Team 435

PATHOLOGY

As a doctor you should know what can threaten your patient's life
should know what makes your patient suffers from pain

That's why you study pathology

Lecture 3

Lecture three: (Restrictive Lung diseases)

Objectives:

A- Understand the structure and constituents of the lung interstitium as well as the restrictive changes which occur in these diseases and lead to the development of symptoms of progressive breathlessness and cough in affected patients. □

B- Appreciate the pathogenesis of interstitial lung diseases regardless of their type. This pathogenesis include the 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 (honey-comb lung).

C- Become aware of the classification of interstitial lung diseases. □

Contents:

1- Definition and causes of restrictive pulmonary diseases.

2- Pathogenesis of restrictive pulmonary diseases which include abnormalities in the chest wall or neuromuscular diseases that restrict lung expansion or conditions leading to interstitial accumulations of cells or non-cellular substances.

3- Brief account on the clinicopathological features of:

A. Adult and neonatal respiratory distress syndromes.
B. Anthracosis and coal worker's pneumoconiosis.
C. Silicosis and asbestosis.
D. Hypersensitivity pneumonitis (extrinsic allergic alveolitis).
E. Goodpasture syndrome.
F. Eosinophilic granuloma.
G. Idiopathic pulmonary fibrosis.
H. Sarcoidosis.

Restrictive Pulmonary Diseases:

A group of disorders characterized by reduced expansion of the lung, reduction in total lung capacity, increased work of breathing and inadequate ventilation and/or oxygenation (decreased lung compliance).

- ❏ Both forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) are reduced with normal to high FEV1/VC and decreased Tco. The expiratory flow rate is near normal.

Dr. Rikabbi's Note:
People who have restrictive lung diseases usually have dyspnea, which may be severe with persistent cough.

- ❏ The reduced lung volume is due to:
  - An alteration in lung parenchyma.
  - A disease of the pleura, chest wall, or neuromuscular apparatus.
- ❏ Stiff Lung.

Examples include:

- **Abnormalities of the chest wall** from bony abnormalities or neuromuscular disease such as the Guillain-Barré syndrome that restrict lung expansion.

Dr. Rikabbi's Note:

Restrictive pulmonary diseases can be caused either by:

- A neuromuscular disease that is affecting the diaphragm or intercostal muscles
- A deformity in the thoracic cage.

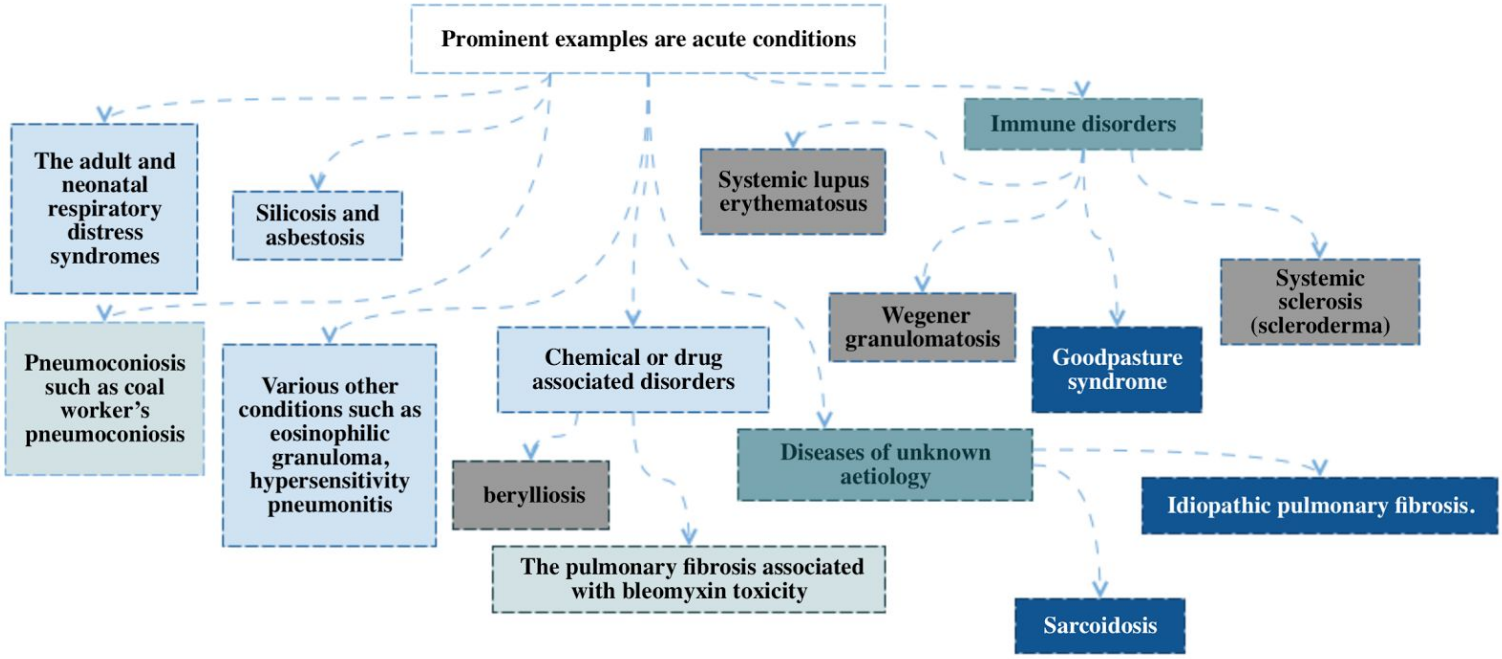
If there's abnormality in the thoracic cage i.e. deformity in thoracic cage and vertebral column which will prevent the lung from expansion causing restrictive lung disease.

Dr. Rikabbi's Note:

Guillain barre syndrome is a viral infection affecting muscles and nerves. If it is mild it affects only limbs, if it's severe it affects the respiratory muscles therefore they don't respond to neural stimulus and they don't expand causing difficulty in breathing. People with this disease need artificial ventilation.

- **Interstitial lung diseases:**

  A heterogeneous group of disorders, characterized by interstitial accumulations of cells or non cellular material within the alveolar walls that restrict expansion and often interfere with gaseous exchange.



The hallmark feature of these disorders is reduced compliance (i.e., more pressure is required to expand the lungs because they are stiff), which in turn causes difficulty in breathing (dyspnea).

Divided into:

1. **Intrinsic lung diseases/ diseases of the lung parenchyma/primary interstitial lung disease:**
   - The diseases cause inflammation or scarring of the lung tissue (interstitial lung disease) 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 therefore there is decreased oxygen-diffusing capacity which leads to reduced compliance of the lung. They can be acute or chronic.
   - End-stage: diffuse interstitial pulmonary fibrosis.
   - Honeycomb lung indicates end stage disease. In it both alveoli and bronchioles coalescence to form cysts lined with cuboidal or columnar epithelium and separated by inflammatory fibrous tissue.
   - Important signs and symptoms:
     - Dyspnea and hypoxia.
     - In advanced cases: severe hypoxia, hypercapnia and cyanosis respiratory failure and cor pulmonale.

Dr. Rikabbi's Note:
When there's fibrosis of the lung there will be resistance to gas exchange which means the heart is putting more effort to pump the blood which will lead to pulmonary hypertension causing cor pulmonale \ right-sided heart failure.

NOTE:
1- FEV1\FVC is normal in restrictive lung disease – in COPD FEV1 is decreased and the ratio FEV1\FVC is decreased
2- If cough is episodic ⟶ asthma – if it persist for long period of time we need to think of restrictive lung disease.

- Interstitial lung diseases affect the connective tissue and interior components of the lung.
  - ❑ **What are the diseases that fall under this category?**
    What we will study in this lecture.

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 respiratory muscles results in respiratory muscle weakness and respiratory failure e.g. myopathy or myositis, quadriplegia, or phrenic neuropathy from infectious or metabolic causes.

Pulmonary interstitium:
It is the area of the lung between the alveolar epithelial and capillary endothelial basement membranes (fused in the thinnest portions)

It is composed of:

- Elastic tissue.
- Fibroblasts.
- A few mast cells.
- Occasional mononuclear cells.

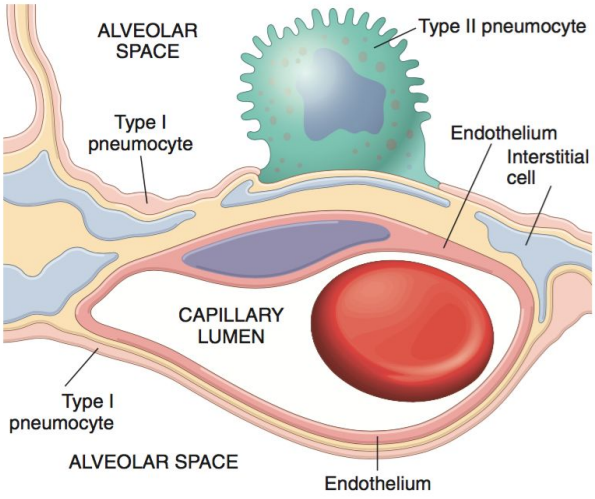


Figure 12–1 Microscopic structure of the alveolar wall. Note that the basement membrane *(yellow)* is thin on one side and widened where it is continuous with the interstitial space. Portions of interstitial cells are shown.

What are the changes that occur?

- ❏ Damage to the alveolar epithelium and interstitial vasculature produces abnormalities in the ventilation–perfusion ratio, leading to hypoxia.
- ❏ Chest radiographs show diffuse infiltration by small nodules, irregular lines, or "ground-glass shadows." With progression, patients can develop respiratory failure, often in association with pulmonary hypertension and cor pulmonale.
- ❏ Advanced forms of these diseases may be difficult to differentiate because they result in scarring and gross destruction of the lung, referred to as end-stage or "honeycomb" lung.

Dr. Rikkabi's Note:
Honeycomb lung is named like this because it's got interstitial fibrosis and it's entrapping those dilated bronchi and bronchiole, so we see a (interstitial fibrosis, the space between the alveolar walls is wide, entrapment of the alveoli, alveolar ducts and bronchioles, which leaves these areas that are full of air, sometimes there is also secretions.

Chronic interstitial lung diseases are categorized based on clinicopathologic features and characteristic histology.

Major Categories of Chronic Interstitial Lung Disease:

1. **Occupational:**
   Pneumoconiosis: - Anthracosis and coal worker's pneumoconiosis. - Silicosis. - Asbestosis.
2. **Fibrosing:** (occupational diseases are also fibrosing diseases)
   Usual interstitial pneumonia (idiopathic pulmonary fibrosis)
3. **Immune diseases:**
   - **Sarcoidosis.** - **Goodpasture syndrome.** - Wegener granulomatosis. - Systemic sclerosis (scleroderma).
   - Systemic lupus erythematosus. - **Hypersensitibity pneumonitis(extrinsic allergic alveolitis).**
4. **Drugs:**
   Chemotherapy, methotrexate, bleomyxin toxicity.
5. **Radiation Reactions.**
6. **Smoking related:**
   - **Eosinophilic granuloma.** - **Desquamative interstitial pneumonia.**
   - **Respiratory bronchiolitis-associated interstitial lung disease.**

Table 12–3 Major Categories of Chronic Interstitial Lung Disease

Fibrosing
Usual interstitial pneumonia (idiopathic pulmonary fibrosis)
Nonspecific interstitial pneumonia
Cryptogenic organizing pneumonia
Associated with collagen vascular disease
Pneumoconiosis
Associated with therapies (drugs, radiation)
Granulomatous
Sarcoidosis
Hypersensitivity pneumonia
Eosinophilic
Loeffler syndrome
Drug allergy–related
Idiopathic chronic eosinophilic pneumonia
Smoking-Related
Desquamative interstitial pneumonia
Respiratory bronchiolitis

Histopathologic features include:

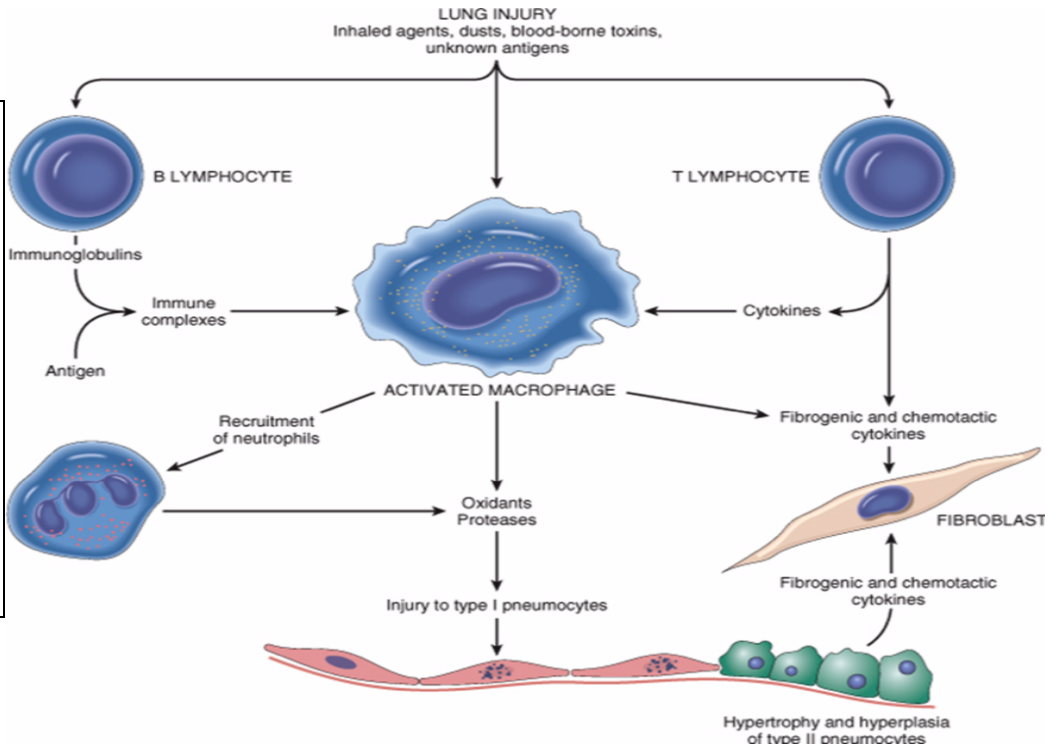
- Inflammation and induction of TH2 type T cell response with eosinophils, mast cells, IL-4, and IL-13 in the lesions.
- Abnormal epithelial repair at the sites of damage and inflammation gives rise to exuberant fibroblastic or myofibroblastic proliferation, leading to the characteristic fibroblastic foci.
- TGF-β1, which is released from injured type I pneumocytes induces transformation of fibroblasts into myofibroblasts leading to excessive and continuing deposition of collagen and ECM.
- Some patients with familial IPF have mutations that shorten telomeres, leading to rapid senescence[1] and apoptosis of pneumocytes. TGF-β1 also down regulates fibroblast caveolin-1, which acts as an endogenous inhibitor of pulmonary fibrosis.

Dr. Rikkabi's Note:
Usual interstitial pneumonitis (UIP) :
We see: patchy interstitial fibrosis, honeycomb lung, and it can be relentless. Here the antigen is unknown, but what we do know is that the antigen has stimulated the macrophages and lymphocytes to secrete specific interleukins and cytokines, specially TGF-B1.. which induces the interstitial lung disease.

Pathogenesis:

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

Dr. Rikabbi's Note: (diagram explanation):
Antigen will activate macrophages ⟶ macrophages release cytokines and recruit more neutrophils secrete protease which will cause injury to type 1 pneumocyte
Other pathway macrophages secrete fibrogenic agent (transforming Growth Factor TGF-B1) which will activate fibroblasts causing fibrosis ⟶ so now we'll have (fibrogenic fibrosis). ⟶ interstitial lung disease.



[1] Loss of a cell's power of division and growth.

Morphology:

Grossly, the pleural surfaces of the lung have the appearance of cobblestones because of the retraction of scars along the interlobular septa.

The cut surface shows fibrosis (firm, rubbery white areas), with lower lobe predominance and a distinctive distribution in the subpleural regions and along the interlobular septa. The histologic hallmark of UIP (usual interstitial pneumonia) is **patchy interstitial fibrosis,** which varies in intensity and worsens with time.

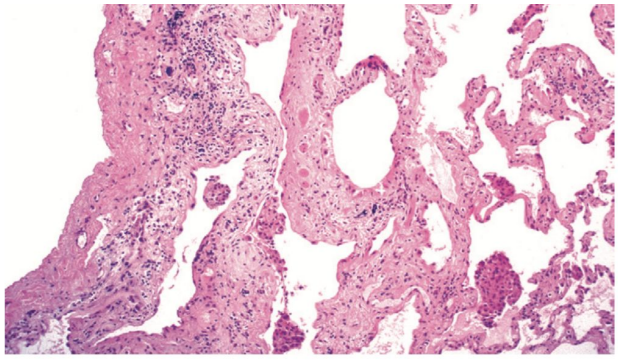


Figure 12–15 Usual interstitial pneumonia. The fibrosis, which varies in intensity, is more pronounced in the subpleural region.

The earliest lesions demonstrate exuberant fibroblastic proliferation and appear as **fibroblastic foci.**

Over time these areas become more collagenous and less cellular.

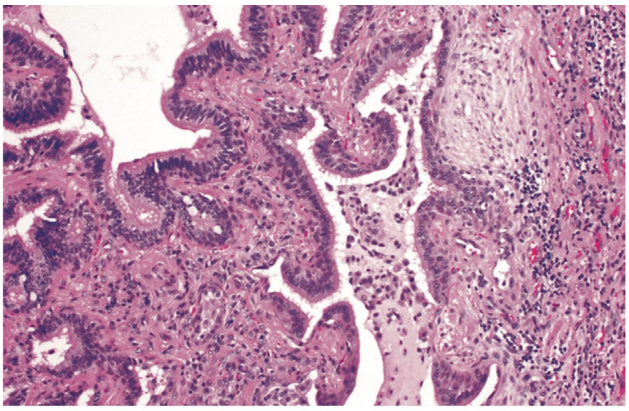


Figure 12–16 Usual interstitial pneumonia. Fibroblastic focus with fibers running parallel to surface and bluish myxoid extracellular matrix. Honeycombing is present to the *left*.

Quite typical is the existence of both early and late lesions **(temporal heterogeneity).** The dense fibrosis causes collapse of alveolar walls and formation of cystic spaces lined by hyperplastic type II pneumocytes or bronchiolar epithelium **(honeycomb fibrosis).** The interstitial inflammation usually is patchy and consists of an alveolar septal infiltrate of mostly lymphocytes and occasional plasma cells, mast cells, and eosinophils. Secondary pulmonary hypertensive changes (intimal fibrosis and medial thickening of pulmonary arteries) are often present.

Acute Respiratory Distress Syndrome (ARDS): (Affects both adults and neonatal)

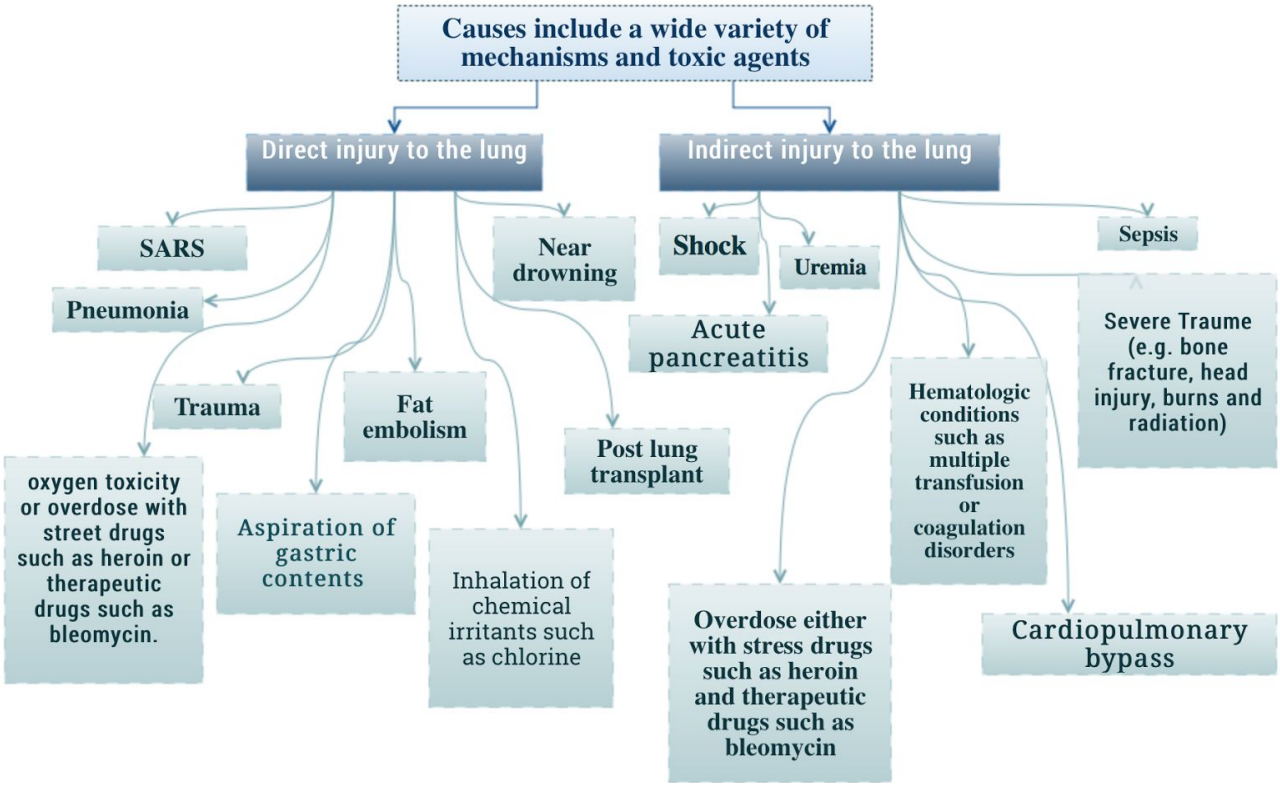
Adult respiratory distress syndrome:

ARDS is a severe form of acute lung injury with diffuse alveolar injury. Produced by diffuse alveolar damage with resultant increase in alveolar capillary permeability, causing leakage of protein-rich fluid into alveoli.

It is also known as shock lung/ diffuse alveolar damage/ adult respiratory failure/acute alveolar injury/ traumatic wet lung.

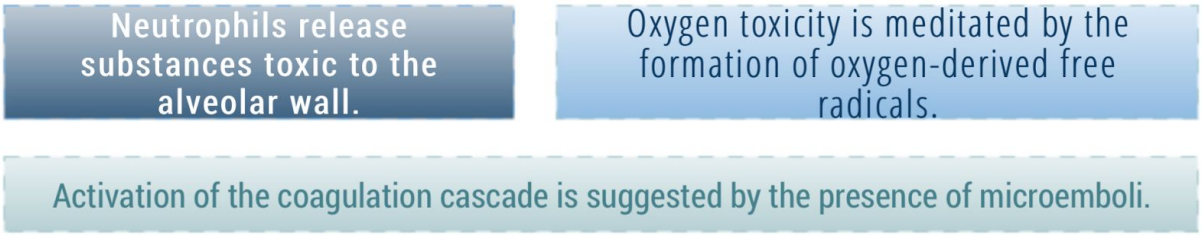
Characteristics include the formation of an **intra-alveolar hyaline membrane** composed of fibrin and cellular debris.

➔ The result is severe impairment of respiratory gas exchange with consequent severe hypoxia.



➔ ARDS can be a manifestation of the severe acute respiratory syndrome (SARS). The SARS virus is coronavirus that destroy the type II pneumocytes and causes diffuse alveolar damage.

➔ ARDS is initiated by damage to alveolar capillary endothelium and alveolar epithelium and is influenced by the following pathogenetic factors:



It is:

- Rapid acute onset progressive severe life threatening respiratory insufficiency, cyanosis, severe arterial hypoxia.
- Decreased arterial oxygen pressure.
- Refractory to oxygen therapy and that may progress to multiorgan failure.
- Bilateral pulmonary infiltrates (edema).
- Absence of evidence of left sided heart failure.
- It is the most common cause of non- cardiogenic pulmonary edema

Dr. Rikabbi's Note:
There are interstitial diseases that start as acute and then develop to chronic interstitial disease.. they can affect neonates and adults. ARDS & NRDS.

Clinical features characterized by:

- Cyanosis.
- May progress to multisystem organ failure.

Dr. Rikabbi's Note:

- Septicemia proliferation of bacteria in blood
- Aspiration of gastric juices flowing major operation because of anesthesia and present with ARDS.

Dr. Rikabbi's Note:

Usually caused by:

- Major trauma
- Aspiration of gastric juice
- Septicaemia
- Severe infections
- Shocks.

➔ These cause damage to type 1 pneumocytes (the alveolar lining cells), or to capillaries, type 1 pneumocytes injury is almost irreversible because they are incapable to multiply. "the damage of the alveolar wall will induce exudating"

➔ When the damage of ARDS happens, it causes a leak of plasma, fibrin, and proteins.

➔ When this happens, a "hyaline membrane" shows, which is formed of exudating proteins, inflammatory cells, cellular depress.

➔ ARDS causes "DAD" (Diffuse Alveolar Damage) which is caused of excessive plasma proteins and formation of hyaline membrane.

➔ In the morphology you see a white lung.

There are two types of ARDS:

- Direct:
  If the injury is in the interstitial area.. like the damage of the lining cells.
- Indirect:
  When there is a septicaemia which can cause some problems to the alveolar capillaries and then the alveoli.

Pathogenesis:

Diffuse alveolar damage which leads to → increase in alveolar capillary permeability which leads to →leakage protein rich fluid which leads to (in order of appearance):

1. **Exudative stage:**

   The protein and necrotic cells layer out on the alveolar septae, forming hyaline membranes (composed of fibrin and cellular debris).

   The lungs become remarkably heavy and stiff due to inflammation and edema.

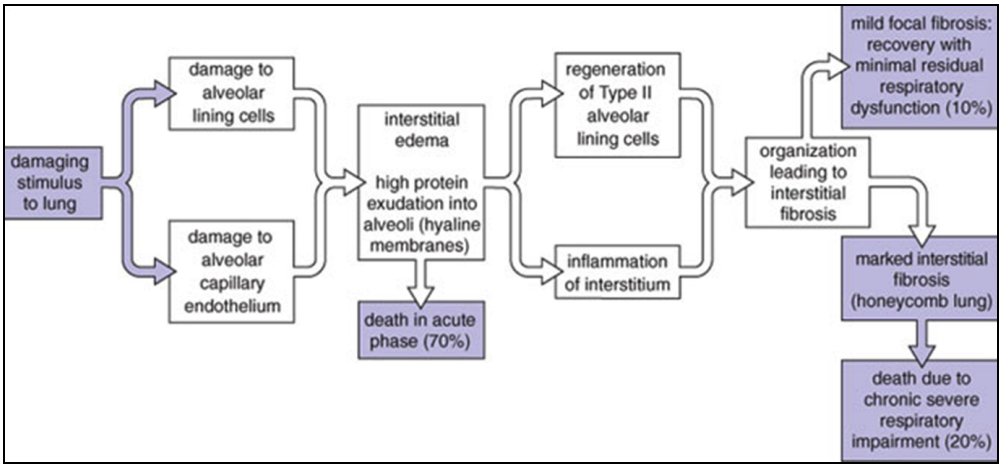
2. **Proliferative stage:**

   Occurs in response to the damage. Type II pneumocytes undergo hyperplasia (type I can't regenerate).

3. **Fibrosis.**

The injury is induced by the:

A. Neutrophils releasing substances toxic to the alveolar wall.
B. Oxygen toxicity (due to formation of free radicals).
C. Activation of the coagulation cascade.



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

Dr. Rikabbi's note:
Alveolar wall is lined by pneumocyte type 1 and this type of cell can not regenerate . most of survived patient depend on type 2 pneumocyte regeneration and they suffer from further fibrosis and inflammation after period of time they may die as shown in the diagram .

Neonatal Respiratory Distress Syndrome (Hyaline Membrane Disease)

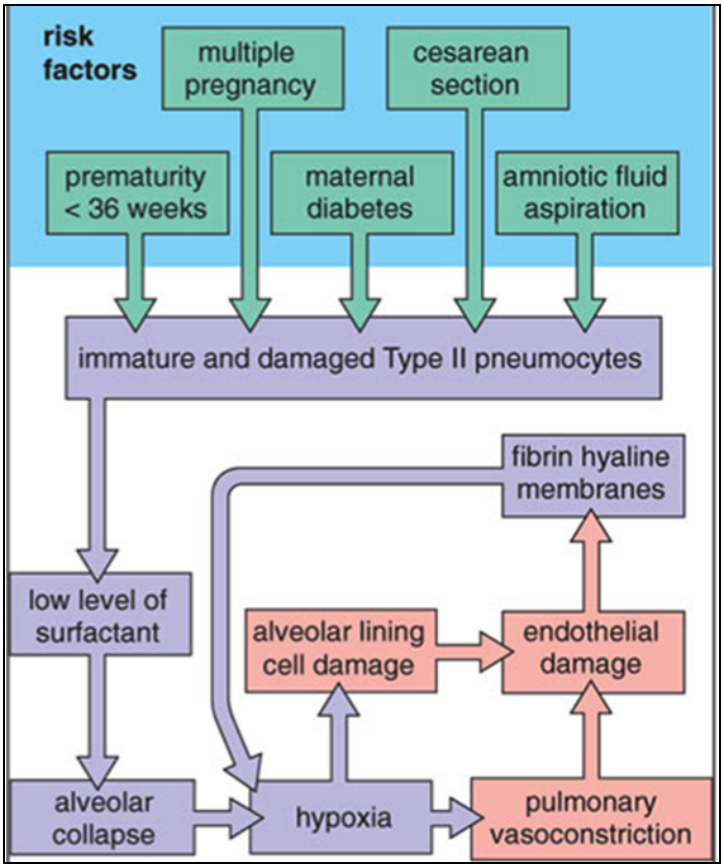
General Considerations:

- Neonatal respiratory distress syndrome 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.
- It too results in diffuse alveolar damage with the development of a hyaline membrane lining the alveoli.
- This syndrome is marked by dyspnea, cyanosis and tachypnea shortly after birth. This syndrome results from deficiency of surfactant, most often as a result of immaturity.

  Why is it because of deficiency of surfactant? Because the surfactant is formed later in pregnancy around the 6th or 7th month and sometimes even later than that. Thus, children are born with a deficiency of surfactant.

Predisposing Factors:

- **Prematurity.**
- **Maternal diabetes mellitus.**
- **Delivery by cesarean section.**
- **Amniotic fluid aspiration.**[2]
- **Multiple births.**[3]



[2] The amniotic fluid may aspirate to the neonate during delivery.
[3] Pregnancy of twins eg: 3 or 4 twins

Fibrosing Diseases:

1. Pneumoconiosis:

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...

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.

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 (1-5m) shape.
- ❏ Their solubility and physiochemical activity.
- ❏ The possible additional effects of other irritants, tobacco smoking.

They are exemplified by the following conditions:

1. **Anthracosis:**
   - Asymptomatic accumulation of coal pigment/carbon particles without consequent cellular reaction.
   - Such accumulation can be found in varying degrees among most urban dwellers and in tobacco smokers.
   - Characterized by **carbon-carrying macrophages,** it results in irregular black patches visible on gross inspection.
   - Inhaled coal dust enters the terminal bronchioles, and the carbon pigment is engulfed by alveolar and interstitial macrophages.

2. **Coal worker's pneumoconiosis:**

Caused by inhalation of **coal dust**, which contains both carbon and silica.

A. **Simple coal worker's pneumoconiosis**:

Marked by **coal macules** around the bronchioles, formed by ingestion of coal dust particles by macrophages. In most cases, it is inconsequential and produces no disability.

- Mostly in the upper zones of the lower and upper lobes of the lungs.
- Patients have slight cough and blackish sputum.

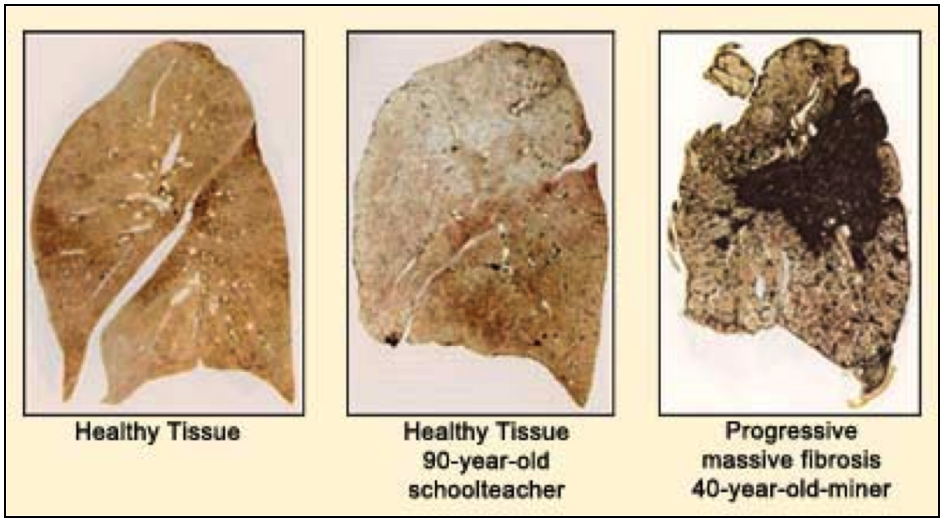
Dr. Rikabbi's Note: The simple "coal worker's pneumoconiosis" does not induce fibrosis, while the severe one does.

B. **Progressive massive fibrosis or complicated coal worker's syndrome depending on the extent of the disease:**

- Marked by fibrotic nodules filled **with necrotic black fluid.** It can result in **bronchiectasis, pulmonary hypertension,** or death from respiratory failure or right-sided heart failure (cor pulmonale).
- Pulmonary massive fibrosis in association with rheumatoid arthritis is known as **Caplan syndrome.**

Morphology:

- Occurs after many years of underground mine work.
- Fibrous scarring appears (complicated CWP) also called progressive massive fibrosis.
- Black scars exceed 2 cm in diameter sometimes up to 10 cm.
- It consists of dense collagen and carbon pigments.
- Complicated coal worker's pneumoconiosis produces cough, dyspnea, and lung function impairment.



3. **Silicosis:**

A chronic occupational fibronodular lung disease seen in miners, glass manufactures and stone cutters. In the Gulf region and in "desert climate", it could be due to inhalation of sand.

The more common chronic forms manifest after several years of exposure. The symptoms may be indolent or progressive. Chronic silicosis can lead to complicated progressive massive fibrosis. Symptoms often manifest only 1 to 3 decades after initial exposure.

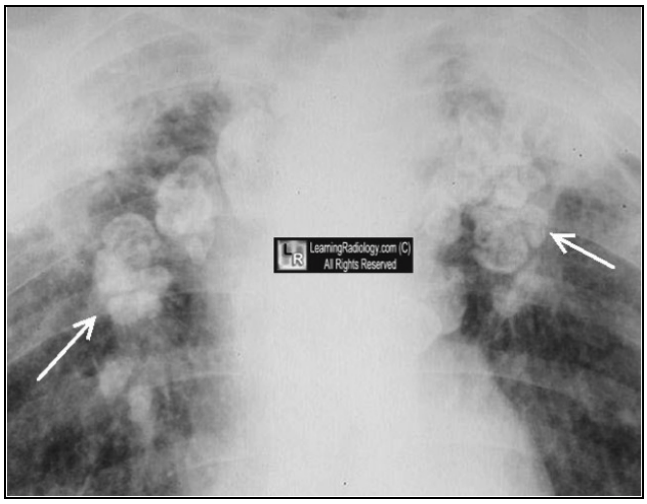
Dr. Rikabbi's Note: Silicosis is the most common pneumoconiosis in the world.

A. **Pathogenesis:**

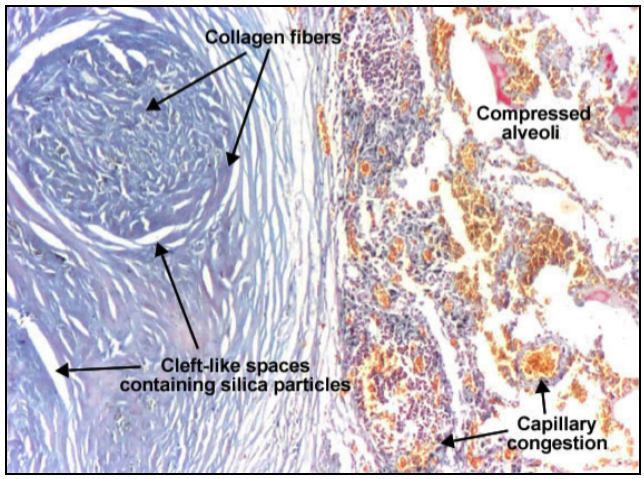
Crystalline silica is highly fibrogenic, the disease is initiated **by ingestion of silica dust by alveolar macrophages.** Scattered lymphocytes and macrophages are drawn rapidly with fibrosis given that silica is highly fibrogenic**; damage to the macrophages initiates an inflammatory response** mediated by lysosomal enzymes and various chemical mediators. Some particles are transported to lymph nodes.

B. **Morphology and clinical features**:

Usually detected on routine chest radiographs obtained in asymptomatic workers. Shows a fine nodularity in the upper zones of the lung (called **Silicotic nodules** that enlarge and eventually obstruct the airways and blood vessels are characteristics), but pulmonary function is either normal or only moderately affected.



- ➔ The lung parenchyma between the scars may be compressed or emphysematous.
- ➔ Calcifications may appear (eggshell calcification) .
- ➔ Similar collagenous nodules within the lymph nodes.
- ➔ Hyalinized collagen fiber surround an amorphous center (fibrous nodules).
- ➔ Cor pulmonale.



C. Silicosis is associated with **increased susceptibility to lung cancer and tuberculosis**; the frequent concurrence is referred to as **silicotuberculosis.**

4. **Asbestosis:**

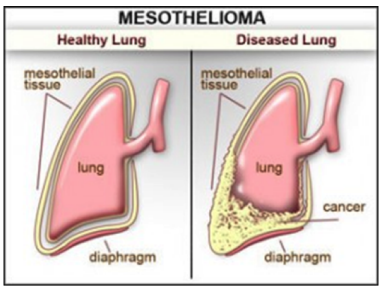
A group of naturally occurring, heat-resistant fibrous silicates. Asbestos fibers are long and thin. They can curved or straight. All types of asbestos (crocidolite and amosite) are fibrogenic to lungs.

- Caused by inhalation of **asbestos fibers.**

Dr. Rikabbi's Note:

Asbestosis may develop into bronchogenic carcinoma and mesothelioma (malignant tumor in the pleura).

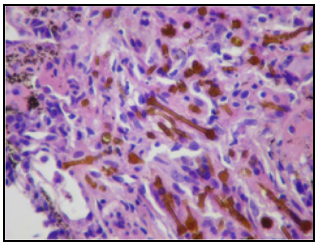
Asbestosis is related to the insulation substances "المواد العازلة"



Why do we get mesothelioma in the peritoneum ?

The peritoneum is lined by mesothelial cells, pleura is lined with mesothelial cells and pericardium is lined by mesothelial cells. so this mesothelioma may go to the pericardium also.

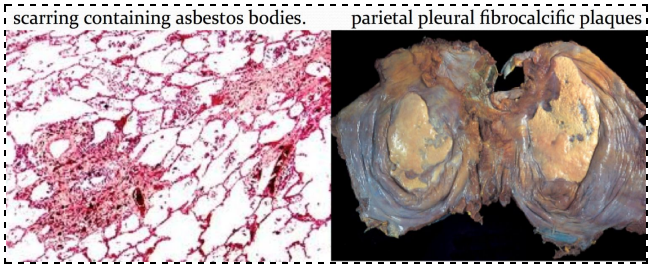
A. **Pathogenesis:**



Occurs decades after exposure has ended. This disease is initiated by uptake (inhalation) of asbestos fibers by alveolar macrophages. A fibroblastic response occurs, probably from release of fibroblast-stimulation growth factors by macrophages and leads **to diffuse interstitial fibrosis mainly in the lower lobes.**

B. **Morphology:**

It is characterized by the presence of **ferruginous bodies** which are yellow-brown, rod-shaped bodies with clubbed ends that stain positively with Prussian blue; these arise from iron and protein coating on asbestos fibers. Dense **hyalinized fibrocalcific plaques of the parietal pleura** are also present.



C. **Clinical Features:**

Characterized by scars containing asbestos bodies. Cigarette smoking further increases the risk of bronchogenic carcinoma. Symptoms usually appear after a latent period of 20 years or longer. This latent period may be shorter after intense exposure. Dyspnea upon exertion is the most common symptom and worsens as the disease progresses. Patients may have a dry cough and chest discomfort.

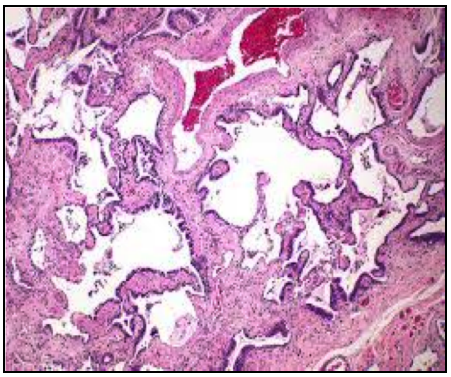
Where can we find Asbestos?

Pipes, sheets, vinyl-asbestos floor tiles, asbestos paper in filtering and insulating products, textile products etc.

Who's at risk? People in the following occupations are at risk: Insulation workers, boilermakers, pipefitters, plumbers.

2. Idiopathic Pulmonary fibrosis (IPF):

- ❏ Immune complex disease with progressive fibrosis of the alveolar wall, which in advanced cases results in severe hypoxemia and cyanosis. Refers to a pulmonary disorder of unknown etiology.
- ❏ It is an idiopathic interstitial pneumonia with diffuse interstitial fibrosis and inflammation.
- ❏ Similar pathologic changes in the lung may be present in well-defined entities such as asbestosis, the collagen vascular diseases, and a number of other conditions.
- ❏ Affects adults from 30 to 50 years.



Morphology:

The morphologic changes vary according to the stage of the disease.

Early cases:

- Intra-alveolar and interstitial 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.

Honeycomb fibrosis: collapse of alveolar walls and formation of cystic spaces lined by hyperplastic type IIpnueumocytes or bronchiolar epithelium.

Clinical Features:

- Nonproductive cough and progressive dyspnea are the most common features.
- On physical examination “dry” or “Velcro”-like crackles during inspiration.
- A chest radiograph and high-resolution computed tomography typically reveals diffuse reticular opacities.
- Cyanosis.
- Peripheral edema may develop in later stages of the disease.
- Histology of IPF shows features of:
  - Usual interstitial pneumonia with a heterogeneous, patchy appearance.
  - There are alternating areas of healthy lung and abnormal lung with interstitial inflammation, fibrosis, and honeycomb change.

How can we diagnose this disease?

The diagnosis of IPF relies on a combination of clinical, laboratory, radiologic, and/or pathologic data.

Etiology:

The etiology of IPF remains undefined. The current hypothesis is that:

1. Exposure to an inciting agent (eg. smoke, environmental pollutants, etc) in a susceptible host leads to alveolar damage, fibrosis and irreversible destruction of the lung parenchyma.
2. Some idiopathic pulmonary fibrosis are familial.
3. Certain medication drugs (bleomycin, and nitrofurantoin) are associated with development of pulmonary fibrosis.

Prognosis:

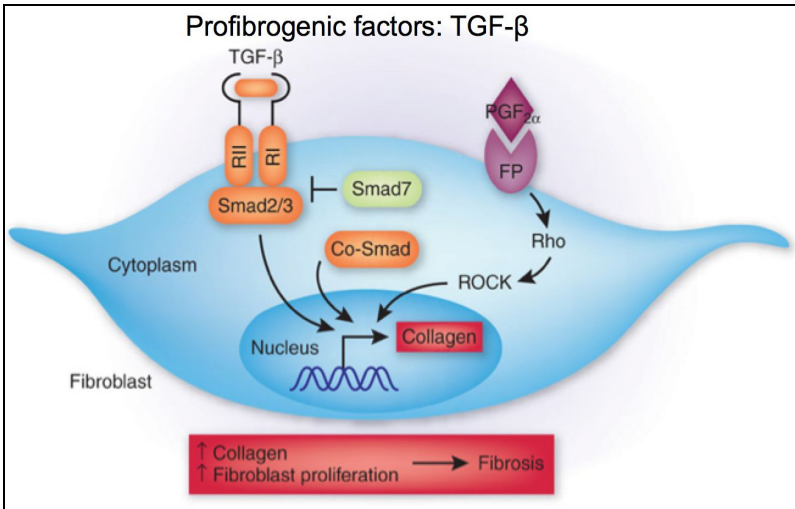
Poor prognosis. Respiratory and heart failure may develop within few years. The mean survival is 3 years or less.

Treatment:

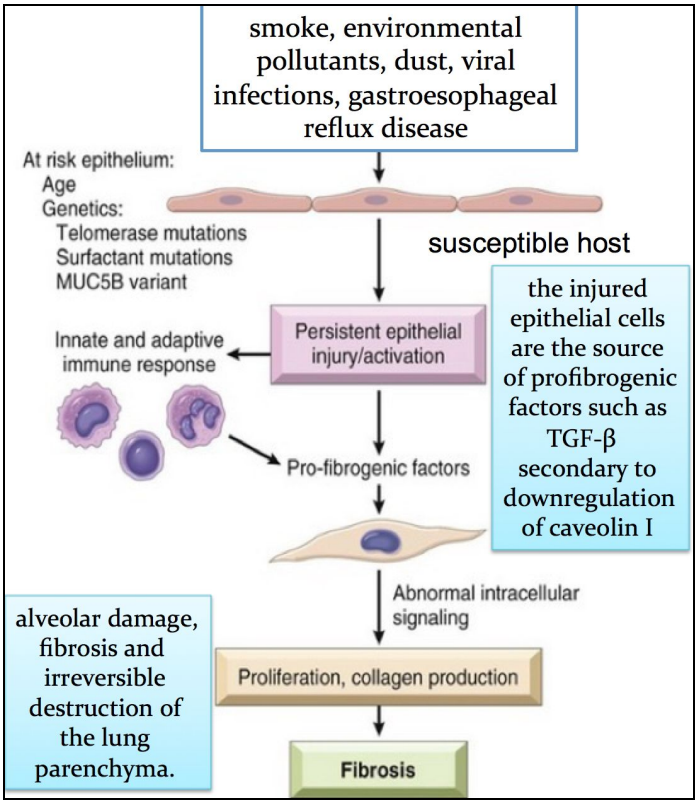
No effective therapy is available for the treatment of idiopathic pulmonary fibrosis. Lung transplant is the only solution.

Pathogenesis:

The recurrent concept is that IPF is caused by "repeated cycles" of epithelial activation/injury by some unidentified agent.



$PGF_{2\alpha}$, produced locally during lung injury or fibrosis binds to its cognate G protein–coupled receptor FP. This binding activates the small GTPase Rho signaling pathway, leading to collagen synthesis through mechanisms yet to be delineated. The potent profibrotic factor TGF-β acts independently through Smads to further enhance collagen production by fibroblasts. The increase in collagen, together with $PGF_{2\alpha}$-FP–induced fibroblast proliferation, contribute to the pathogenesis of *in vivo* pulmonary fibrosis.



Granulomatous Diseases:

1. **Hypersensitivity pneumonitis:**

An immunologically mediated (type III and IV) interstitial lung disease caused by intense and often prolonged exposure to inhaled organic dust(i.e. dusts containing organic antigens) affecting irways and interstitium. It manifests as a predominantly restrictive lung disease with decreased diffusion capacity, lung compliance, and total lung volume.

- ❑ An immunologically mediated inflammatory lung disease 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.
- ❑ Poultry and other bird handlers are commonly exposed to droppings, feathers, and serum proteins of pigeons.
- ❑ 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.
- ❑ Hypersensitivity pneumonitis can present as acute, subacute (intermittent) or chronic progressive.

Table 12–5 Selected Causes of Hypersensitivity Pneumonitis

Syndrome	Exposure	Antigens
Fungal and Bacterial Antigens		
Farmer's lung	Moldy hay	*Micropolyspora faeni*
Bagassosis	Moldy pressed sugar cane (bagasse)	Thermophilic actinomycetes
Maple bark disease	Moldy maple bark	*Cryptostroma corticale*
Humidifier lung	Cool-mist humidifier	Thermophilic actinomycetes, *Aureobasidium pullulans*
Malt worker's lung	Moldy barley	*Aspergillus clavatus*
Cheese washer's lung	Moldy cheese	*Penicillium casei*
Insect Products		
Miller's lung	Dust-contaminated grain	*Sitophilus granarius* (wheat weevil)
Animal Products		
Pigeon breeder's lung	Pigeon droppings	Pigeon serum proteins in droppings
Chemicals		
Chemical worker's lung	Chemical industry	Trimellitic anhydride, isocyanates

Farmer's lung
Thermophilic actinomycetes in hay

Pigeon breeder's

Air-condition lung
Thermophilic bacteria

Sugarcane bagasse (Bagassosis)

How does it all take place?

1. **First exposure:** patient develop precipitating IgG antibodies (present in serum)
2. **Second exposure:**
   - Antibodies combine with inhaled allergen to form immune complex (type 3 hypersensitivity)
   - Immunocomplexes produce an inflammatory reaction in lung tissue.
3. **Chronic exposure:** additional component of interstitial granulomatous inflammation (type 4 hypersensitivity)(increased numbers of CD4+ and CD8+ T cells)(macrophages stimulates →CD4+ Th1 cells →Activated CD8+ T cells destroy target cells)lead to interstitial fibrosis.

Characterized by: Diffuse inflammation of lung parenchyma and airways in previously sensitized persons.

Morphology:

- Noncaseating interstitial granulomas (IV hypersensitivity reaction)
- Bronchiolitis.
- Interstitial pneumonitis.
- Diffuse interstitial fibrosis.

Clinical Features : Clinical course is variable.

Hypersensitivity pneumonitis may manifest either as an:

1. **Acute Hypersensitivity Pneumonitis:**
   Characterized by fever, cough, dyspnea, and constitutional signs and symptoms arising 4 to 8 hours after exposure, resolves with removal of the exposure.
2. **Chronic Hypersensitivity Pneumonitis:**
   Characterized by insidious onset (developing gradually) cough, dyspnea, malaise, and weight loss.

   Failure to remove the inciting agent from the environment eventually results in an irreversible chronic interstitial pulmonary disease.

2. **Sarcoidosis:** (do NOT confuse between scoliosis "abnormal lateral curvature of the spine" & Sarcoidosis)

Multisystem inflammatory disease of unknown etiology characterized by noncaseating (non-necrotizing) granulomas in affected organ tissues. 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.
- Affecting all races and both sexes equally

Clinical features: (increased incidence in nonsmokers)

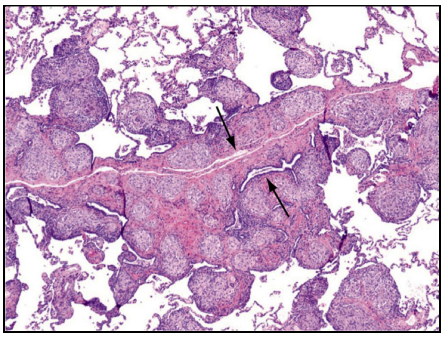
- **Asymptomatic patients:**

  Present with hilar lymphadenopathy[4] discovered by chest radiograph or occasional finding at autopsy. OTHER commonly presenting manifestations (almost any tissue can be involved): Peripheral lymphadenopathy, cutaneous lesions, eye involvement, splenomegaly(تضخم الطحال), hepatomegaly.

- **Symptomatic cases:**

  There is gradual appearance of respiratory symptoms (shortness of breath, dry cough, or vague substernal discomfort, dyspnea on exertion and chest pain) or constitutional signs and symptoms (fever, fatigue, weight loss, anorexia, night sweats and arthralgias).

  Depending on the organs involved the patient can have dermatological, occular, cardiac or neural(rare) manifestations.



Sarcoidosis granuloma in the lung

Goodpasture Syndrome: (Anti GBM disease)

Hemorrhagic pneumonitis and glomerulonephritis caused by antibodies directed against glomerular basement membranes.

A rare disease which is a triad of:

- Diffuse pulmonary hemorrhage.
- Glomerulonephritis.
- Circulating anti-alveolar and anti-glomerular basement membrane (anti-GBM) antibodies

Also called anti-GBM disease and it is an autoimmune disorder. The anti-GBM antibody can usually be found in serum.

Clinical presentation : Most of the patients have:

1. **Pulmonary symptoms:**
   - Hemoptysis - Dyspnea
2. **Renal symptoms (which occur later):**
   - Hematuria. - Proteinuria. - Red cell casts. - Renal failure. - Progressing to uremia(blood in urine) and death.
3. **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.

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

Iron stain in sputum

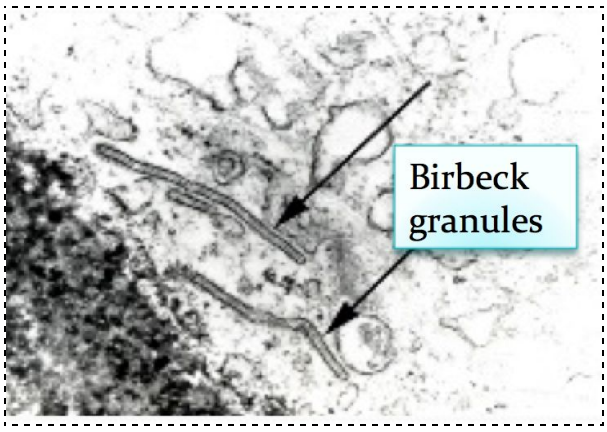
[4] Enlargement of mediastinal lymph nodes.

Eosinophilic Granuloma:

pulmonary histiocytosis X / pulmonary Langerhan cell histiocytosis X

Eosinophilic granuloma: Proliferation of histiocytic cells related to Langerhan's cells of the skin.

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



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قال صلى الله عليه وسلم: من سلك طريقاً يلتمس به علماً سهل الله له به طريقاً إلى الجنة.

دعواتنا لكم بالتوفيق.