PATHOLOGY OF THE REPIRATORY SYSTEM

LEC 3

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Lung Pathology Outline

- Congenital anomalies
- Atelectasis
- Acute respiratory distress syndrome
- Diffuse lung diseases
- Pulmonary disease of vascular origin
- Infections
- Lung tumors

Restrictive Lung Diseases

- A heterogeneous group of disorders characterized by **bilateral,** often **patchy, pulmonary fibrosis** mainly affecting the walls of them alveoli

➢The hallmark of these disorders is **reduced compliance** (i.e., more pressure is required to expand the lungs because they are stiff); total lung capacity (**TLC) is reduced** (while in obstructive lung diseases FEV1 is reduced)

➢Occur in two general conditions:

- Chest wall disease: the defect outside the lung (e.g., neuromuscular diseases such as poliomyelitis, severe obesity, pleural diseases, and kyphoscoliosis)
- Chronic interstitial and infiltrative lung diseases: e.g. pneumoconiosis, interstitial fibrosis , sarcoidosis ,connective tissue diseases.

➢Clinical features:

- Dyspnea, tachypnea, cyanosis, without wheezing or other evidence of airway obstruction.

➢**Pulmonary function test (PFT):** reductions in diffusion capacity, lung volume, and lung compliance.

➢**Chest radiographs**: bilateral lesions appear as small nodules, irregular lines, or ground-glass shadows, all corresponding to areas of interstitial fibrosis.

- Although the entities can often be distinguished in their early stages, **advanced forms** are hard to differentiate because all result in diffuse scarring of the lung, often referred to as **end-stage lung or honeycomb lung.**

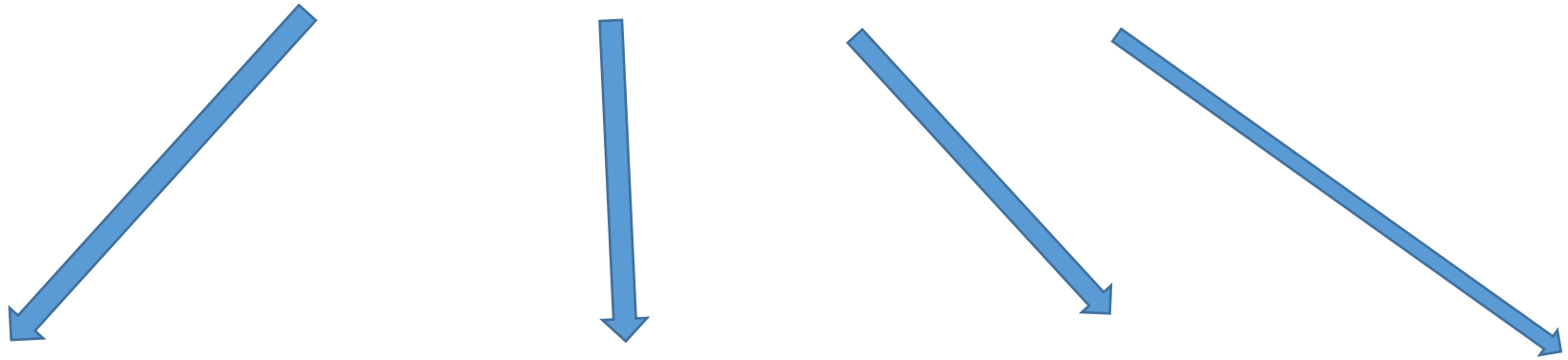
➢Complications:

1- Secondary pulmonary hypertension

2- Right sided heart failure (cor-pulmonale) may result.

- **Major Categories of Restrictive Lung Diseases:**
- **FIBROSING**
- **GRANULOMATOUS**
- **EOSINOPHILIC**
- **SMOKING RELATED**

Major Categories of Restrictive Lung Disease

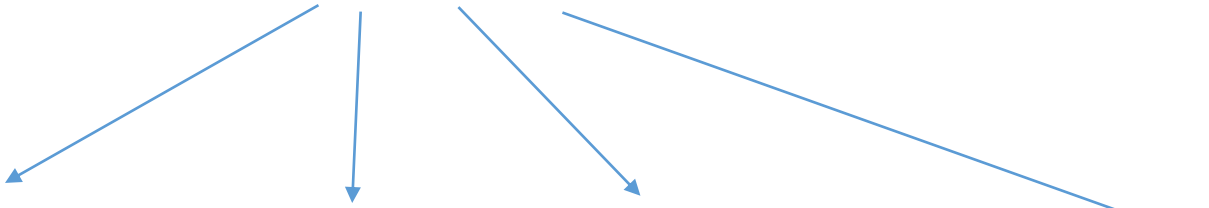


FIBROSING

GRANULOMATOUS
sarcoidosis

EOSINOPHILIC

SMOKING RELATED

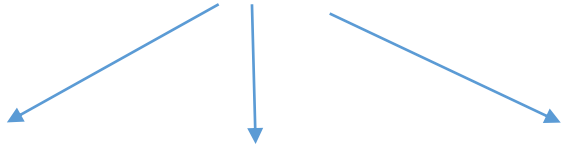


Idiopathic Pulmonary Fibrosis (IPF)

Other Fibrosing Diseases

Drug- and Radiation-Induced Pulmonary Disease

Pneumoconioses



Coal Workers Pneumoconiosis

Silicosis

Asbestosis

Fibrosing Diseases

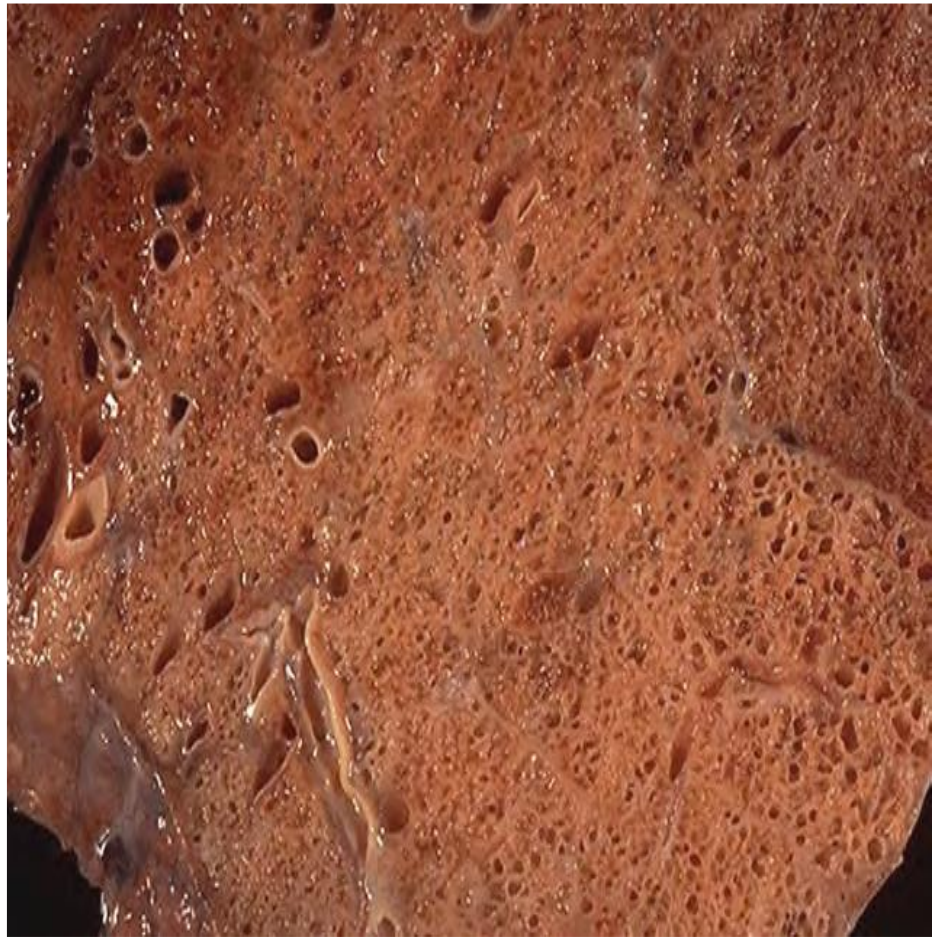
❖Idiopathic Pulmonary Fibrosis (IPF)

- Also called **cryptogenic fibrosing alveolitis; Usual interstitial pneumonia**
- It is a pulmonary disorder **of unknown etiology** that is characterized by patchy, progressive bilateral interstitial fibrosis.
- Males are affected more often than females.
- It is a **disease of aging,** virtually never occurring before 50 years of age.
- Because similar pathologic changes in the lung may be present in entities such as **asbestosis**, **collagen vascular diseases**, and **other conditions**; Therefore, IPF is a diagnosis of exclusion.

Pathogenesis:

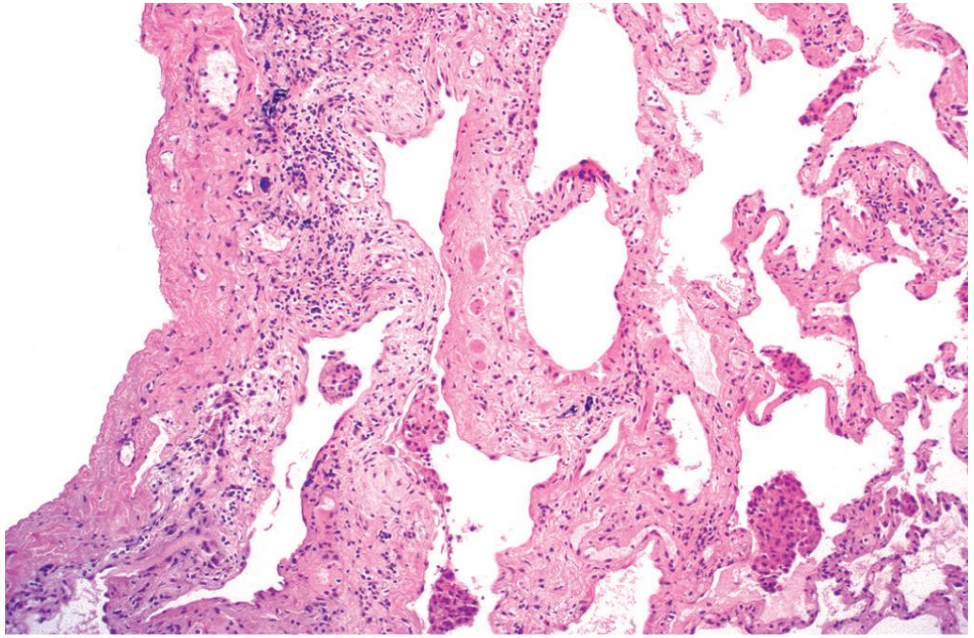
- The exact cause of idiopathic pulmonary fibrosis is unknown, recurrent Injuries to alveolar epithelial cells by environmental exposures like cigarette smoking , air pollution or in certain occupations in genetically predisposed individuals lead to **increased local production of fibrogenic cytokines**, such as **TGF-β** that is secreted either from injured epithelial cells or from immune cells as part of the host response to epithelial cell damage.

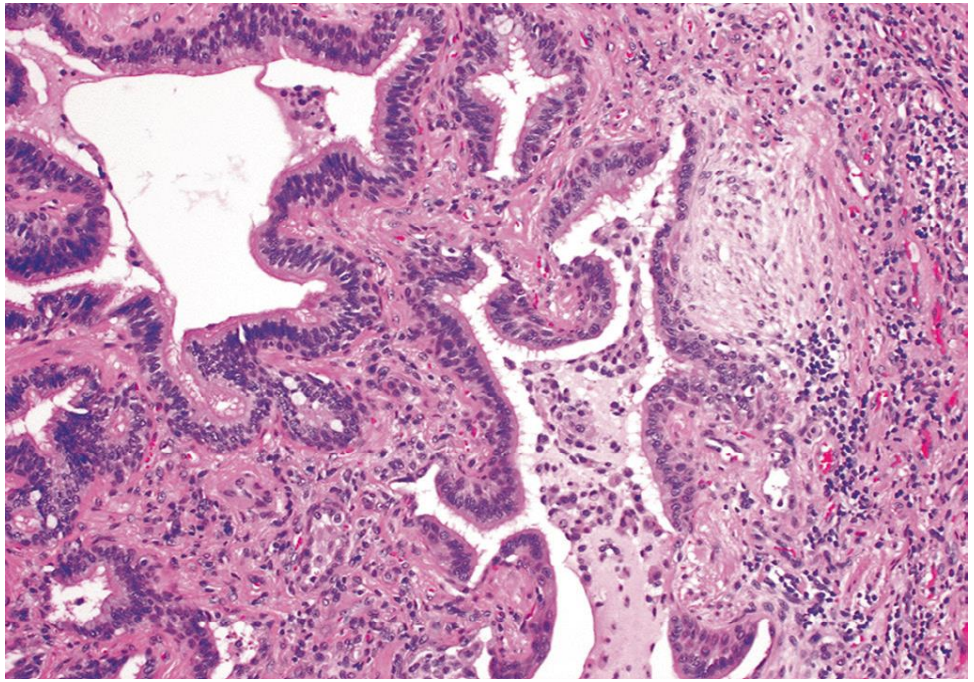
- **Grossly:**
- The **pleural surfaces** of the lung have cobblestone appearance because of the retraction of scars along the interlobular septa.
- The cut surface shows firm, rubbery white areas of fibrosis.



"Honeycomb lung" because of the appearance of the irregular residual small dilated airspaces between bands of dense fibrous interstitial connective tissue.

- **The histologic hallmark is:**
  - Patchy interstitial fibrosis, which varies in intensity (new, cellular **fibroblastic foci** with moderate inflammation coexist with older, more densely fibrotic areas).
  - The dense fibrosis causes collapse of alveolar walls and formation of cystic spaces lined by hyperplastic type II pneumocytes (**honeycomb lung**).
  - The interstitial inflammation usually is patchy and consists of an alveolar septal infiltrate of inflammatory cells mainly lymphocytes.





Clinical Features

- IPF begins with gradually increasing dyspnea on exertion and dry cough.
- Hypoxemia, cyanosis, and clubbing occur late in the course.
- The course in individual patients is unpredictable.

Prognosis:

- Usually there is slowly progressive respiratory failure, but some patients have acute exacerbations and follow a rapid clinical course.

Treatment:

- Lung transplantation is the only definitive therapy; however TGF-β antagonist, shown to slow disease progression and represent the first effective targeted therapies for IPF.

❖ Other Fibrosing Diseases

- Other **rare** pulmonary diseases **associated with fibrosis** need to be considered in the differential diagnosis of IPF

➢ **Nonspecific interstitial pneumonia (NSIP)**

- Is a diffusely fibrosing disease of unknown etiology, manifesting with chronic dyspnea and cough. The histologic pattern shows chronic inflammation and/or fibrosis that is patchy but uniform in the areas involved without the heterogeneity seen in UIP. The prognosis is better than UIP.

➢ **Cryptogenic organizing pneumonia.**

- Has an unknown etiology. It presents with cough and dyspnea, and chest radiographs demonstrate subpleural or peribronchial patchy areas of consolidation. Histologically, there are loose fibrous tissue plugs (Masson bodies) within bronchioles, alveolar ducts, and alveoli, but there is no interstitial fibrosis or honeycombing. Some patients recover spontaneously while most require treatment, usually with oral steroids.

➢ **Pulmonary involvement in connective tissue diseases**

- Also in the differential diagnosis of fibrosing pulmonary disorders are several connective tissue diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, and scleroderma). Prognosis is variable (depending on the underlying disease) but is better than for idiopathic UIP.

❖Drug- and Radiation-Induced Pulmonary Disease

- **Drugs** can cause a variety of acute and chronic alterations in respiratory structure and function. For example, bleomycin, an anti-cancer agent, **causes pneumonitis and interstitial fibrosis** as a **result of direct toxicity of the drug** and by stimulating the influx of inflammatory cells into the alveoli.
- Amiodarone, an anti-arrhythmic agent, also is associated with risk for **pneumonitis and fibrosis.**
- **Radiation pneumonitis** is a well-known complication of irradiation of pulmonary and other thoracic tumors. Acute radiation pneumonitis, which typically **occurs 1 to 6 months after therapy** in as many as **20%** of the patients, is manifested by fever, dyspnea out of proportion to the volume of irradiated lung, pleural effusion, and pulmonary infiltrates in the irradiated lung bed. These signs and symptoms may resolve with corticosteroid therapy or progress to chronic radiation pneumonitis, associated with pulmonary fibrosis.

❖ Pneumoconioses

- **Interstitial fibrosis of lung due to inhalation of mineral dusts**
- The three most common of these result from exposure to:
- **Coal dust,**
- **Silica, and**
- **Asbestos**;
- nearly always due to exposure in the **workplace.**

Pathogenesis

- The reaction of the lung to mineral dusts depends on the size, shape, solubility, and reactivity of the particles.
- Particles that are **1 to 5 µm** are the most dangerous, because they lodge at the bifurcation of the distal airways.
- Coal dust is relatively inert, and large amounts must be deposited in the lungs before the disease is clinically apparent.
- Silica, asbestos are more reactive than coal dust, resulting in fibrotic reactions at lower concentrations.
- The pulmonary alveolar macrophage play central role in the initiation and progression of lung injury and fibrosis.
- Tobacco smoking **worsens** the effects of all inhaled mineral dusts, but **particularly asbestos** particle.

1. Coal Workers' (miners lung , black lung) Pneumoconiosis:

- The **spectrum of lung findings** in coal workers includes:

a. Asymptomatic anthracosis;

- Mild asymptomatic mild type of pneumoconiosis
- In which pigment accumulates without cellular reaction (NO fibrosis). It is also commonly seen in all urban dwellers and tobacco smokers. Inhaled carbon pigment is engulfed by alveolar or interstitial macrophages, which then accumulate in the connective tissue.

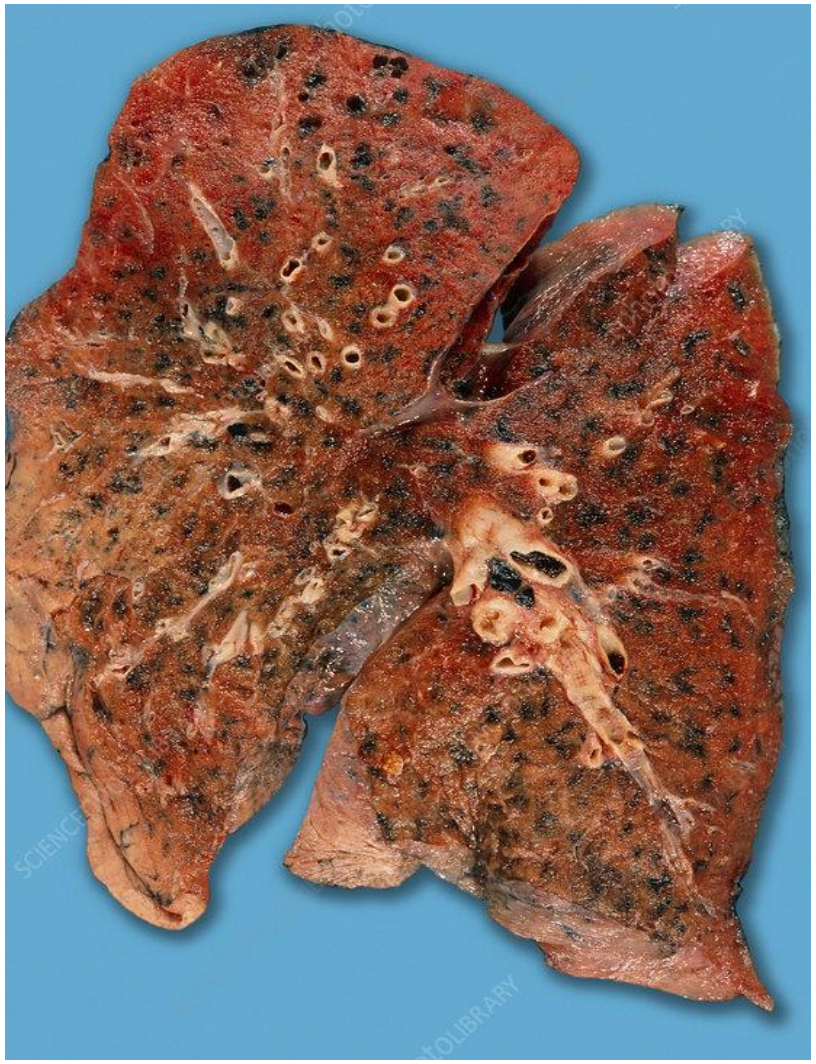
b. Simple coal workers' pneumoconiosis;

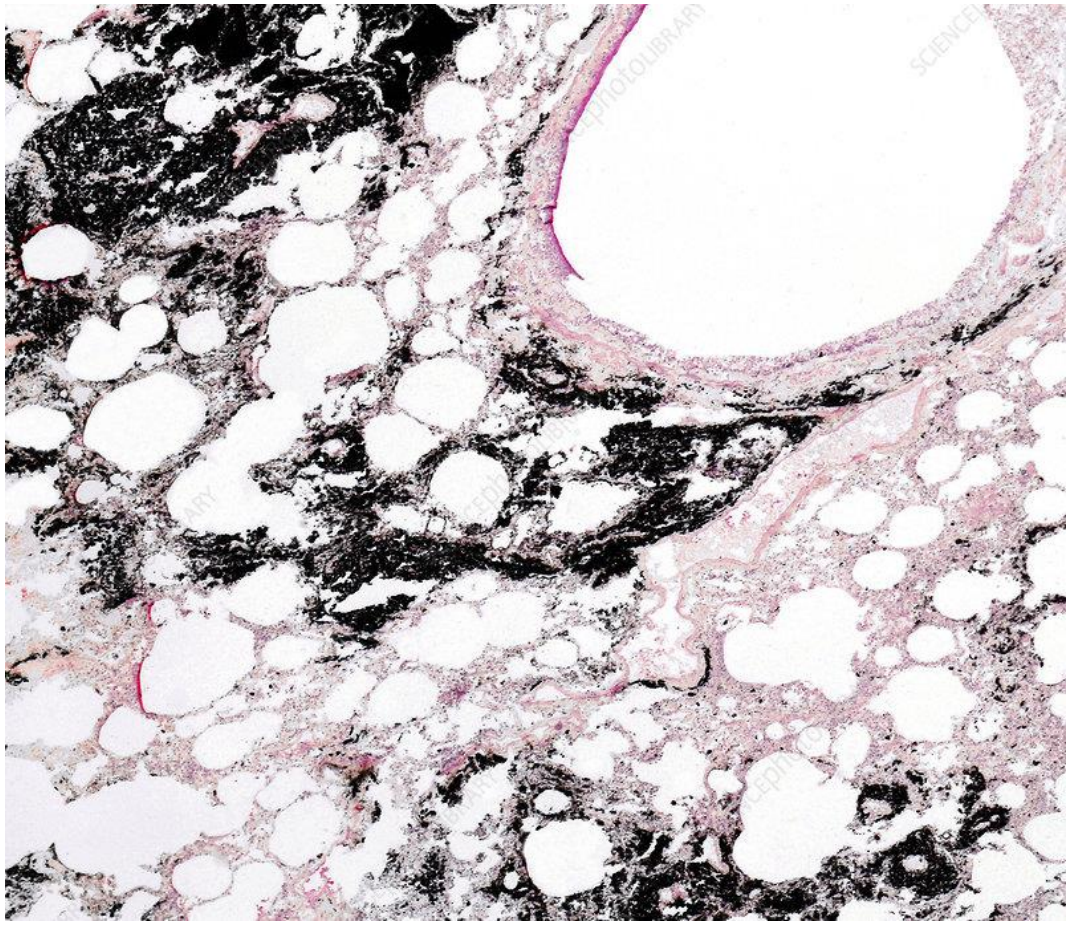
- Is characterized by formation of fibrotic nodules

c. Progressive massive fibrosis develops in **10%** of those with the above; it occurs through the **coalescence of the fibrotic nodules**.

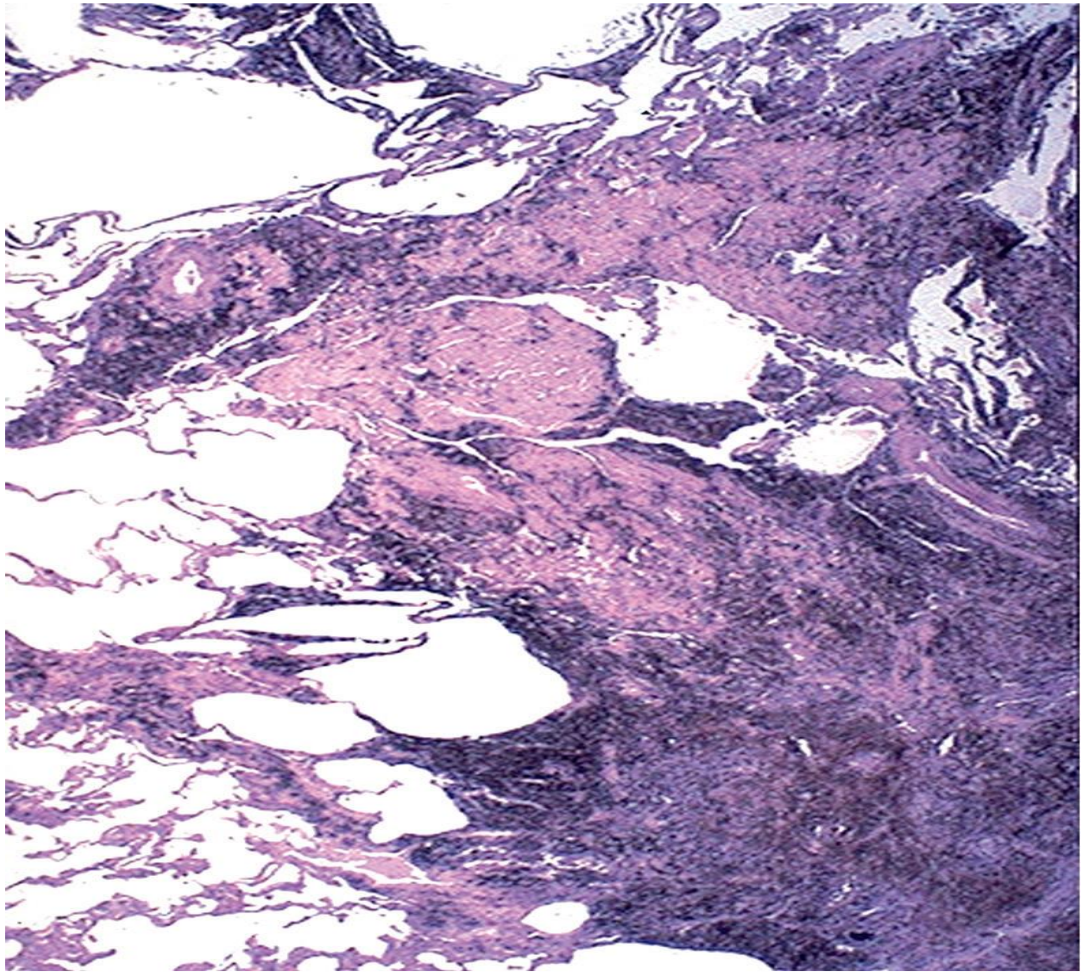
- **There is NO increased frequency of bronchogenic carcinoma**

Anthracosis





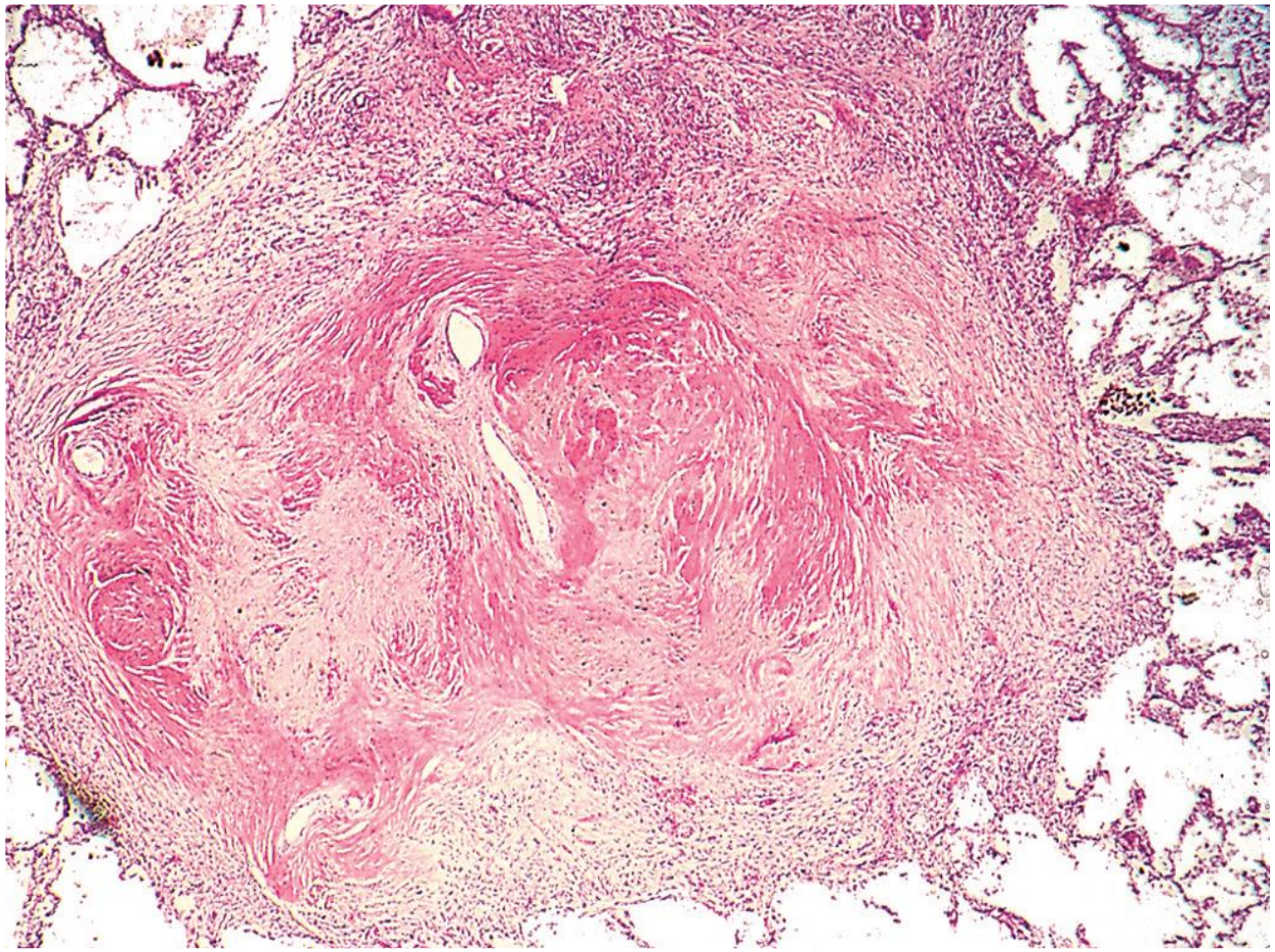
Asymptomatic anthracosis: pigment accumulates in the lungs without cellular reaction.



Progressive massive fibrosis in a coal worker.
A large amount of black pigment is associated with fibrosis

2- Silicosis:

- Silicosis is the most common chronic occupational disease in the world.
- It is caused by inhalation of silica crystals mostly quartz
- The condition is characterized by the formation of silicotic nodules involving the **upper zones of the lungs.**
- Silicosis is associated with an increased susceptibility to tuberculosis because crystalline silica inhibits the ability of pulmonary macrophages to kill phagocytosed mycobacteria
- Silica from occupational sources is carcinogenic in humans. However, this subject continues to be controversial.



Coalescent collagenous silicotic nodules.

3. Asbestosis and Asbestos-Related Diseases

- Asbestos is a family of silicate crystals with a fibrous spatial arrangement.
- It cause a **wide spectrum of diseases** depending on concentration, size, shape, and solubility
- Occupational exposure to asbestos is associated with :

1- Localized fibrous plaques or, rarely, diffuse pleural fibrosis

2- Recurrent pleural effusions.

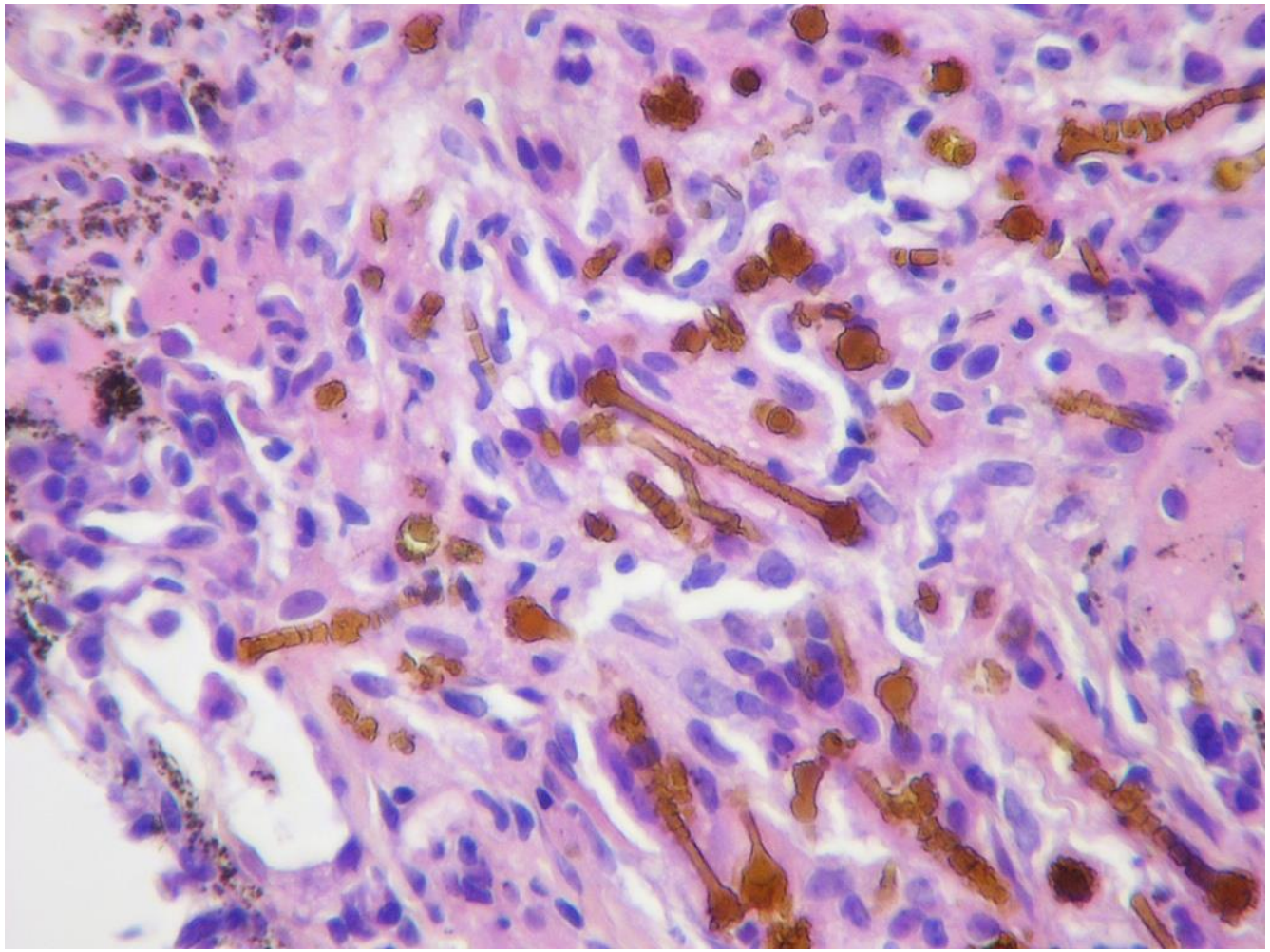
3- Parenchymal interstitial fibrosis

4- Lung carcinoma

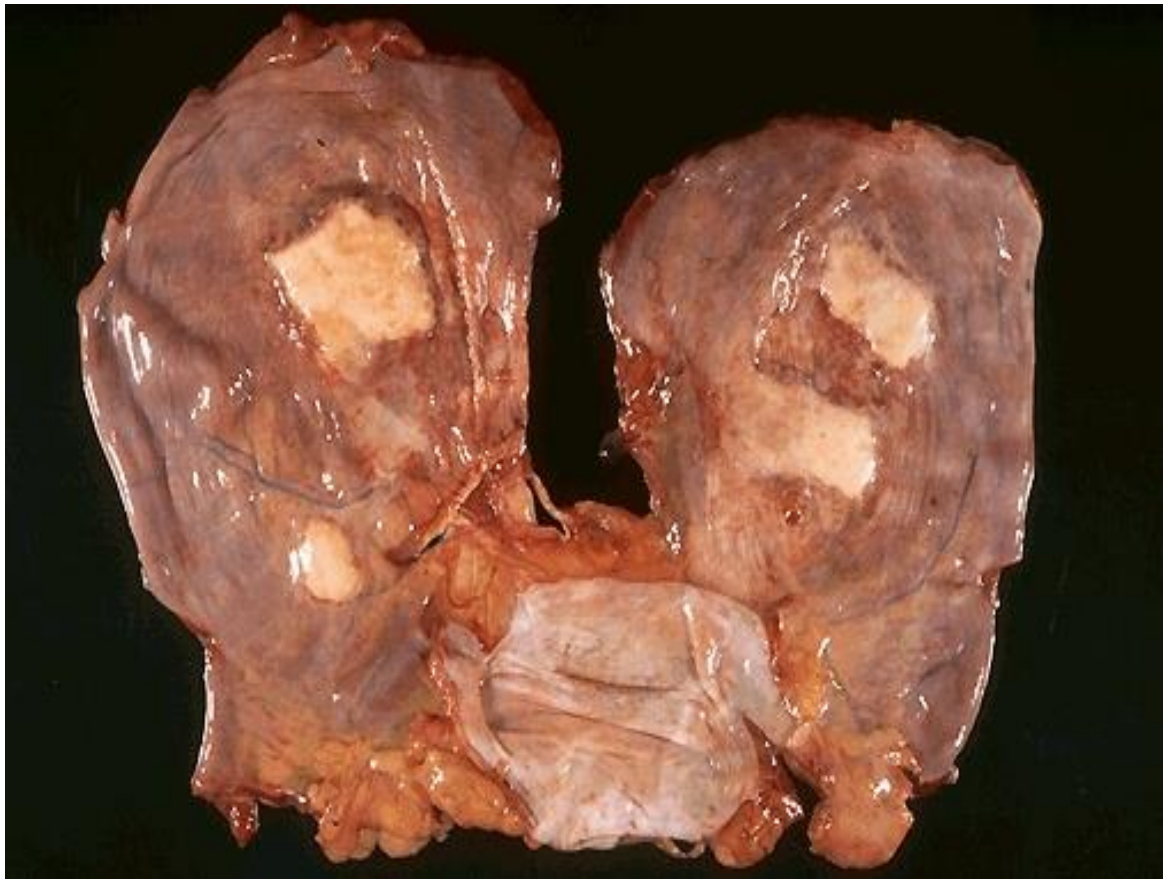
5- Mesothelioma (pleural, peritoneal)

6- Laryngeal, ovarian, and perhaps other extrapulmonary neoplasms, including colon carcinoma

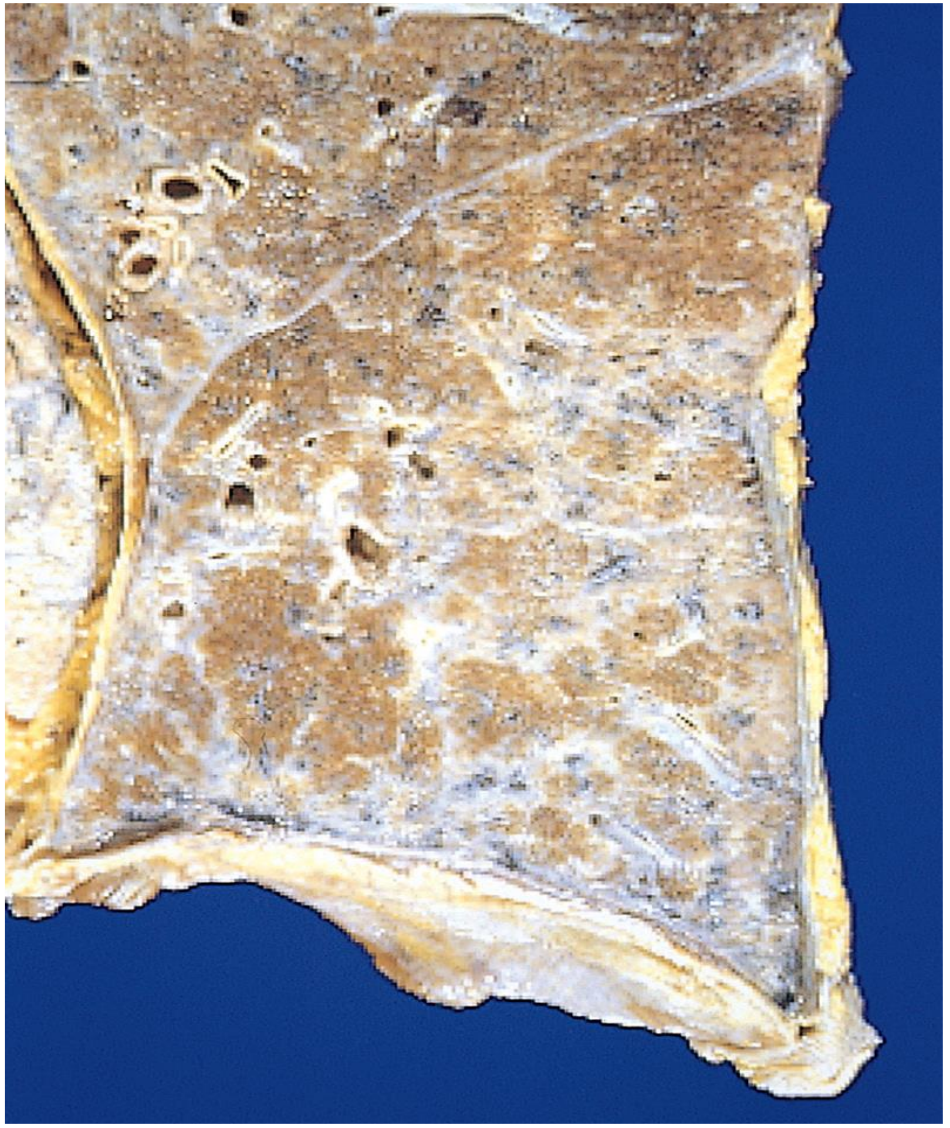
- **Asbestosis** : diffuse pulmonary **interstitial fibrosis** & characteristically shows the presence of **asbestos bodies**, which are seen as golden brown, beaded rods. They consist of asbestos fibers coated with an iron-protein material.
- **Pleural plaques** are the most common manifestation of asbestos exposure and are **well-circumscribed patches of dense collagen** that develop most frequently on the **parietal pleura** and over the domes of the diaphragm.
- The risk of bronchogenic carcinoma is increased about **five times** for asbestos workers.
- The risk for mesotheliomas, normally a very rare tumor, is more than **1000 times** greater.
- Concomitant **cigarette smoking** greatly increases the risk of **bronchogenic carcinoma** but not that of mesothelioma.
- The carcinoma & mesothelioma associated with asbestos exposure have a particularly **poor prognosis.**



Asbestos bodies: golden brown, beaded rods.
They consist of asbestos fibers coated with an iron-protein material.



Asbestosis with fibrous pleural plaque well-circumscribed patches of dense collagen that develop most frequently on the parietal pleura and over the domes of the diaphragm.



Asbestosis. Markedly thickened visceral pleura covers the lateral and diaphragmatic surface of the lung. Note also severe interstitial fibrosis diffusely affecting the lower lobe of the lung.

Granulomatous Diseases

❖Sarcoidosis:

- Is a systemic granulomatous disease of unknown etiology characterized by noncaseating granulomas in many tissues and organs.
- Other diseases, including **mycobacterial or fungal infections** also produce noncaseating granulomas; therefore, the histologic diagnosis of sarcoidosis is one of exclusion.
- Bilateral hilar lymphadenopathy &/or parenchymal lung involvement is the major presenting manifestations in 90% of cases.
- Spleen and liver are microscopically affected in 75% of patients.
- Eye and skin involvement are also frequent and may occasionally be the presenting feature of the disease.
- Sarcoidosis occurs throughout the world, affecting both sexes and all races and ages. There is a predilection for adults younger than 40 years of age.
- Sarcoidosis is one of the few pulmonary diseases **with a higher prevalence among nonsmokers.**
- Although the etiology of sarcoidosis remains unknown, it is probably a disease of disordered immune regulation in genetically predisposed individuals exposed to certain environmental agents.

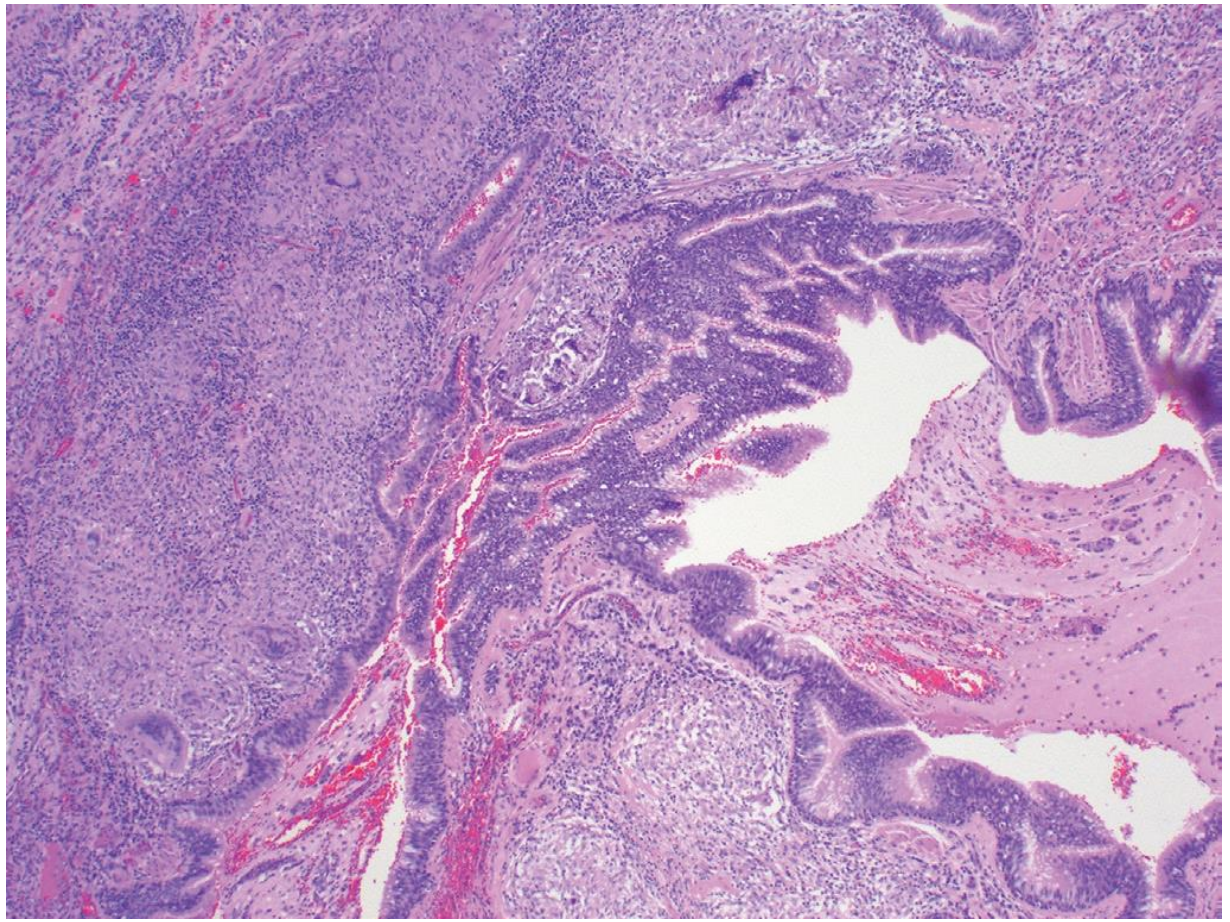
• Pathologic features

- **Noncaseating epithelioid granulomas** are the histopathologic marker of sarcoidosis . composed of aggregates of tightly clustered epithelioid macrophages, often with giant cells.
- Two other microscopic features are sometimes seen in the granulomas:

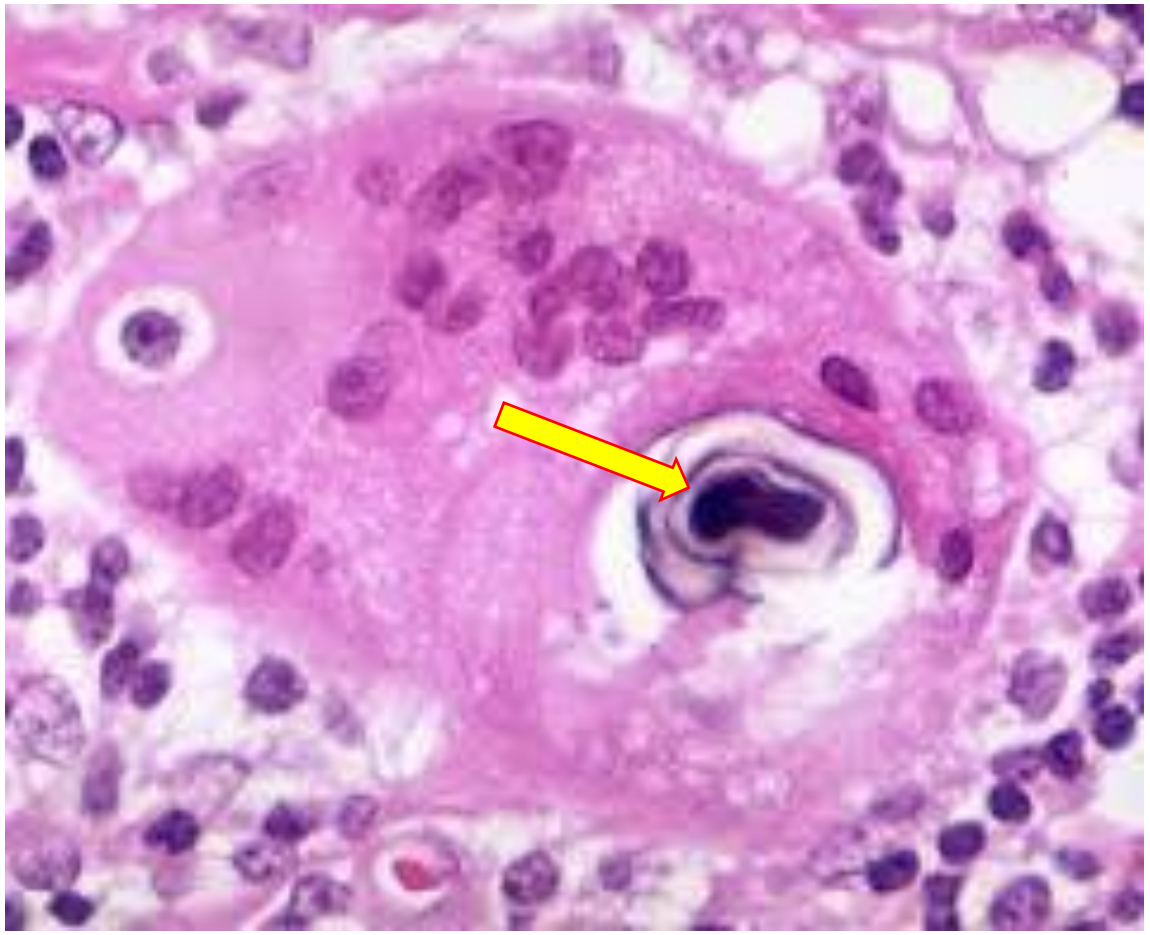
1. Schaumann bodies, laminated concretions composed of calcium and proteins;

2. Asteroid bodies, stellate inclusions enclosed within giant cells. They are neither specific nor required to make the diagnosis.

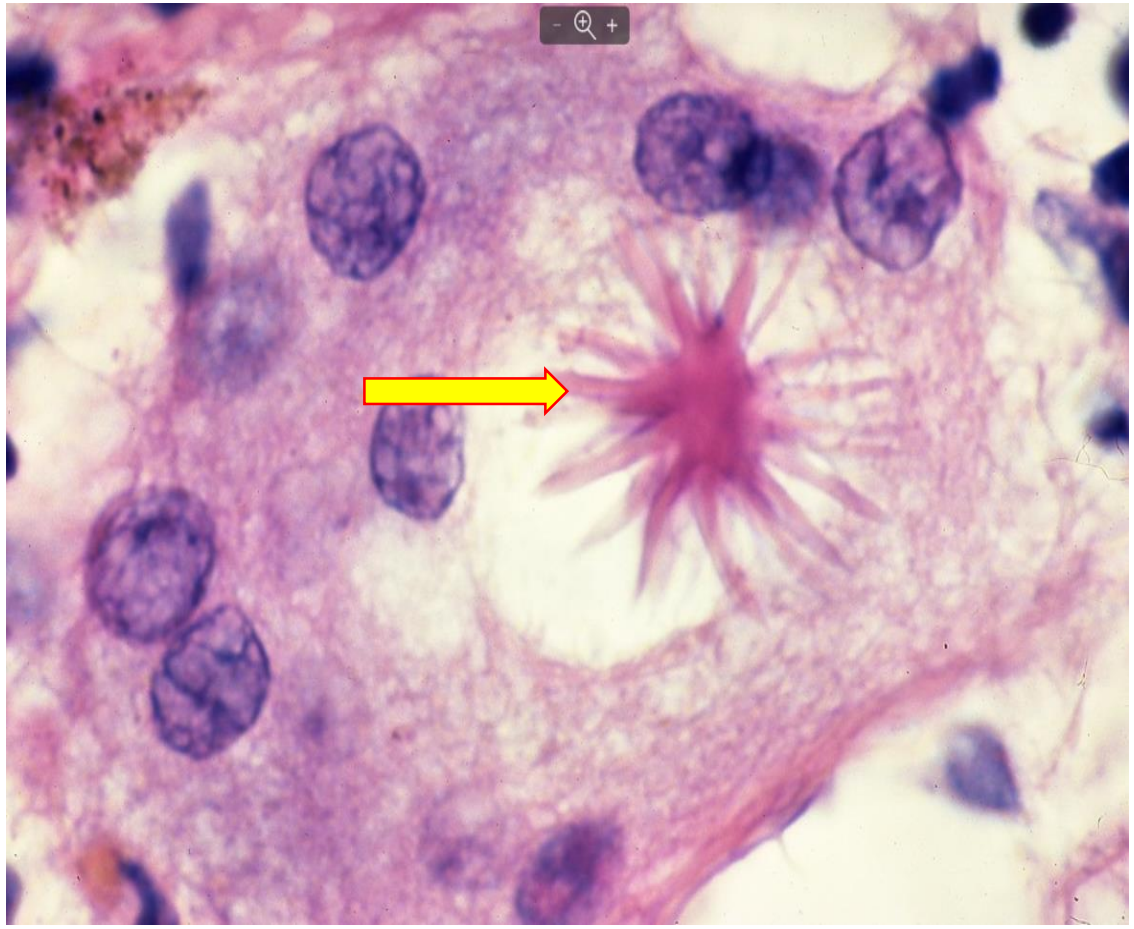
- **Caseation necrosis (typical of tuberculosis) is absent.**
- The lungs are involved in 90% of patients. The granulomas predominantly involve the interstitium rather than airspaces. later result in honeycomb lung which may lead to pulmonary hypertension & cor pulomanle.
- Intrathoracic hilar and paratracheal lymph nodes are enlarged in the majority of patients.



Sarcoidosis:. Characteristic peribronchial **noncaseating granulomas** with many giant cells are present.



Schaumann bodies are calcium and protein inclusions inside the giant cell



Asteroid bodies, stellate inclusions enclosed within giant cells

EOSINOPHILIC (Pulmonary Eosinophilia)

- A number of disorders are characterized by pulmonary infiltrates rich in eosinophils, which are recruited to the lung by local release of chemotactic factors.
- These diverse diseases generally are of immunologic origin, but the etiology is not understood. Pulmonary eosinophilia is divided into the following categories:

- Acute eosinophilic pneumonia with respiratory failure: Unknown etiology; rapid onset of fever, dyspnea, and hypoxia, and prompt response to corticosteroids
- Simple pulmonary eosinophilia (Loeffler syndrome): Uncertain etiology: transient infiltrates with prominent eosinophilia in blood and lung
- Tropical eosinophilia: Caused by microfilariae
- Secondary eosinophilia: Induced by infections, hypersensitivity, asthma, or allergic bronchopulmonary aspergillosis
- Idiopathic chronic eosinophilic pneumonia: Unknown etiology; it is manifested by focal lung consolidation with extensive lymphocyte and eosinophil infiltration, and is steroid responsive.

Smoking-Related Interstitial Diseases

- In addition to obstructive lung disease (COPD), smoking is also being associated with restrictive or interstitial lung diseases.
- *Desquamative interstitial pneumonia (DIP)* and *respiratory bronchiolitis* are two related examples of smoking-associated interstitial lung disease.
- The most striking histologic feature of **DIP** is the accumulation of large numbers of macrophages containing dusty-brown pigment *(smoker's macrophages)* in the air spaces. The alveolar septa are thickened by a sparse lymphocytic infiltrate and interstitial fibrosis when present, is mild. patients with DIP **have a good prognosis and an excellent response to steroids and smoking cessation.**
- **Respiratory bronchiolitis** is a common lesion found in smokers that is characterized by the presence of pigmented intraluminal macrophages similar to those in DIP, but in a "bronchiolocentric" distribution. Mild peribronchiolar fibrosis also is seen. As with DIP, affected patients present with gradual onset of dyspnea and dry cough, and the symptoms recede with smoking cessation.

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PULMONARY DISEASES OF VASCULAR ORIGIN

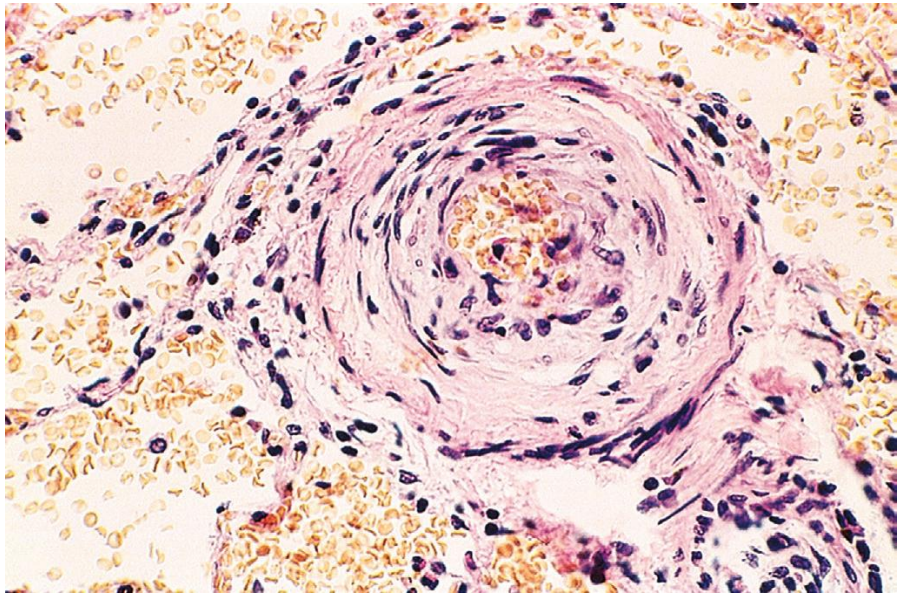
• Pulmonary Embolism, Hemorrhage, and Infarction

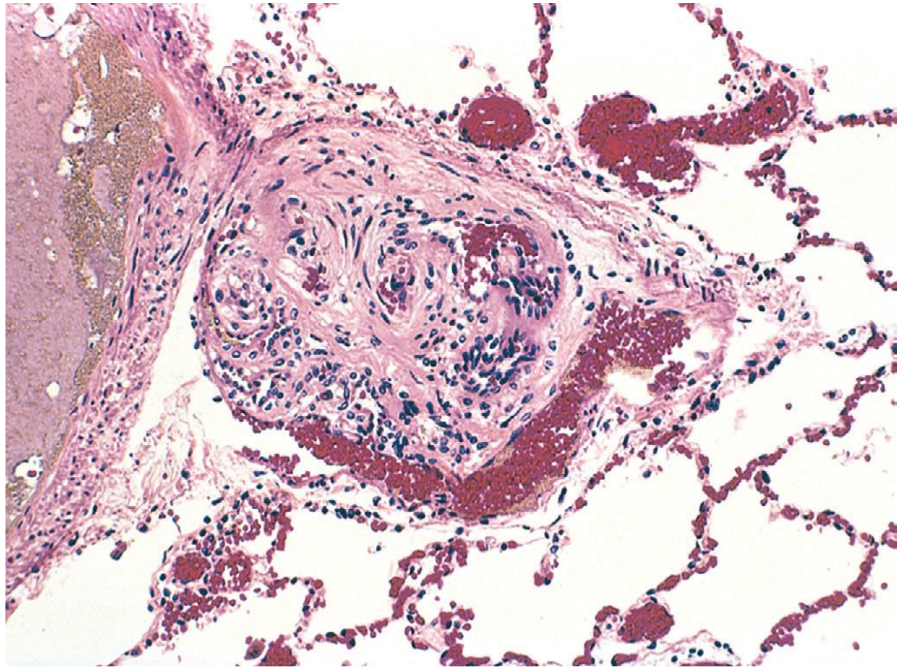
- More than 95% of all **pulmonary emboli** arise from thrombi within the large deep veins of the legs, most often those that have propagated to involve the popliteal vein and larger veins above it.
- **Predisposing causes:** prolonged bed rest, surgery, especially orthopedic surgery, severe trauma (including burns or multiple fractures), congestive heart failure; disseminated cancer, hypercoagulability, pregnancy or the use of oral contraception pills (high estrogen)
- **The consequences** of pulmonary thromboembolism depend largely on the size of the embolus and the cardiopulmonary status of the patient.
- There are two important consequences (1) Pulmonary hypertensionfrom blockage of flow, diminished cardiac output, right sided heart failure *(acute cor-pulmonale),* and sometimes sudden death. (2) Pulmonary infarction.

- lungs are oxygenated not only by the pulmonary arteries but also by bronchial arteries and directly from air in the alveoli. Thus, **ischemic necrosis (infarction)** is the exception rather than the rule, occurring in as few as 10% of patients with thromboemboli. It occurs only if there is compromise in cardiac function or bronchial circulation, or if the region of the lung at risk is underventilated as a result of underlying pulmonary disease.
- About 75% of infarcts affect the lower lobes, and more than half are multiple.
- Wedge shaped coagulative necrosis, may be with hemorrhage, fibrinous exudate on the pleura.

- **Pulmonary hypertension** **(defined as pressures of 25 mm Hg or more)**
- Causes include:
- Chronic obstructive or interstitial lung disease
- Congenital or acquired heart disease with left-sided heart failure
- Recurrent PE
- Connective tissue diseases
- Obstructive sleep apnea
- Idiopathic or familial forms of PH (rare)

- **MORPHOLOGY**
- Medial hypertrophy of the pulmonary muscular and elastic arteries, pulmonary arterial a therosclerosis.
- The vessel changes can involve the entire arterial tree,
  from the main pulmonary arteries down to the arterioles.
- An uncommon but characteristic pathologic change is the **plexiform lesion,** so called because a tuft of capillary formations is present producing a network, or web





Diffuse Alveolar Hemorrhage Syndromes

- This may be secondary, complicating for e.g. necrotizing bacterial pneumonia, bleeding diathesis. Or **primary** represented by group of immune mediated diseases that present as hemoptysis, anemia and radiographic diffuse pulmonary infiltrates. These are;
- ***Goodpasture Syndrome:*** is an autoimmune disease in which lung and kidney injury are caused by circulating autoantibodies against certain domains of type IV collagen that are intrinsic to the **basement membranes** of renal glomeruli and pulmonary alveoli.
- ***Granulomatosis and Polyangiitis: (Wegener granulomatosis)*** More than 80% of patients develop upper-respiratory or pulmonary manifestations at some time in their course. The lung lesions are characterized by a combination of necrotizing vasculitis and parenchymal necrotizing granulomatous inflammation. Anti-neutrophil cytoplasmic antibodies (ANCAs) are present in close to 95% of cases

THANK YOU