Respiratory block
2017

Restrictive Lung Disease

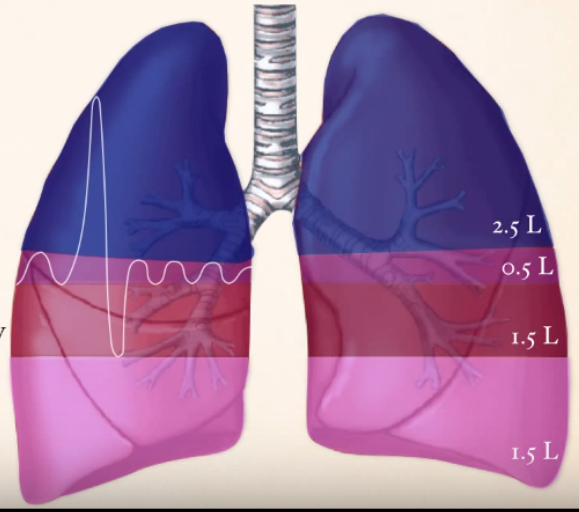
Dr. Maha Arafah and Prof. Rikabi

Objectives

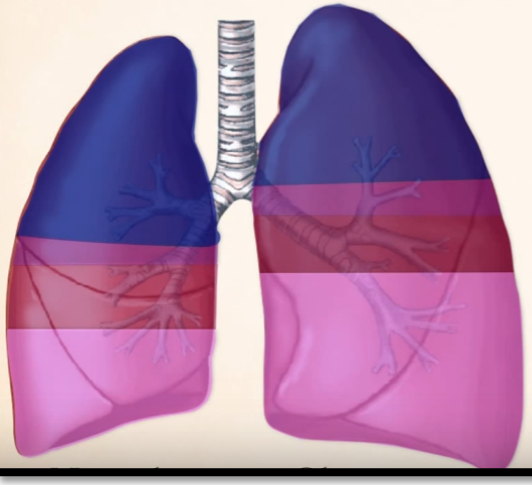
- Understand the structure and constituents of the lung interstitium as well as the restrictive changes which occur in diseases of the interstituim (ILD)
- Know the symptoms of ILD: progressive breathlessness and cough
- Know subtypes of ILD: acute and chronic
- Discuss the causes, morphology and outcome of acute ILD
- Appreciate the pathogenesis of chronic ILD regardless of their type.
- Become aware of the classification of interstitial lung diseases.
- Discuss examples of interstitial lung diseases including:
  - **idiopathic pulmonary fibrosis**
  - **Pneumoconiosis**
  - **Hypersensitibity pneumonitis**
  - **Goodpasture syndrome**
  - **Sarcoidosis**

INTRODUCTION
LUNG VOLUMES AND CAPACITIES

- Inspiratory Reserve Volume
- Tidal Volume
- Expiratory Reserve Volume
- Residual Volume
- Inspiratory Capacity
- Functional Residual Capacity
- Vital Capacity
- Total Lung Capacity

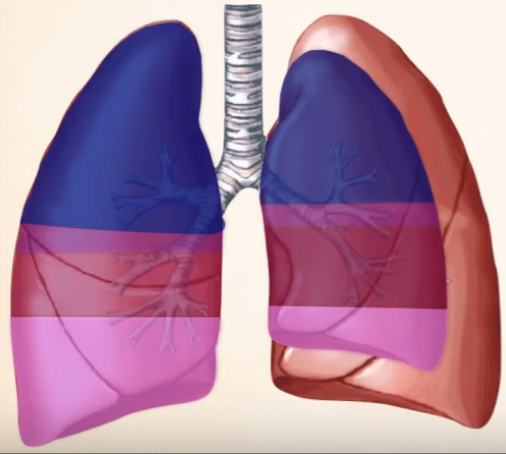


OBSTRUCTIVE



- Forced Expiratory Volume in 1sec ↓↓
- Forced Vital Capacity ↓
- FEV_1 / FVC ↓↓
- Total Lung Capacity ↑
- Residual Volume ↑↑

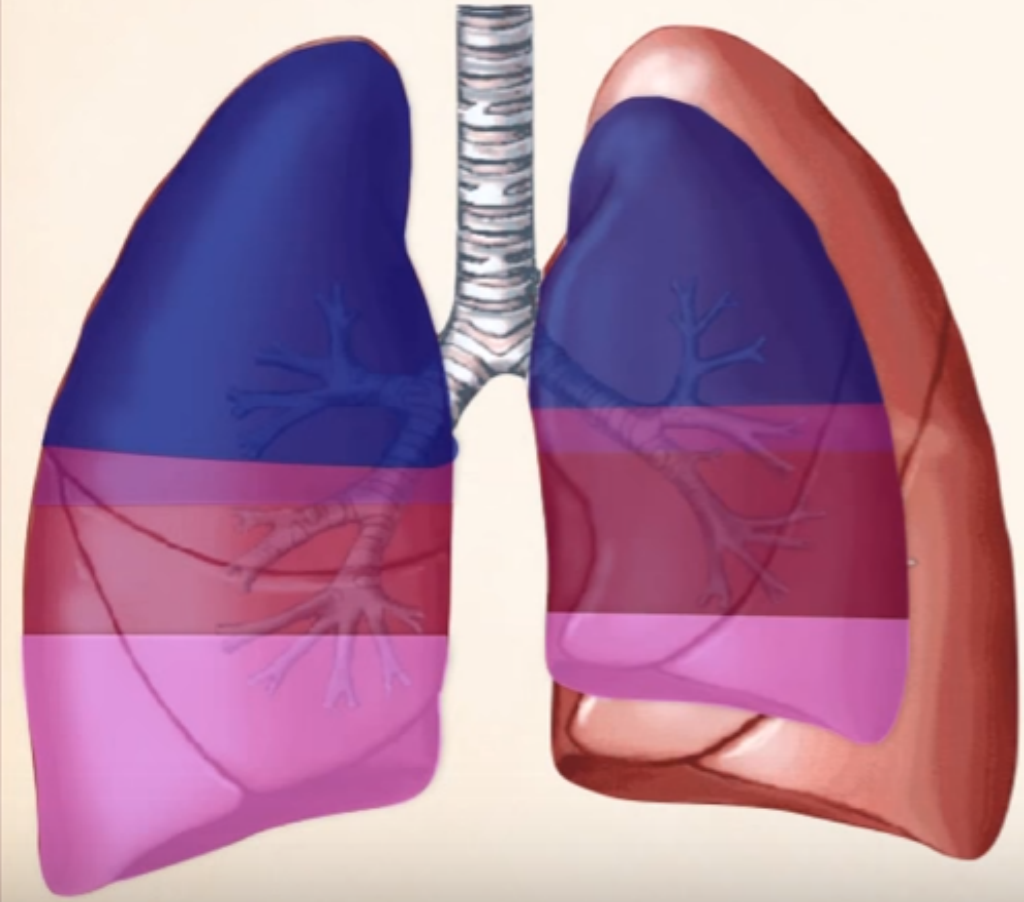
RESTRICTIVE



- Forced Expiratory Volume in 1sec ↑
- Forced Vital Capacity ↓↓
- FEV_1 / FVC ↑
- Total Lung Capacity ↓↓

Both forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) are reduced with normal to high FEV1/VC

RESTRICTIVE



Forced Expiratory Volume in 1sec ↑

Forced Vital Capacity ↓↓

FEV_1 / FVC ↑

Total Lung Capacity ↓↓

Restrictive Lung Disease

The restrictive lung diseases are divided into:

1. **Intrinsic lung diseases/ diseases of the lung parenchyma/primary ILD:**

The diseases cause inflammation or scarring of the lung tissue (ILD) or result in filling of the air spaces with exudate and debris (pneumonitis). They are characterized by inflammatory infiltrates in the interstitial space and the interstitium becomes thickened and fibrotic (Stiff Lung). Therefore there is decreased oxygen-diffusing capacity.
They are acute or chronic.

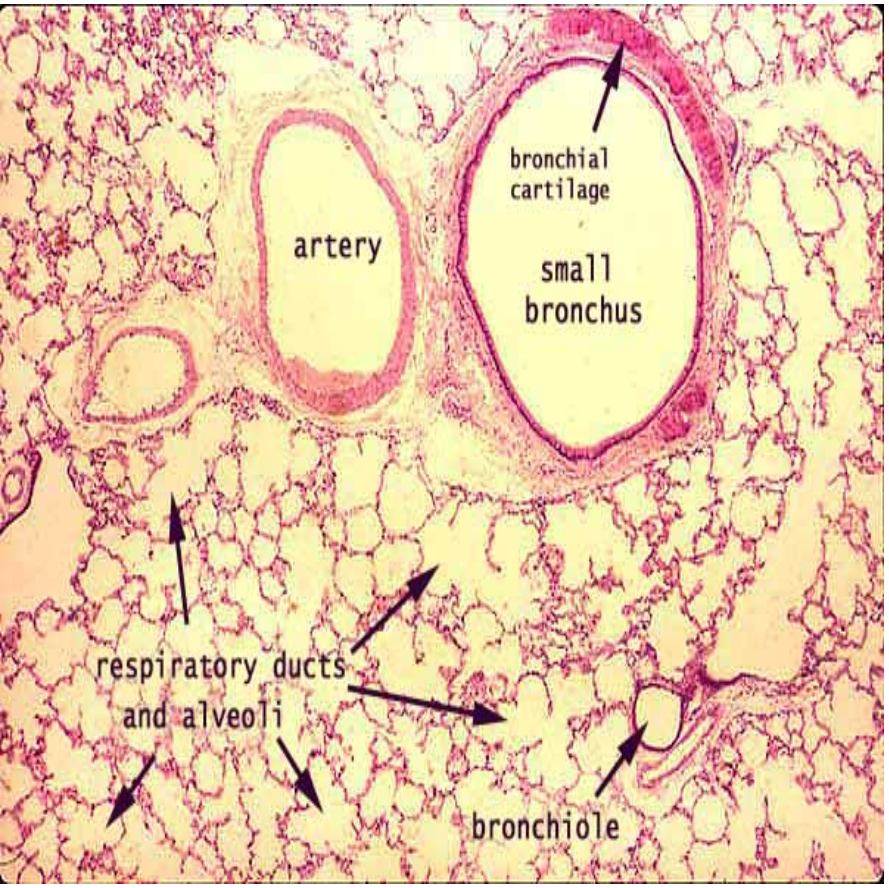
2. **Extrinsic disorders or extraparenchymal diseases:**

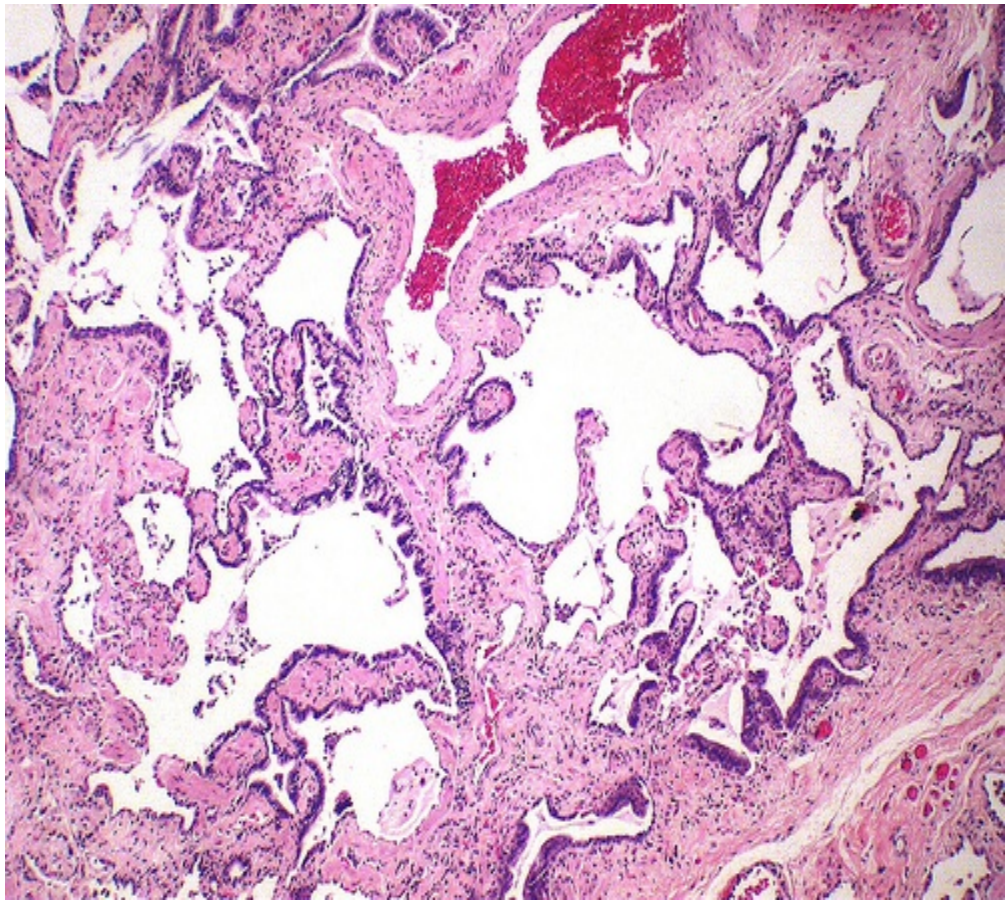
The chest wall, pleura, and respiratory muscles are the components of the respiratory pump, and they need to function normally for effective ventilation. Abnormalities of the chest wall include:

- **bony abnormalities (kyphosis or kypho-scoliosis)**
- **massive pleural effusion,**
- **morbid obesity**
- **neuromuscular disease of respiratoy muscles results in respiratory muscle weakness and respiratory failure e.g. myopathy or myositis, quadriplegia, or phrenic neuropathy from infectious or metabolic causes**

Intrinsic type of Restrictive lung diseases

- Characterized by reduced compliance of the lung.
- It can be:
  - Acute.
  - Chronic.
- Important signs and symptoms:
  - Dyspnea.
  - Hypoxia.
  - In advanced cases of restrictive lung disease, there is severe hypoxia, hypercapnia and cyanosis, respiratory failure and cor pulmonale.
- The final stage of all restrictive lung disease is extensive fibrosis with honeycomb lung. The lung becomes more stiff and solid.
- Honeycomb lung indicates end stage disease. In it both alveoli and bronchioles coalescence to form cysts lined with cuboidal or columnar epithelium and seperated by inflammatory fibrous tissue.


bronchial
cartilage
artery
small
bronchus
respiratory ducts
and alveoli
bronchiole



Acute restrictive lung diseases (INTRINSIC TYPE)

1. **Adult respiratory distress syndromes**
2. **Neonatal respiratory distress syndromes**

Adult Respiratory Distress Syndrome (ARDS)

- ARDS is a severe form of acute lung injury with diffuse alveolar injury.
- known as shock lung/ diffuse alveolar damage/ adult respiratory failure/acute alveolar injury/ traumatic wet lung
- Features
  - rapid acute onset progressive severe life threatening respiratory insufficiency, cyanosis, severe arterial hypoxia
  - refractory to oxygen therapy and that may progress to multi-organ failure
  - bilateral pulmonary infiltrates (edema) in the absence of evidence of left sided heart failure
- It is the most common cause of non- cardiogenic pulmonary edema

Adult respiratory distress syndromes (ARDS)

Can be caused by many conditions:

Pneumonia and sepsis are the most common causes

Direct injury to lung

- Pneumonia
- Aspiration of gastric contents
- Pulmonary trauma
- Fat embolism
- Near drowning
- Toxic inhalation injury (irritants such as chlorine, O2 toxicity)
- Post lung transplant
- Severe acute respiratory syndrome (SARS): The virus is a coronavirus that destroys the type II pneumocytes and causes diffuse alveolar damage

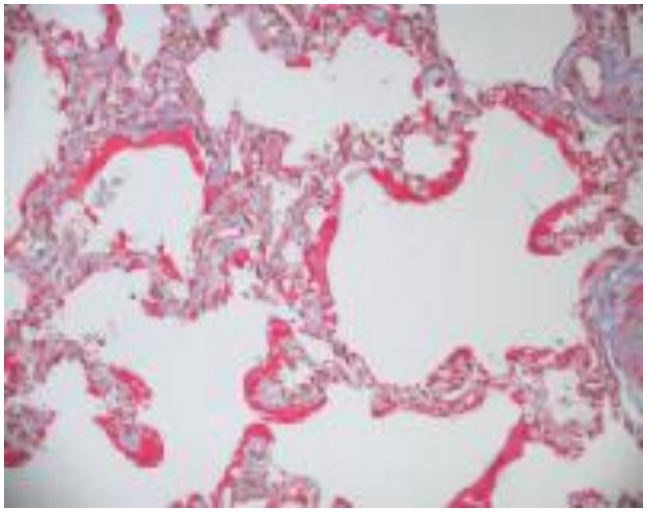
Indirect injury to lung:

- Sepsis
- Severe trauma (e.g. bone fractures, head injury, burns, radiation)
- Shock
- Cardiopulmonary bypass
- Acute pancreatitis
- Transfusion
- Uremia
- Overdose with street drugs such as heroin
- Therapeutic drugs such as bleomycin
- Hematologic conditions e.g multiple transfusion, coagulation disorders

Adult Respiratory Distress Syndrome

Pathophysiology

- ARDS is associated with diffuse alveolar damage.
- It is initiated by injury to:
  1. alveolar capillary endothelium a with resultant increase in alveolar capillary permeability
  2. alveolar epithelium

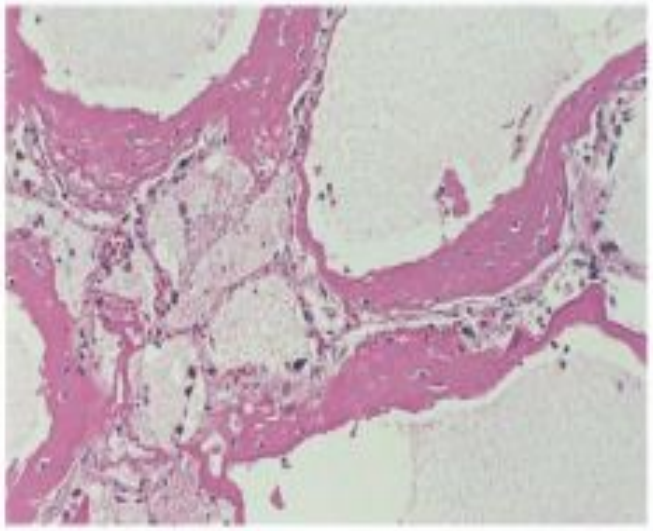


- The injury is induced by the:

(a) Neutrophils releasing substances toxic to alveolar wall.

(b) Activation of the coagulation cascade.

(c) O2 toxicity (due to formation of free radicals).



Pathophysiology of ARDS

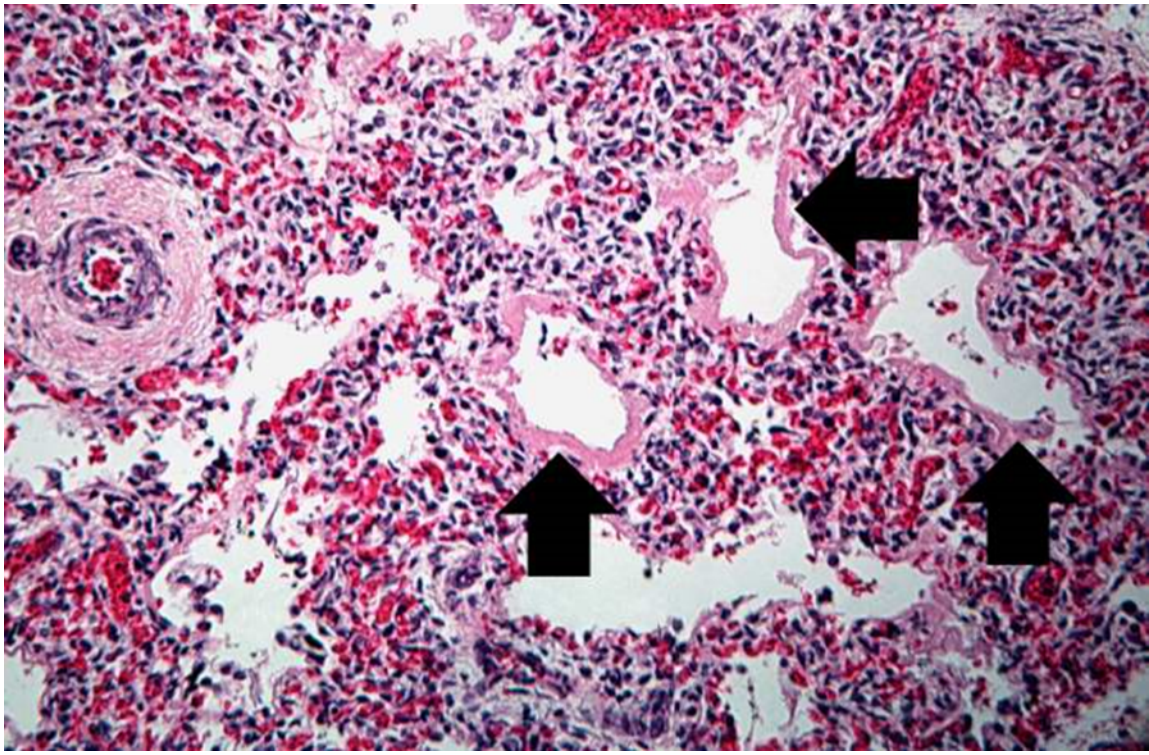
- This causes leakage of protein-rich fluid into alveoli, formation of alveolar hyaline membrane lining the inner surface of alveoli
- The membrane is composed of fibrin and cellular debris.
- The lungs become remarkably heavy and stiff due to inflammation and odema and later interstitial fibrosis.
- Chest x-ray: bilateral and diffuse pulmonary infiltrates

Outcome of ARDS:

- Mortality was 100%
- Now 30 -40% with good ICU support
- Poor prognosis: old age, multisystem failure, high level of IL-1

Neonatal Respiratory Distress Syndrome/Hyaline membrane disease

- It is the most common cause of respiratory failure in the newborn and is the most common cause of death in premature infants.
- It is the same as ARDS except that it is caused by a deficiency of pulmonary surfactants in new borns, most often as a result of immaturity.



Chronic restrictive lung disease

(INTRINSIC TYPE)

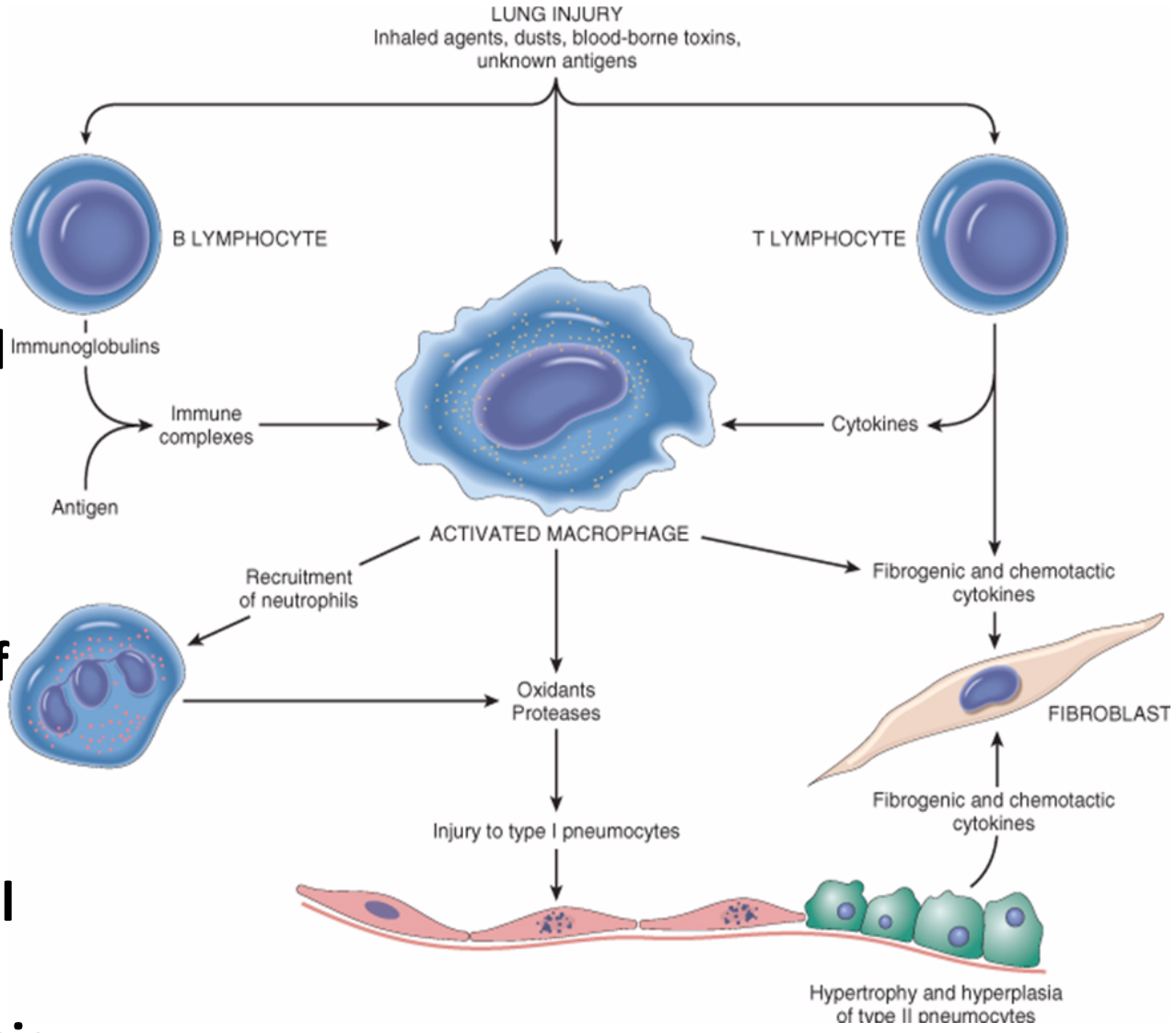
Chronic restrictive lung disease (INTRINSIC TYPE)

Definition

- **Are a heterogenous group of diseases.**
- **Many entities are of unknown cause and pathogenesis.**
- **They have similar clinical signs, symptoms, radiographic alterations and pathophysiologic changes.**
- **Account for about 15% of non-infectious lung diseases.**
- **End-stage: diffuse interstitial pulmonary fibrosis.**

Pathogenesis of intrinsic chronic ILD

- **Lung injury**
- **Influx of inflammatory cells into the alveoli and alveolar walls**
- **Distortion of the normal structure of alveoli**
- **Release of chemical mediators and Promotion of fibrosis**



Chronic restrictive lung disease

Major Categories of Chronic Interstitial Lung Disease

Idiopathic fibrosing:

Usual interstitial pneumonia (idiopathic pulmonary fibrosis)

Drug:

Chemotherapy, methotrexate, bleomyxin toxicity

Occupational: Pneumoconiosis

Anthracosis and coal worker's pneumoconiosis,
Silicosis
Berylliosis
Asbestosis

Smoking related:

Eosinophilic granuloma
Desquamative interstitial pneumonia
Respiratory bronchiolitis-associated interstitial lung disease

Immune diseases:

Sarcoidosis
Goodpasture syndrome
Hypersensitibity pneumonitis (extrinsic allergic alveolitis)
Systemic lupus erythematosus
Systemic sclerosis (scleroderma)
Wegener granulomatosis

Radiation Reactions

Occur after radiation with diffuse alveolar damage, severe atypia of hyperplastic type II cells and fibroblasts

Idiopathic Pulmonary Fibrosis/ Fibrosing Alveolitis/ Hamman-Rich Syndrome /

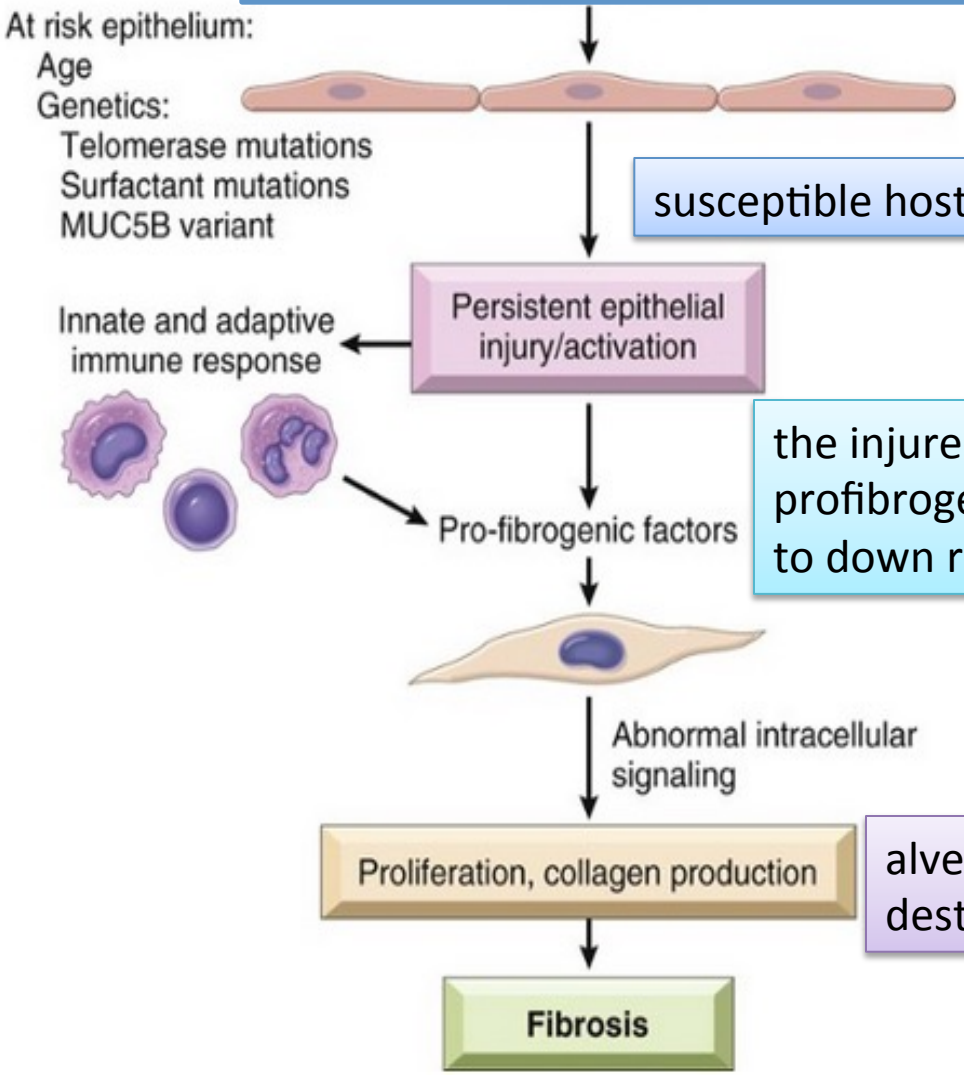
Usual Interstitial Pneumonia (UIP)

Idiopathic Pulmonary Fibrosis (UIP)

- UIP is progressive fibrosing disorder of unknown cause. It is an idiopathic interstitial pneumonia with diffuse interstitial fibrosis and inflammation.
- Age: Adults 30 to 50 years
- Prognosis: poor.
  - Respiratory and heart failure may develop within few years. No effective therapy is available for the treatment of idiopathic pulmonary fibrosis. Lung transplant is the only solution.

Pathogenesis of Idiopathic Pulmonary Fibrosis/ usual interstitial pneumonia/ fibrosing alveolitis/ Hamman-Rich syndrome (UIP)

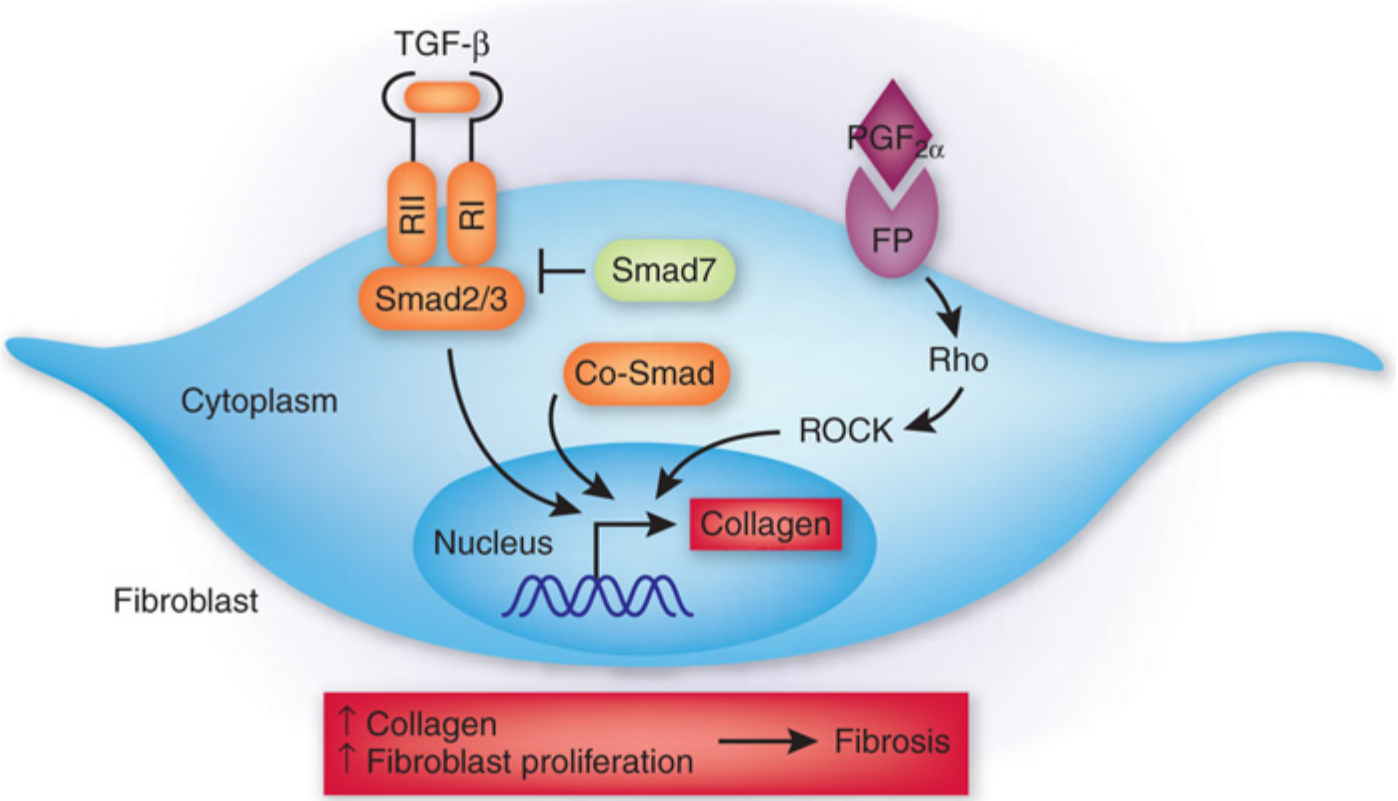
smoke, environmental pollutants, dust, viral infections, gastroesophageal reflux disease



the injured epithelial cells are the source of profibrogenic factors such as TGF-β secondary to down regulation of caveolin I

alveolar damage, fibrosis and irreversible destruction of the lung parenchyma.

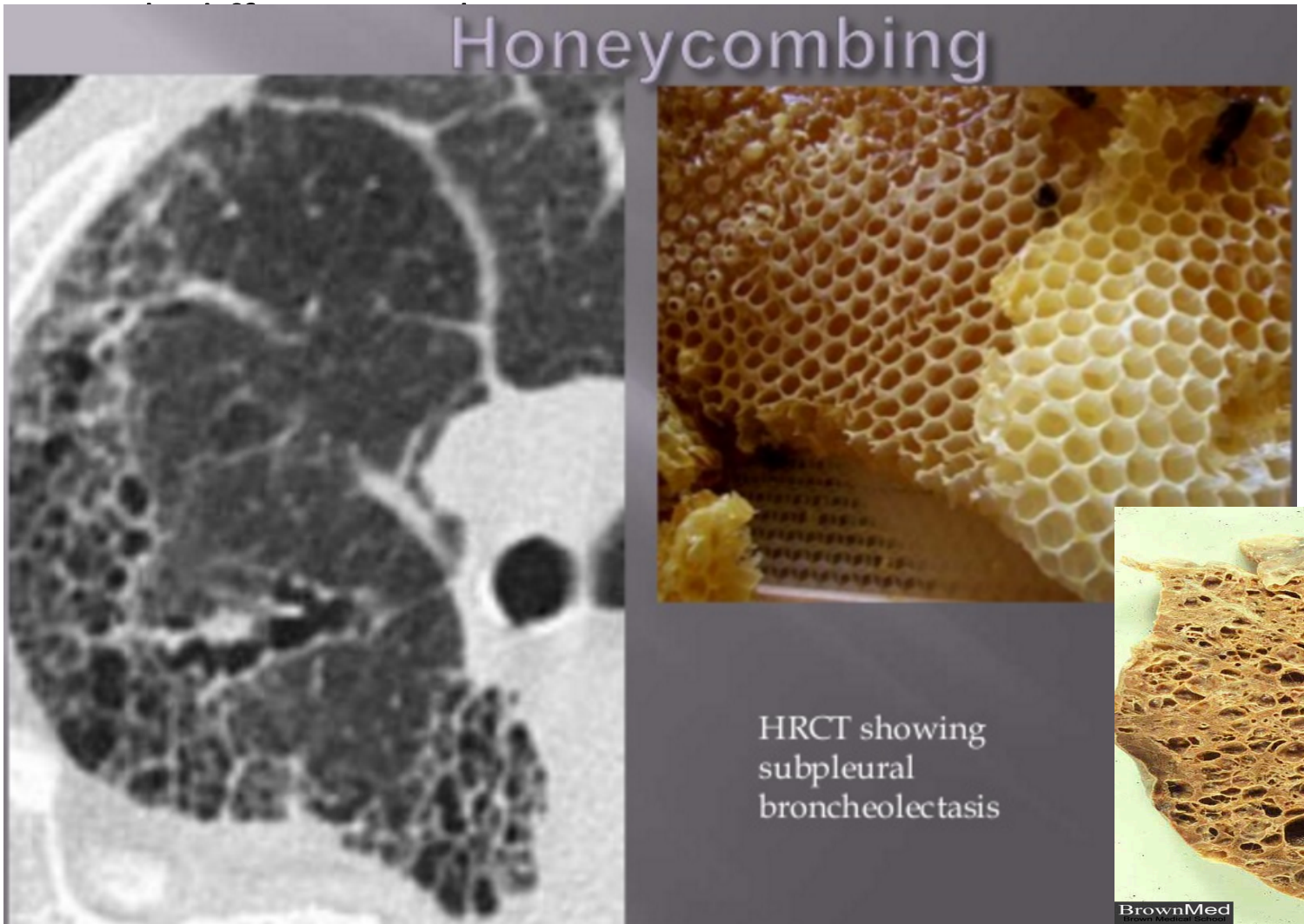
Profibrogenic factors: TGF-β



The potent profibrotic factor TGF-β acts independently through Smads to enhance collagen production by fibroblasts. The increase in collagen, together with $PGF_{2\alpha}$-FP–induce fibroblast proliferation, contribute to the pathogenesis of pulmonary fibrosis.

Clinical Features of UIP

- Most patients present with exertional dyspnea and a nonproductive cough
- A chest radiograph and high-resolution computed tomography typically



Morphology of UIP

- The morphologic changes vary according to the stage of the disease.
- Early cases:

  -Intra-alveolar and interstial inflammation.

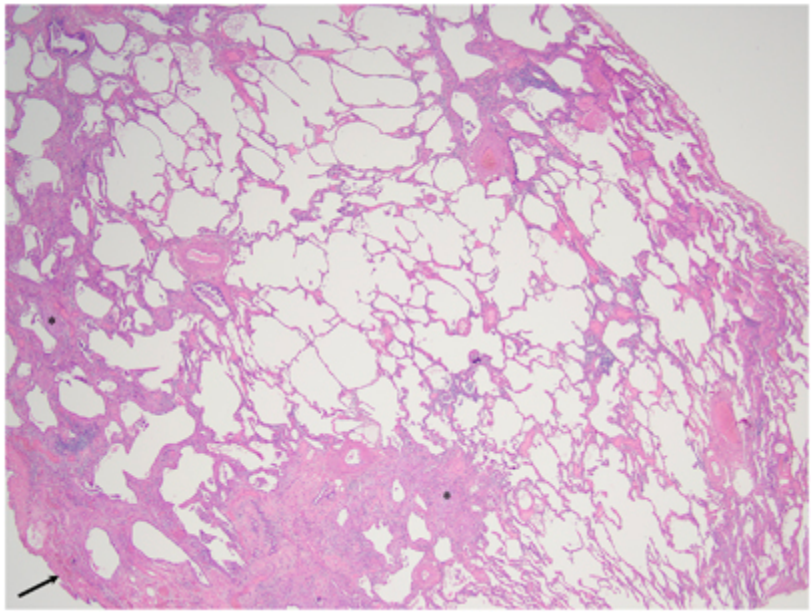
  - Hyperplasia of type II pneumocytes

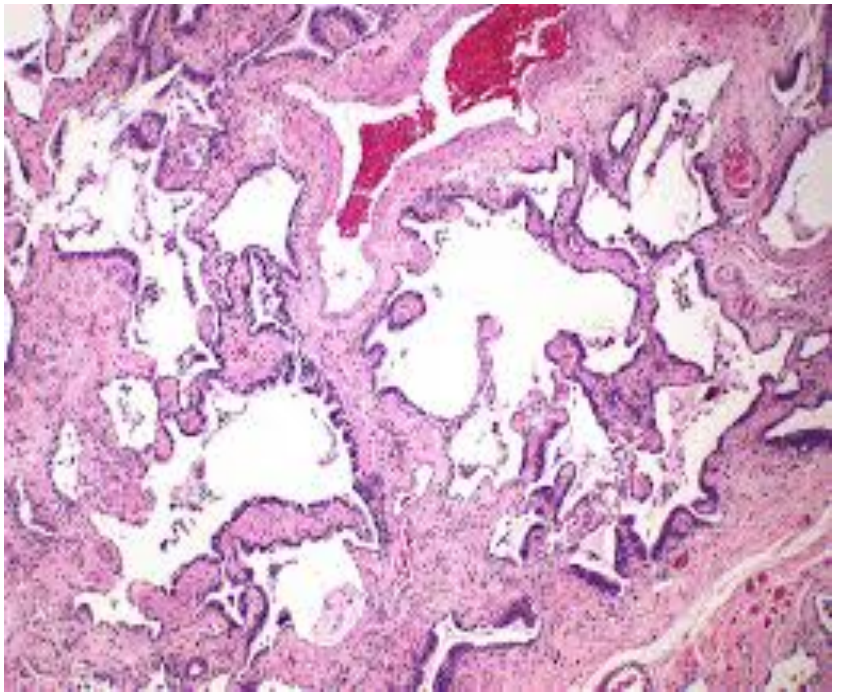
- Advancing disease:

  -prominent interstitial fibrosis.

  -Alternating areas of fibrosis and normal tissue will be seen.

- In the end, the lung consists of spaces lined by cuboidal or columnar epithelium separated by inflammatory fibrous tissue (honeycomb lung). It is the end stage of lung disease





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Wegener granulomatosis

Radiation Reactions

Pneumoconiosis

- Pneumoconiosis is a group of pulmonary diseases caused by chronic exposure to inorganic mineral dust inhalation and this leads to lung damage.
- More than 40 inhaled minerals can cause lung problems.
- They include **carbon dust, silica, asbestos**, beryllium etc.
- Pathophysiology:
  - Alveolar macrophages ingest the particles, become activated, and release cytokines and chemotactic factors that recruit other inflammatory cells.
  - The ensuing inflammation damages lung cells and also damages the interstitium of the lung by degrading the extracellular matrix glycoproteins.
  - The inhaled particles also stimulate the fibroblasts to proliferate and produce collagen; fibrosis results.
  - As the disease progresses the blood vessels become compromised, and ischemic necrosis ensues.

Pneumoconiosis

The development of pneumoconiosis is dependent on:

- The amount of dust retained in the lung and airways.
    a. Concentration of the dust in the ambient air.
    b. Duration of the exposure.
    c. Effectiveness of the clearance mechanisms.
- The size (1-5μ) shape.
- Their solubility and physiochemical activity.
- The possible additional effects of other irritants, tobacco smoking.

Pneumoconiosis

Entity	Example	Pathological features	Comment
coal worker's pneumoconi-osis	coal dust in coal miners	-Simple coal worker's -Complicated coal worker's pneumoconiosis (with rheumatoid arthritis is called Caplan syndrome)	**Anthracosis** is the accumulation of coal without consequent cellular reaction in air polution /smoker
Silicosis	**silicon dioxide**	industries: mining of gold, tin, copper and coal, sandblasting, metal grinding, ceramic manufacturing	-Complicated progressive massive fibrosis -Predispose to lung cancer and TB
Berylliosis	Beryllium Mining, Aerospace manufacturing	non-necrotizing granulomata distributed in the parenchyma, LN and other organs	Pedispose to lung cancer
Asbestosis	Pipes, sheets, vinyl-asbestos floor tiles, asbestos paper in filtering and insulating products	Pulmonary fibrosis Pleural fibrosis	Bronchogenic Carcinoma and Malignant Mesothelioma

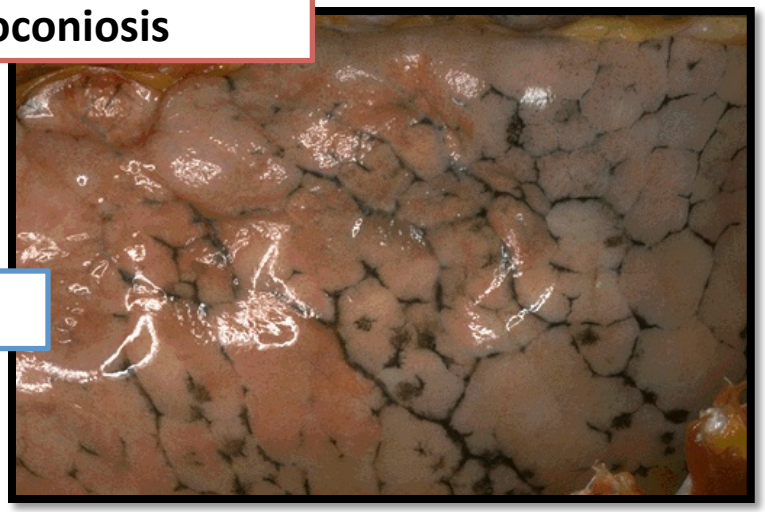
Coal Worker's Pneumoconiosis

- Coal worker's pneumoconiosis (CWP) can be defined as the accumulation of coal dust in the lungs and the tissue's reaction to its presence.
- The disease is divided into 2 categories:

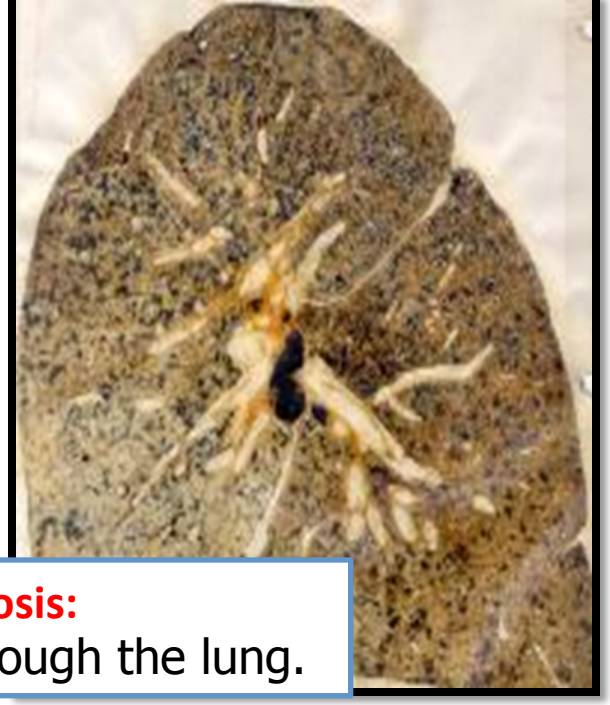
1. Simple coal worker’s pneumoconiosis
2. Complicated coal worker’s pneumoconiosis (CCWP), or pulmonary massive fibrosis (PMF), depending on the extent of the disease.

- Pulmonary massive fibrosis in association with rheumatoid arthritis is known as Caplan syndrome.

Coal Worker's Pneumoconiosis



Anthracosis



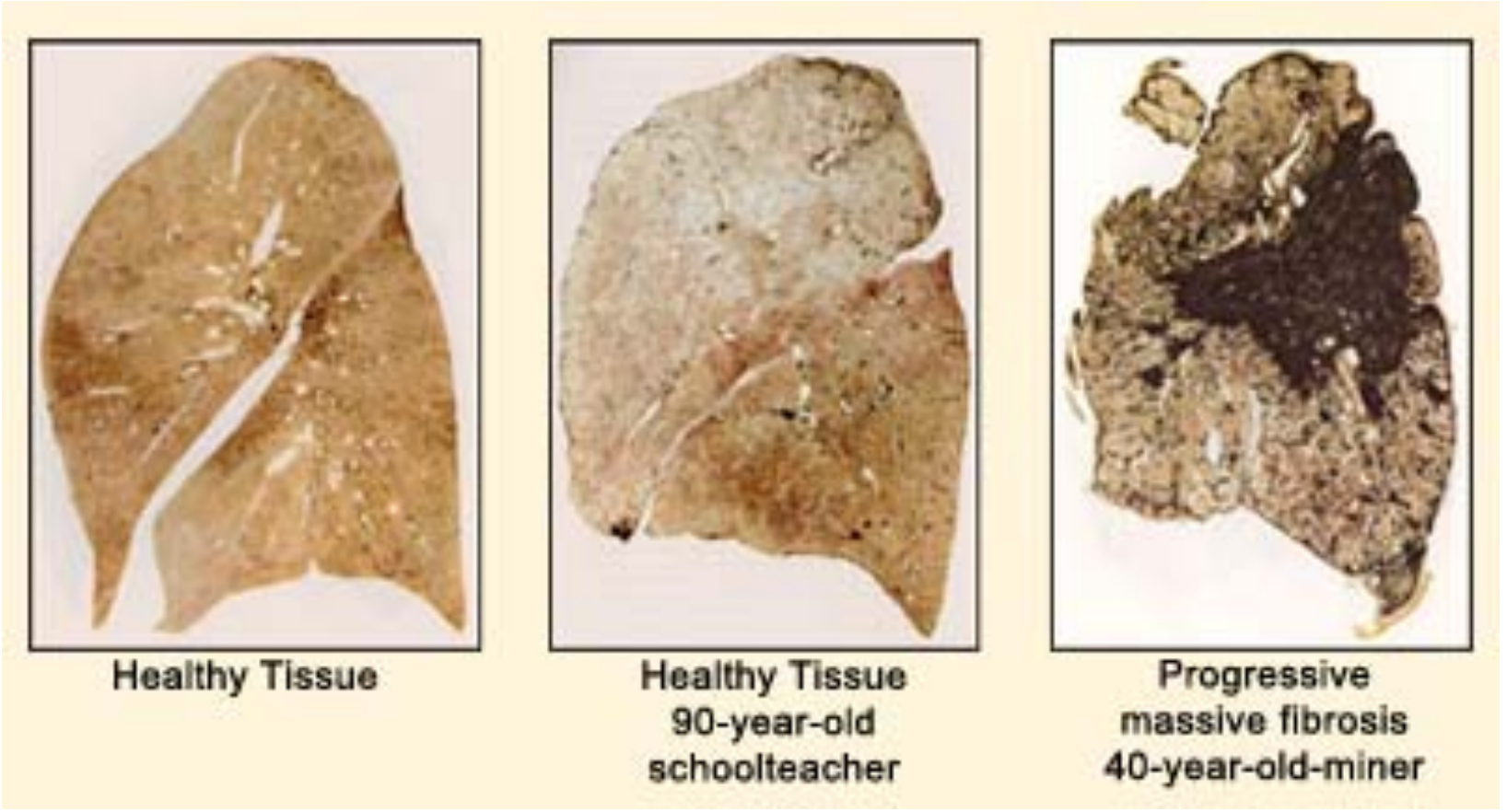
Simple Coal worker pneumoconiosis:

Black macules)1 to 5 mm are scattered through the lung.

Complicated coal worker's pneumoconiosis:

- Black scars exceed 2 -10 cm
- Fibrous scarring appears (progressive massive fibrosis)
- produces cough, dyspnea, and lung function impairment.
- cor pulmonale
- no convincing evidence that coal dust increases susceptibility to tuberculosis or cancer (non-smoker)

Coal Worker's Pneumoconiosis

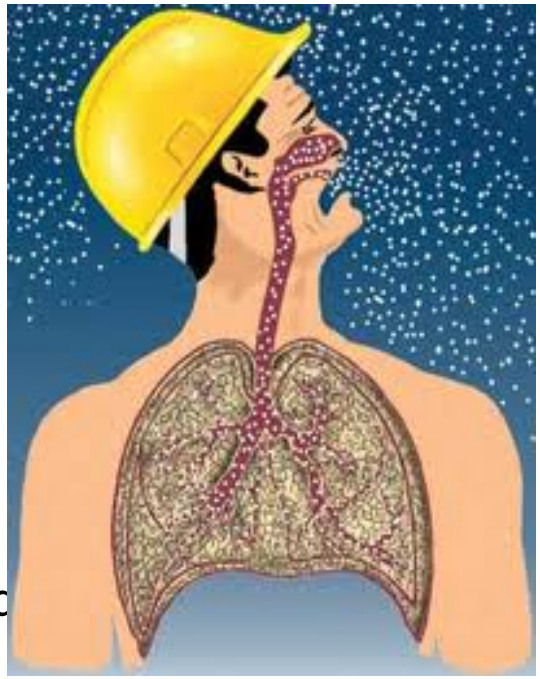


Healthy Tissue

Healthy Tissue
90-year-old
schoolteacher

Progressive
massive fibrosis
40-year-old-miner

Silicosis

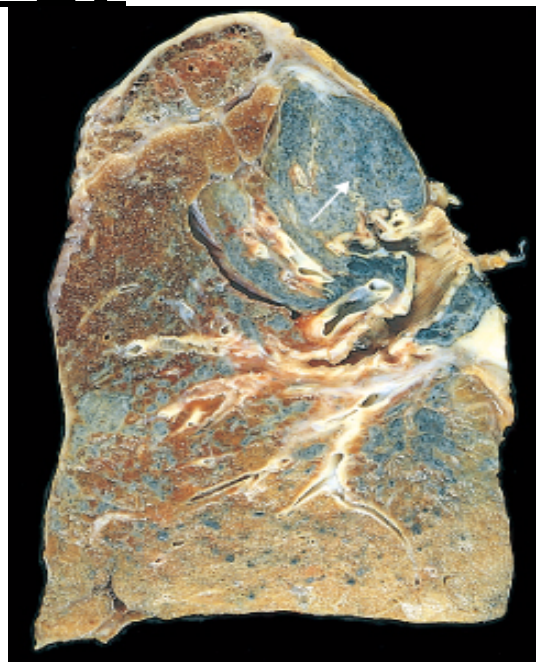


- Silicosis is a fibro-nodular lung disease caused by long term exposure to inhalation of crystalline silica particles (alpha-quartz or silicon dioxide).
- Industrial exposure: mining of gold, tin, copper and coal, sandblasting, metal grinding, ceramic manufacturing.
- Chronic forms manifest after several years of exposure
- The symptoms may be indolent or progressive: complicated progressive massive fibrosis.
- Silicosis predispose to lung cancer and tuberculosis.

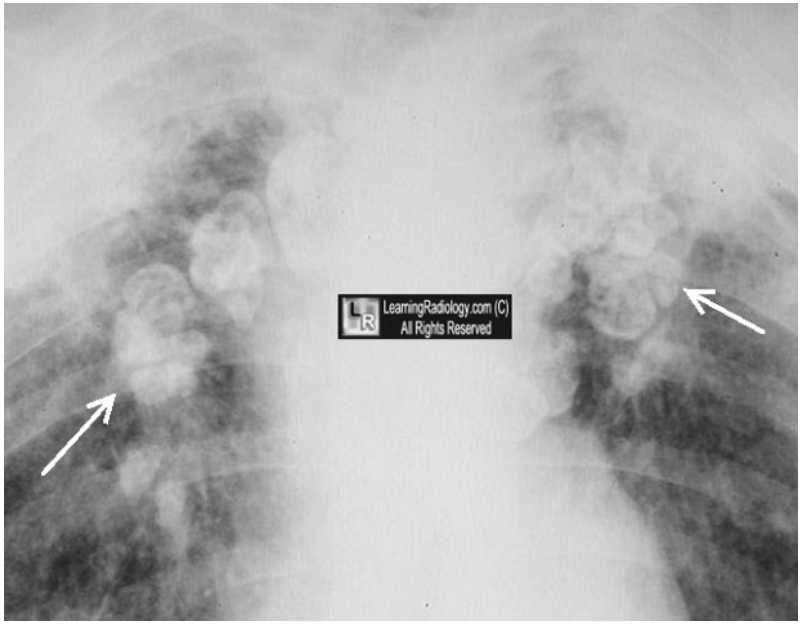
Pathogenesis:

- Crystalline silica is highly fibrogenic.
- Scattered lymphocytes and macrophages are drawn rapid with fibrosis.
- Some particles are transported to lymph nodes.

Morphology



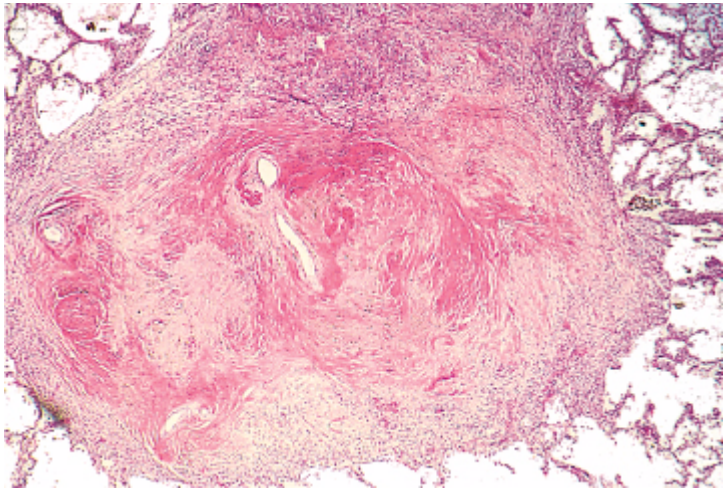
- Tiny collagenous nodules that enlarge forming stony-hard large fibrous scars usually in the upper lobes.
- The lung parenchyma between the scars may be compressed or emphysematous.
- Calcifications may appear (eggshell calcification) .
- Similar collagenous nodules within the lymph nodes.
- Fibrous pleural plaques may develop.



Morphology:

-Hyalinized collagen fiber surround an amorphous center (fibrous nodules).

- Scarring progress to progressive massive fibrosis.

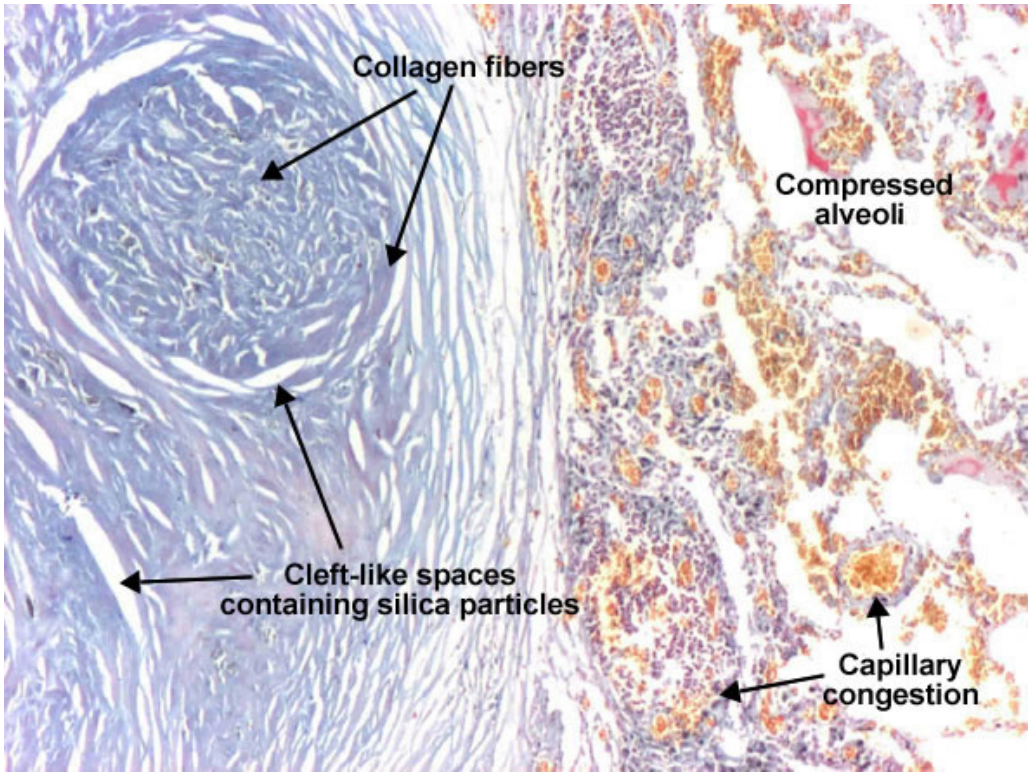


Prognosis:

- Scarring extending and encroching the pulmonary arteries leading to Cor pulmonale.

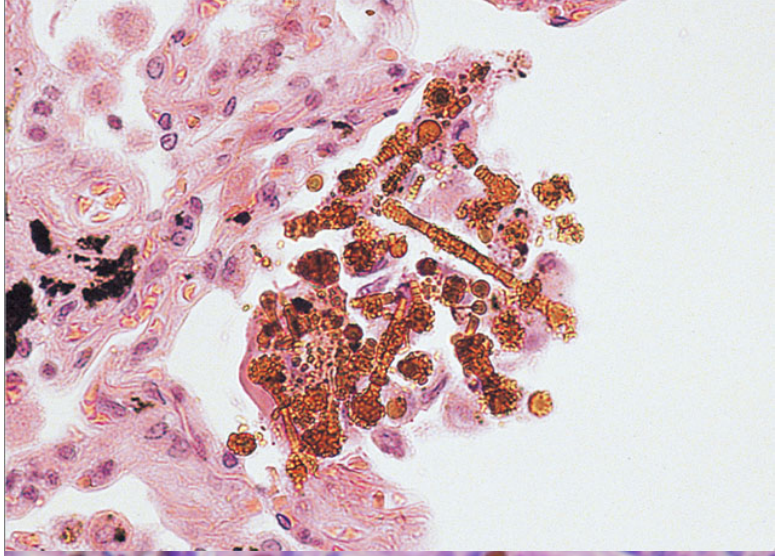
-Increased susceptibility to tuberculosis (crystalline silica inhibits the ability of pulmonary macrophages to kill phagocytosed mycobacteria)

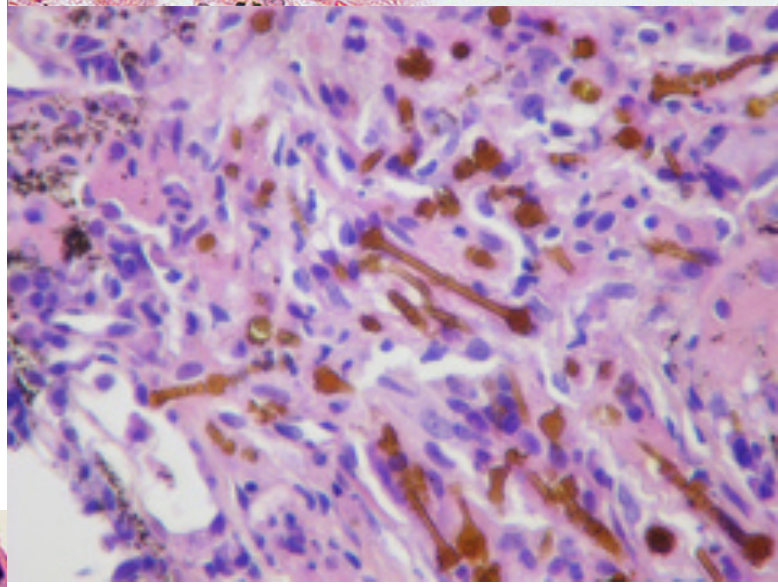
-Patients with silicosis have double the risk for developing lung cancer

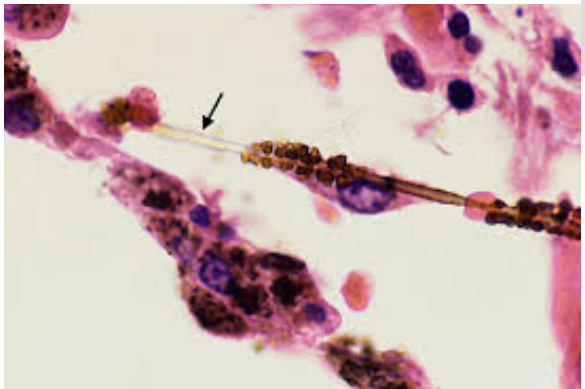


Asbestosis

- Caused by asbestos inhalation
- Asbestos fibers are long and thin. They can curved or straight.
- All types of asbestos (crocidolite and amosite) are fibrogenic to lungs.
- **Asbestosis** occurs decades after exposure has ended.
- Characterized by scars containing asbestos bodies.
- They can cause
  - pleural effusion.
  - pleural adhesions.
  - parietal pleural fibrocalcific plaques
  - Some types of asbestos are carcinogenic (especially crocidolite) and prolong asbestos exposure can predisposes to bronchogenic carcinoma and malignant mesothelioma.



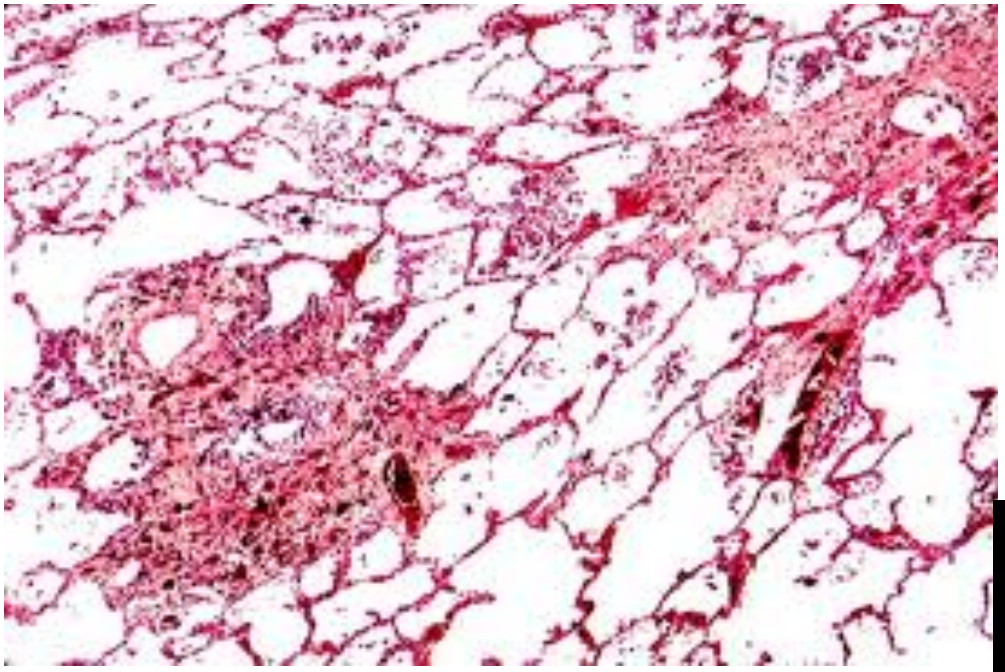


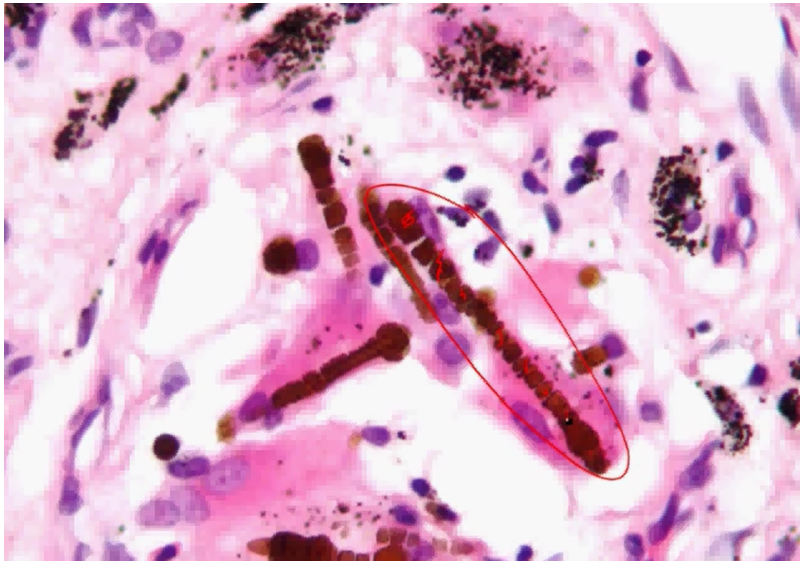


Asbestos bodies are long, thin asbestos fibers coated with hemosiderin and protein to form brown filaments with a beaded or drumstick pattern.

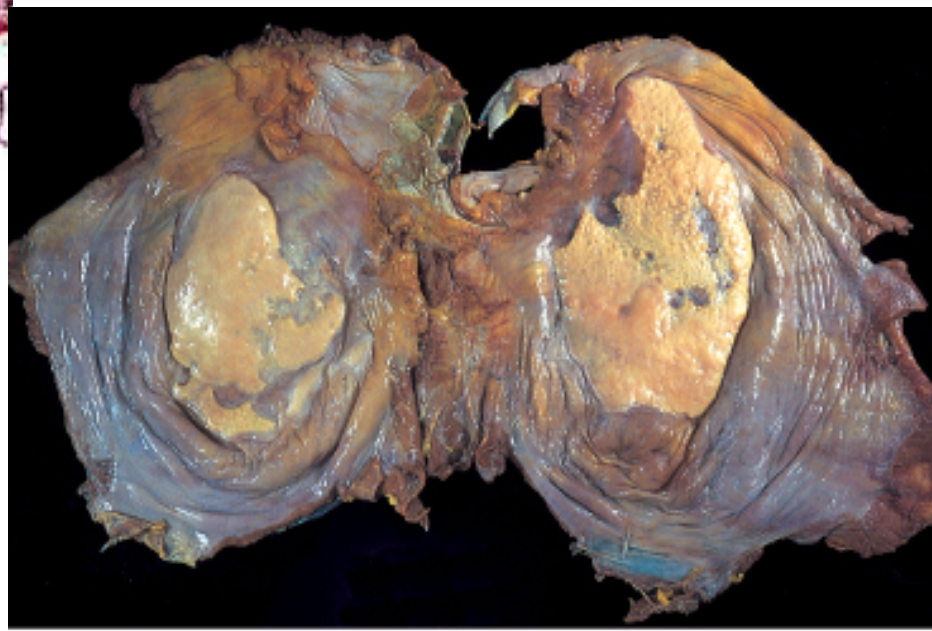
Pneumoconiosis : Asbestosis

- scarring containing asbestos bodies (ferruginous bodies).





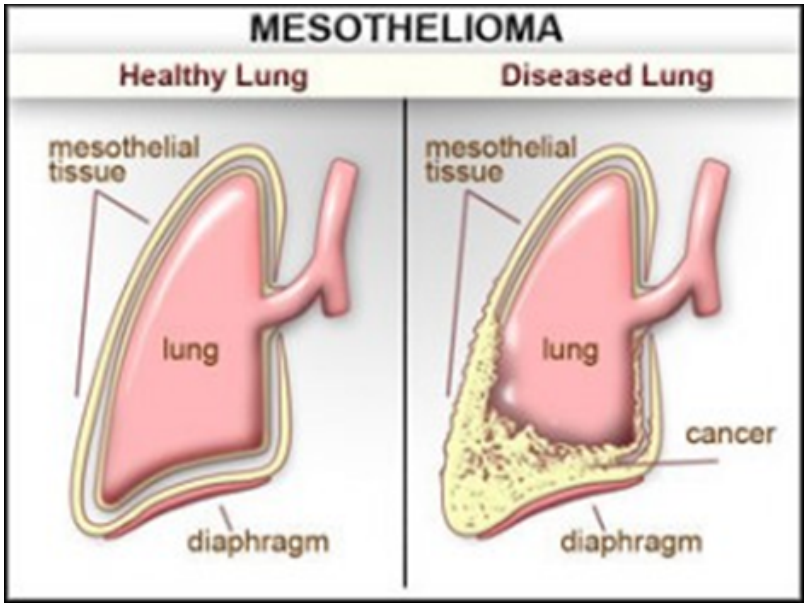
- parietal pleural fibrocalcific plaques

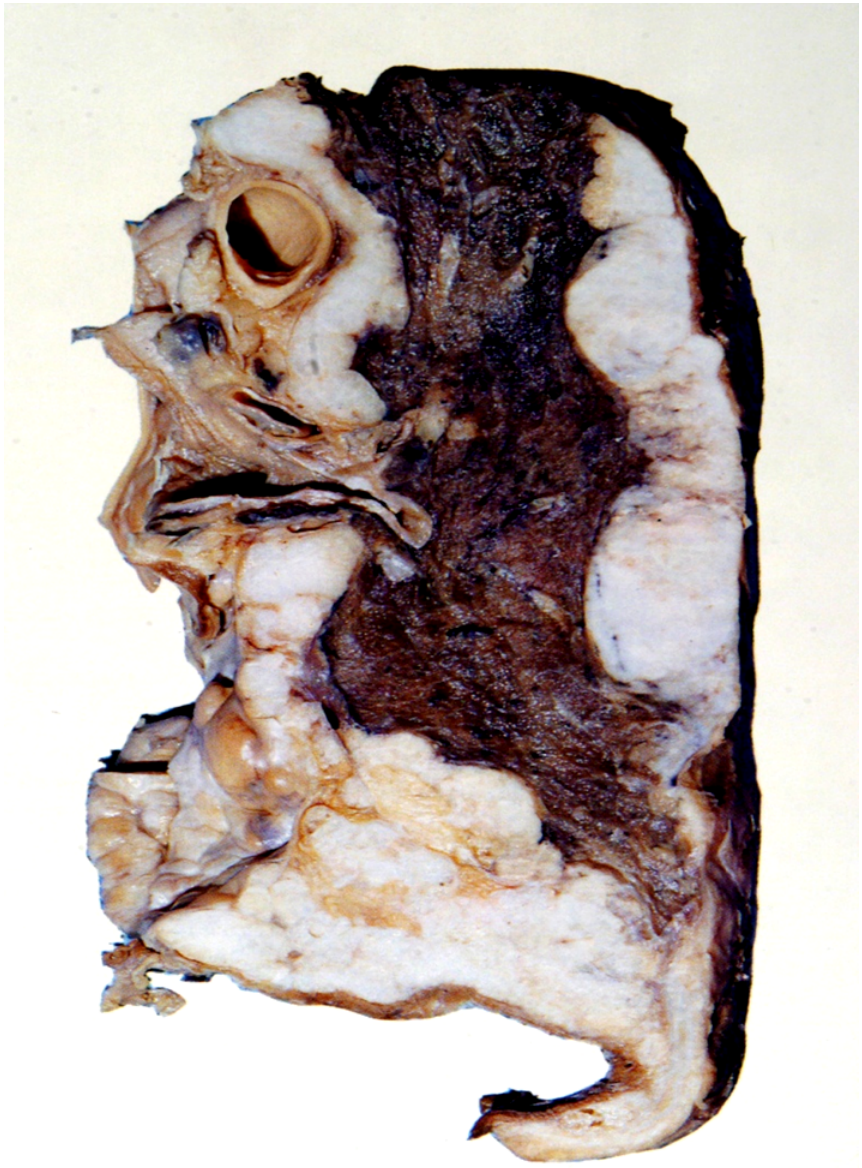


Pneumoconiosis : Asbestosis

- **Both bronchogenic carcinoma and mesothelioma develop in workers exposed to asbestos.**

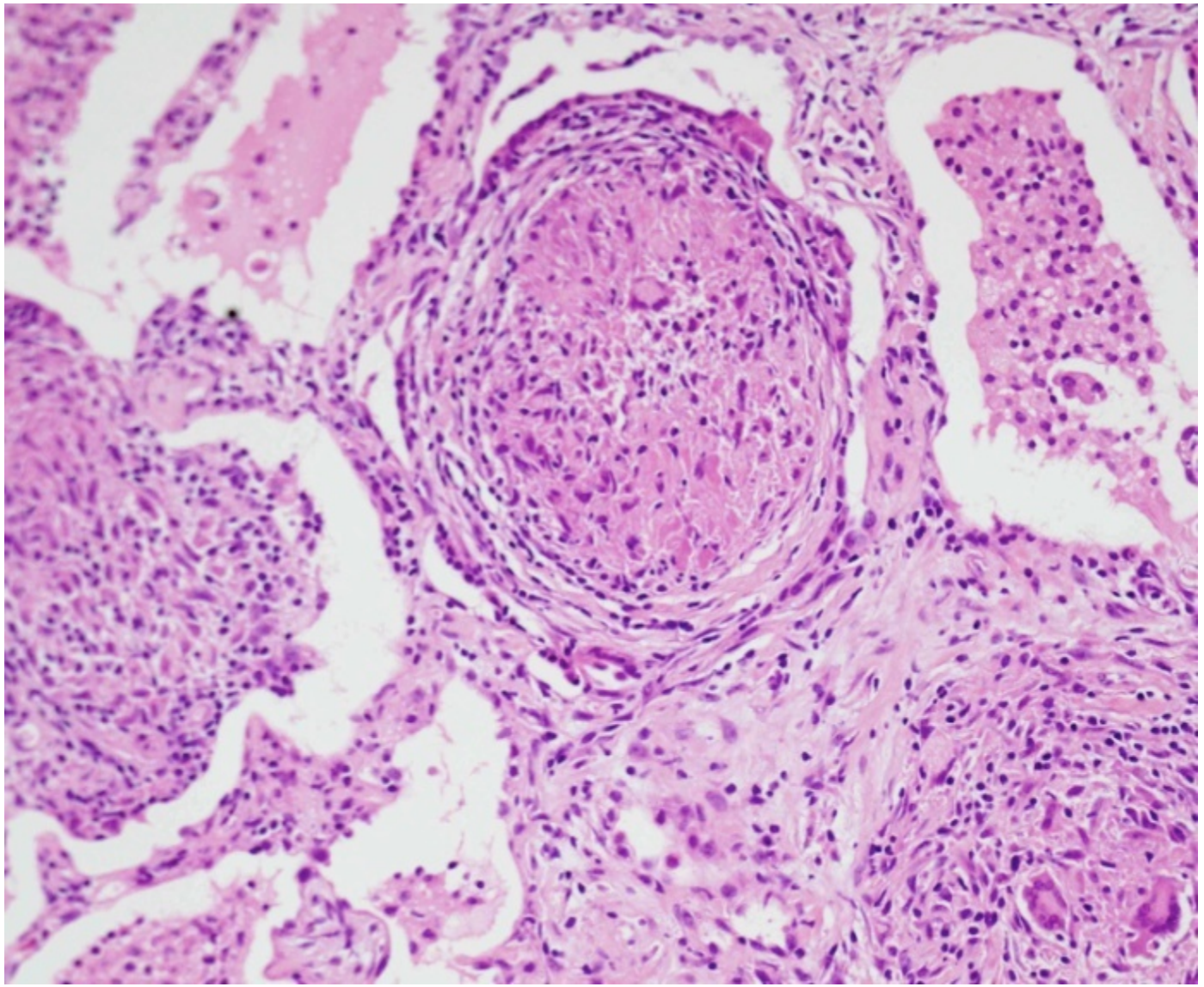
The risk of bronchogenic carcinoma is fivefold and for mesothelioma is 1000 fold greater





Pleural mesothelioma

Berylliosis



Chronic restrictive lung disease

Major Categories of Chronic Interstitial Lung Disease

Idiopathic fibrosing:

Usual interstitial pneumonia (idiopathic pulmonary fibrosis)

Drug:

Chemotherapy, methotrexate, bleomyxin toxicity

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Goodpasture syndrome
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Systemic sclerosis (scleroderma)
Wegener granulomatosis

Radiation Reactions

Hypersensitivity pneumonitis

Prolonged exposure to inhaled organic antigens

- **Hypersensitivity pneumonitis an immunologically mediated (type III and IV)**
- **Caused by intense and often prolonged exposure to inhaled organic dust**
- **It primarily affects the alveoli and is therefore often called allergic alveolitis**
- **These dusts come from sources such as dairy and grain products, animal droppings and animal proteins etc. Poultry and other bird handlers are commonly exposed to droppings, feathers, and serum proteins of pigeons etc.**
- **The most common antigens are thermophilic *Actinomycetes* species and avian proteins and the most common diseases are farmer's lung and bird fancier's/handler's lung.**
- **It is an occupational restrictive disease**

Hypersensitivity pneumonitis

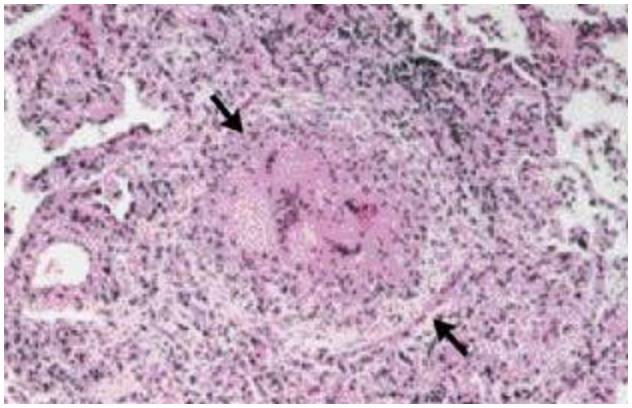
- **Immunologically mediated disorder affecting airways and interstitium**

Farmer's lung
Thermophilic actinomycetes in hay

Pigeon breeder's

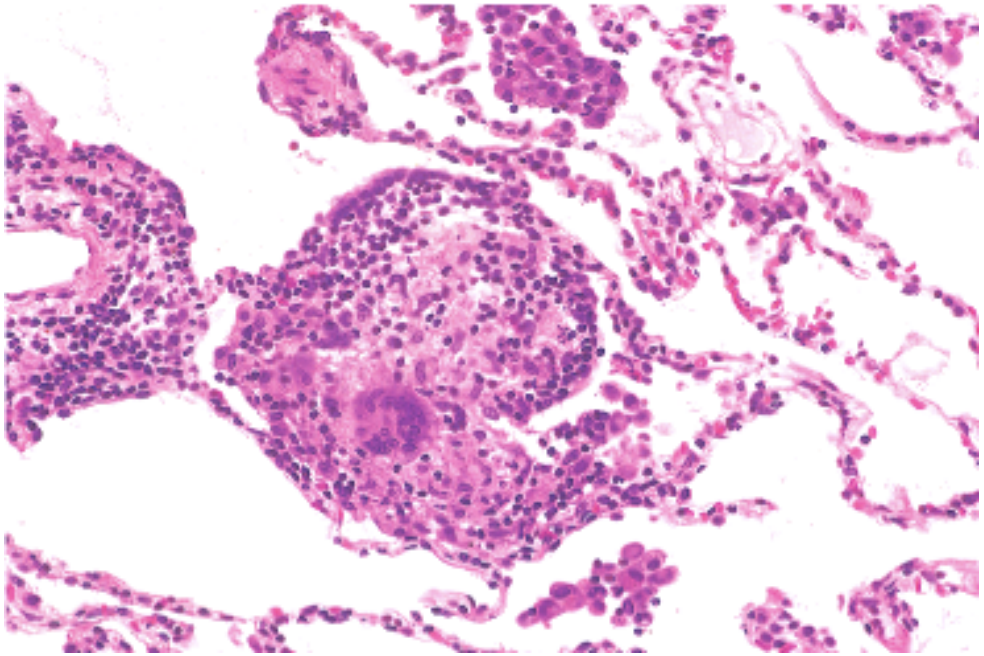
Air-condition lung
Thermophilic bacteria

Sugarcane bagasse
(Bagassosis)



Hypersensitivity Pneumonitis

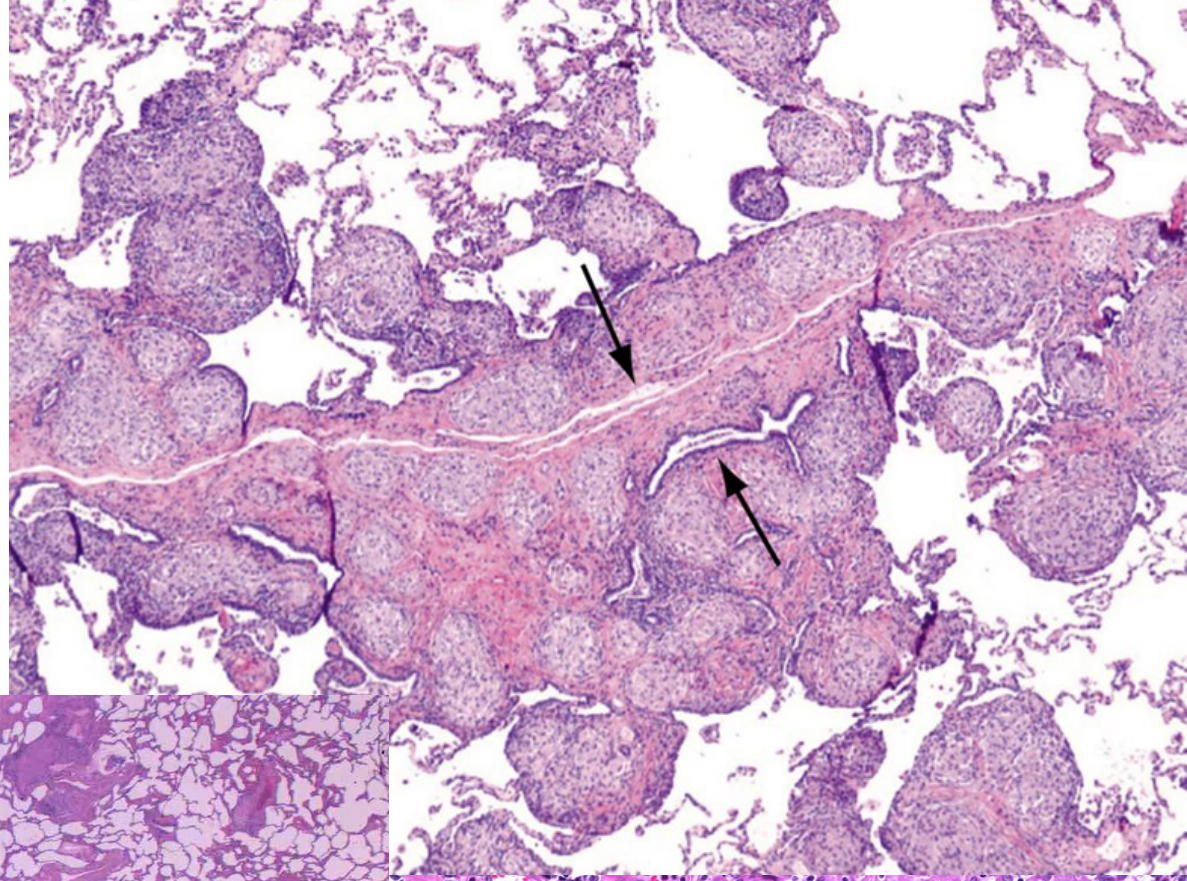
- **Hypersensitivity pneumonitis can present as acute, subacute (intermittent) or chronic progressive.**
- **Morphology: noncaseating interstitial granulomas (IV hypersensitivity reaction), bronchiolitis, interstitial pneumonitis, and diffuse interstitial fibrosis.**
- **Clinical course is variable**

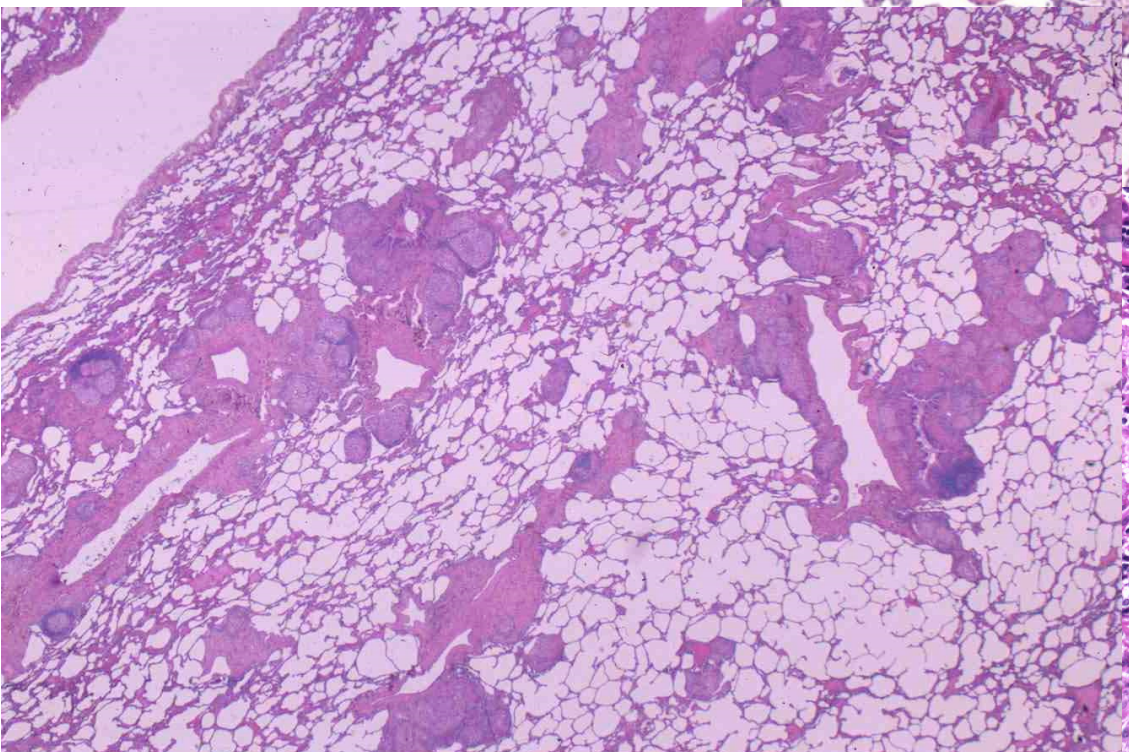


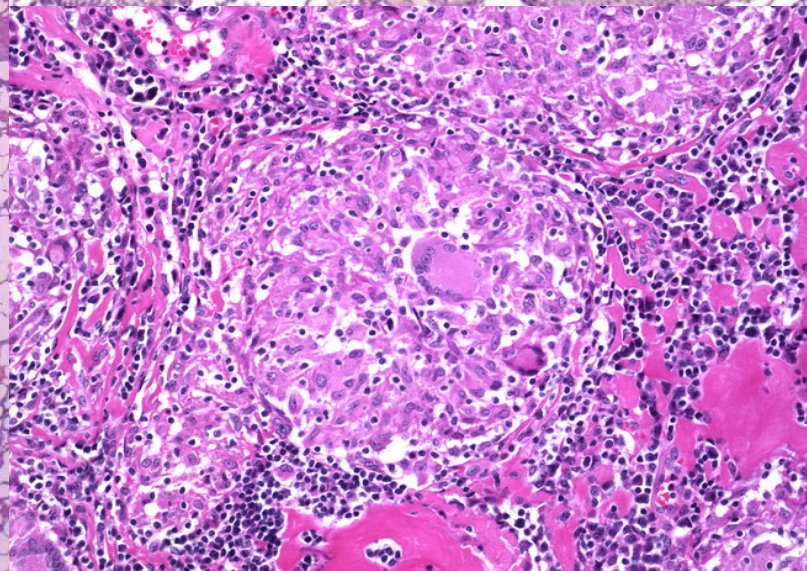
Sarcoidosis

- **Sarcoidosis is a multisystem inflammatory disease of**
    - **unknown cause/etiology**
    - **that predominantly affects the lungs and intrathoracic lymph nodes.**
    - **characterized by non-caseating/ non-necrotizing granulomas in affected organ tissues.**
    - **affecting all races**
    - **affecting both sexes equally**
- **Other organs that may be involved include eyes, skin, liver, spleen and bone marrow. Occasionally kidney, heart, CNS and endocrine organs may be involved.**

- Sarcoidosis granulomas in the lung





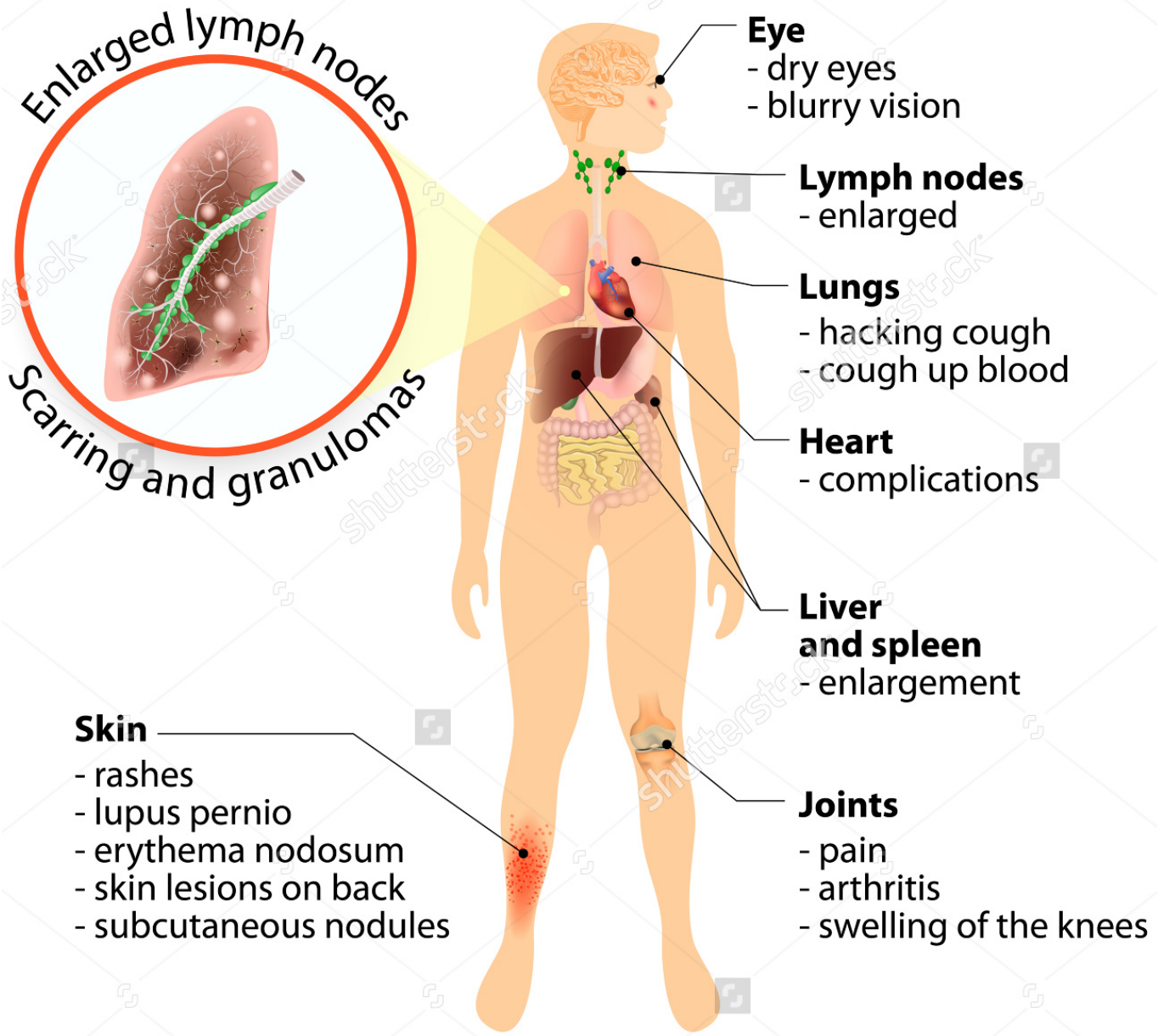


Sarcoidosis

- Clinically the patient may present with fever, anorexia, and arthralgias, dyspnea on exertion, cough and chest pain. Depending on the organs involved the patient can have dermatological, occular, cardiac or neural(rare) manifestations.

- The prognosis of sarcoidosis is unpredictable. It can progressive and chronic. It may present as episodes of activity. Majority of the patients respond well to treatment. A small percentage of patients may die of the complications of sarcoidosis.

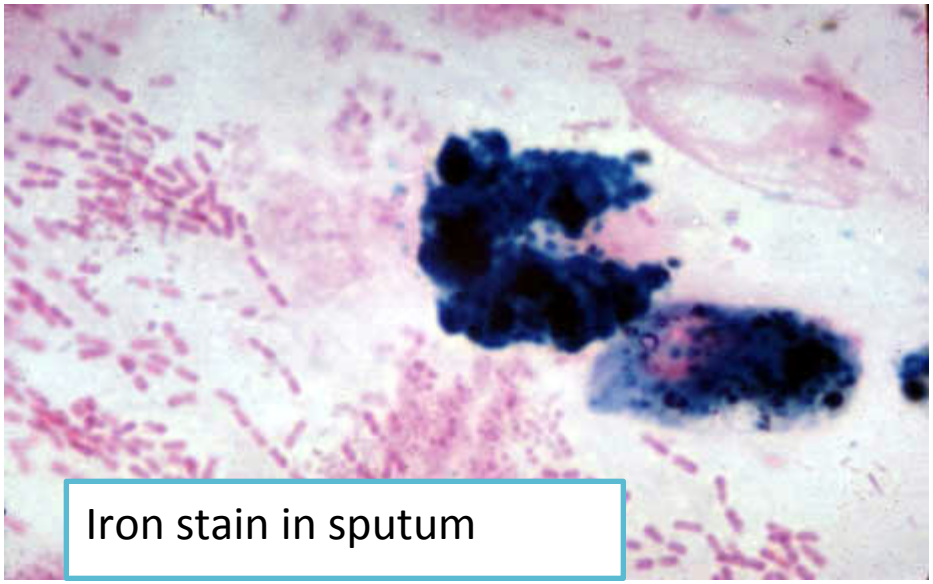
Sarcoidosis

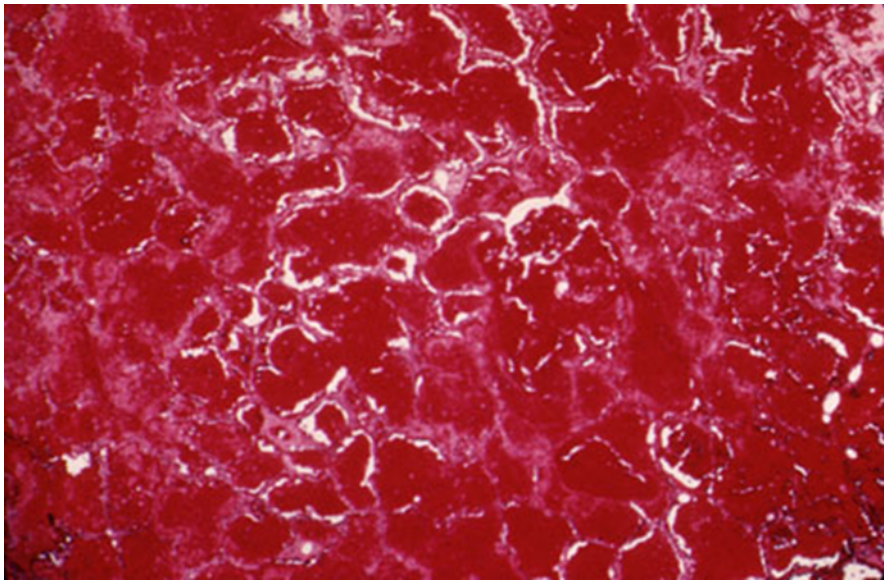


Goodpasture Syndrome/ Anti-GBM disease

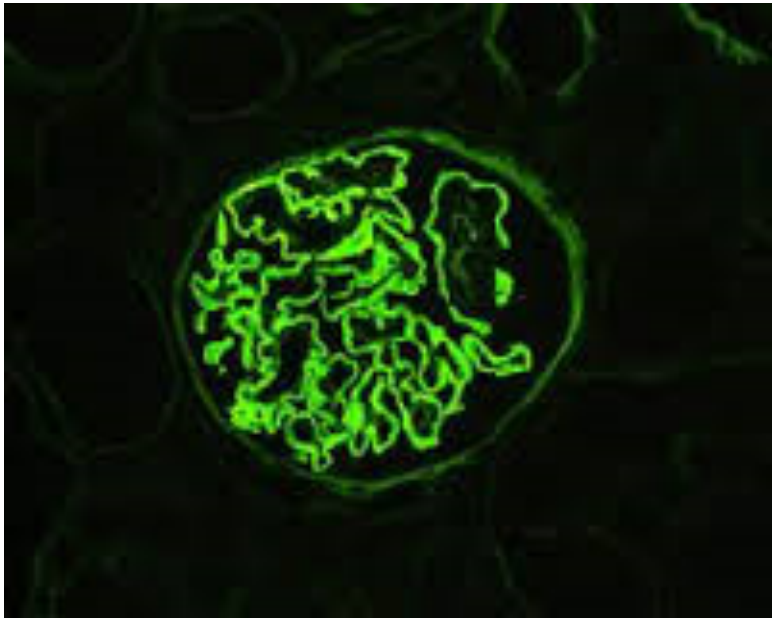
- Rare disease
- Is a triad of
  - diffuse pulmonary hemorrhage,
  - glomerulonephritis,
  - circulating anti-alveolar and anti-glomerular basement membrane (anti-GBM) antibodies
- Anti-GBM disease is an autoimmune disorder.
- The antibody can usually be found in serum.
- Most of the patients have pulmonary symptoms (hemoptysis and dyspnea) and renal symptoms (hematuria, proteinuria, red cell casts and renal failure) and arthralgias.
- The lung will show features of acute necrotizing alveolitis with marked hemorrhage.
- Kidney may show rapidly progressive glomerulonephritis that may lead to renal failure.

Goodpasture syndrome





Immunofluorescence of renal biopsy staining for IgG in a linear pattern in patient with anti-glomerular basement membrane (anti-GBM) disease



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Radiation Reactions

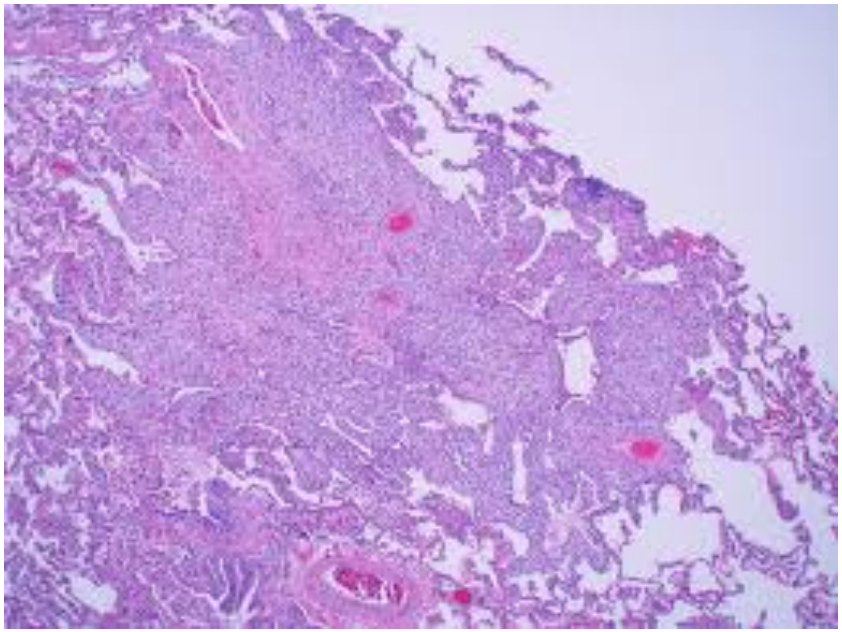
Eosinophilic Granuloma/pulmonary histiocytosis X/pulmonary Langerhan cell histiocytosis X

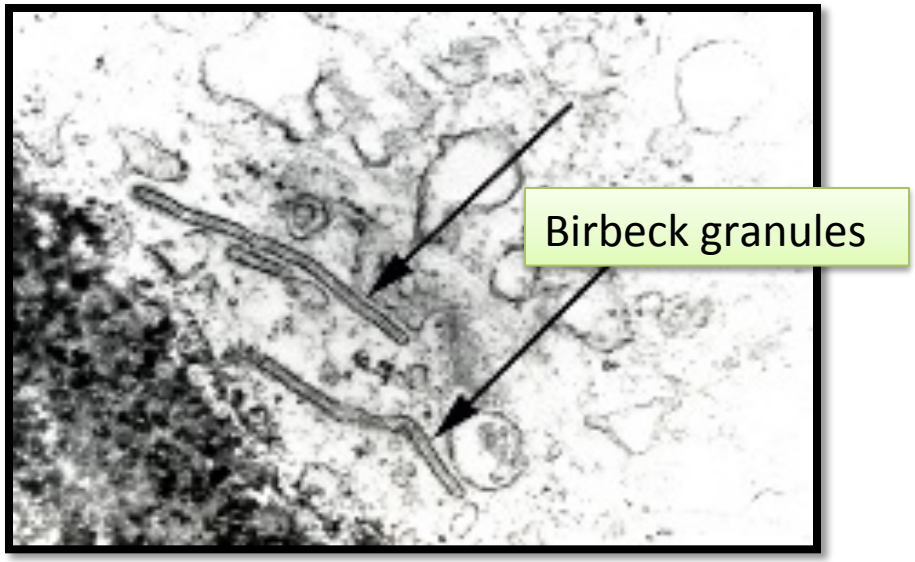
- is an uncommon interstitial lung disease in which there is accumulation of Langerhans cells in the lungs.
- It is considered as a form of smoking-related interstitial lung disease.
- Some patients recover completely after they stop smoking, but others develop long-term complications such as pulmonary fibrosis and pulmonary hypertension.
- It chiefly affects young adults in the third or fourth decades of life.
- It is a localized form of Langerhan cell histiocytosis.
- It commonly involves the lungs. Other organ systems like bone, skin and lymph nodes may also be affected.

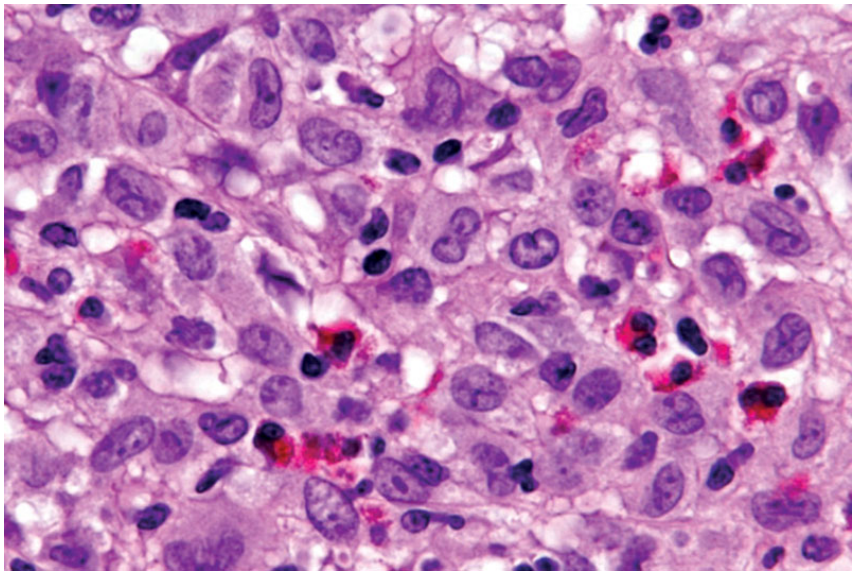
Eosinophilic Granuloma

- In pulmonary Langerhans cell histiocytosis X there is infiltration of the lungs by activated Langerhans cells and eosinophils. They form nodules around the bronchioles, causing destruction of the airway walls. In late stages of the disease, fibrotic stellate scarring.

- They may be identified by immunohistochemical staining with CD1a or by the presence of rod like Birbeck granules via electron microscopy.







Summary

Restrictive lung disease could be acute or chronic

Acute: Adult respiratory distress syndrome most commonly due to pneumonia or septic shock

Idiopathic fibrosing:

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Chemotherapy, methotrexate, bleomyxin toxicity

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Radiation Reactions