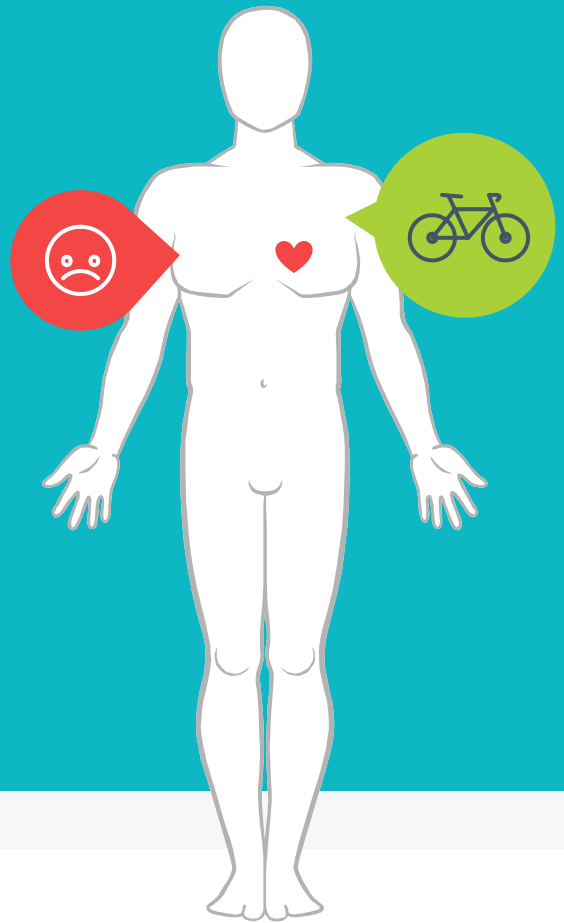
Respiratory System Pathology:

CHRONIC INTERSTITIAL (RESTRICTIVE, INFILTRATIVE) LUNG DISEASES



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CHRONIC INTERSTITIAL (RESTRICTIVE, INFILTRATIVE) LUNG DISEASES:

- A heterogeneous group of disorders characterized by **bilateral**, often **patchy**, pulmonary fibrosis mainly affecting the **walls of alveoli**.
- The hallmark of these disorders: reduced lung **compliance** (stiff lungs) → necessitates increased effort to breathe (dyspnea).
- Damage to the alveolar epithelium & interstitial vasculature produces abnormalities in the ventilation-perfusion ratio→ **hypoxia**.
- Chest radiographs: small nodules, irregular lines, or “ground-glass shadows.”
- With progression, patients may develop respiratory failure, pulmonary hypertension, and cor pulmonale.

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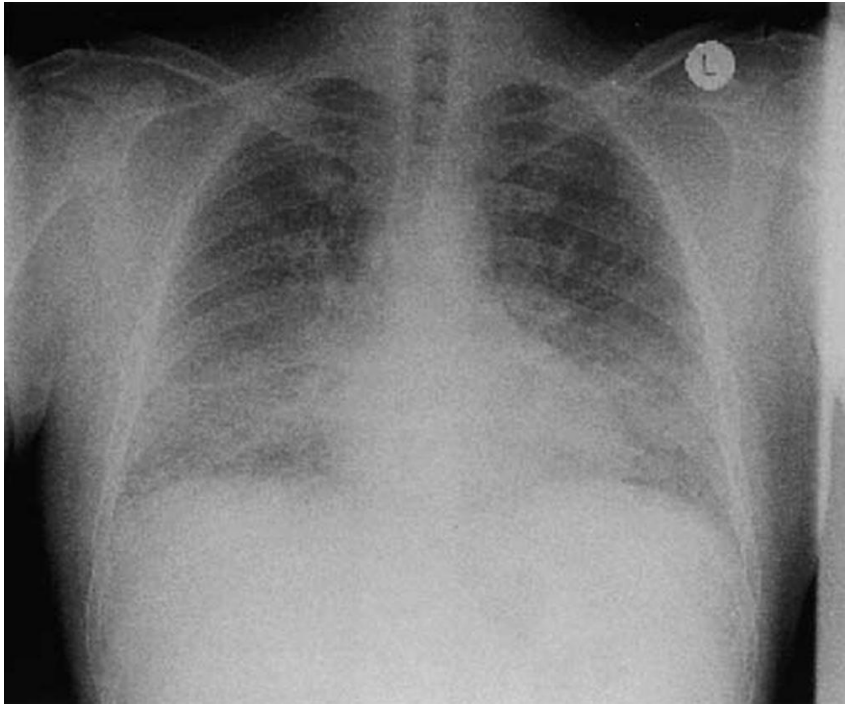
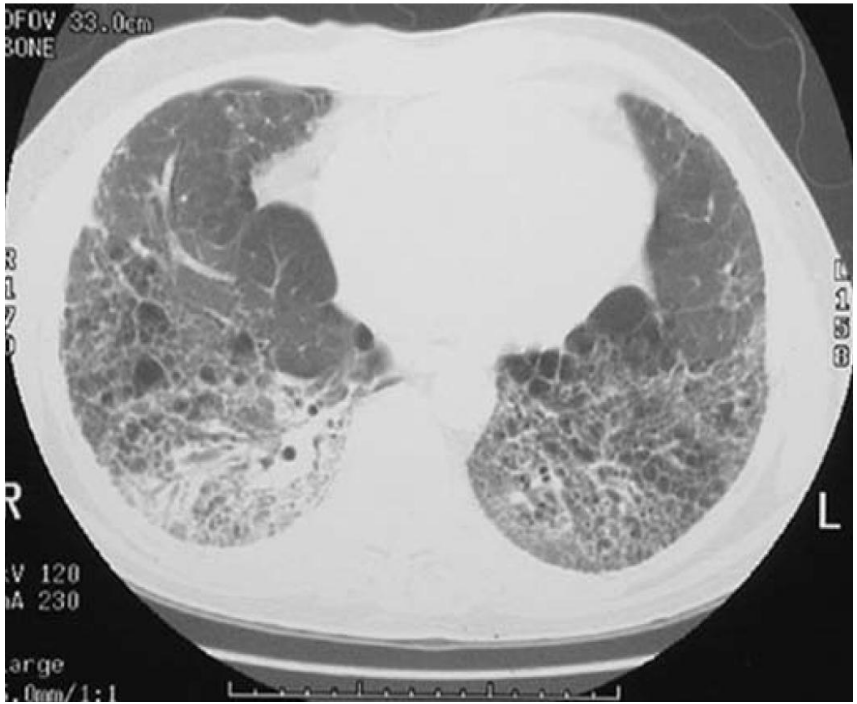




Major Categories of Chronic Interstitial Lung Disease

Fibrosing
Idiopathic pulmonary fibrosis/usual interstitial pneumonia
Nonspecific interstitial pneumonia
Cryptogenic organizing pneumonia
Collagen vascular disease-associated
Pneumoconiosis
Therapy-associated (drugs, radiation)
Granulomatous
Sarcoidosis
Hypersensitivity pneumonia
Eosinophilic
Loeffler syndrome
Drug allergy—associated
Idiopathic chronic eosinophilic pneumonia
Smoking-Related
Desquamative interstitial pneumonia
Respiratory bronchiolitis

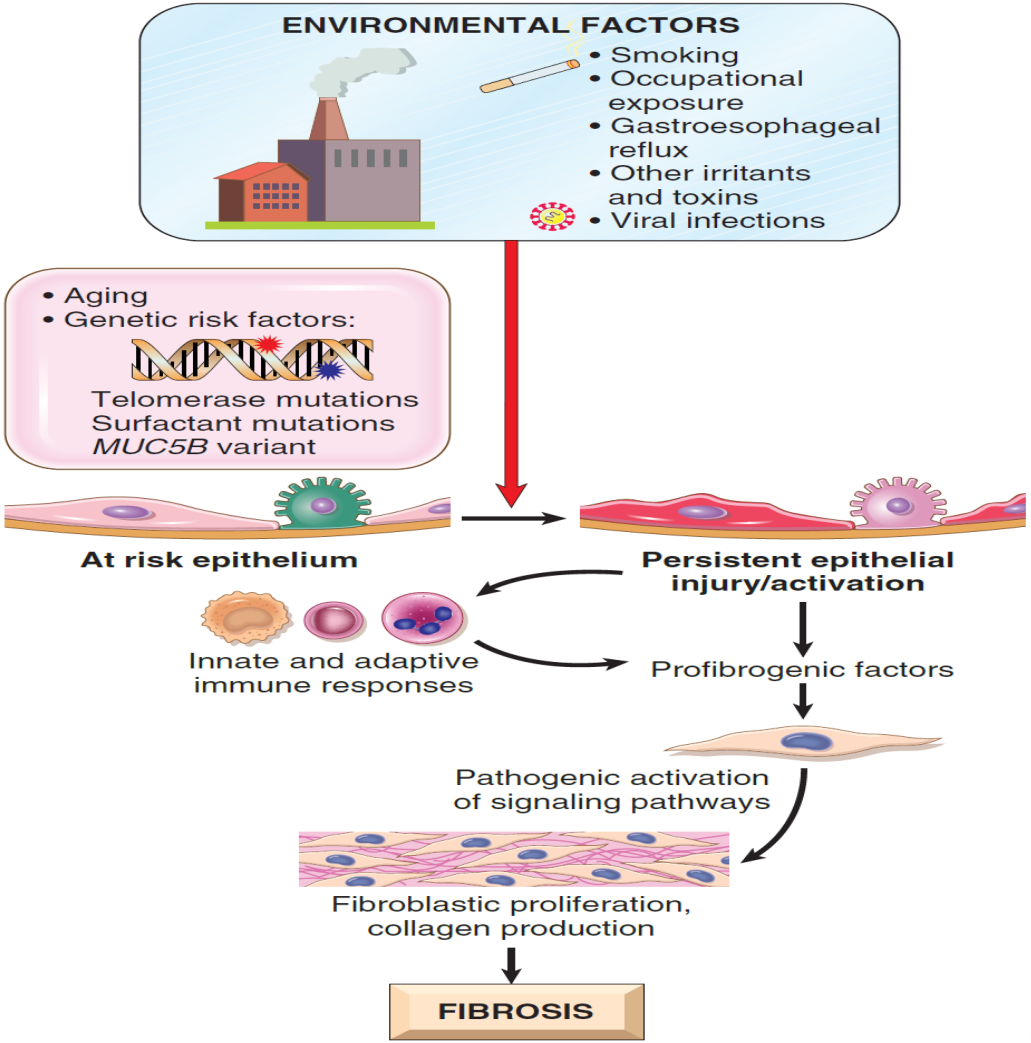
1.
Fibrosing Diseases

Idiopathic Pulmonary Fibrosis (Usual Interstitial Pneumonia)

- IPF is a pulmonary disorder of unknown etiology.
- Patchy, progressive bilateral interstitial fibrosis.
- The radiologic & histologic pattern of fibrosis is referred to as usual interstitial pneumonia (UIP) → required for the diagnosis of IPF.
- known as cryptogenic organizing alveolitis. (unknown etiology)
- Males > females, a disease of older adults, never before 50
- Diagnosis of exclusion → similar pathologic changes may be present in asbestosis, collagen vascular diseases, and other conditions

IPF – Pathogenesis

- The interstitial fibrosis that characterizes IPF is believed to result from repeated injury & defective repair of alveolar epithelium, often in a genetically predisposed individual



IPF – Morphology

- Grossly, the pleural surfaces of the lung are cobblestoned due to retraction of scars along the interlobular septa. The cut surface shows firm, rubbery, white areas of fibrosis.

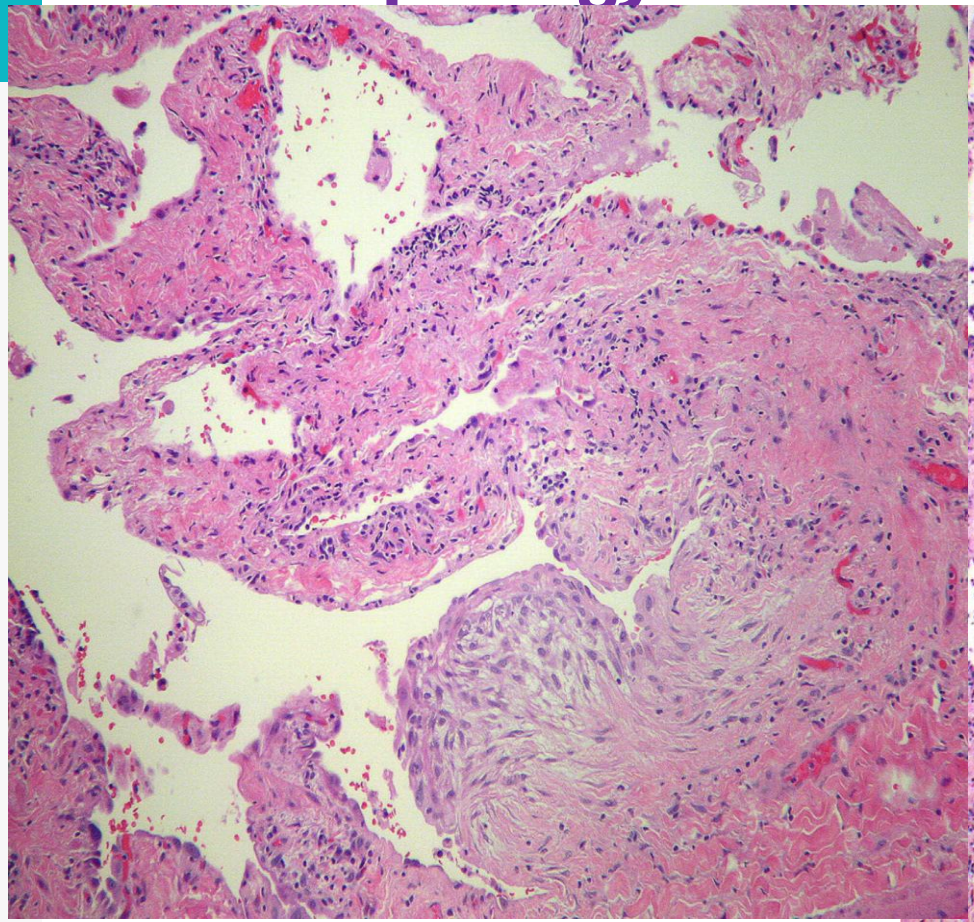
IPF – Morphology

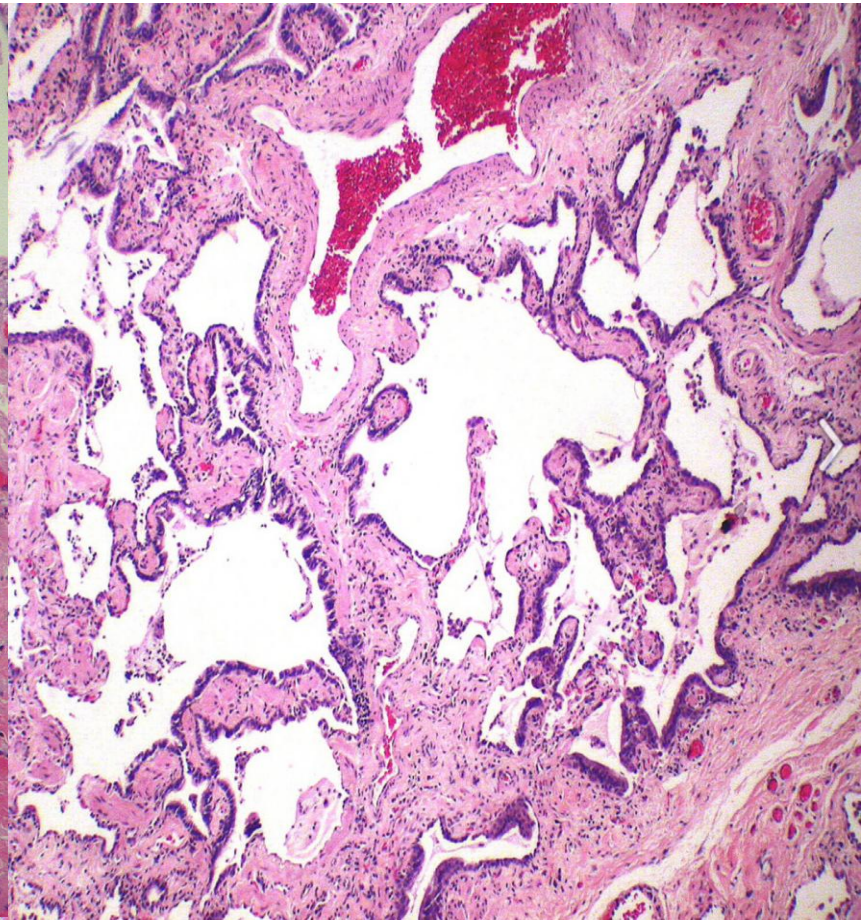
- Histologically, the hallmark is patchy interstitial fibrosis, varies in amount & worsens with time.
- within the **lower lobe, subpleural regions**, & along interlobular septa.
- The earliest lesions: exuberant fibroblastic proliferation (fibroblastic foci)
- Late: over time these areas become more collagenous & less cellular.

IPF – Morphology

- A typical finding: coexistence of both early & late lesions.
- Dense fibrosis causes collapse of alveolar walls and formation of cystic spaces (honeycomb fibrosis) lined by hyperplastic type II pneumocytes or bronchiolar epithelium.
- The interstitial inflammation consists of alveolar septal infiltrates of lymphocytes and occasional plasma cells, mast cells, and eosinophils.
- Secondary pulmonary hypertensive changes: (intimal fibrosis and medial thickening of pulmonary arteries) are often present.

IPF – Morphology





IPF – Clinical features

- Gradual onset of a nonproductive cough & progressive dyspnea.
- On P/E: characteristic “dry” or “velcro-like” crackles during inspiration.
- Cyanosis, cor pulmonale, & peripheral edema may develop in later stages of the disease.
- Clinical & radiologic findings: subpleural and basilar fibrosis, reticular abnormalities, and “honeycombing” are often diagnostic
- Overall prognosis remains poor, survival is only 3 to 5 years, & lung transplantation is the only definitive treatment.

Pneumoconiosis

- A term originally coined to describe lung disorders caused by inhalation of mineral dusts.
- Now include diseases induced by organic and inorganic particulates, by some chemist, regard chemical fume- and vapor induced lung diseases as pneumoconioses.
- The mineral dust pneumoconiosis most commonly caused by inhalation of coal dust, silica, and asbestos (exposure in the workplace).

Pneumoconiosis – Pathogenesis

- The reaction of the lung to mineral dusts depends on:

1. The size
2. Shape.
3. Solubility of the particles
4. Inherent proinflammatory properties.

- Silica, asbestos, & beryllium stimulate greater immune response than coal dust, resulting in fibrotic reactions at lower concentrations.

Pneumoconiosis – Pathogenesis

- The pulmonary alveolar macrophage is a key cellular element in the initiation and perpetuation of inflammation, lung injury, and fibrosis.
- Phagocytosis →particles activate inflammasome and induce production of the proinflammatory cytokine IL-1 & other→ initiate an inflammatory response →fibroblast proliferation & collagen deposition.
- Tobacco smoking worsens the effects of all inhaled mineral dusts, more so with asbestos than other particles.

A. Coal Workers' Pneumoconiosis

- The spectrum of lung findings in coal workers is wide:

1. Asymptomatic anthracosis: carbon pigment deposits without a perceptible cellular reaction.
2. simple CWP: macrophages accumulate with little to no pulmonary dysfunction
3. Complicated CWP or progressive massive fibrosis (PMF): fibrosis is extensive and lung function is compromised

- Less than 10% of cases of simple CWP progress to PMF
- Risk of CWP is higher in miners in areas in which coal has higher levels of contaminating chemicals & minerals.

A. Coal Workers' Pneumoconiosis – Morphology

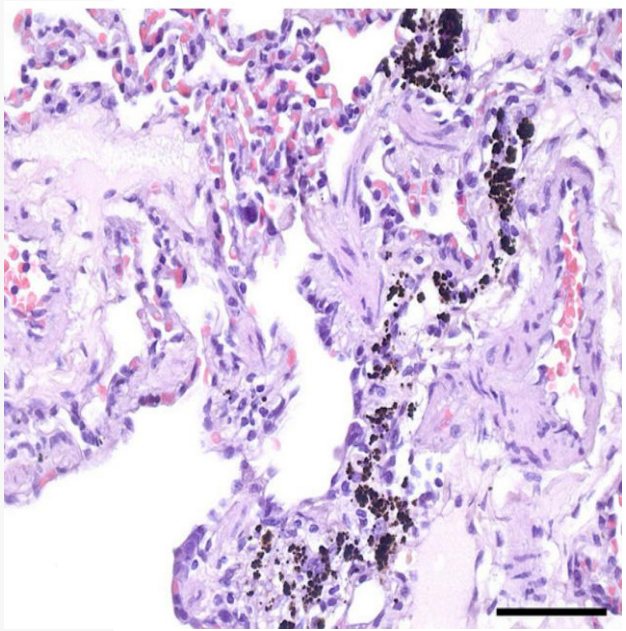
- Pulmonary anthracosis: Inhaled carbon pigment is engulfed by alveolar or interstitial macrophages → accumulate in the connective tissue along the pulmonary & pleural lymphatics & in draining lymph nodes.
- Simple CWP: coal macules & larger coal nodules.

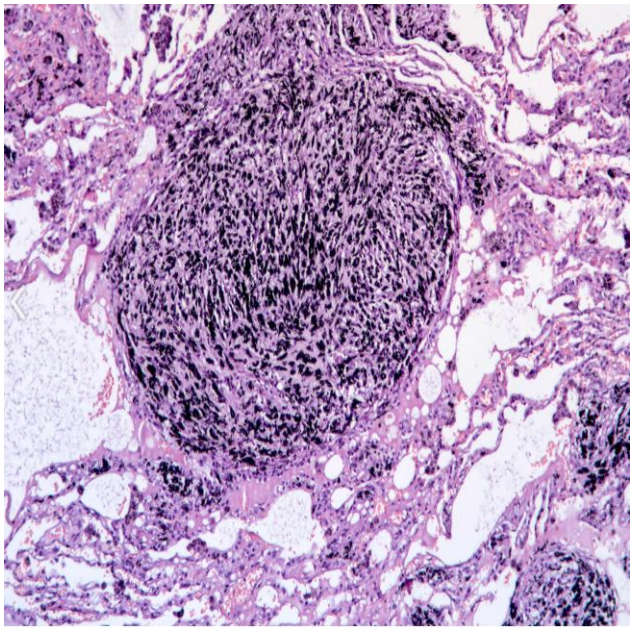
The coal macule consists of dust-laden macrophages & small amounts of collagen fibers arrayed in a delicate network. (upper lobes and upper zones of the lower lobes are more heavily involved).

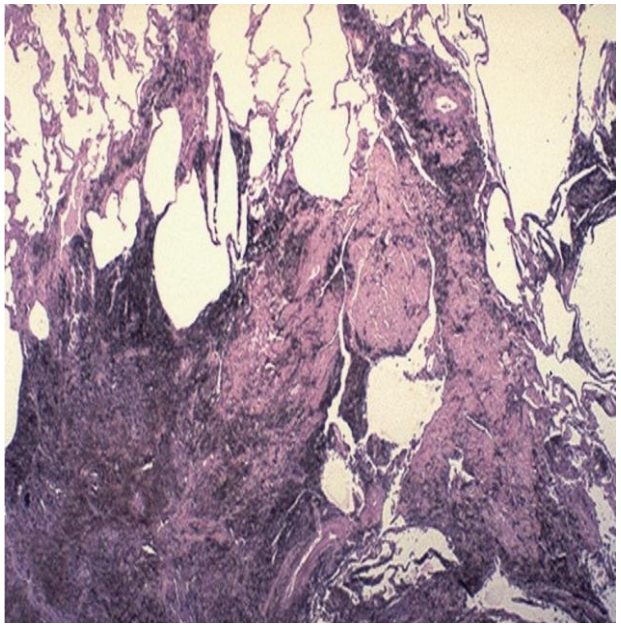
- Complicated CWP (PMF): coalescence of coal nodules & generally develops over many years.

Multiple, dark black scars larger than 2 cm consist of dense collagen and pigment.

A. Coal Workers' Pneumoconiosis – Morphology







A. CWP – Clinical features

- CWP usually is a benign disease that produces little defect in lung function.
- If PMF develops, there is increasing pulmonary dysfunction, pulmonary hypertension, and cor pulmonale.
- There is no increased frequency of lung carcinoma in coal miners, a feature that distinguishes CWP from both silica and asbestos exposures

B. Silicosis

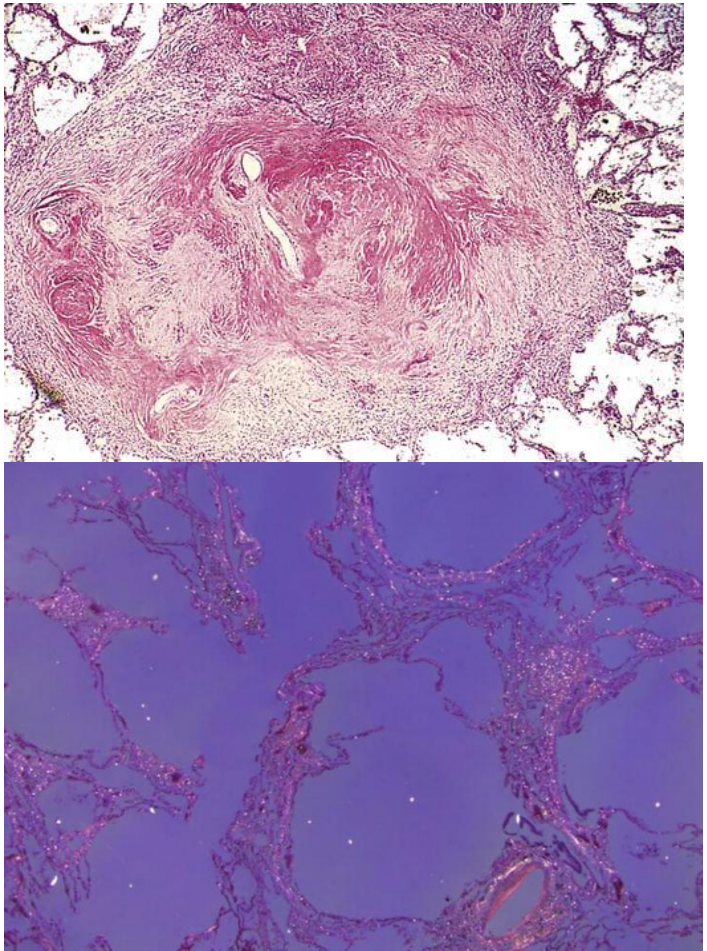
- Silicosis is currently the most prevalent chronic occupational disease in the world.
- It is caused by inhalation of crystalline silica, mostly in occupational settings (sandblasting and hardrock mining)
- Silica occurs in both crystalline and amorphous forms, but crystalline forms (e.g; quartz-most common) are by far the most toxic and fibrogenic.

B. Silicosis – Pathogenesis

- After inhalation, silica particles are ingested by alveolar macrophages → lysosomal damage → activation of the inflammasome → release of inflammatory mediators, including IL-1, TNF, lipid mediators, oxygen-derived free radicals, and fibrogenic cytokines.
- As the disease progresses, individual nodules may coalesce into hard, collagenous scars, with eventual progression to PMF.
- The intervening lung parenchyma may be compressed or overexpanded → honeycomb pattern may develop.

B. Silicosis – Morphology

- Silicotic nodules in early stages are tiny, barely palpable, discrete, pale-to-black (if coal dust is present) nodules in the upper zones of the lungs.
- Microscopically: Silicotic nodule demonstrates concentrically arranged hyalinized collagen fibers surrounding an amorphous center.
- The "whorled" appearance of collagen fibers is quite distinctive for silicosis.
- Nodules on polarized microscopy: weakly birefringent silica particles. .



B. Silicosis – Clinical

- Silicosis usually is detected in asymptomatic workers on routine chest radiographs → show a fine nodularity in the upper zones of the lung.
- Most patients do not develop shortness of breath until late in the course.
- Patients with PMF develop pulmonary hypertension & cor pulmonale as a result of chronic hypoxia–induced vasoconstriction and parenchymal destruction.
- Silicosis is associated with an increased susceptibility to tuberculosis

C. Asbestos-Related Diseases

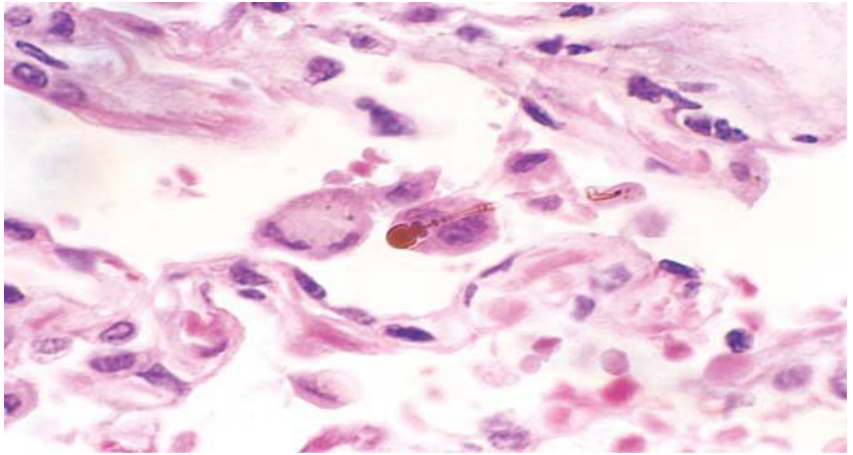
- Asbestos is a family of crystalline hydrated silicates with a fibrous geometry.
- Occupational exposure to asbestos is linked to: 1.Prenchymal interstitial fibrosis (asbestosis). 2. localized fibrous plaques. 3. pleural effusions. 4. lung carcinoma. 5. malignant pleural and peritoneal mesothelioma. 6. laryngeal carcinoma.
- Increased incidence of asbestos-related cancers in family members of asbestos workers.

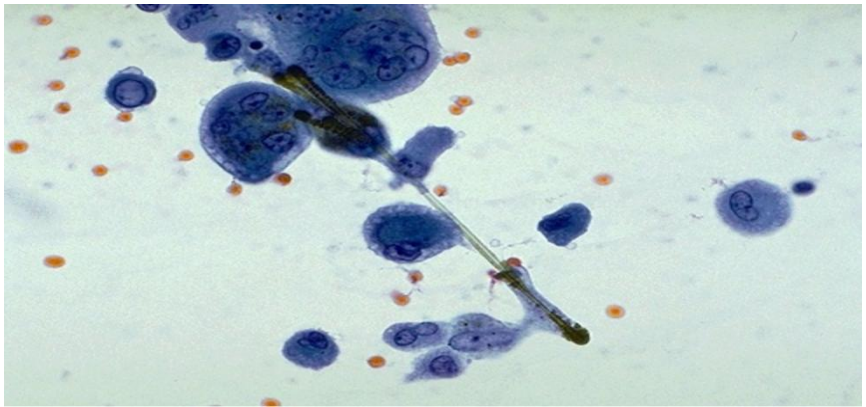
C. Asbestos – Pathogenesis

- Once phagocytosed by macrophages, asbestos fibers activate the inflammasome and damage phagolysosomal membranes, stimulating the release of proinflammatory factors and fibrogenic mediators.
- In addition to cellular and fibrotic lung reactions, asbestos probably also functions as both a tumor initiator and a promoter.

C. Asbestos – Morphology

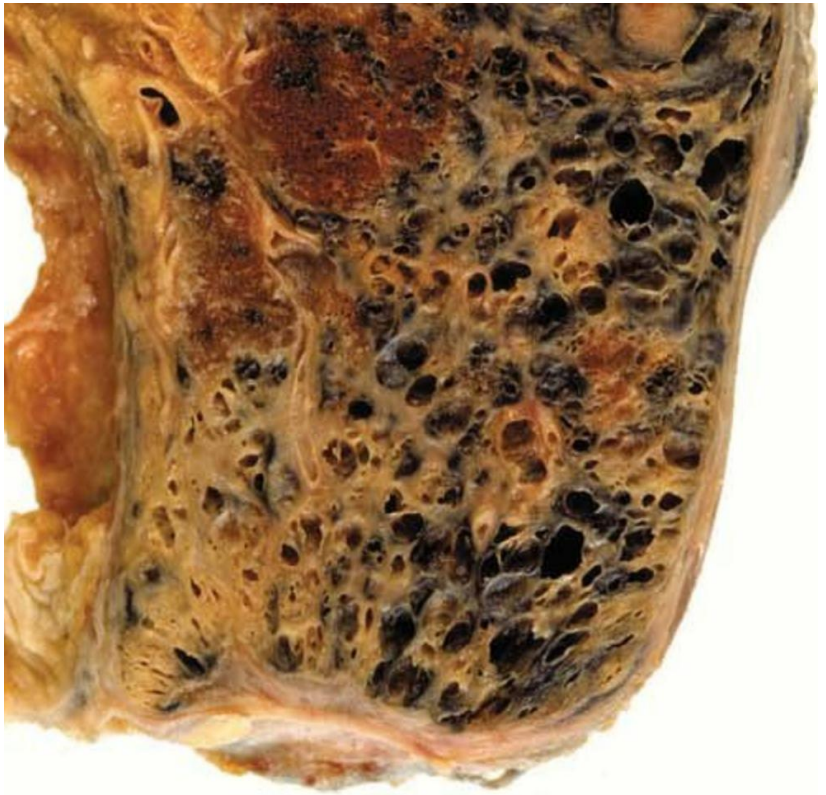
- Marked by diffuse pulmonary interstitial fibrosis, characterized by the presence of asbestos bodies→ golden brown, fusiform or beaded rods with a translucent center.
- Asbestos bodies formed when macrophages attempt to phagocytose asbestos fibers; the iron “crust” is derived from phagocyte ferritin.





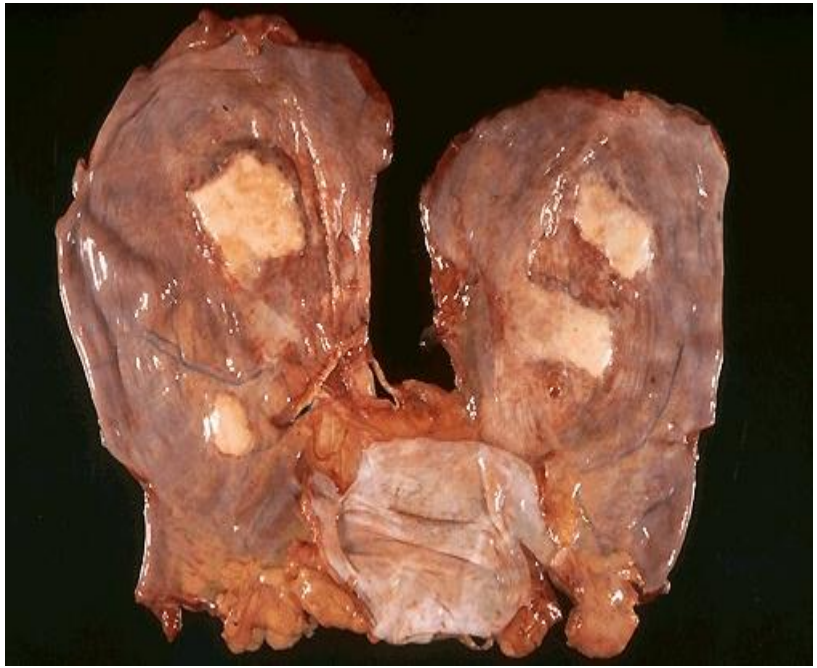
C. Asbestos – Morphology

- Asbestosis begins in the lower lobes and subpleurally, spreading to the middle and upper lobes of the lungs as the fibrosis progresses.
- Contraction of the fibrous tissue distorts the normal architecture, creating enlarged air spaces enclosed within thick fibrous walls; eventually, the affected regions become honeycombed



C. Asbestos – Morphology

- Pleural plaques: the most common manifestation of asbestos exposure.
- A well-circumscribed plaques of dense collagen often containing calcium.
- At the anterior & posterolateral aspects of the parietal pleura & over the domes of the diaphragm.
- Uncommon: pleural effusion or diffuse pleural fibrosis.



C. Asbestos – Clinical

- Progressively worsening dyspnea appears 10 to 20 years after exposure, accompanied by cough and production of sputum.
- The disease may remain static or progress to congestive heart failure, cor pulmonale, and death.
- Exposed people at markedly increased risk of lung carcinoma (poor prognosis) and malignant mesothelioma.
- Concomitant cigarette smoking greatly increases the risk for lung carcinoma

2. Granulomatous Diseases

Sarcoidosis

Sarcoidosis

- A multisystem disease of unknown etiology characterized by noncaseating granulomatous inflammation in many tissues and organs.
- Can manifest in many different ways: Bilateral hilar lymphadenopathy or lung involvement (or both), visible on chest radiographs, is the major finding at presentation in most cases.
- Eye and skin involvement each occurs in about 25%

Sarcoidosis – Pathogenesis

- Etiology of sarcoidosis remains unknown, evidence suggest that it is a disease of disordered immune regulation in genetically predisposed individuals exposed to undefined environmental agents.
- Immunologic abnormalities in sarcoidosis suggest the development of a cell-mediated response to an unidentified antigen → driven by CD4+ helper T cells

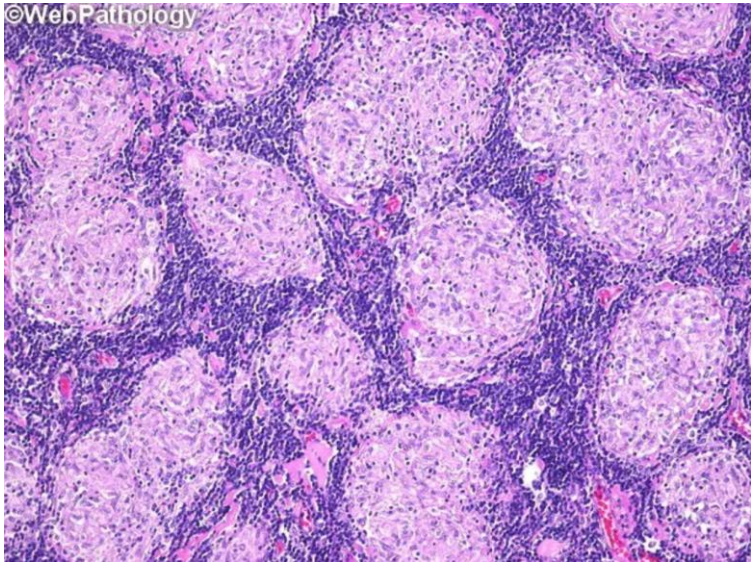
Sarcoidosis – Pathogenesis

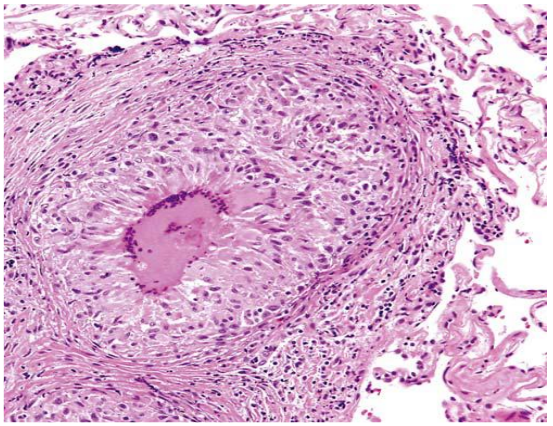
- CD4+ clues:

1. Intraalveolar and interstitial accumulation of CD4+ TH1 cells.
2. Low peripheral CD4+ T cell.
3. Increases in TH1 cytokines such as IL-2 and IFN-γ, resulting in T cell proliferation and macrophage activation, respectively.
4. Oligoclonal expansion of CD4+ Th1 T cells within the lung as determined by analysis of T-cell receptor rearrangements

Sarcoidosis – Morphology

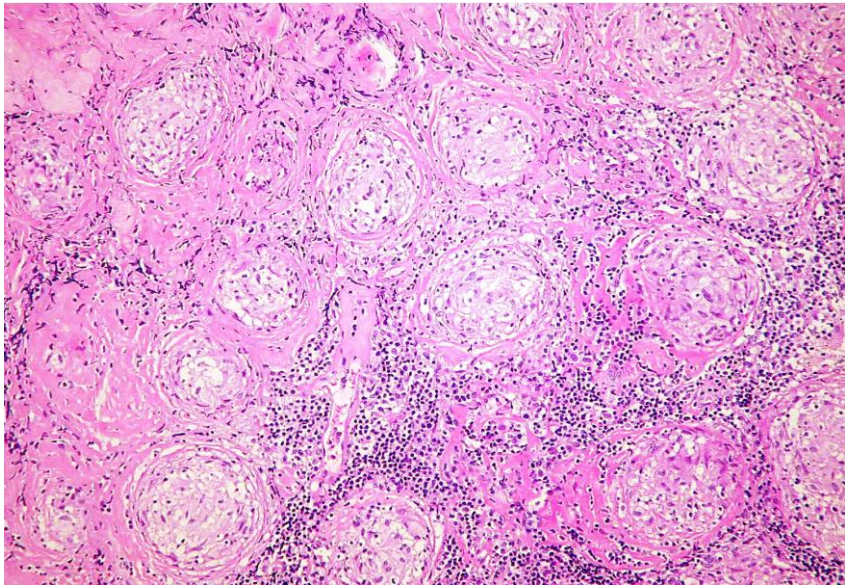
- The cardinal histopathologic feature of sarcoidosis is the nonnecrotizing epithelioid granuloma.
- This is a discrete, compact collection of epithelioid macrophages rimmed by an outer zone rich in CD4+ T cells.
- It is not uncommon to see intermixed multinucleate giant cells formed by fusion of macrophages.





Sarcoidosis – Morphology

- Early on, a thin layer of laminated fibroblasts is found peripheral to the granuloma; over time, these proliferate and lay down collagen that replaces the entire granuloma with a hyalinized scar.

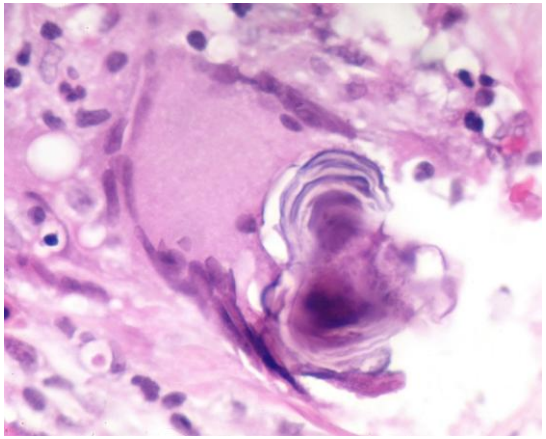


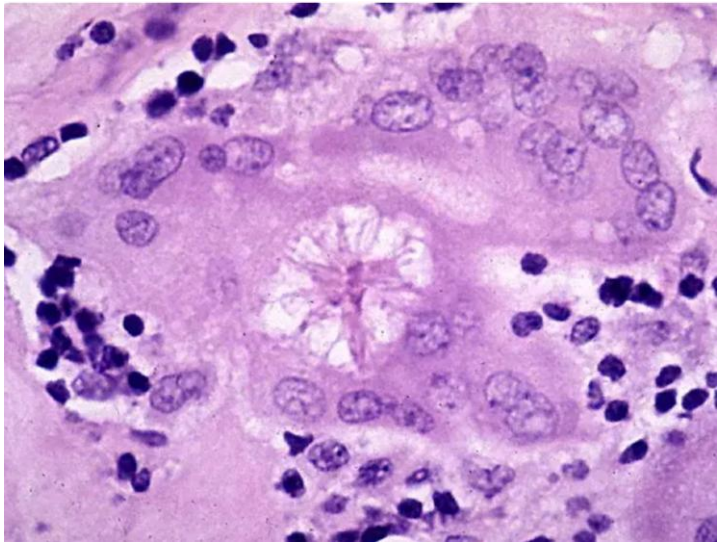
Sarcoidosis – Morphology

- Two other microscopic features sometimes seen in granulomas:

1. Schaumann bodies, laminated concretions composed of calcium & proteins.
2. Asteroid bodies, stellate inclusions enclosed within giant cells.

- not required for diagnosis of sarcoidosis, & may be found in granulomas seen in other disorders



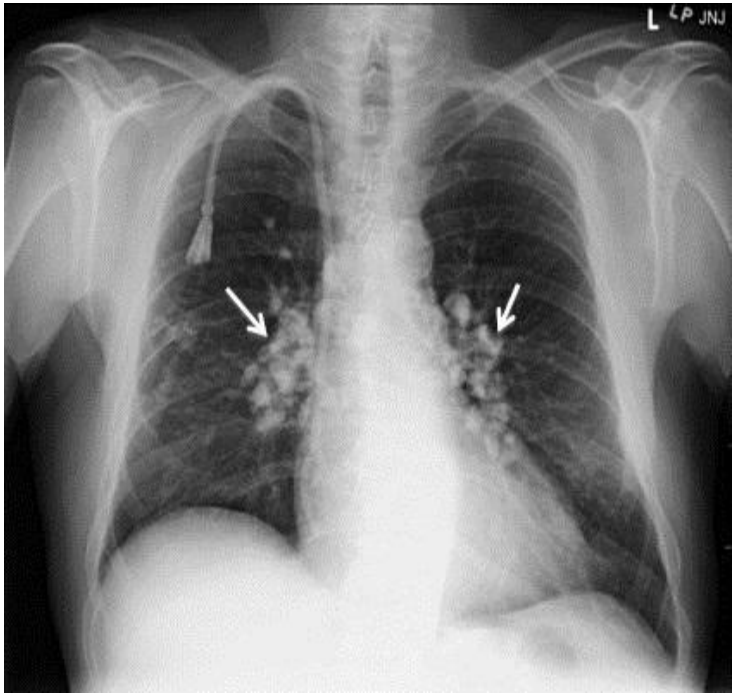


Sarcoidosis – Clinical

- The lungs are involved at some stage of the disease in 90% of patients.
- The granulomas predominantly involve the interstitium rather than air spaces with tendency to localize in the connective tissue around bronchiolesand pulmonary venules and in the pleura (“lymphangitic” distribution).
- In 5% to 15% of patients, the granulomas are eventually replaced by diffuse interstitial fibrosis, resulting in a so-called “honeycomb lung”

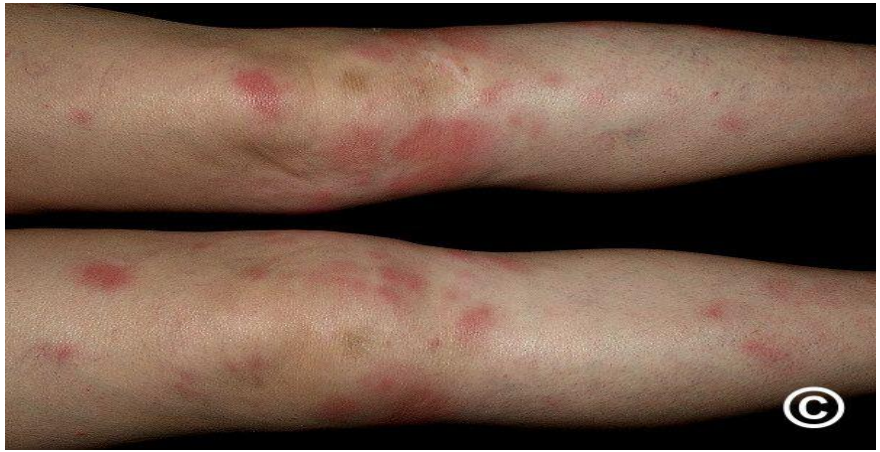
Sarcoidosis – Clinical

- Intrathoracic hilar and paratracheal lymph nodes are enlarged in 75-90% of patients; nodes are painless and have a firm, rubbery texture. Unlike in tuberculosis, lymph nodes in sarcoidosis are “nonmatted” (nonadherent) & do not undergo necrosis.



Sarcoidosis – Clinical

- Skin lesions are encountered in approximately 25% of patients: Erythema nodosum, a hallmark of acute sarcoidosis, presents as bilateral raised, red, tender nodules on the anterior aspects of the legs. It is a form of panniculitis.



Sarcoidosis – Clinical

- Many asymptomatic, discovered on routine chest films as bilateral hilar adenopathy or as an incidental finding at autopsy.
- In some patients, symptoms of peripheral lymphadenopathy, cutaneous lesions, eye involvement, splenomegaly, or hepatomegaly.
- Respiratory symptoms (shortness of breath, dry cough, or vague substernal discomfort). ☒
- Definitive diagnostic test for sarcoidosis does not exist, and establishing a diagnosis requires the presence of clinical and radiologic findings. (Exclusion)
- Sarcoidosis follows an unpredictable course characterized by either progressive chronicity or periods of activity interspersed with remissions

‘ Thank you

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