become more marked. As the upper lobes contract, large densities appear on the roentgenogram, similar to those encountered in complicated silicosis.

In simple silicosis, obliterative nodules are the prime elements composing the pattern of reaction. In the advanced and complicated stages of the disease, masses appear in the upper lobes, which contract, while areas of bullous emphysema are often marked at the lung bases. Silicosis is frequently complicated by mycobacterial infection with atypical patterns of cavitation. In accelerated silicosis, the effects of infection at the lung bases can be prominent, with breakdown in the lower lobes.

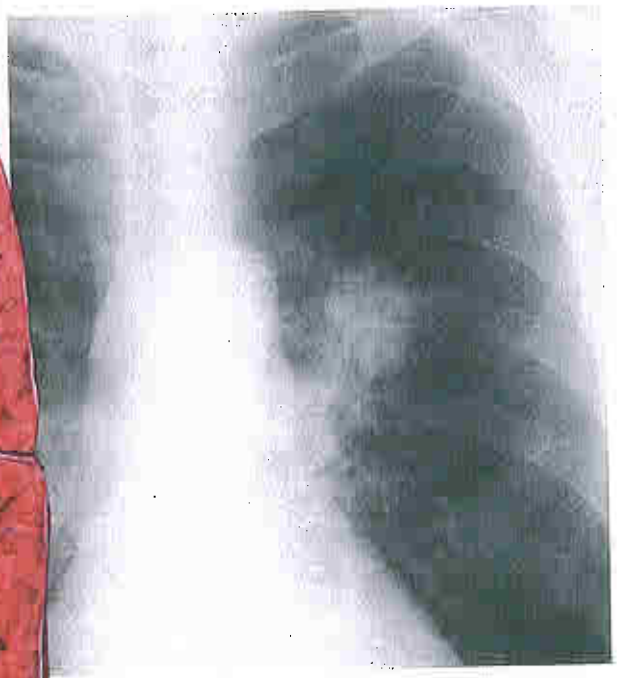
On the roentgenogram, an appearance similar to that seen in classic silicosis is encountered in coal worker's pneumoconiosis. In these cases, nodular densities are typical, but progressive massive fibrosis, although infrequent, does occur. In rare cases, individuals with rheumatoid disease will develop groups of enlarging nodules that simulate the appearance of tumor metastases (Caplan's nodules, as seen in Plate 7).

Bronchogenic Carcinoma: Adenocarcinoma

Different histologic types of bronchogenic carcinoma cannot be distinguished by gross specimens or roentgenogram alone. However, a peripherally located tumor < 4 cm in diameter is most likely to be adenocarcinoma

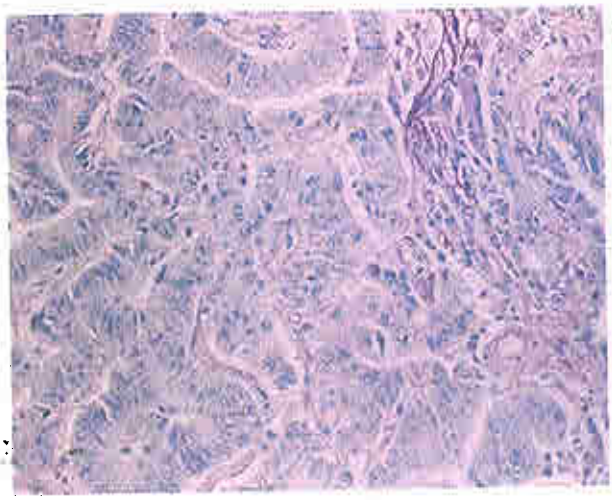


Small, peripherally placed tumor

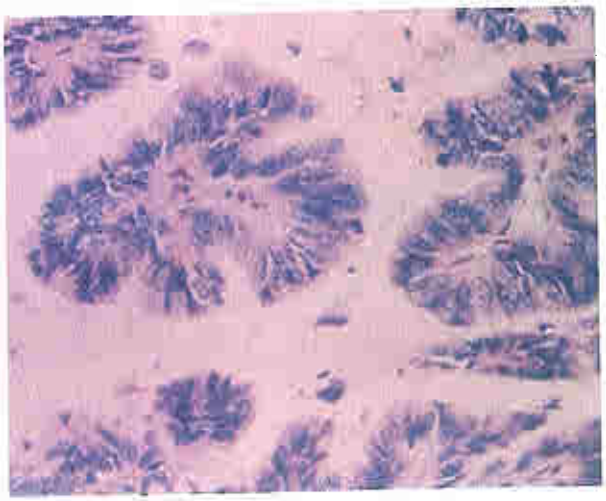


F. Netter, M.D. © CIBA

Varied histology of adenocarcinoma



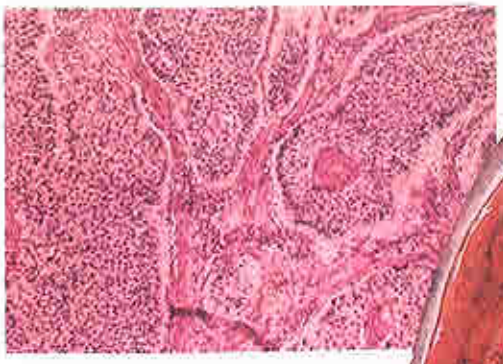
Tumor cells form glandlike structures with or without mucin secretion



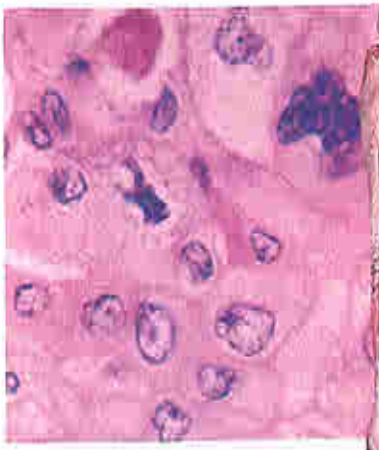
Tumor cells may also form papillary structures

Plate 13

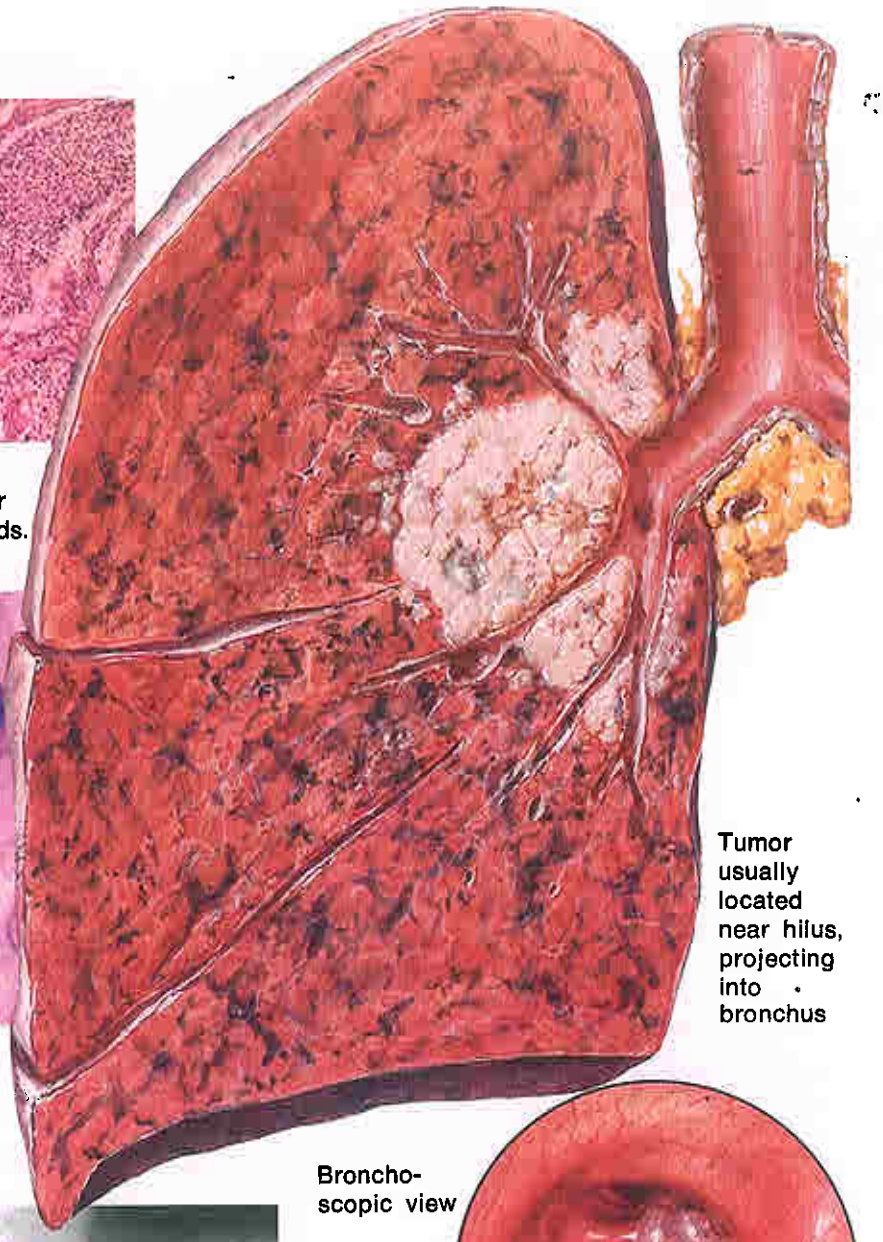
Bronchogenic Carcinoma: Squamous Cell Type



Low-power section (H and E stain) showing nests of tumor cells separated by fibrous bands. Keratin (horn) pearls present

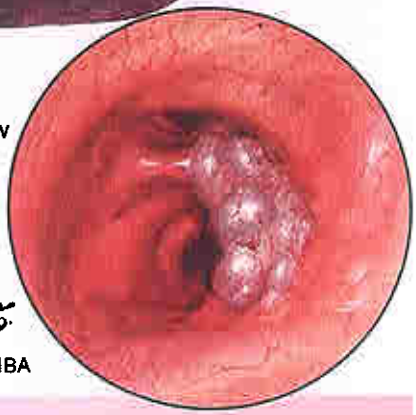


High-power section showing nuclear pleomorphism and individual cell keratinization (pink)

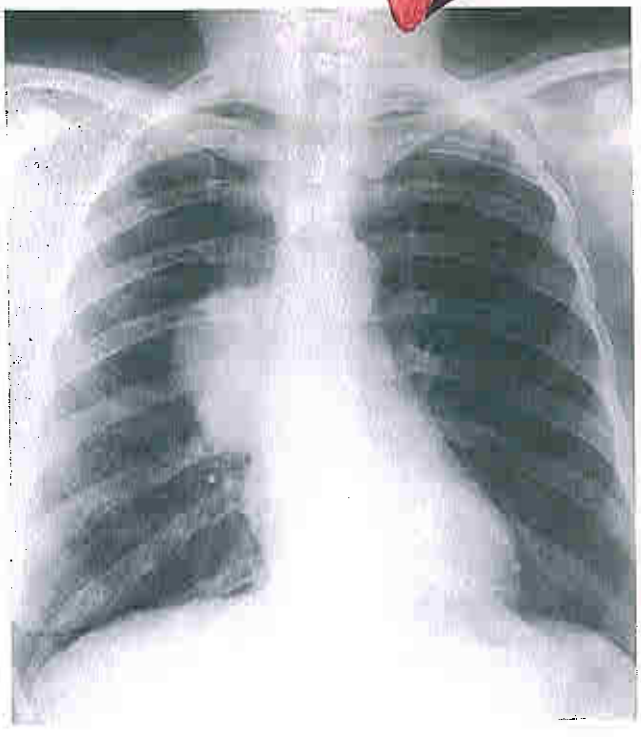


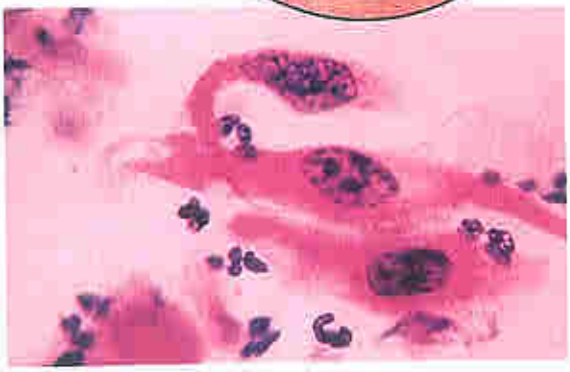
Tumor usually located near hilus, projecting into bronchus

Broncho-scopic view



F. Netter M.D. © CIBA





Cytologic smear from sputum or broncho-scopic scraping showing cells with dark nuclei and cytoplasm strongly pink because of keratin

In the presence of diffuse obstructive changes as seen in chronic byssinosis and chronic obstructive pulmonary disease, enlargement of the lungs with attenuation of vascularity will appear on the roentgenogram. The heart appears relatively small, and the diaphragm will be depressed.

Localized Disease. Peripheral neoplasms that show up clearly on x-ray film are encountered in asbestos, chromate and nickel workers. These groups of workers may develop endobronchial carcinomas that produce obstruction and infiltration of pulmonary lobes and additional masses within the mediastinal lymph nodes. Involvement of lymph nodes is also commonly associated with the granulomatosis and fibrosis of chronic beryllium disease. Peripheral "eggshell" calcification of the lymph nodes is often seen in individuals with silicosis.

Cardiac changes are also seen with occupational pulmonary disease. In restrictive disorders in which pulmonary fibrosis adjacent to the heart is severe, the cardiac borders appear indistinct and shaggy on the x-ray film. On the other hand, in the presence of pleural disease with calcified pleural plaques, which develops following asbestos exposure, the heart borders may be well defined although partially calcified.

Changes within the pleura are not uncommon in occupational lung disease, and extensive pleural thickening accompanying lobar contractions is seen in silicosis (Plate 5) and in some cases of chronic hypersensitivity pneumonia. The most striking changes in the pleura, however, are those associated with asbestos exposure. In individuals with long exposure to asbestos, the development of hyaline and calcified pleural plaques is common (Plate 8). On chest x-ray films, the plaques are usually best demonstrated along the lateral chest walls, but they may be seen *en face* or over the diaphragm. Noncalcified plaques must be distinguished from the intercostal companion muscle shadows that accompany the ribs.

In addition to the benign pleural changes described above, malignant mesothelioma is specifically associated with asbestos exposure (Plate 14), most commonly with exposure to blue asbestos (crocidolite). This tumor greatly thickens the walls of the pleural spaces and contains a cavity from which bloody fluid can be aspirated. The tumor can become massive, and it compresses the lung and depresses the diaphragm. Metastases are not common but sometimes occur.

DIAGNOSTIC TESTS

The diagnosis of occupational pulmonary diseases may require specific laboratory tests. Evidence of cellular reactions and mineral content in the lungs may be obtained by examination of tissue specimens or samples of sputum or bronchial washings. In certain types of diseases, serologic and skin tests may confirm the diagnosis suggested by the historical, physical and roentgenologic findings. The development of characteristic reactions after the inhalation of aerosols containing specific industrial products may also help support a diagnosis.

Tissue specimens obtained by biopsy or autopsy may show cellular reactions or patterns of degeneration characteristic of occupational lung diseases. Lung biopsy is rarely necessary in diseases that produce diffuse pulmonary reactions, although in certain situations specific treatment should not be begun unless the diagnosis is absolutely secure; it is never required in disorders that cause bronchospasm and hyperinflation of the lungs. Biopsy is indicated, however, when carcinoma is suspected. It is also advised when disease is found in a young person, or when there is a possibility of an occupational hazard to a group and diagnosis is important to protect others also.

A biopsy sample may be obtained by transbronchial biopsy through a fiberoptic bronchoscope, while larger specimens are obtained through the rigid bronchoscope or via a thoracotomy.

Bronchial washings will provide living cells for tissue culture that can be used in macrophage and lymphocyte stimulation tests after routine studies have been carried out. In addition, pathologic studies should be initiated and tissue samples should be examined for mineral content. Tissue samples can be examined by light and electron microscopy and crystallography. Transmission electron microscopy (TEM) can be utilized to identify trace elements, including silicon and metals. The sputum should be also examined for tumor cells and infectious organisms such as mycobacteria.

Cellular reactions or patterns of degeneration characteristic of specific diseases may be revealed by tissue examination. These include nodular fibrosis in silicosis, characterized by

27

central whorls of hyalinized collagen (Plate 6), and a reaction unfamiliar to many pathologists and radiologists which occurs in acute silicosis (silicoproteinosis). On examination of tissue sections, free silica will be demonstrated in the affected tissues together with areas of early nodulation or linear fibrosis provoked by the free silica.

Although asbestos fibers have been demonstrated in tissues that show no fibrotic reaction, if fibrosis has developed from exposure to asbestos, characteristic asbestos (ferruginous) bodies will be seen (Plate 8).

The presence of potentially toxic material which has not provoked any reaction is a phenomenon that occurs in all tissues of the body. Materials that are inhaled or ingested and have a slow release time before excretion will be encountered in biopsies, particularly when ultramicroscopic methods are employed. For example, using chemical methods or electron microscopy, beryllium may be demonstrated in tissues even though no reaction is present and beryllium disease has not developed. Thus, to make a definitive diagnosis of beryllium disease, it is not enough simply to demonstrate the presence of the metal alone—the granulomatous and fibrous reactions to beryllium must be present.

Serologic and Skin Tests. The presence of precipitins to specific thermophilic actinomycetes strongly supports the diagnosis of hypersensitivity to organic dusts, although the same response can be found in individuals who have not developed the disease. However, patients with active disease are very likely to have positive precipitin tests. In some cases, a positive skin test to antigen may also be present; but this is a delayed (Arthus) reaction that occurs several hours after the application of the antigen, and results in a lasting lesion in which necrosis may take place. Because the antigens for these reactions are impure and skin reactions are inconstant and often excessive, the search for Arthus reactions in these diseases is not routinely carried out.

Antinuclear antibodies may be found in patients with asbestosis and silicosis, and help support these diagnoses.

Provocative tests using aerosols containing low concentrations of irritant substances are commonly employed in testing for specific bronchial hyperactivity. In individuals who are sensitive to low concentrations of industrial materials, even in the absence of antibody production, tests of this sort are diagnostic. They have been used in testing for sensitivity to cotton dust, thermophilic actinomycetes, the diisocyanates and western red cedar dust.

PULMONARY FUNCTION TESTS

Spirometry provides a simple and sensitive technique for quantitative evaluation of pulmonary function. Pulmonary function tests are used to confirm evidence of disease found on physical examination, chest x-ray films and immunologic testing, or to demonstrate the existence of a functional disorder when structural aspects of disease cannot yet be objectively delineated. The studies can be repeated after a time interval to demonstrate progression of disease or monitor the pulmonary response to treatment or changes in working conditions. In addition, arterial-blood gas studies provide other useful information concerning respiratory function.

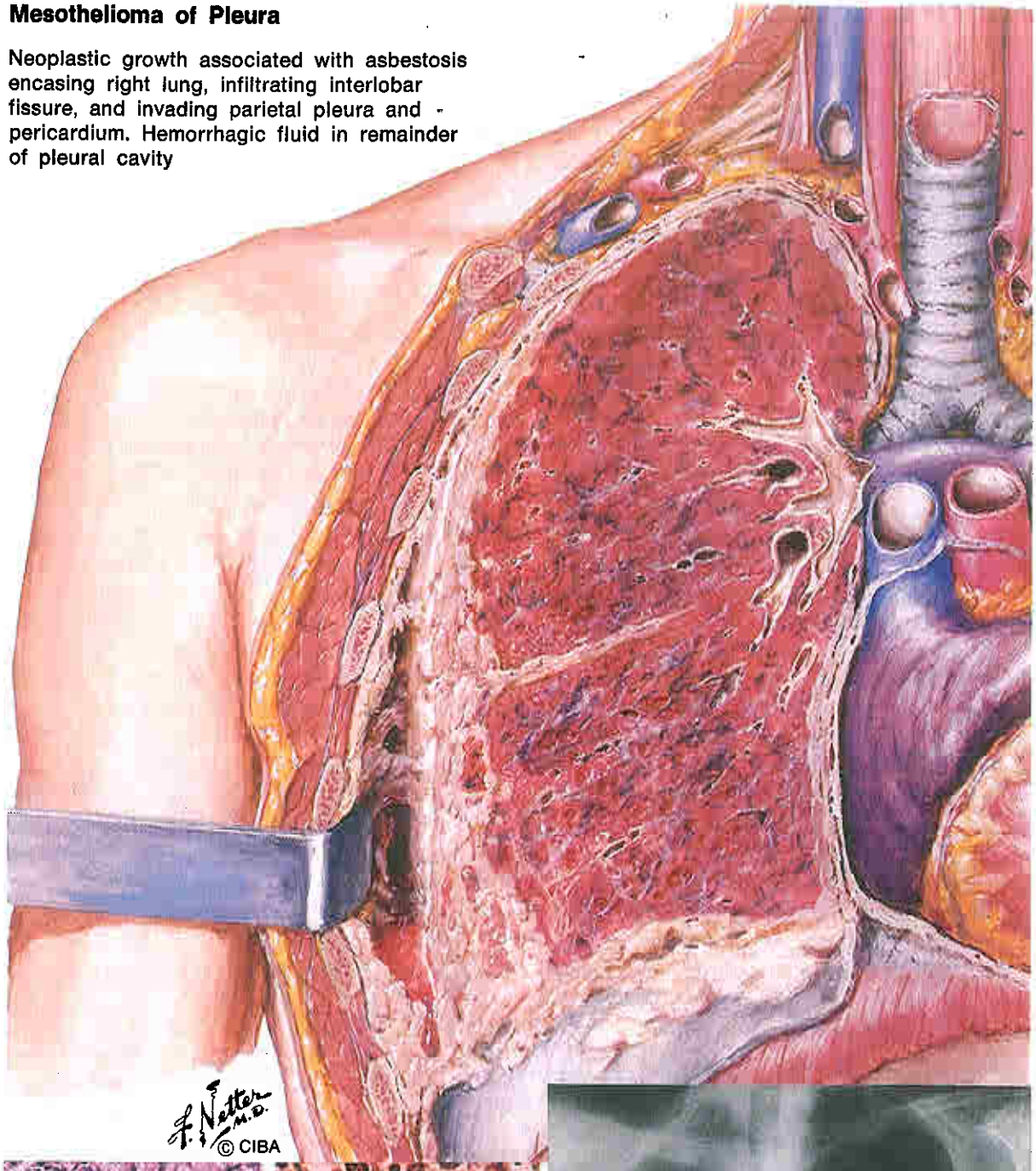
Characteristics of Pulmonary Function Tests in Industry. Pulmonary function tests used in industrial medicine should be sufficiently sensitive to detect early stages of pulmonary disease and minimal changes in progression, and simple enough for the subject to cooperate effectively. In addition, studies should be easily repeatable and provide reproducible data that correlate with the stage of the patient's lung disease. Although these tests do not differ substantially from those performed on patients with pulmonary disorders not attributable to industrial exposure, the tests preferred for field surveys are simpler and more economical.

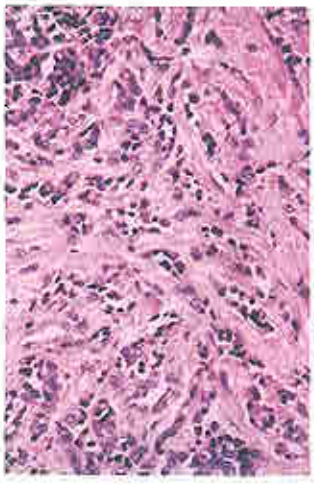
The technical personnel administering the tests and the types of spirometer used are important factors in surveying industrial populations. Most spirometric tests require maximal cooperation and effort on the part of the subject, and a highly trained technician must administer the test to obtain meaningful and reproducible results. Water-balanced spirometers are still generally employed, although waterless spirometers have specific mechanical advantages and can be equipped for instantaneous readout. In any event, a permanent graphic record, which can be analyzed and stored for later study, must be obtained from spirometric tests in an industrial setting.

The availability of a vehicle serving as a mobile laboratory makes it possible to carry out an extensive battery of diagnostic tests

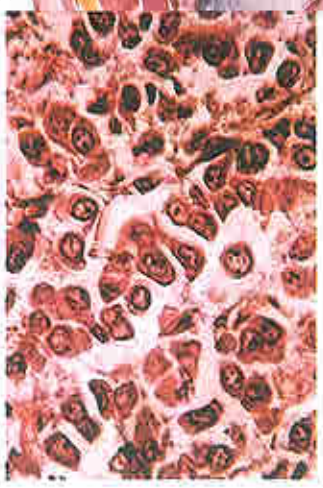
Mesothelioma of Pleura

Neoplastic growth associated with asbestosis encasing right lung, infiltrating interlobar fissure, and invading parietal pleura and pericardium. Hemorrhagic fluid in remainder of pleural cavity

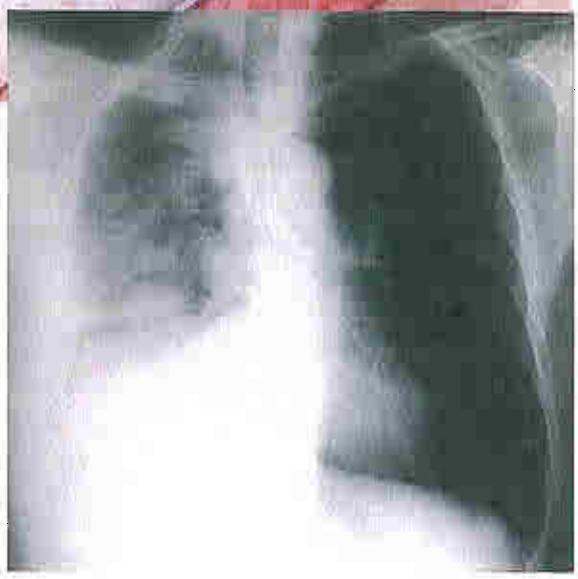




Fibrosarcomatous type of tumor



Epithelial cell type of tumor



Mottled shadow over right lung, with effusion. In advanced cases, lung may be totally obscured

on an industrial population. Arterial-blood gas studies are rarely performed in such field work, but venous blood for serologic or other studies can be drawn.

Patterns of disturbances of pulmonary function in industrial workers have been demonstrated by studies of both individuals and groups, with the earliest changes usually showing up on spirometry. Reduced vital capacity has been demonstrated in patients with asbestosis whose chest x-ray films still appear normal. Yet in diseases that involve small airways (less than 2 millimeters in diameter), spirometric measurements may themselves appear to be normal. In these cases, special techniques for measuring airflow in small airways may be of value, although some useful information can still be obtained from the spirograms taken during forced expiration, especially the FEF 25-75% in which airflow through narrowed airways in particular is being measured.

Disturbances in function in progressive occupational pulmonary disease will become obvious and increase in degree with continuing exposure to the agent concerned. For instance, pulmonary function is well maintained in simple silicosis, but it is markedly disturbed in so-called acute silicosis in which many fine airspaces are filled and their walls are thickened. Function is also impaired in complicated silicosis, in which there is lobar contraction and distortion of the airways.

Arterial-blood gas studies are helpful in uncovering disturbances of oxygenation caused by maldistribution of air in the lungs, and a fall of oxygen tension during exercise is indicative of marked reduction in the area of the pulmonary diffusing surface. Similarly, carbon dioxide retention in patients with pneumoconiosis is an indication of advanced, preterminal disease. In general, a reduction of pulmonary diffusing capacity indicates widespread lung involvement. However, this may be partially counterbalanced by an increase in total lung capacity in diseases complicated by emphysema in which alveolar volume is increased. It must be remembered that obstructive disorders with reduced airflow rates and other functional changes may be the result of factors unconnected with an industrial environment. One very important factor that disturbs the rate of airflow is prolonged and heavy cigarette smoking.

Industrial diseases resulting in reversible airways obstruction are well suited for spirometric study. In cases of industrial asthma, it is easy to measure the reduced vital capacity as well as the response to bronchodilator therapy, and monitor the seasonal variations in obstructive disorders and the variations in obstruction throughout a work shift. In studies of byssinosis, spirometric measurements demonstrate clearly the decrease in airflow that occurs on the first day of reexposure to cotton dust following a weekend away from work.

Serial determinations can demonstrate the progression of obstruction and the development of fixed resistance to airflow. Inhalation challenges can be instituted and monitored to determine a worker's hypersensitivity to substances suspected of causing bronchospasm. Positive reactions to such provocative tests may be correlated with positive serologic and skin tests. Studies of reactions to organic dusts have been useful in demonstrating respiratory sensitivity to thermophilic actinomycetes in moldy hay or bagasse, an approach fortified by studies of atopic status (sensitivity to common allergens) and bronchial hyperactivity using challenges with inhaled methacholine chloride.

SUMMARY

In summary, requirements for the diagnosis of occupational pulmonary disease include: (1) a history of significant exposure to a toxic substance; (2) physical signs; (3) abnormal roentgenologic findings; (4) evidence of mineral content, characteristic reactions and patterns of degeneration in tissue samples obtained by biopsy or autopsy; (5) the presence of antibodies in sera or the presence of antinuclear antibodies in asbestosis and silicosis; (6) positive reactions to provocative tests in hypersensitivity diseases; and (7) evidence of abnormal pulmonary function obtained by spirometric tests. As the tests can often detect disease in early stages, a diseased worker can be separated promptly from the cause of his illness, and an annual functional examination is now becoming a requirement in those occupations in which there is a respiratory hazard.

TREATMENT

Occupational pulmonary disease includes a great variety of pathologic conditions and symptoms, and the treatment varies accordingly. For many of these disorders, however, there is no treatment for the underlying

PULMONARY REACTIONS TO INDUSTRIAL SUBSTANCES

	Substances	Usual Reaction	X-ray Findings	Pathologic Findings
Airways	Irritant gases: chlorine, sulfur dioxide, ammonia	acute bronchitis	nonspecific	nonspecific
	Organic dusts: TDI, western red cedar dust	asthma	nonspecific	nonspecific
	Cotton dust	"Monday fever"	nonspecific	nonspecific
	Particulates: mineral and organic	chronic bronchitis	nonspecific	nonspecific
Lungs	Dusts carrying thermophilic actinomycetes	hypersensitivity pneumonia	granular haziness; occasionally, nodular densities	acute inflammation; granulomas; fibrosis
	Phosgene	edema	butterfly pattern	edema; secondary pneumonia
	Mercury, cadmium	pneumonia	diffuse airspace filling	acute inflammation
	Nitrogen dioxide	edema; small airways disease	butterfly pattern	bronchioloalveolar tufts
	Ammonia	supperative pneumonia; bronchiectasis	contracted lobes; obstructive emphysema	acute and chronic inflammation
	Tin, barium, iron	dust deposits	dense acinar pattern	dust deposits
	Silica	nodular and massive fibrosis	nodules in upper lung fields	hyaline nodules
	Asbestos, tungsten	diffuse fibrosis	linear (interstitial) shadows in lung bases	asbestos bodies; interstitial fibrosis
	Beryllium	pneumonia; granulomatosis	butterfly pattern; granular or nodular fibrosis	inflammation; granulomas
	Asbestos, nickel, chromate	cancer	masses, atelectasis	adenocarcinoma, squamous cell carcinoma
	Coal dust, carbon	coal macules; massive fibrosis	nodules	indurated coal deposits; fibrosis
Pleura	Asbestos	pleural plaques	pleural thickening, calcification	no cellular reaction
	Asbestos	mesothelioma	marked thickening of pleural walls	specific neoplasm

disease, and only symptomatic treatment or treatment for complications may be available. *Thus, for all occupation-linked diseases the principal emphasis is on prevention.*

Acute edema and pneumonia following exposure to toxic gases are treated with oxygen therapy and antibiotics. Positive-pressure oxygen breathing may be necessary if excessive damage to the respiratory tract has occurred. The acute bronchospastic response to TDI, western red cedar dust, and proteolytic enzymes may be relieved with the use of bronchodilators.

If a condition is not progressive but recurs frequently, as is the case with some of the hypersensitivity pneumonias, removal of the patient from the industrial location will be sufficient for cure, although corticosteroids may be required to treat acute episodes. Also, removal from the source of exposure usually prevents simple coal worker's pneumoconiosis from developing into complicated disease.

However, progressive disorders that result from exposure to respirable dusts such as free silica, asbestos and beryllium will remain active even after exposure is terminated. In

these disorders, the only treatment available is administration of antituberculous drugs for mycobacterial infection or corticosteroids for cases complicated by autoimmune disorders. To date, there have been no long-term studies in humans of attempts to control the progressive cellular reaction in silicosis.

PREVENTION

Because occupational pulmonary diseases are generally preventable, it is important to discover industrial hazards as early as possible. Some authorities propose that all *newly introduced materials* be regarded as hazardous until proved otherwise, although determining the toxicity of materials is often difficult and usually requires long-term animal experiments. In any event, efforts should first be made to minimize the workers' contact with new, potentially hazardous materials until safe levels of exposure have been conclusively established, and the workers exposed to any vapors, fumes and dusts should be examined regularly and frequently. In addition, the peaks and fluctuations in the concentration of these substances in the factory's atmosphere should be carefully monitored. Such a program will make it possible to detect any adverse reactions in workers as early as possible and to correlate the reactions with changes in the atmospheric concentrations of the industrial substances.

In industries where there is a *known hazard*, everything must be done to reduce the concentration of the material in the atmosphere to a level known as the threshold limit value (TLV), below which no disease develops. The goal of physicians and others concerned with industrial hygiene is to determine whether there is, indeed, a no disease level for the material concerned and to achieve that level.

Control measures for toxic substances include enclosing them, diluting their concentration in the air with adequate ventilation, and reducing worker contact with them by the use of protective devices such as respirators, masks and air-supplied hoods.

Another method of reducing industrial disease is the use of inert substances. Recognition of the hazards of sandblasting led to the substitution of coal ash, coal slag and steel grit for silica. To date, no respiratory diseases have been attributed to these substitutes. However, the possibilities of injury to the airways and of deposition of dusts within the airspaces makes it essential to regularly monitor workers who are chronically exposed to high concentrations of even so-called innocuous dusts.

Using such methods, the incidence of disease in industrial populations can be sharply reduced. Unfortunately, it was the experience in industries using asbestos products that asbestosis may make its appearance 20 years after the original exposure. Since this occurred using supposedly safe levels of exposure, the aim for the future must be to further reduce exposure of workers to industrial products, at the same time as collecting data to ensure that the health of succeeding cohorts of workers continues to improve.

REFERENCES

Bates DV, Macklem PT, Christie RV: *Respiratory Function in Disease*, 2nd ed., Philadelphia: W.B. Saunders, 1971

Baum GL, Editor: *Textbook on Pulmonary Diseases*, 2nd ed., Boston: Little, Brown and Company, 1974

Becklake MR: *Asbestos-related disease of the lung and other organs: their epidemiology and implications for clinical practice*, Am. Rev. Respir. Dis. 114:187, 1976

Gilson JC: *Occupational bronchitis*, Proc. R. Soc. Med. 63:857, 1970

Jones RN, Weill H: *Occupational lung disease*, Basics of RD 6:1, 1978

Morgan WKC, Lapp NL: *Respiratory disease in coal miners*, Am. Rev. Respir. Dis. 113:531, 1976

Morgan WKC, Seaton A: *Occupational Lung Diseases*, Philadelphia: W.B. Saunders, 1975

Parkes WR: *Occupational Lung Disorders*, London: Butterworth, 1974

Weill H, George R, Schwarz M, Ziskind MM: *Late evaluation of pulmonary function after acute exposure to chlorine gas*, Am. Rev. Respir. Dis. 99:374, 1969

Ziskind MM, Jones RN, Weill H: *Silicosis*, Am. Rev. Respir. Dis. 113:643, 1976