Respiratory block
2018

Restrictive Lung Disease

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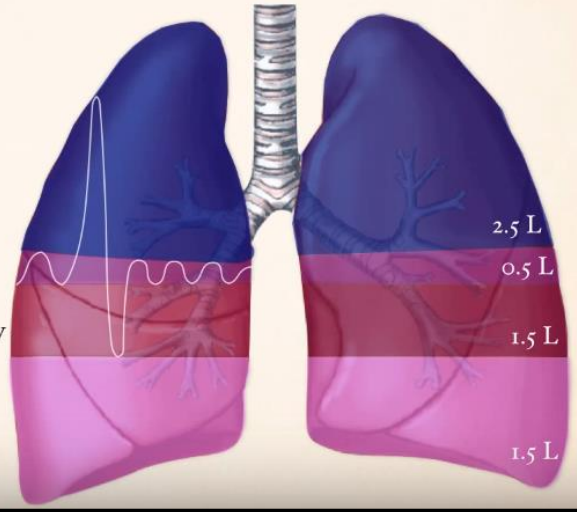
Objectives

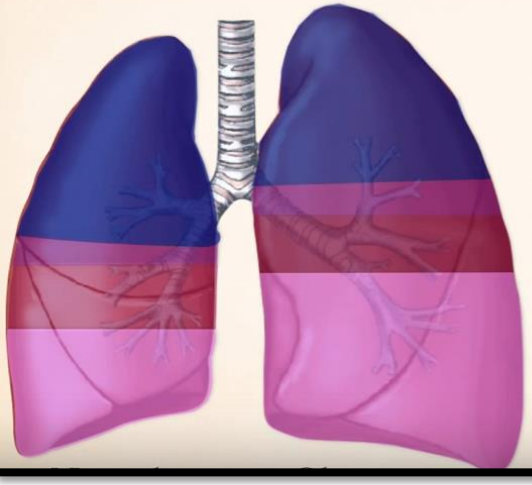
- Understand the structure and constituents of the lung interstitium as well as the restrictive changes which occur in diseases of the interstituim (ILD)
- Know the symptoms of ILD: progressive breathlessness and cough
- Know subtypes of ILD: acute and chronic
- Discuss the causes, morphology and outcome 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

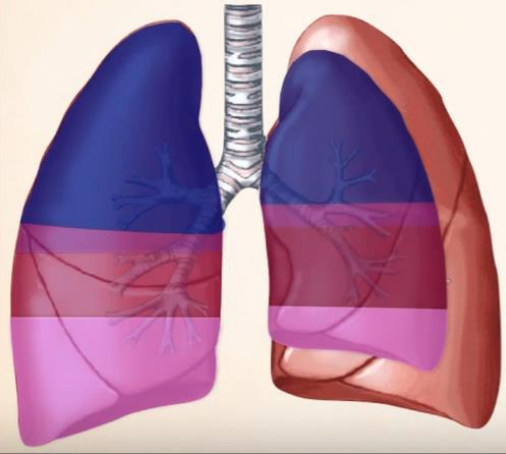


OBSTRUCTIVE



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

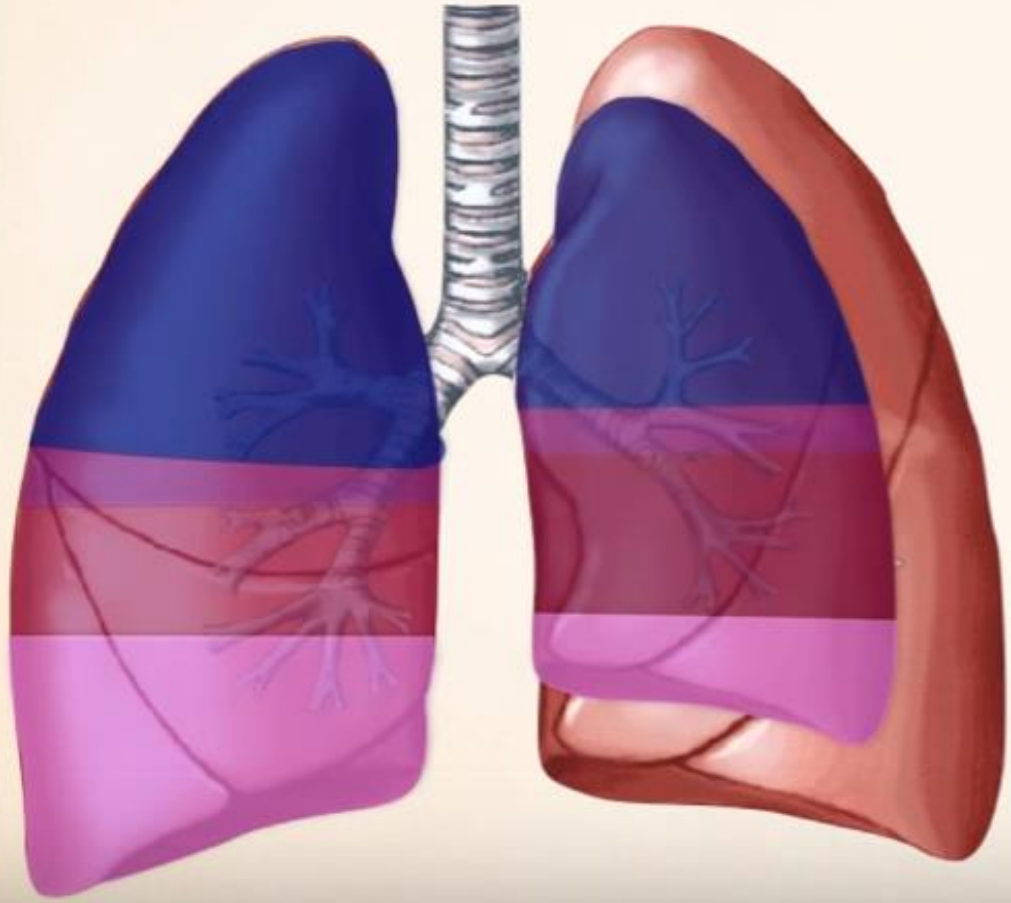
RESTRICTIVE



- 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



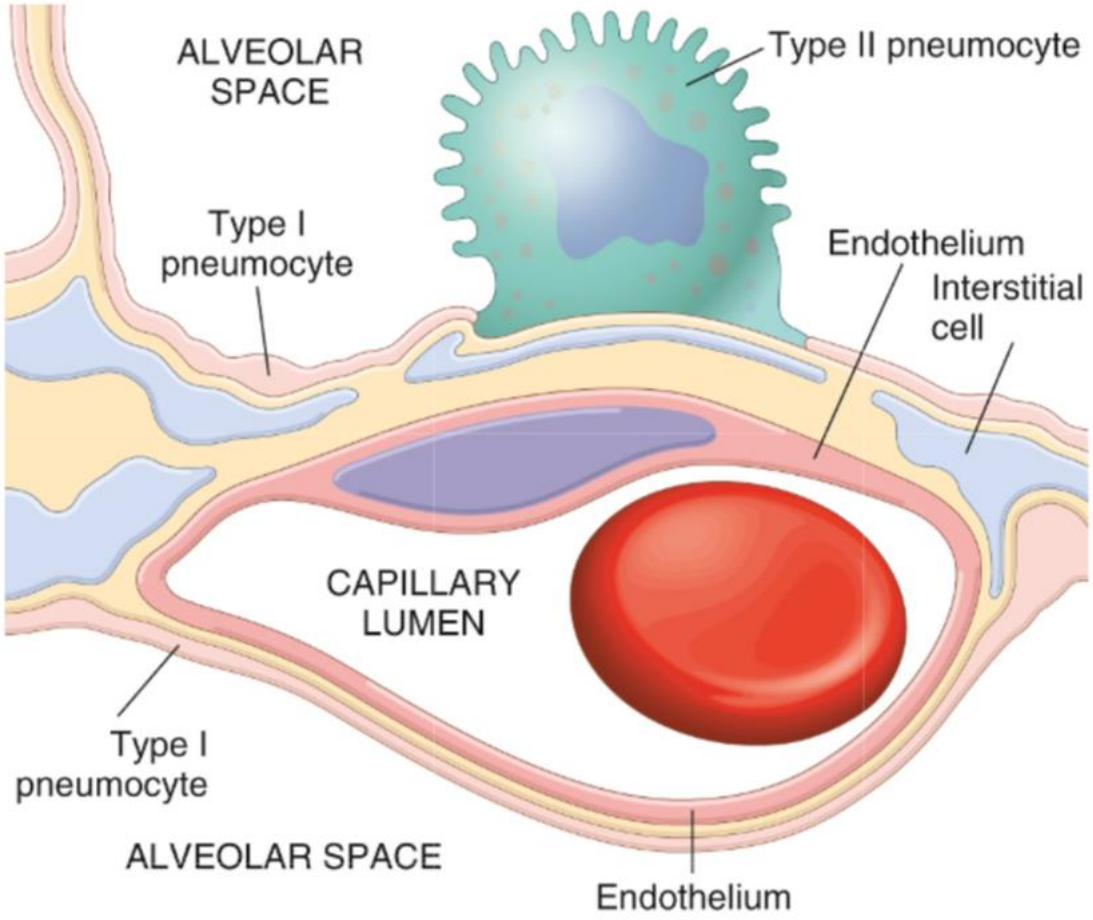
Forced Expiratory Volume in 1sec ↑

Forced Vital Capacity ↓↓

FEV_1 / FVC ↑

Total Lung Capacity ↓↓

Constituents of the lung interstitium



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:

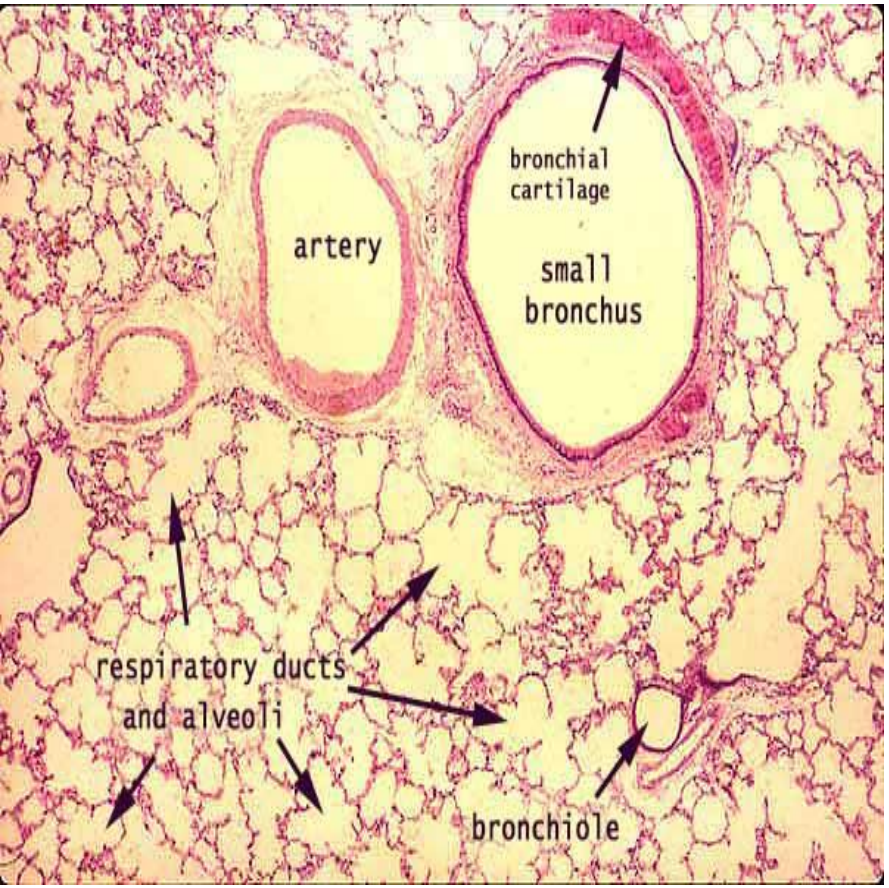
- **bony abnormalities (kyphosis or kypho-scoliosis)**
- **massive pleural effusion,**
- **morbid obesity**
- **neuromuscular disease of respiratoy muscles results in respiratory muscle weakness and respiratory failure e.g. myopathy or myositis, quadriplegia, or phrenic neuropathy from infectious or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

Intrinsic type of Restrictive lung diseases

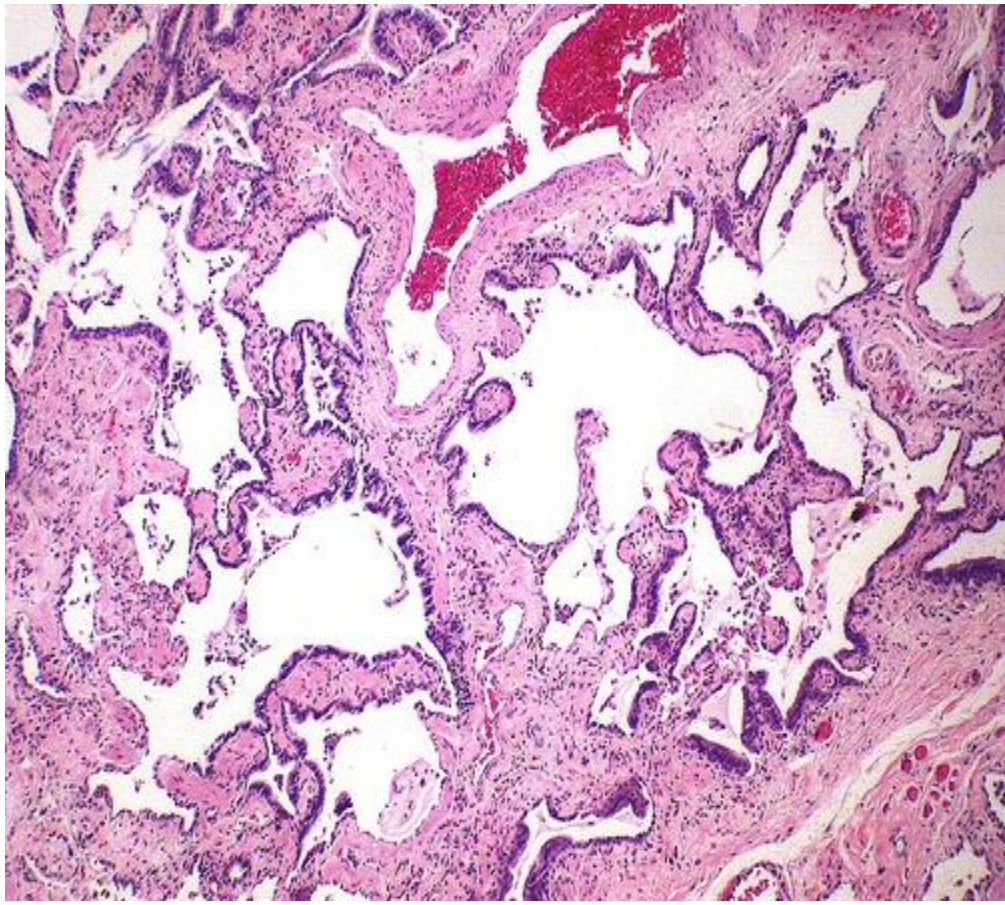
- Characterized by reduced compliance of the lung.
- It can be:
  - Acute.
  - Chronic.
- Important signs and symptoms:
  - Dyspnea.
  - Hypoxia.
  - In advanced cases of restrictive lung disease, there is severe hypoxia, hypercapnia and cyanosis, respiratory failure and cor pulmonale.
- The final stage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

Interstitial lung diseases

Normal



Honeycomb lung



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 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

ARDS

Can be caused by many conditions:

Pneumonia and sepsis are the most common causes

Direct injury to lung

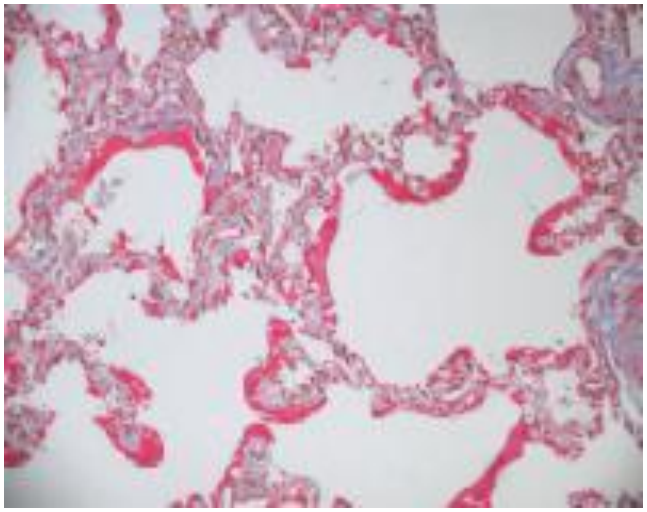
- Pneumonia
- Aspiration of gastric contents
- Pulmonary trauma
- Fat embolism
- Near drowning
- Toxic inhalation injury (irritants such as chlorine, O2 toxicity)
- Post lung transplant
- Severe acute respiratory syndrome (SARS): The virus is a coronavirus that destroys the type II pneumocytes and causes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

ARDS

Pathophysiology

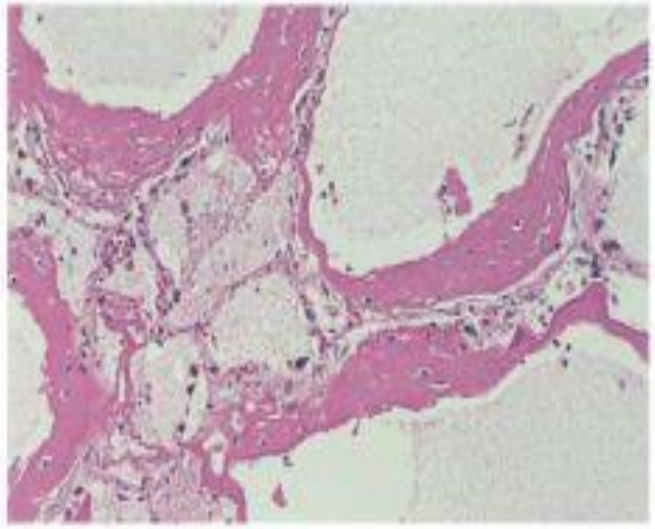


- **ARDS is associated with diffuse alveolar damage.**
- **It is initiated by injury to:**
  1. **alveolar capillary endothelium with a resultant increase in alveolar capillary permeability**
  2. **alveolar epithelium**
- **The injury is induced by the:**

(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

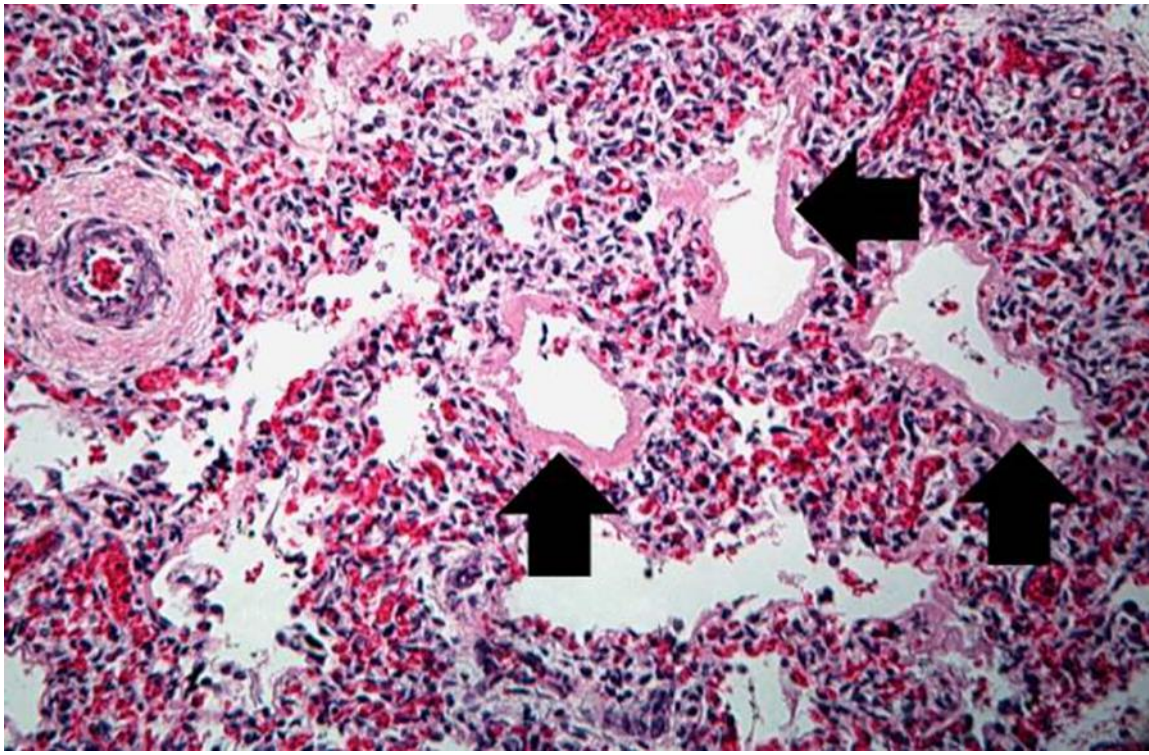
- This causes leakage of protein-rich fluid into alveoli, form alveolar hyaline membranes, line the inner surface of alveoli (the membrane is composed of fibrin and cellular debris)
- The lungs become remarkably heavy and stiff due to inflammation and odema and later interstitial fibrosis.
- Chest x-ray: 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)

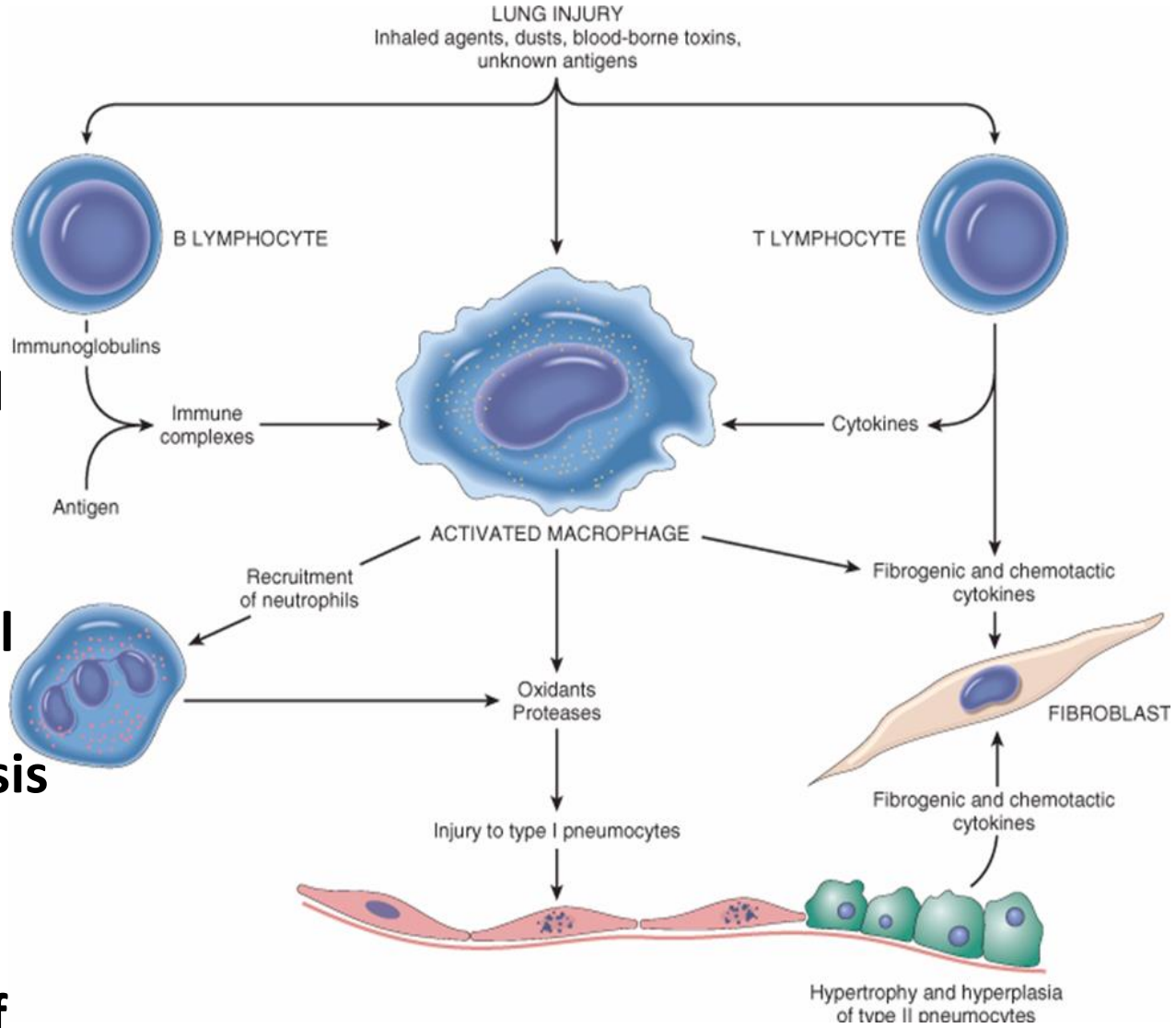
Chronic restrictive lung disease (INTRINSIC TYPE)

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**
- **Release of chemical mediators and promotion of fibrosis**
- **Distortion of the normal structure of alveoli**



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 (Scars formation along the interlobular septa)
- 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

Idiopathic Pulmonary Fibrosis: Pathogenesis

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

At risk epithelium:
Age
Genetics:
Telomerase mutations
Surfactant mutations
MUC5B variant

susceptible host

Persistent epithelial injury/activation

Innate and adaptive immune response

Pro-fibrogenic factors

Abnormal intracellular signaling

Proliferation, collagen production

Fibrosis

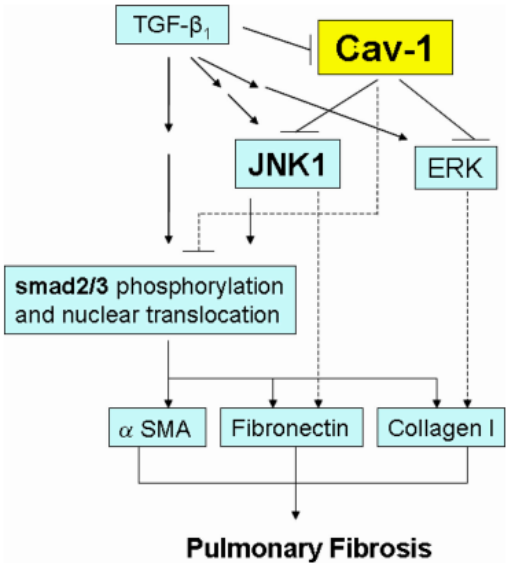


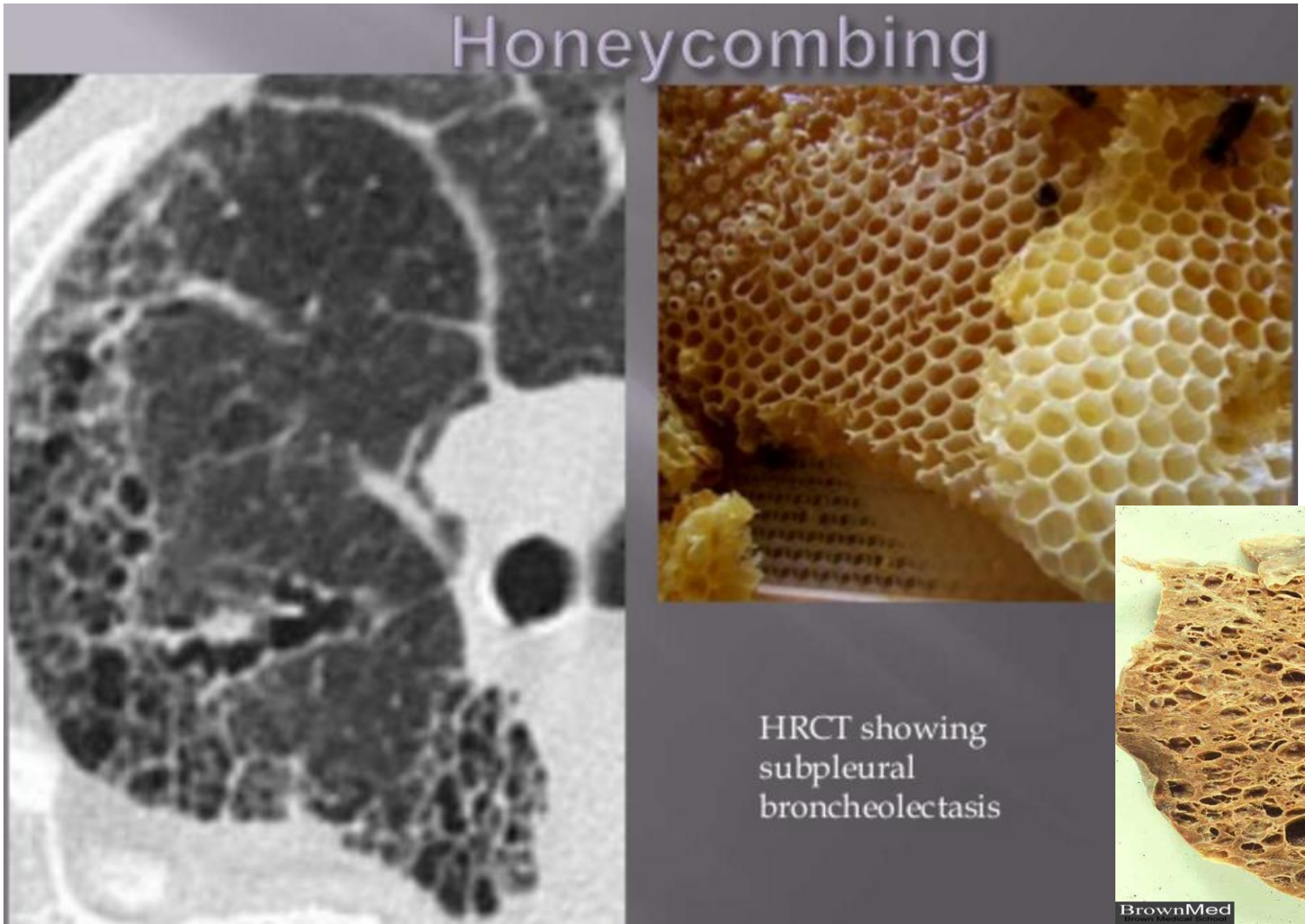
Figure 7. Summary of the role of cav-1 in pulmonary fibrosis. cav-1 modulates TGF-β1–induced JNK1 and smad-2/3 activity and inhibits α-SMA, fibronectin, and collagen type I production.

the injured epithelial cells are the source of profibrogenic factors such as down regulation of caveolin-1 by transforming growth factor Beta I

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

Clinical Features of UIP

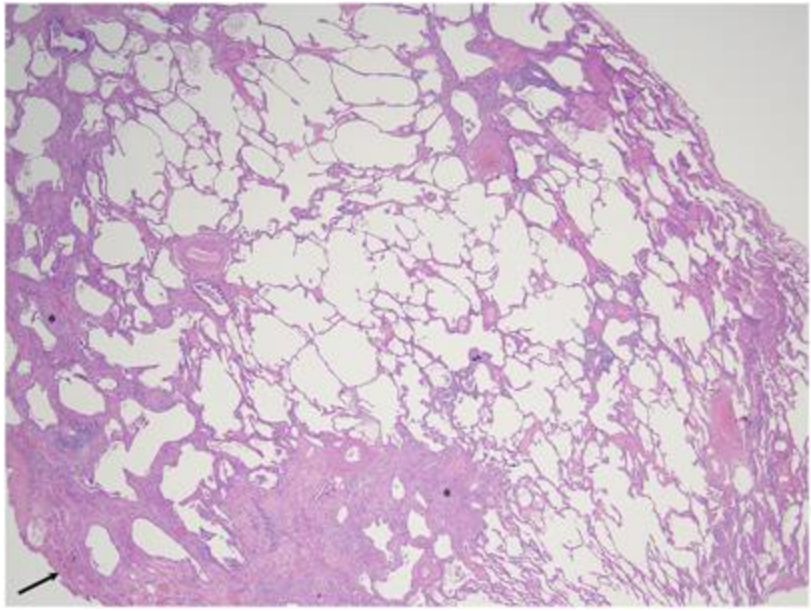
- Most patients present with exertional dyspnea and a nonproductive cough
- A chest radiograph and high-resolution computed tomography typically reveals diffuse reticular opacities.



Morphology of UIP

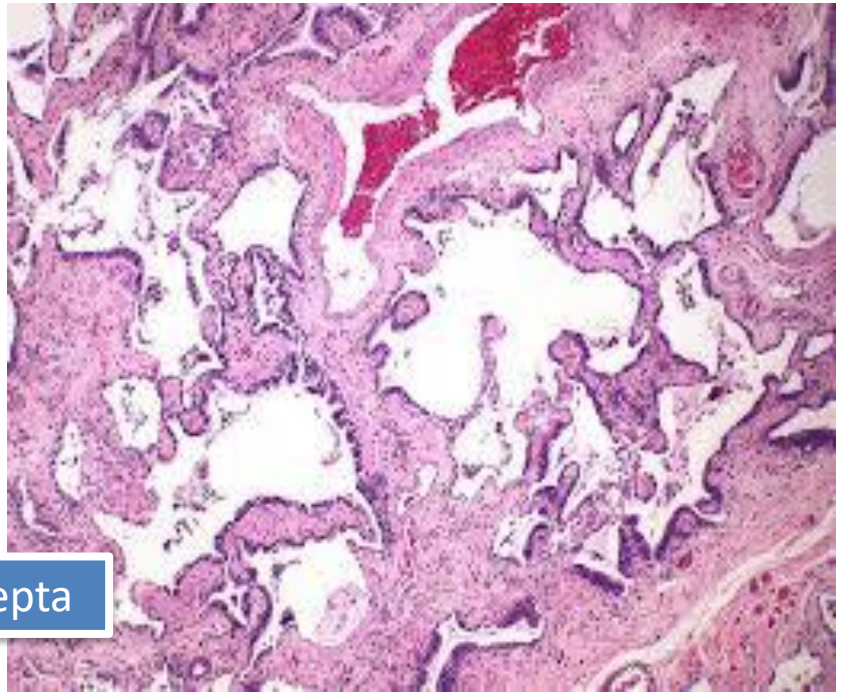
- The morphologic changes vary according to the stage of the disease.
- **Early cases:**

  - 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 pperipheral cystic spaces lined by cuboidal or columnar epithelium separated by inflammatory fibrous tissue (honeycomb lung). Foci of normal lung tissue were also seen. It is the end stage of lung disease



Scars formation along the interlobular septa

Chronic restrictive lung disease

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Silicosis
Berylliosis
Asbestosis

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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.
  - Inflammation damages lung cells and damages the interstitium of the lung by degrading the extracellular matrix glycoproteins
  - Fibroblasts are stimulated and proliferated to produce collagen; fibrosis results
  - As the disease progresses the blood vessels become compromised, and ischemic necrosis may occur

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.

Coal Worker's Pneumoconiosis

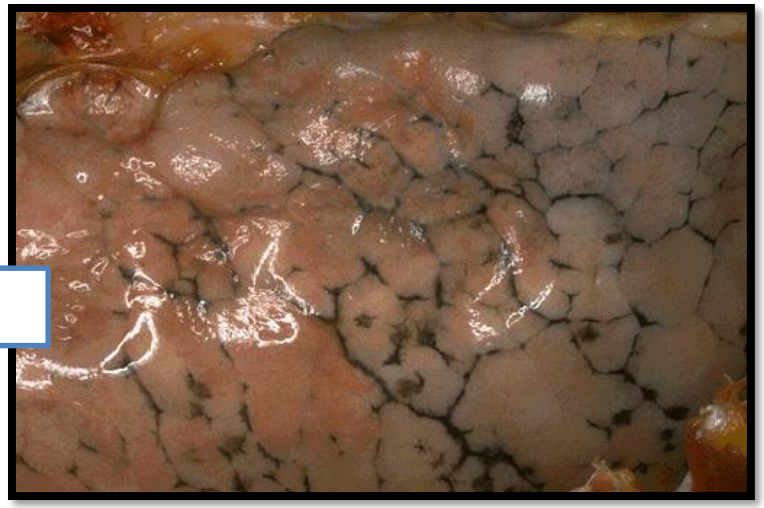
- Coal worker's pneumoconiosis (CWP) can be defined as the accumulation of coal dust in the lungs and the tissue's reaction to its presence.
- The disease is divided into 2 categories:

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.

Occupational: Coal

Anthracosis



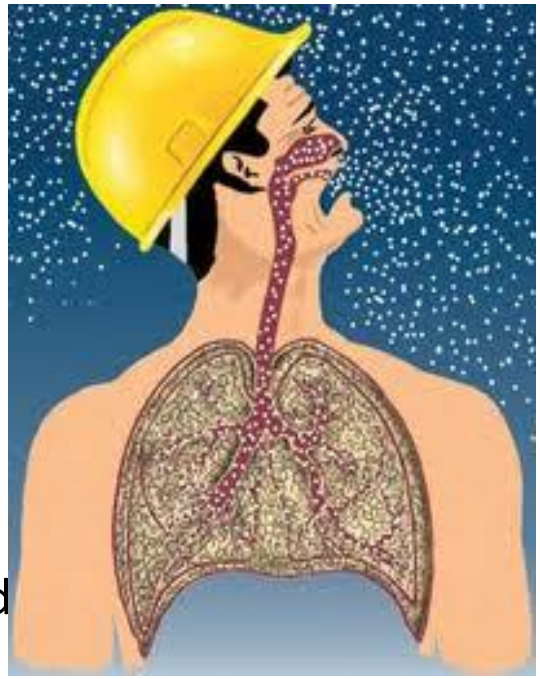
Simple Coal worker pneumoconiosis:

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)

Silicosis



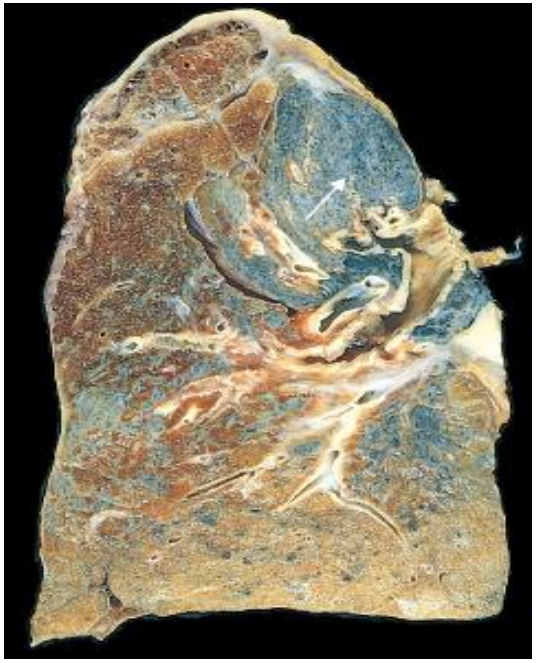
- Silicosis is a fibro-nodular lung disease caused by long term exposure to inhalation of crystalline silica particles (alpha-quartz or silicon dioxide).
- Industrial exposure: mining of gold, tin, copper and coal, sandblasting, metal grinding, ceramic manufacturing.
- Chronic forms manifest after several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

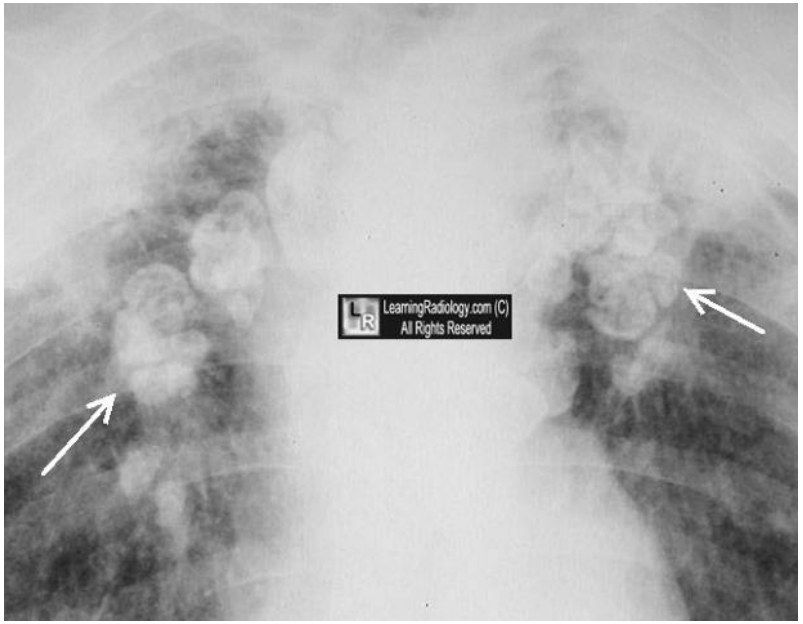
Pathogenesis:

- Crystalline silica is highly fibrogenic.
- Scattered lymphocytes and macrophages are drawn rapidl 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.
- Calcifications may appear (eggshell calcification)
- Similar collagenous nodules within the lymph nodes.
- Fibrous pleural plaques may develop.



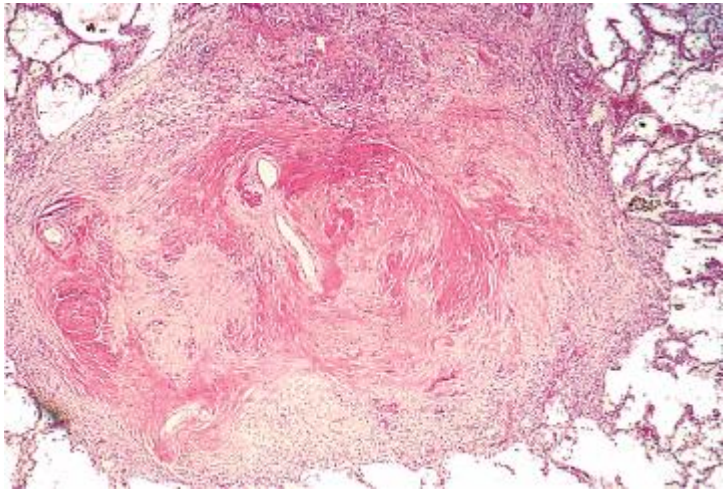


Occupational: Silicosis

Morphology:

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

- Scarring progress to progressive massive fibrosis.

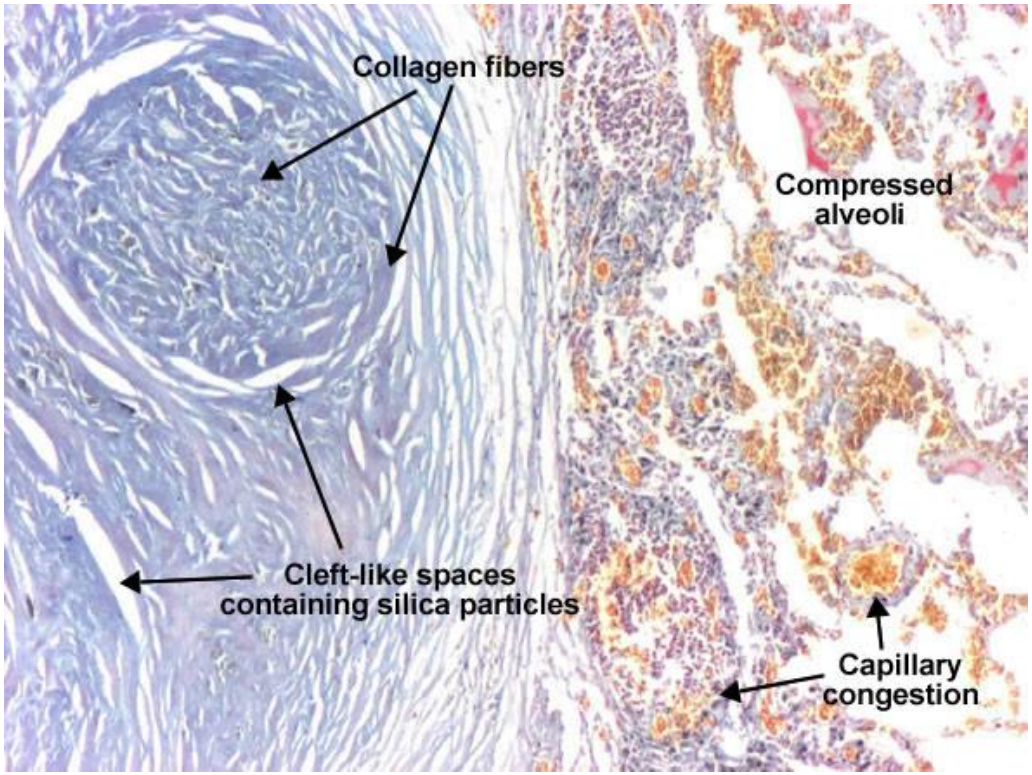


Prognosis:

- 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)

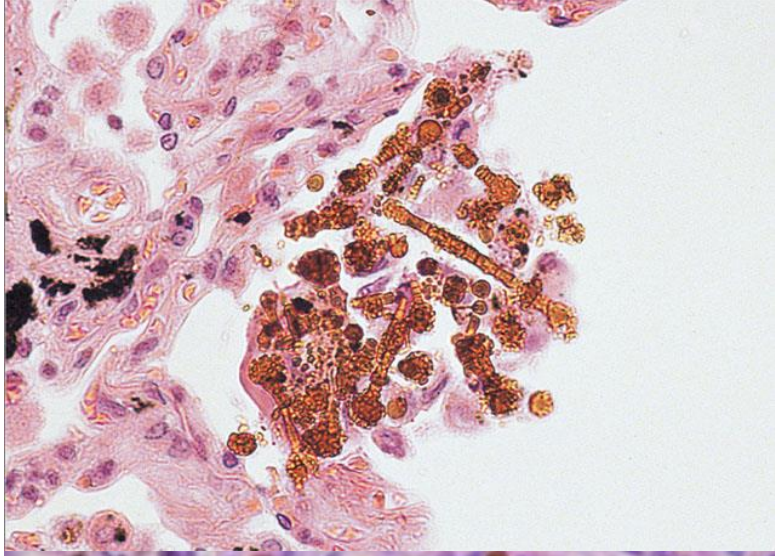
-Patients with silicosis have double the risk for developing lung cancer

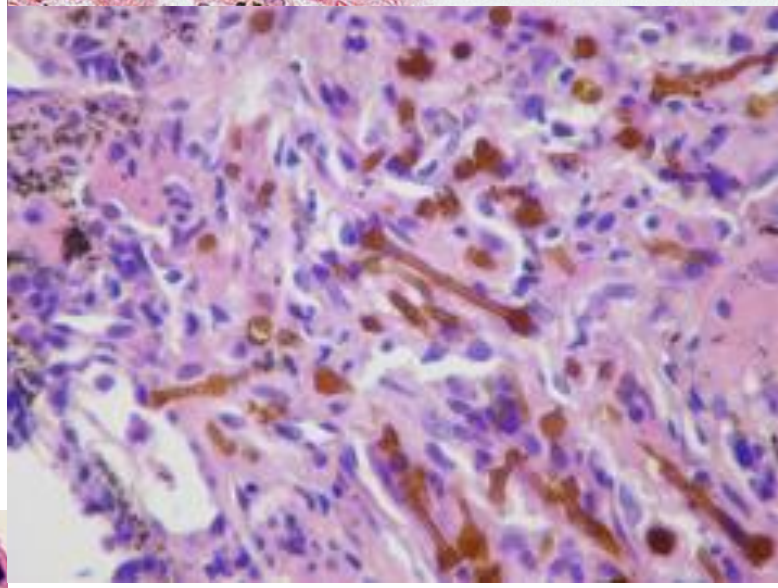


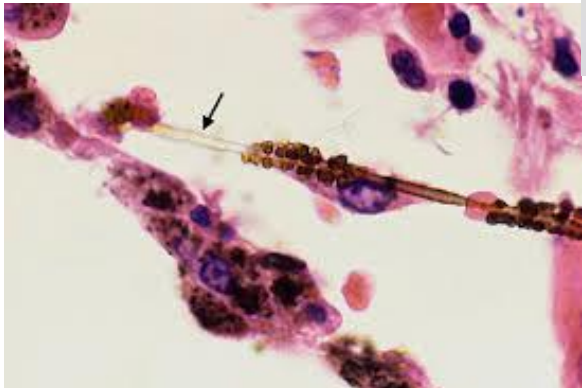
Occupational: Asbestosis

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.



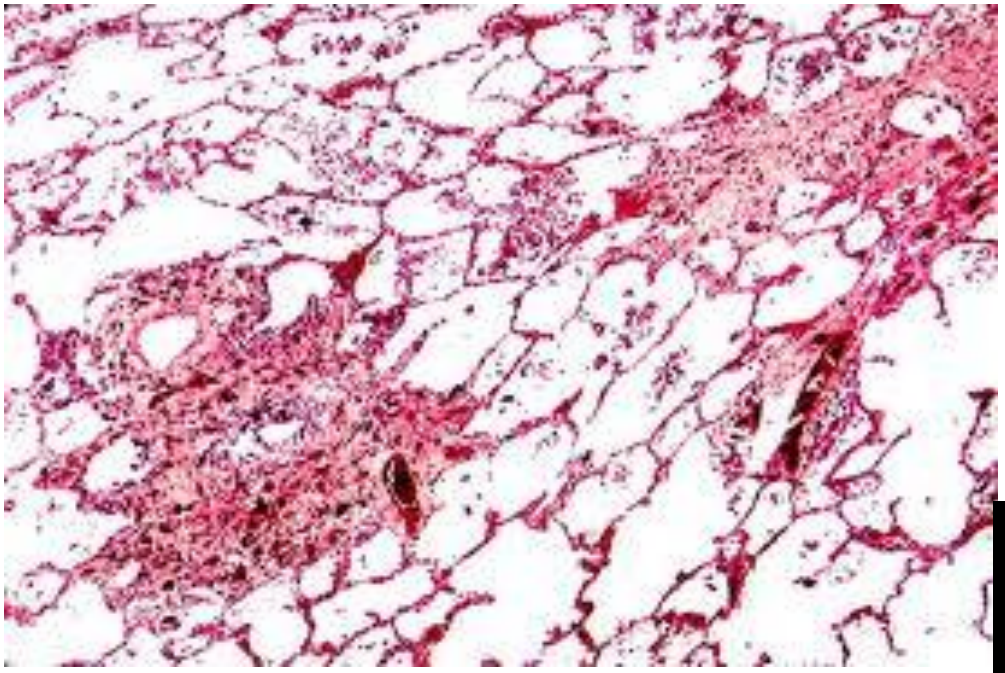


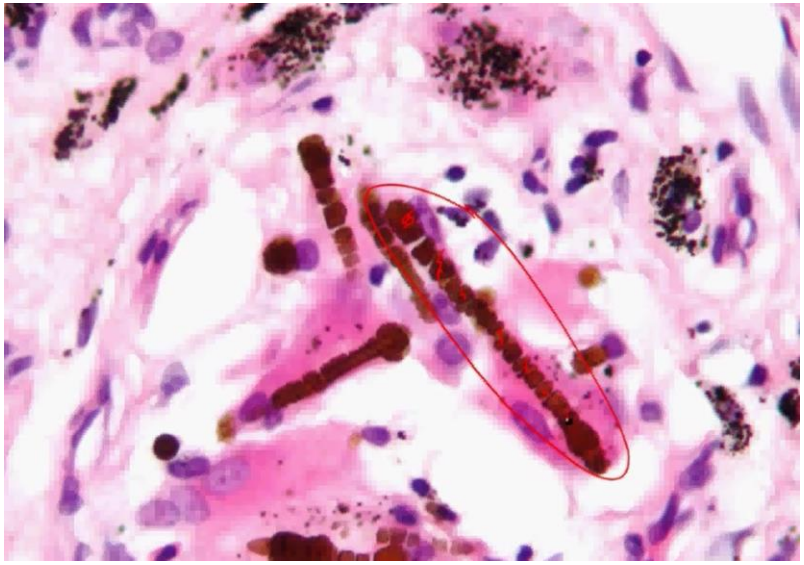


Asbestos bodies are long, thin asbestos fibers coated with hemosiderin and protein to form brown filaments with a beaded or drumstick pattern.

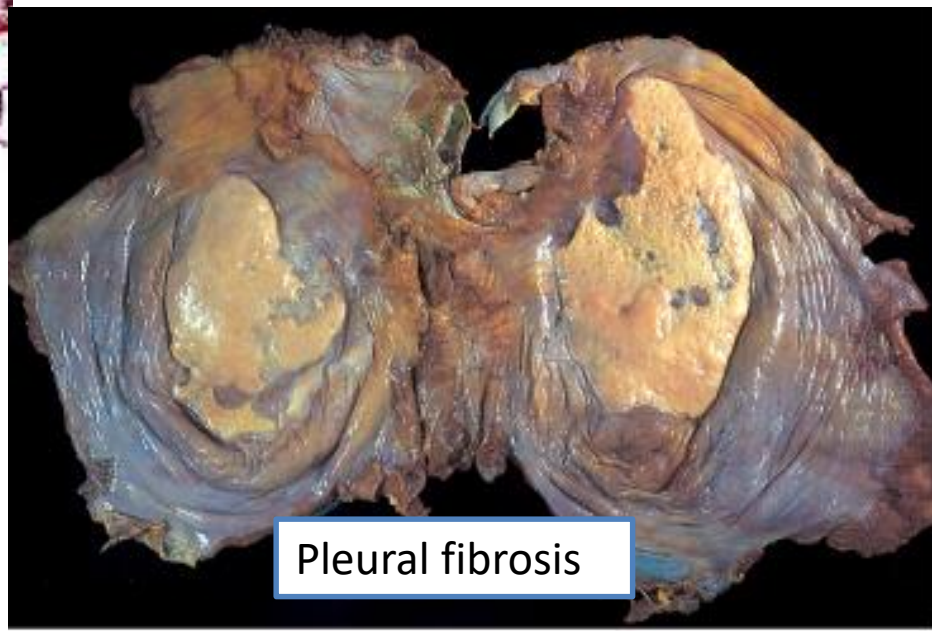
Occupational: Asbestosis

- scarring containing asbestos bodies (ferruginous bodies).





- parietal pleural fibrocalcific plaques

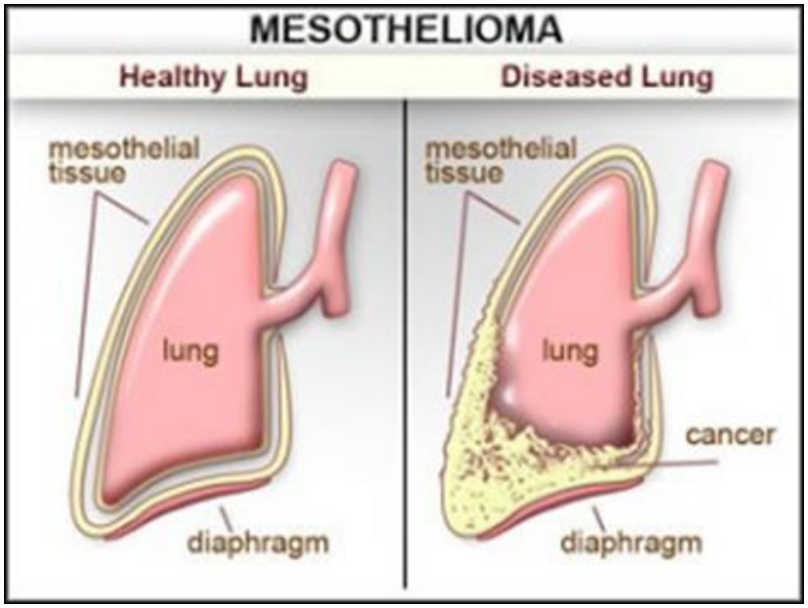


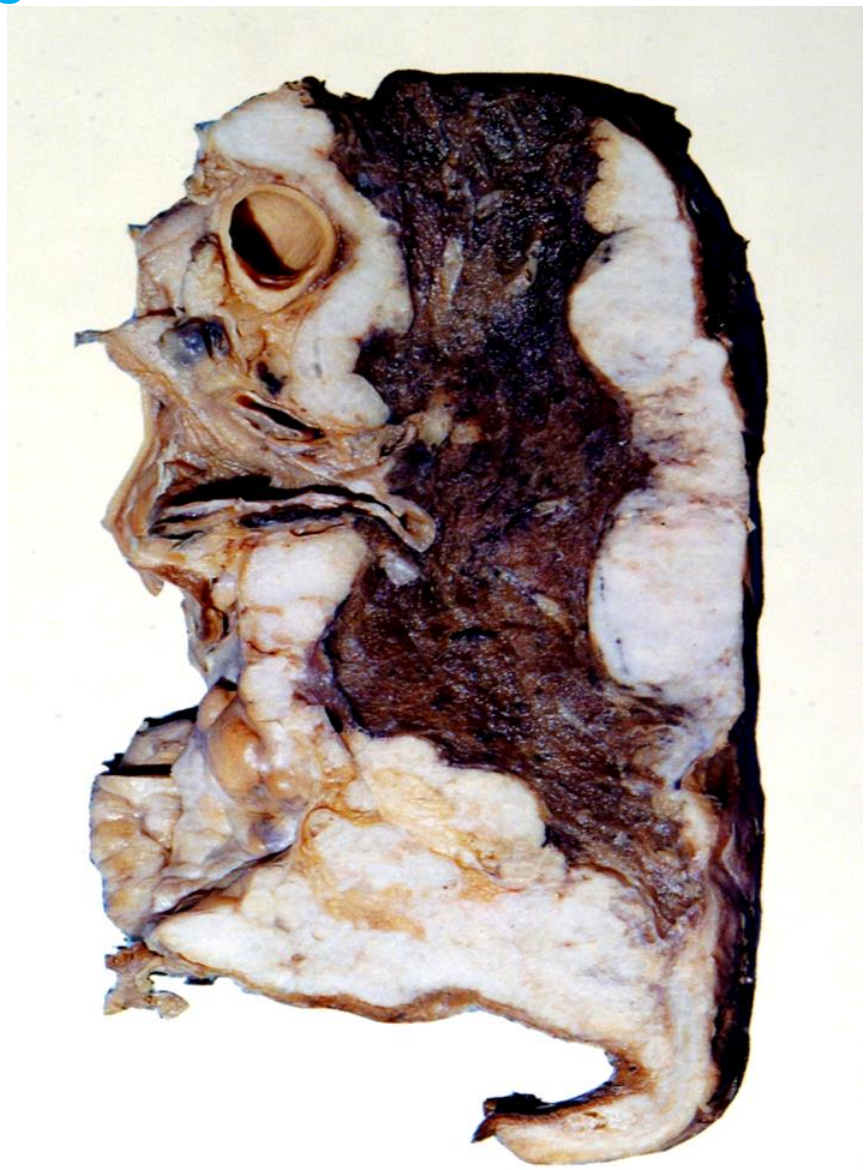
Occupational: Asbestosis

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





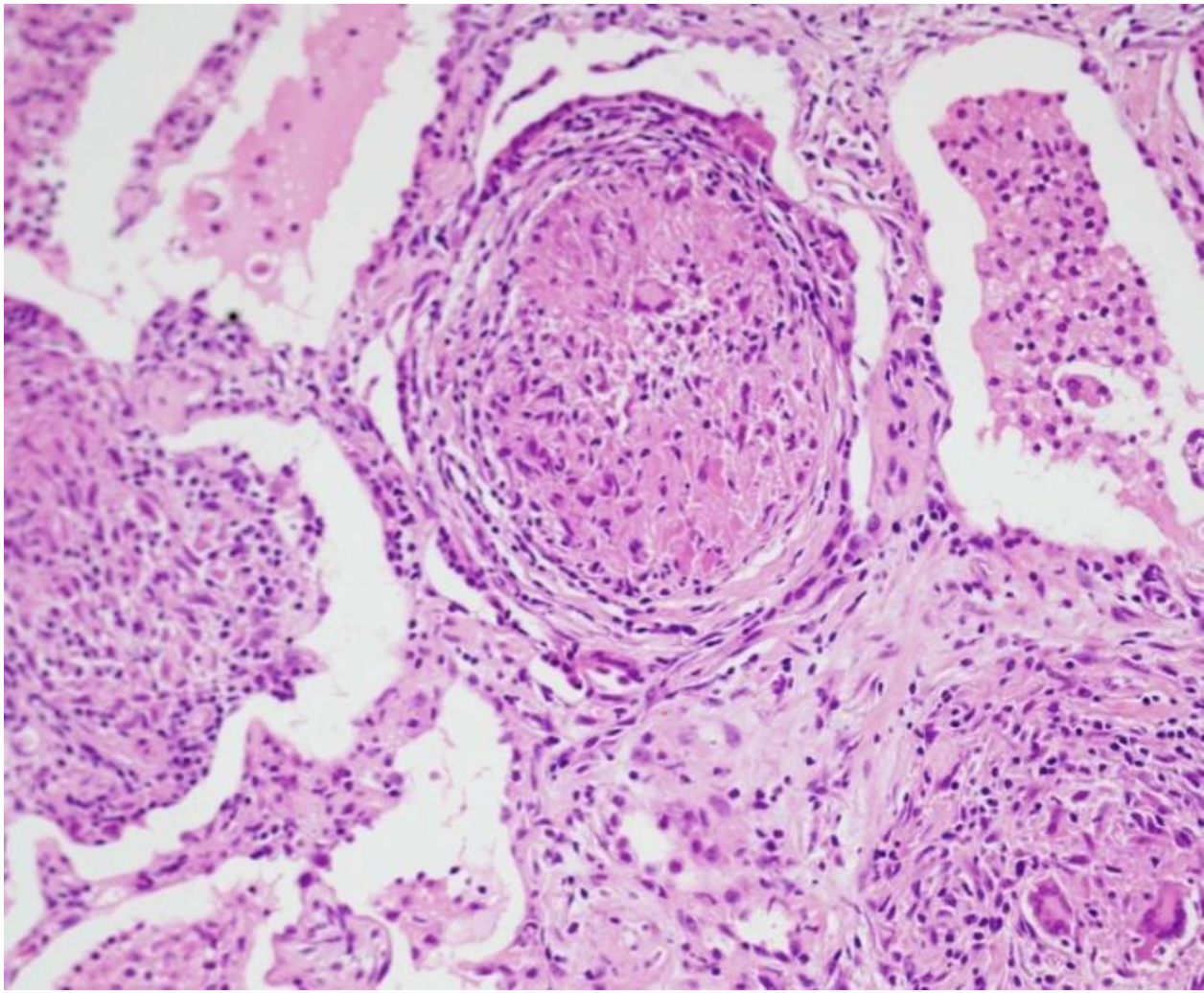
Pleural mesothelioma

Berylliosis

- Beryllium Mining, Aerospace manufacturing

-non-necrotizing granulomata distributed in the parenchyma, LN and other organs

-Pedispose to lung cancer



Occupational: 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

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

Radiation Reactions

Hypersensitivity pneumonitis

Prolonged exposure to inhaled organic antigens

- **Hypersensitivity pneumonitis an immunologically mediated (type III or 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:**
  1. **Evaporative coolers (Desert coolers/ wet air cooler) type AC**
  2. **Dairy and grain products**
  3. **Animal droppings and animal proteins**
  4. **Poultry and other bird handlers are commonly exposed to droppings, feathers, and serum proteins of pigeons etc.**

- **The most common antigens are thermophilic *Actinomycetes* and avian proteins**
- **The most common diseases are farmer's lung and bird fancier's/handler's lung.**

Hypersensitivity pneumonitis

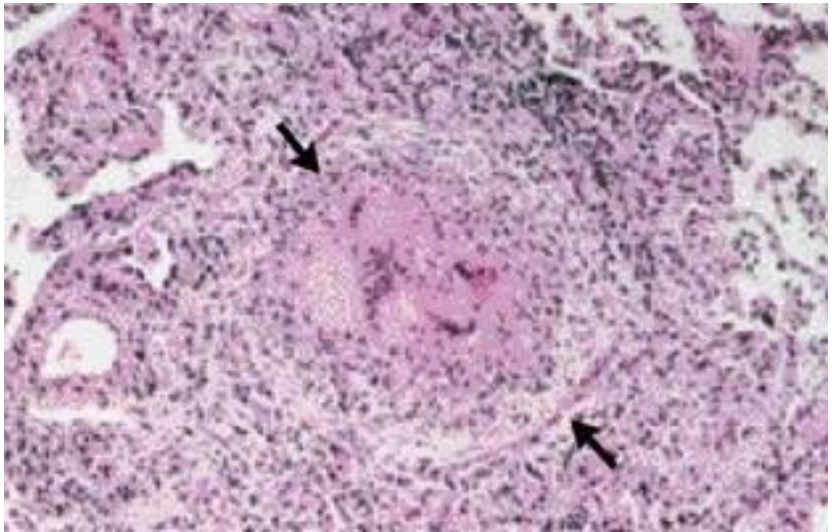
- **Causes: It is an occupational restrictive disease**

Farmer's lung
Thermophilic actinomycetes in hay

Pigeon breeder's

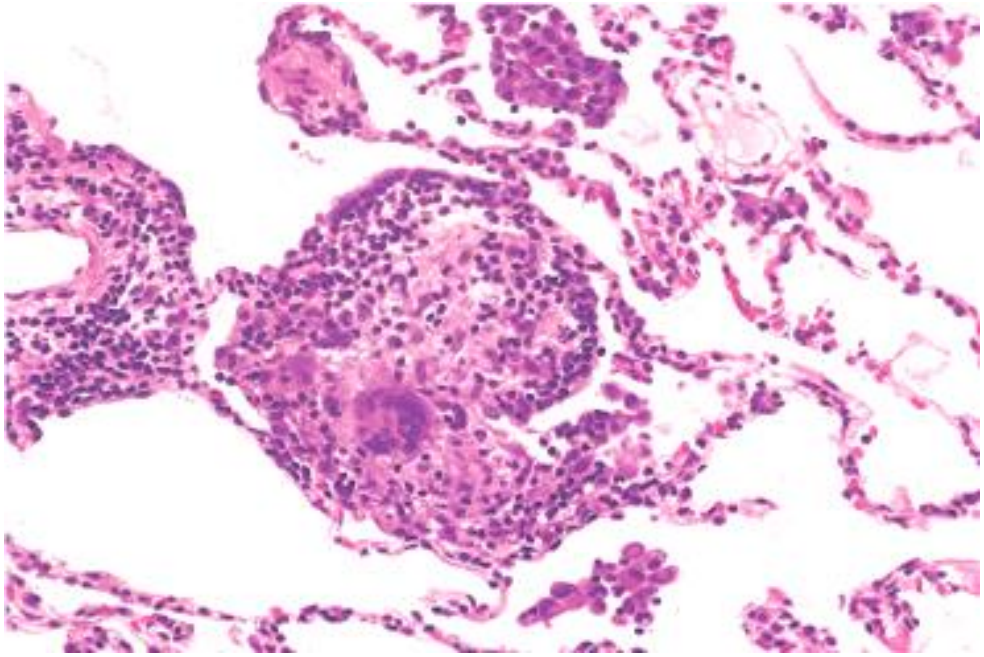
Air-cooler lung
Thermophilic bacteria

Sugarcane bagasse (Bagassosis)



Hypersensitivity Pneumonitis

- **Morphology: noncaseating interstitial granulomas (IV hypersensitivity reaction), bronchiolitis, interstitial pneumonitis, and diffuse interstitial fibrosis.**
- **Clinical course is variable**



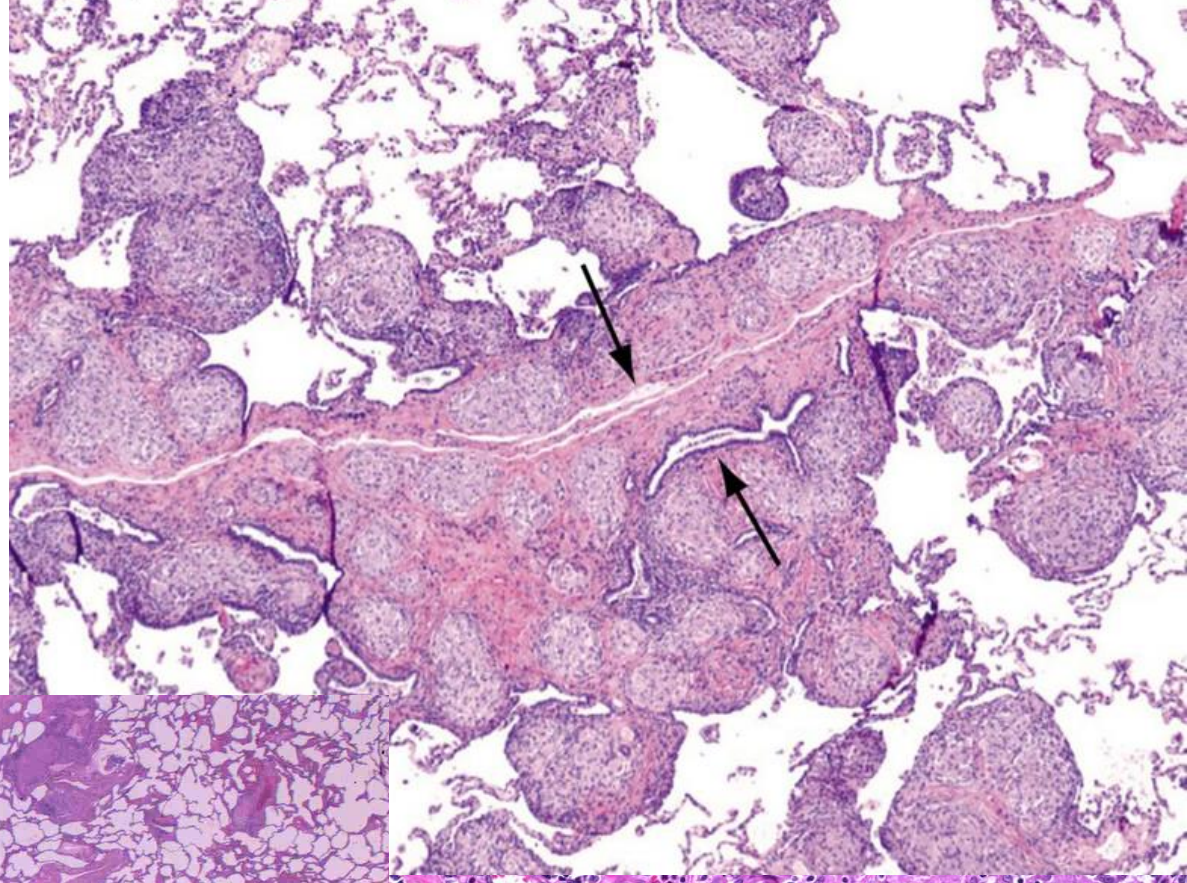
- **Hypersensitivity pneumonitis can present as:**
  1. **Acute:** fever, cough, dyspnea
  2. **Subacute (intermittent)**
  3. **Chronic progressive:** cough, dyspnea, malaise, and weight loss

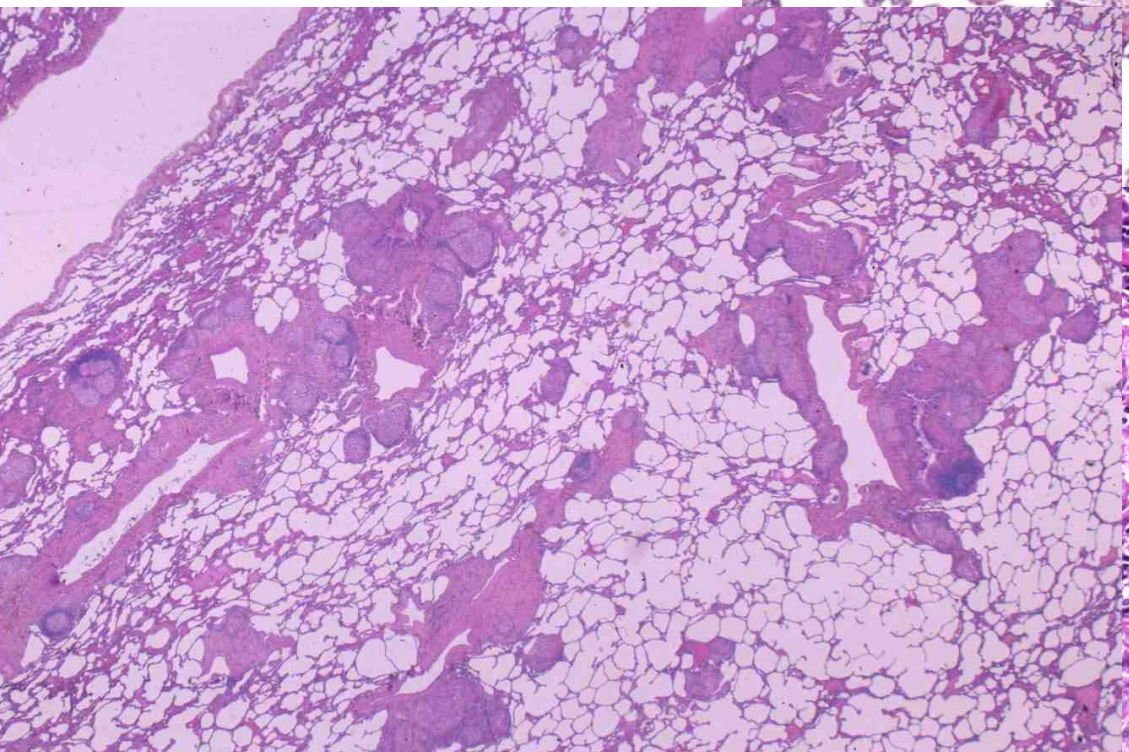
Sarcoidosis

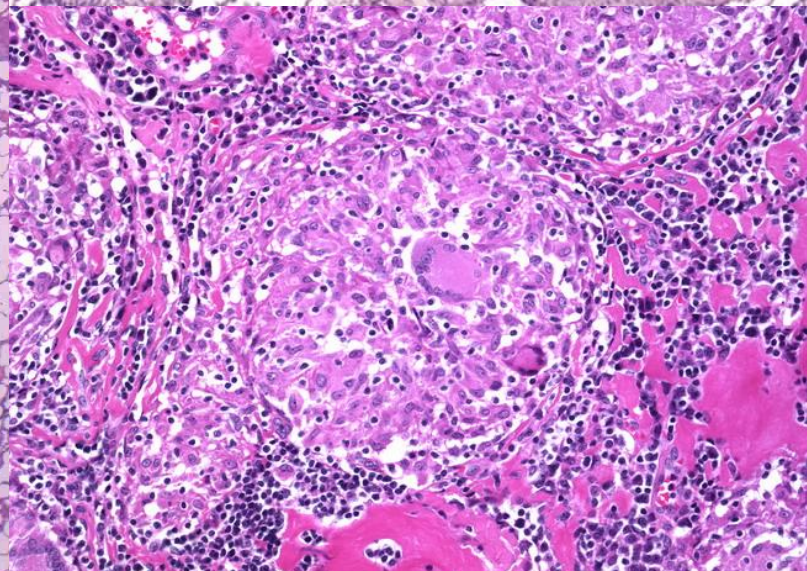
- Sarcoidosis is an inflammatory disease
  - Epidemiology: affecting all races and both sexes equally
  - Cause: unknown
  - Sites: predominantly affects the lungs and intrathoracic lymph nodes
    - Other organs that may be involved include eyes, skin, liver, spleen and bone marrow.
    - Occasionally kidney, heart, CNS and endocrine organs may be involved.
  - Morphology: non-caseating/ non-necrotizing granulomas in affected organ tissues.

Immune diseases: Sarcoidosis

- Sarcoidosis granulomas in the lung



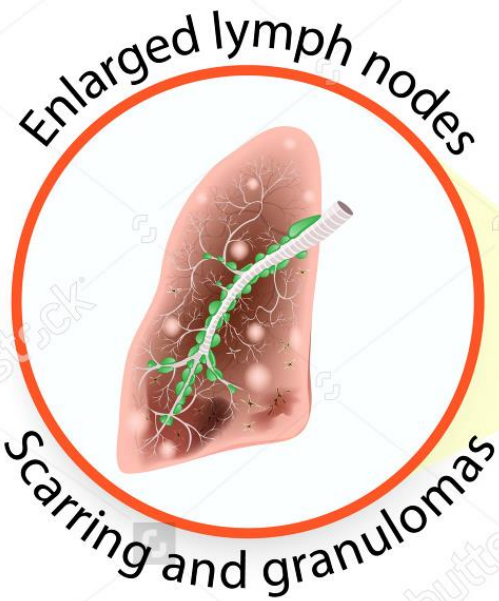




Sarcoidosis

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.



Eye
- dry eyes
- blurry vision

Lymph nodes
- enlarged

Lungs
- hacking cough
- cough up blood

Heart
- complications

Liver and spleen
- enlargement

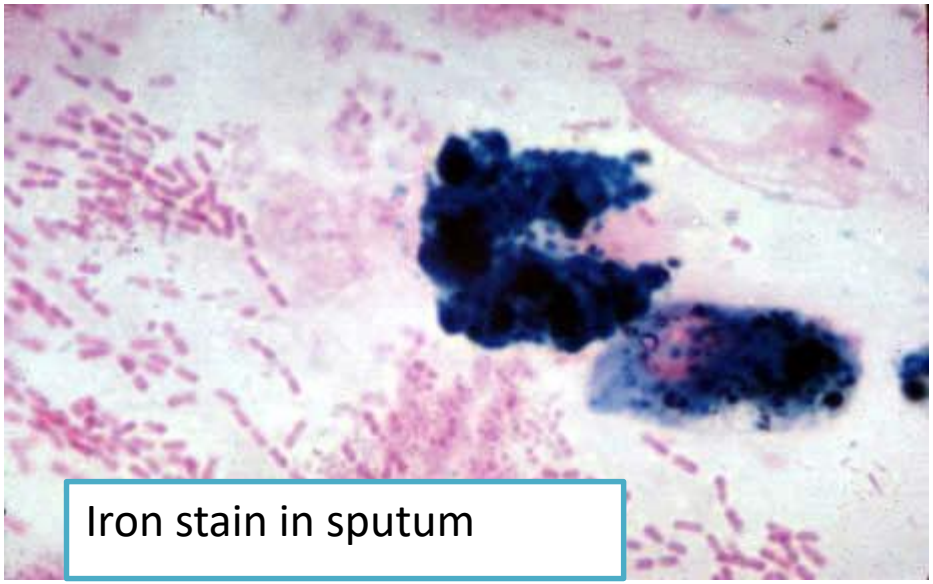
Skin
- rashes
- lupus pernio
- erythema nodosum
- skin lesions on back
- subcutaneous nodules

Joints
- pain
- arthritis
- swelling of the knees

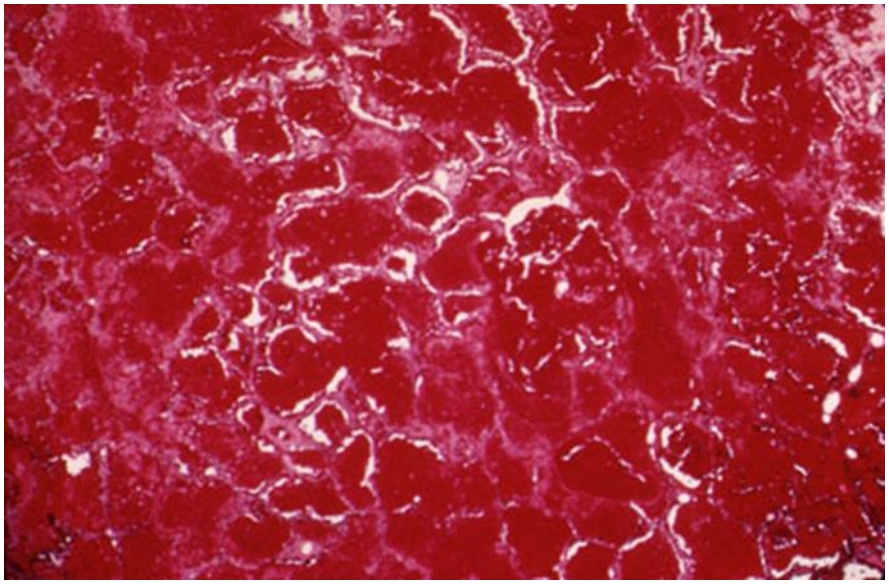
Goodpasture Syndrome/ Anti-GBM disease

- Rare autoimmune disorder
- Is a triad of
  - diffuse pulmonary hemorrhage,
  - glomerulonephritis,
  - circulating (anti-GBM) antibodies against alveolar and glomerular basement membranes
- The antibody can usually be found in serum.
- Morphology:
  - The lung: acute necrotizing alveolitis with hemorrhage
  - Kidney: rapidly progressive glomerulonephritis, may lead to renal failure
- Clinical features:
  1) Pulmonary symptoms (hemoptysis and dyspnea)
  2) Renal symptoms (hematuria, proteinuria, RBC casts and renal failure)
  3) Arthralgias

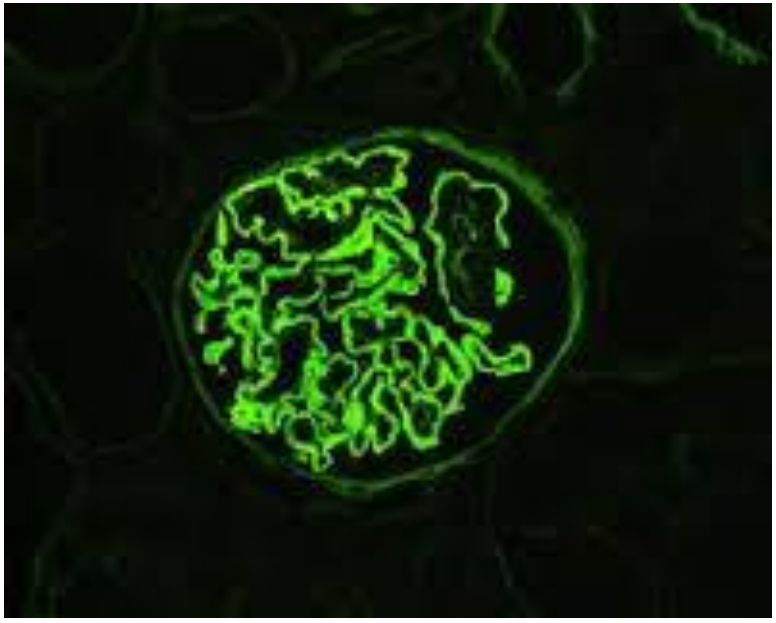
Goodpasture syndrome



Iron stain in sputum



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



Summary

Restrictive lung disease could be acute or chronic

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

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Drug:

Chemotherapy, methotrexate, bleomyxin toxicity

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