Lec1: in this lecture we are going to talk about 2 obstructive diseases, **ASTHMA** and **BRONCHIECTASIS**

firstly let's revise the definition of obstructive and restrictive airways diseases (just for revision):

1- Obstructive airways diseases:

characterized by an increase in resistance to airflow caused by partial or complete obstruction at any level (difficulty to exhale, it's easy to fill them and get the air in, but they are abnormal, such as emphysema, the elastic fibers are damaged, there is compliance and expansion, but there is no recoil so it's very difficult to exhale, so air accumulates inside the lung causing lung hyperinflation, and the volumes in the lung are normal or increased).

2- Restrictive diseases:

characterized by reduced expansion of lung parenchyma (because the compliance is less, it is difficult to inhale, there is restriction to the entry of the air) and decreased total lung capacity.

now, let's start with **ASTHMA**, the doctor talked about asthma in these points:

1-definition
2-hallmarks
3-major factors that contribute to the development of Asthma
4-triggers
5-pathogenesis: -sensitization
-re exposure : -early phase
-late phase
6-airway remodeling and a comparison between normal and asthmatic airways
7-types of asthma: -atopic and how to diagnose it
-non atopic
-drug induced
-occupational
8-morphology
9-clinical features
10-status asthmaticus
11-management

1-definition: asthma is a **chronic** inflammatory disorder of the airways that causes recurrent episodes of wheezing, Dyspnea, chest tightness and dry cough particularly at night and/or early in the morning

2-hallmarks:

A. Intermittent (not continuous) and reversible (not permanent) airway obstruction (bronchospasm).
B. Chronic bronchial inflammation with eosinophils infiltrate.
c. Bronchial smooth muscle cell hypertrophy and hyper-reactivity.
d. increased mucus secretion.

3-major factors that contribute to the development of Asthma:

- Genetic predisposition to type I hypersensitivity (atopy), specifically mediated by IgE.
- Acute and chronic airway inflammation
- Bronchial hyper responsiveness to a variety of **stimuli**, we need certain exposure for asthma to occur. **4-Example of triggers (stimuli):**
  - -respiratory infections (especially viral)
  - -airborne irritants (smoke, fumes)
  - -cold air
  - -Stress
  - -Exercise

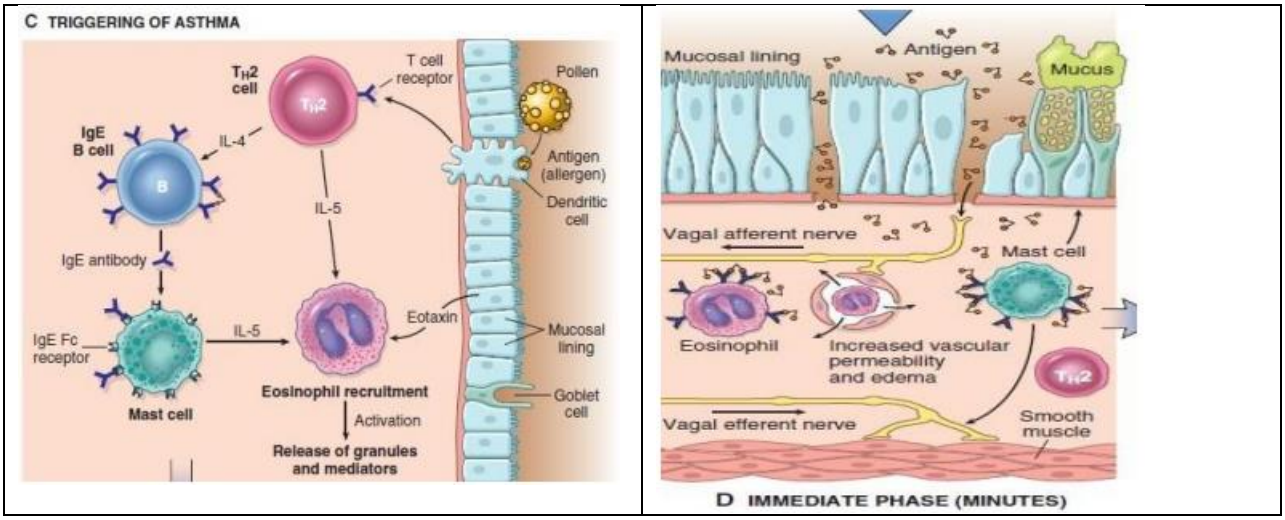
5-pathogenesis:

Upon initial exposure (sensitization) to an inhaled allergen, antigen-presenting cells (APC) or dendritic cells in the epithelial lining recognize the allergen, activating type 2 T helper lymphocytes. This activation leads to the release of inflammatory mediators, including IL-4 and IL-13, stimulating IgE production. IL-5 activates eosinophils, while IL-13 stimulates mucous production. Upon re-exposure, IgE coats submucosal mast cells, triggering two reactions:

A-an early or immediate phase (immediately and within minutes) (triggered by Ag-induced cross-linking of IgE bound to Fc receptors on mast cells) dominated by **bronchoconstriction, increased mucus production, vasodilation, increased vascular permeability and recruitment of leukocytes**, mediated by histamine, prostaglandin D2, leukotrienes (C4, D4, and E4) which are released by mast cells, and reflex neural pathways.

B-late phase (it will take hours to make the response) **characterized by an inflammatory response** initiated by mast cell contents stimulating epithelial cells to produce eotoxin, so in this phase Mast cell degranulation triggers the release of inflammatory mediators, stimulating epithelial cells to produce chemokines like eotoxin (potent chemo attractant). These chemokines attract TH2 cells, eosinophils, and other leukocytes, amplifying the

inflammatory reaction. Again, this phase is characterized by an inflammatory response involving recruited leukocytes (neutrophils, eosinophils, basophils, lymphocytes, and monocytes) to the site of reaction. These cells release mediators, activating more leukocytes and further amplifying the inflammatory reaction, ultimately contributing to the late phase of asthma. Eosinophils release major basic protein and eosinophil cationic protein, causing damage to the epithelium.



6-airway remodeling and a comparison between normal and asthmatic airways:

Repeated bouts of inflammation lead to structural changes in the bronchial wall called **airway remodeling**, including: *(some extra points will be mentioned in morphology)*

- Thickening of submucosal basement membrane to protect mucosa
- We need large amounts of mucus so goblet cells metaplasia will occur.
- deposition of subepithelial collagen
- hypertrophy and hyperplasia of bronchial smooth muscle (increase in size and number)
- hypertrophy of Mucus glands
- increased vascularity

Normal airways	Asthmatic airways
• Thin layer of mucus on the surface. • Epithelium with scattered goblet cells. • Desensitized basement membrane. • Hypocellular lamina propria (no inflammatory cells).	• Thick layer of mucus lining the epithelial surface (accumulation of mucus in the bronchial lumen) • Increased goblet cells in the surface epithelium. • Thickening of the basement

• Smooth muscle layer with a normal thickness. • Scattered mucus-secreting glands.	membrane due to increased deposition of type 1 and type 3 collagen, leading to sub-basement membrane fibrosis. • Dense chronic inflammation in lamina propria with numerous cells, mainly eosinophils. • Hypertrophy and hyperplasia of smooth muscle. • Hypertrophy of mucus-producing glands (submucosal glands)

In summary, asthma is characterized by notable changes such as increased mucus, goblet cells, basement membrane thickening, chronic inflammation with eosinophils, and structural alterations in smooth muscle and mucus-secreting glands compared to the features of a normal airway.

7-types of asthma: (atopic - non atopic - drug induced - occupational)

Atopic Asthma

-Characteristics:

- Most common type.
- Type I IgE–mediated hypersensitivity reaction.
- Typically begins in childhood.
- Positive family history of atopy and/or asthma.
- Attacks preceded by allergic rhinitis, urticaria, or eczema.
- Triggered by allergens (dust, pollen, animal dander, food) or infections.

-Mechanism:

1. Exposure to the antigen leads to excessive activation of type 2 helper cells.
2. Cytokines production: IL-4 and IL-13 stimulate IgE, IL-5 activates eosinophils, IL-13 stimulates mucus production.
3. IgE coats submucosal mast cells and upon re-exposure, there will be the release of Mast cell–derived mediators, and that produce Two waves of reaction: early (immediate) phase (caused by degranulation of mast cells) and late phase (inflammatory in nature).

-Diagnosis:

- Skin test with the antigen (eg: skin prick test, the most common allergy skin test): immediate wheal-and-flare reaction.
  1. We draw a series of the drops of the antigens
  2. Using a needle, small pricks are made below every drop to allow for the antigens to react with the body.
  3. Redness and itchiness will result around the pricks that contain antigens to which the patient is allergic to.

- Serum radioallergosorbent tests (RASTs): blood test using radioimmunoassay to detect specific IgE antibodies.
  In serum RASTS, a blood sample is taken, and I look for antibodies against certain allergic antigens.

-Triggers:

Allergens, infections.

Non-Atopic Asthma

-Characteristics:

- No evidence of allergen/antigen sensitization.
- Negative skin test.
- Positive family history of asthma is less common.

-Triggers:

viral respiratory infections (rhinovirus, parainfluenza virus)
inhaled air pollutants (sulfur dioxide, ozone, nitrogen dioxide).

-Mechanism:

Mechanism is not well understood, but, eventually, the same cellular and humoral mediators are released as in Atopic Asthma, so they are treated in the similar way.

Drug-Induced Asthma

-Example:

Aspirin-induced asthma.

-Presentation (Aspirin-induced asthma):

Recurrent rhinitis, nasal polyps, urticaria, bronchospasm.

-Pathogenesis:

- Precise pathogenesis unknown.
- Involves abnormality in prostaglandin metabolism from inhibition of cyclooxygenase by aspirin.

Occupational Asthma

- Asthma attacks usually develop after repeated exposure to antigens at the workplace.
- **Triggered by** fumes (plastics), organic and chemical dusts (wood, cotton, platinum), gases (toluene), and other chemicals.
  (Extra from the doctor: Examples include (farmers, animal handlers, manufacturers of foam mattresses, bakers, food processors, cotton workers , manufacturers of metals))

-Development:

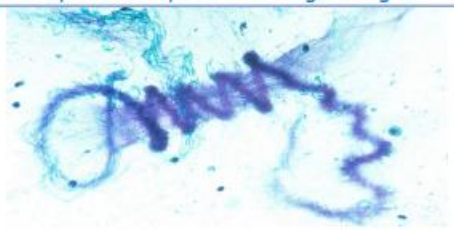
- Develops after a long time (e.g., 5 years).
- Once developed, individuals are not allowed to enter their workplace to prevent recurrent exposure.

8-morphology: (slides 25,26,27,28,29,30 in the modified slides file, so you can see the figures)

MORPHOLOGY

- occlusion of bronchi and bronchioles by thick **mucous plugs**
- mucous plugs contain whorls of shed epithelium called **Curschmann spirals.**

When sputum samples and smeared on slides, we can sometimes see the whorls. Called Curschman Spirals. They are not specific findings though.



Curschman Spirals in sputum

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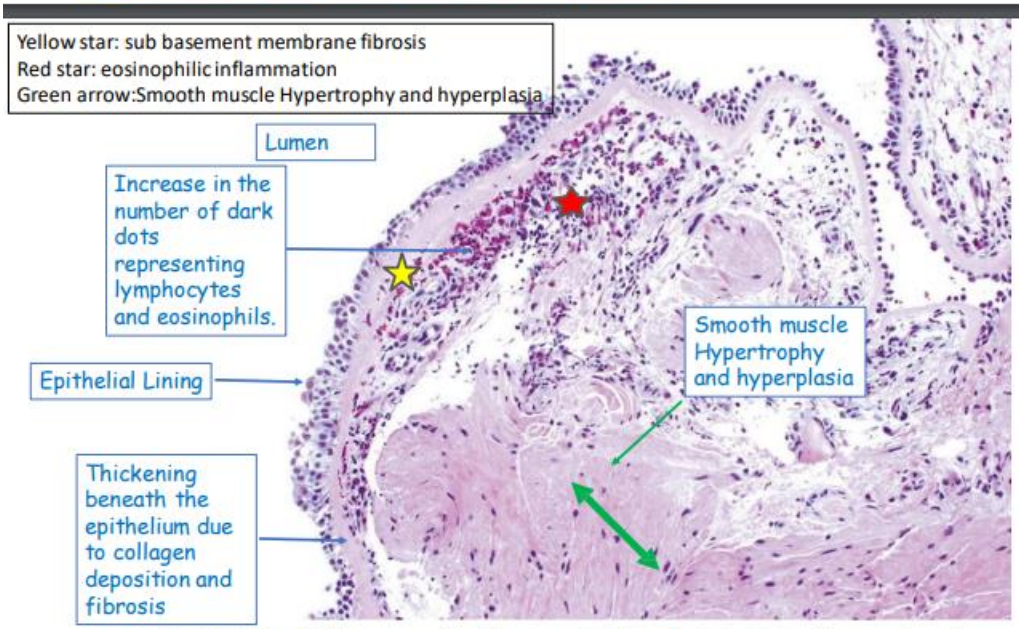
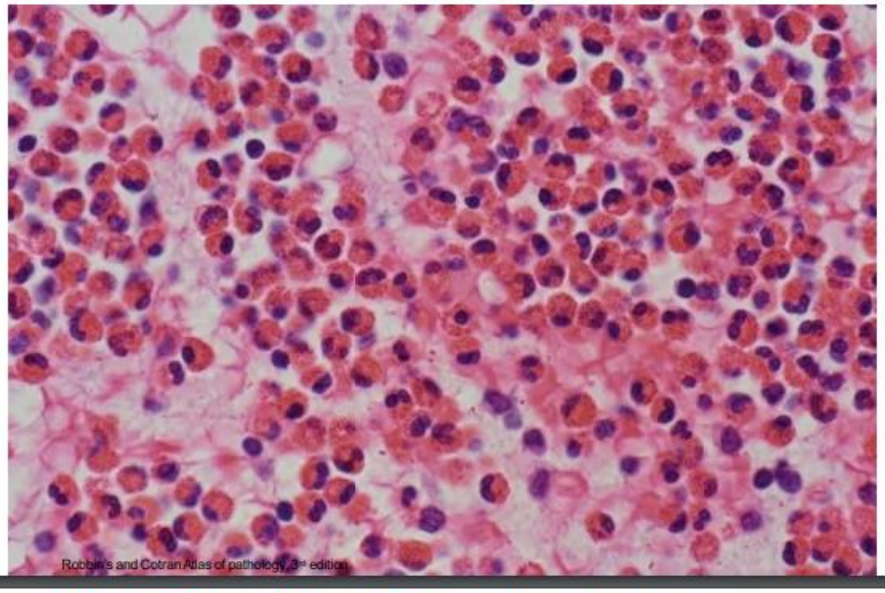
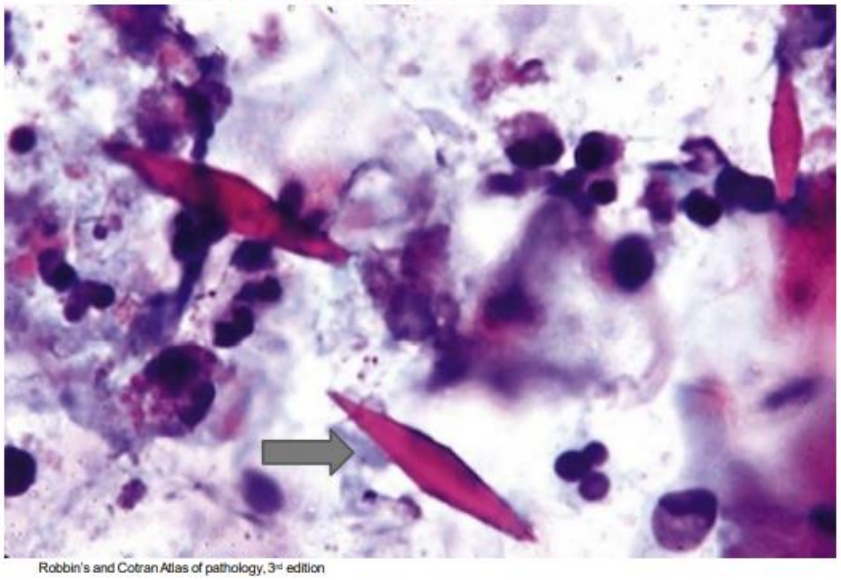


Fig. 13.11 Bronchial biopsy specimen from an asthmatic patient showing sub basement membrane fibrosis, eosinophilic inflammation, and smooth muscle hyperplasia

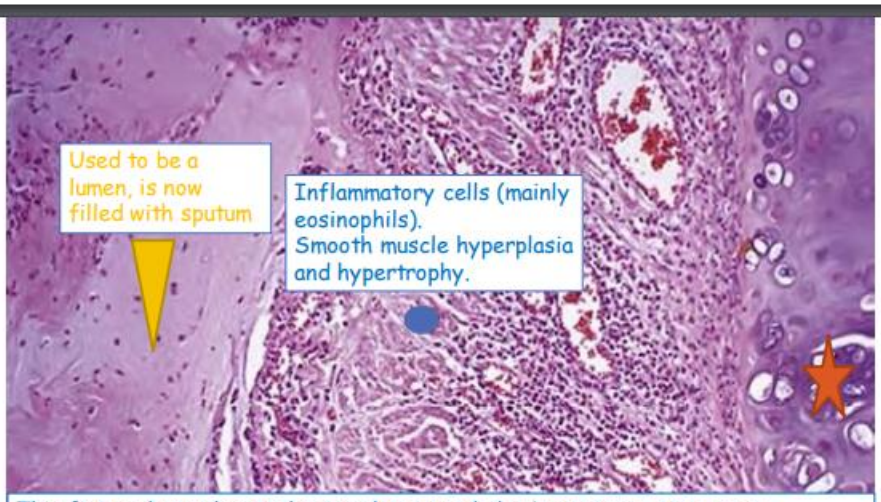
- eosinophils Main inflammatory cells



- **Charcot-Leyden crystals:** crystalloids made up of the eosinophil protein galectin-10



- **airway remodeling, including:**
  - Thickening of airway wall
  - Sub-basement membrane fibrosis
  - Increased submucosal vascularity
  - An increase in size of the submucosal glands and goblet cell metaplasia of the airway epithelium
  - Hypertrophy and/or hyperplasia of the bronchial muscle
  - In fetal cases : distension of lung



This figure shows the predominantly expanded sub mucousa , as you can appreciate the the sub mucousa lies between the bronchial cartilage on the right which is marked by the red star and the bronchial lumen that is stuffed and filled with mucous which marked by yellow arrow on the left , the sub mucousa is widened by smooth muscles hypertrophy edema and inflammatory cells mainly eosinophils .

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Additional ***External*** Summary for Clarifying Asthma Morphology:

Microscopic examination of sputum cytology may show Curschmann spirals (twisted mucus plugs admixed with sloughed epithelium), eosinophils, or Charcot-Leyden crystals (protein crystalloids from broken down eosinophils).

In patients dying from disease, autopsy findings include mucous plugs, increased mucous glands with goblet cell hyperplasia, inflammation (especially with eosinophils), edema; hypertrophy and hyperplasia of bronchial wall smooth muscle, and thickened basement membranes.

9-clinical features:

-Coughing:

- Worsens at night or in the morning.

-Wheezing:

- Audible wheezing sounds, especially during expiration.
- May be heard without a stethoscope.

-Chest Tightness:

- Sensation of something wheezing or sitting in the chest.

-Shortness of Breath (Dyspnea):

- Feeling unable to catch one's breath or breathe deeply enough.
- Asthma is typically associated with difficulty in expiration.
- Asthmatic attacks last for several hours, with the option to end spontaneously or require medication.
- Between attacks, patients are symptom-free.

-Note:

- Asthma is reversible except in severe cases.

10-status asthmaticus:

Definition: Severe and prolonged asthma paroxysm (episode).
Responsiveness: Does not respond to therapy.
Duration: Persists for days or weeks.
Risks: Associated with hypercapnia, acidosis, and severe hypoxia, which can be fatal.
Management: Requires immediate hospitalization.
Objective: In the hospital, efforts are made to abort the asthmatic attack due to its life-threatening nature.

11-management:

Standard therapies include:

• Anti-inflammatory drugs(glucocorticoids) like cortisone
• Bronchodilators (beta-adrenergic drugs)
• Leukotriene inhibitors (potent broncho dilators, those agents can Block specific immune mediators such as: IL4 and IL5) (the doctor said Leukotriene inhibitors are potent bronchoconstrictors, but in fact leukotrienes themselves are bronchoconstrictors and the Leukotriene inhibitors are broncho dilators)

We are done with **ASTHMA**, let's proceed with **BRONCHIECTASIS**, the doctor talked about bronchiectasis in these points:

1- overview
2- pathogenesis
3- the conditions that most commonly predispose to bronchiectasis
4- morphology: -MACROscopic
-MICROscopic
5- clinical features

1- overview:

-Definition: Permanent dilation of bronchi and bronchioles due to destruction of smooth muscle and supporting elastic tissue.

-Etiology: Typically associated with chronic necrotizing infections; not a primary disorder, always secondary to persistent infection or obstruction.

-Reversibility: Irreversible condition.

-Clinical Features:

- Symptoms: Cough and expectoration of copious amounts of purulent sputum.
- Diagnosis: Established through an appropriate clinical history and radiographic evidence demonstrating bronchial dilation.

Purulent Sputum:
-Description: Purulent sputum is characterized as pussy, yellow to green in color, indicating the presence of white blood cells (WBCs) and cellular debris.
-Clinical Significance: A clue of an ongoing infection.
-Distinguishing from Chronic Bronchitis:
Chronic Bronchitis: Clear sputum due to the absence of infection.
Bronchiectasis: Large amounts of green sputum due to the presence of infection.

2- pathogenesis:

-Contributing Processes: Two intertwined processes contribute to bronchiectasis: obstruction and chronic infection (as we said, it is secondary process resulting from either obstruction or chronic infection, if it starts with obstruction this will lead to chronic infection, and if it starts with chronic infection, it leads to obstruction).

-Sequence of Events:

- Obstruction:
  Impairs clearance of secretions → Superimposed infection follows → Inflammatory damage to bronchial wall and accumulating exudate → Airways distention leading to irreversible dilation.

- Persistent Necrotizing Infection:
  Persistent Necrotizing Infection in the bronchi or bronchioles results in poor clearance of secretions, obstruction, inflammation → Peribronchial fibrosis and damage to bronchial walls → Irreversible dilation of the airways.

Origin of Obstruction or Infection: As we said before, it's a secondary process not a primary disease, resulted from either obstruction or chronic infection,
Obstruction Start: Obstruction leads to chronic infection.
Infection Start: Chronic infection leads to obstruction.

-Scenario with Obstruction Start:
Cause: Foreign body or tumor obstructing main airways.
Consequence:
Obstruction blocks secretion clearance.
Accumulated secretions become a medium for infection.
Infection causes inflammation, fibrosis, and destruction of elastic tissue and smooth muscle, and this will lead to permanent dilation of bronchus, especially if the obstruction and the infection are both chronic.

-Scenario with Infection Start:
Cause: Persistent necrotizing infection in bronchi or bronchioles.
Consequence:
Excessive mucin production, inflammation, and edema lead to obstruction.
Obstruction becomes refractory to treatment.
Consequently, chronic damage to tissue, smooth muscle, and elastic fibers, leading to permanent enlargement of bronchi and bronchioles, resulting in irreversible dilation.

3- The conditions that most commonly predispose to bronchiectasis:

(bronchial obstruction, Congenital or hereditary conditions, Necrotizing, or suppurative, pneumonia)

-Bronchial Obstruction:
Causes: Tumors, foreign bodies, mucus impaction OR as a Complication of Atopic asthma and chronic bronchitis.
Localization: Bronchiectasis occurs locally.

-Congenital or Hereditary Conditions:

=Cystic Fibrosis:
Hereditary disease affects lungs and digestive system.
Characterized by thick and sticky mucous production which may block the lung and obstruct the pancreas.
Result: Widespread severe bronchiectasis due to obstruction by abnormally viscid mucus and secondary infections.

=Immunodeficiency States:
Causes: Recurrent bacterial infections.
Distribution: Can be localized or diffuse.

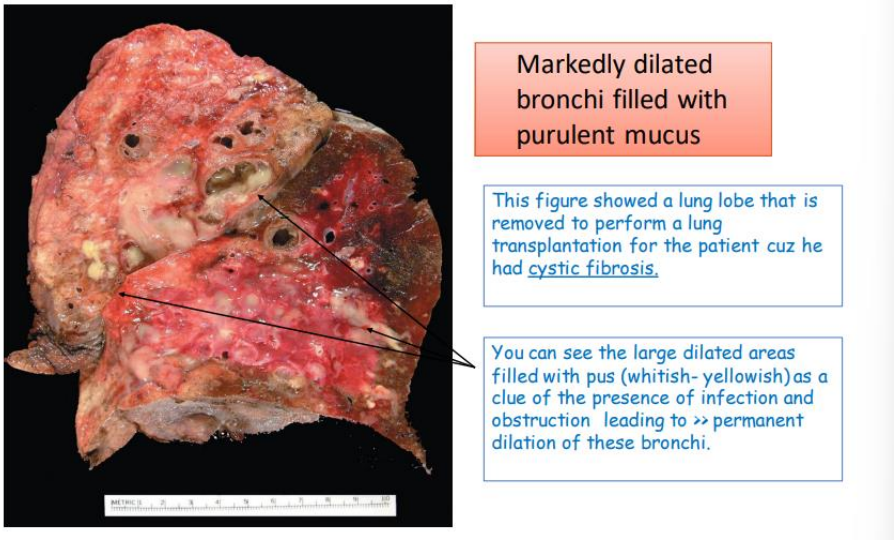
=Primary Ciliary Dyskinesia (Immotile Cilia Syndrome):
Rare autosomal recessive disorder.
It is caused by inherited abnormality of cilia, and this type of abnormality impairs the mucous ciliary clearance of the airways leading to persistent infections.
Associated Features (associated with): Bronchiectasis + sterility in males.

-Necrotizing or Suppurative Pneumonia:
Occurs particularly with virulent organisms such as Staphylococcus aureus or Klebsiella spp.

4- morphology:

-Macroscopic:
location: Lower lobes bilaterally (Predominantly observed in both lower lobes of the lungs)
Most severe involvement: Distal bronchi and bronchioles exhibit the most severe

damage.
The airways may be dilated to as much as four times as their usual diameter so that the changes are prominent (can be recognized)



-Microscopic:

In Full-Blown Active Cases:

Inflammatory Exudate: Intense acute and chronic inflammatory exudate present within the walls of bronchi and bronchioles leading to Desquamation of lining epithelium and Extensive ulceration.

Sputum Culture: Mixed flora cultured from sputum, Usual organisms include Staphylococcus, Streptococcus, Pneumococcus, and anaerobic bacteria.

Histological Features:
Inflammation and Ulceration: Acute or chronic inflammation with ulceration of the epithelium, beneath it a plethora of inflammatory cells.
Progression leads to fibrosis and destruction of underlying layers.

During Healing:

Regeneration of Epithelium: Lining epithelium may regenerate completely.
Structural Changes: Abnormal dilation and scarring.
Fibrosis of bronchial and bronchiolar walls.
Peribronchiolar fibrosis.

Abscess formation in some cases, indicating the accumulation of inflammation in one area.

Resulting Damage: Severe damage to the walls with fibrosis and scarring, Damage to smooth muscles and elastic fibers.

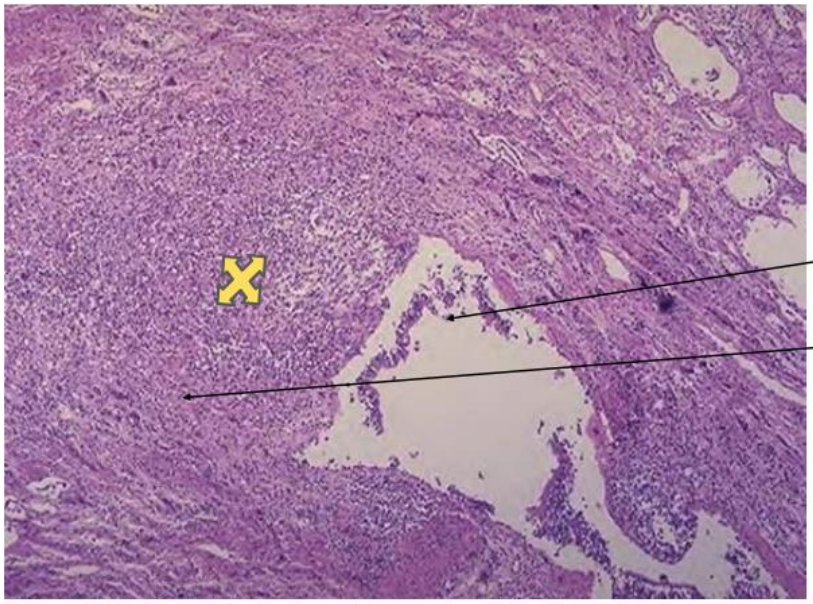


Figure 5-34 **Bronchiectasis, microscopic** dilated bronchus in which the mucosa and bronchial wall are not seen clearly because of the necrotizing inflammation with tissue destruction.
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5- clinical features:

-Primary Symptom: Severe, Persistent Cough (characterized by mucopurulent sputum).

-Other Symptoms:
Dyspnea (Shortness of breath)
Rhinosinusitis (Inflammation of the nose and sinuses)
Hemoptysis (Coughing up blood)

-Symptoms occur episodically.

-Precipitating Factors:
Symptoms are often precipitated by Upper Respiratory Tract Infections URTIs.
Especially significant in immunodeficient patients.

-Complications in Severe Widespread Bronchiectasis:

- Significant obstructive ventilatory defects
- Hypoxemia and Hypercapnia (Reduced oxygen levels and increased carbon dioxide levels)
- Pulmonary Hypertension
- Cor Pulmonale (Right-sided heart failure due to long-term lung disease)
- Congestive Heart Failure
- Decreased Gas Exchange

We are done with **BRONCHIECTASIS**.

The modified slides file contains a summary table of the 4 obstructive lung diseases and some questions, we advise you to read them in slides 48-55.

Lec 2+3+4: in these 3 lectures we are going to talk about **CHRONIC INTERSTITIAL (RESTRICTIVE, INFILTRATIVE) LUNG DISEASES**

let's start,
the doctor talked about **CHRONIC INTERSTITIAL (RESTRICTIVE, INFILTRATIVE) LUNG DISEASES** as follows**:**

 # overview of CHRONIC INTERSTITIAL (RESTRICTIVE, INFILTRATIVE) LUNG DISEASES

categories of chronic interstitial lung diseases:

- GRANULOMATOUS DISEASES:
1- Sarcoidosis
2- Hypersensitivity pneumonia

- FIBROSING DISEASES:
1- Idiopathic Pulmonary Fibrosis
2- Nonspecific Interstitial Pneumonia
3- Cryptogenic Organizing Pneumonia
4- Pneumoconiosis: =Coal Worker's Pneumoconiosis (CWP)
=Silicosis
=Asbestosis and Asbestos-Related Diseases

- SMOKING-RELATED INTERSTITIAL DISEASES:
1- Desquamative interstitial pneumonia (DIP)
2- respiratory bronchiolitis- Associated interstitial lung disease

Table 15.5 Major Categories of Chronic Interstitial Lung Disease

Fibrosing
Usual interstitial pneumonia (idiopathic pulmonary fibrosis)
Nonspecific interstitial pneumonia
Cryptogenic organizing pneumonia
Connective tissue disease–associated
Pneumoconiosis
Drug reactions
Radiation pneumonitis
Granulomatous
Sarcoidosis
Hypersensitivity pneumonitis
Eosinophilic
Smoking-Related
Desquamative interstitial pneumonia
Respiratory bronchiolitis–associated interstitial lung disease
Other
Langerhans cell histiocytosis
Pulmonary alveolar proteinosis
Lymphoid interstitial pneumonia

 # overview of CHRONIC INTERSTITIAL (RESTRICTIVE, INFILTRATIVE) LUNG DISEASES:

Clinical Features and Characteristics:

1. Difficulty in Inhalation:
   - Decreased lung compliance, leading to stiff lungs.
   - Difficulty in filling the lungs with air during inspiration (so it is hard to get the air in, hard to inhale)

2. Reduced Lung Volume and Capacity:
   - Total lung capacity (TLC) is decreased.
   - Lung compliance is diminished.

• Total lung capacity: (TLC) is the volume of air in the lungs upon the maximum effort of inspiration.
• lung compliance is a measure of the lung's ability to stretch or expand

3. Common Features:
   - Characterized by inflammation and fibrosis of the lung interstitium (may involve intra-alveolar spaces).
   - pulmonary function studies Indicative of restrictive lung disease with reduced lung volume and compliance.
   - About 75% of cases have unknown causes and pathogenesis, so it has idiopathic or cryptogenic etiology
   - Overlapping features among various entities.

4. Nomenclature:
   - Interstitial: Involvement of the interstitium layer.
   - Restrictive: Stiff lungs restricted from being filled with air.
   - Infiltrative: (related to histology) Cellular/acellular infiltration, mainly in the interstitium and it can happen in the intra-alveolar spaces.

5. Clinical Presentation:
   - Symptoms: Dyspnea (increased effort to breathe), tachypnea (it will INCREASE the respiratory rate in an attempt of inspiring more air)
   - Physical Examination: End-inspiratory crackles (the small restrictive airways that are facing the restrictive lung disease (trying to enter air in lung)), eventual cyanosis.

6. Radiographic Findings:
   - Bilateral lesions on chest radiographs, present as small nodules and reticular modular pattern, irregular lines, or ground glass appearance, patchy process rather than diffuse.

7. Pathophysiology and Complications:
Ventilation-Perfusion Imbalance:

Damage to alveolar epithelium and interstitial vasculature results in Abnormal ventilation-perfusion ratio leading to hypoxia.

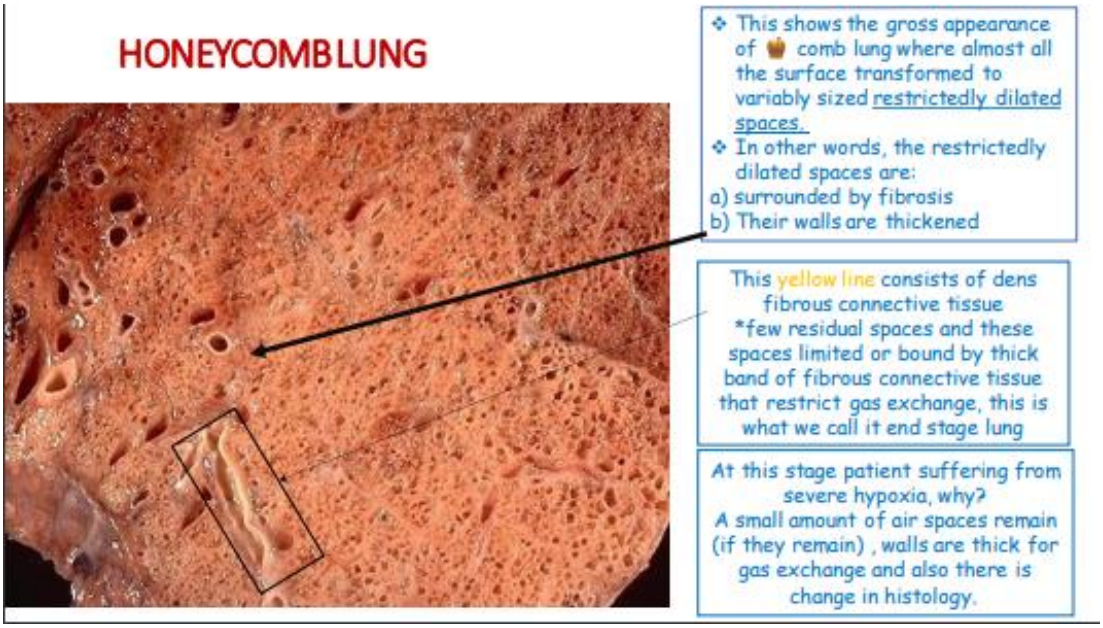
With Progression: vasoconstriction reward blood from area with low O2 to high O2 and with chronic hypoxia cause structural change and thickening in the vessel's wall leading to pulmonary hypertension, so:

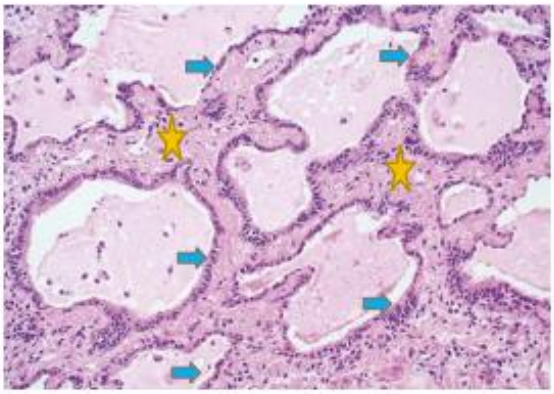
- Pulmonary hypertension develops.
- Respiratory failure and cor pulmonale may occur.

8. Categories and Differentiation:
   - Categorized based on clinical features and histology.
   - Entities share inflammation and a restrictive pattern but differ in etiology and unique findings.
   - Early stages allow for easier differentiation; advanced stages show bilateral extensive fibrosis.

9. Advanced Stage Features:
   - Diffuse scarring and destruction of the lung, termed "honeycomb" lung or end stage lung.
   - Hypoxia, secondary pulmonary hypertension, and cor pulmonale.

10. Challenges in Diagnosis:
   - Identifying underlying etiology becomes difficult in advanced stages.
   - Distinguishing between different restrictive lung diseases is easier at the early stage.





Recap: We will find histological features that restricts gas exchange and gives the honeycomb appearance:
I) Expansion of the alveolar septa and **fibrosis**
II)**Cystically dilated spaces** lined by meta-plastic bronchioles epithelium

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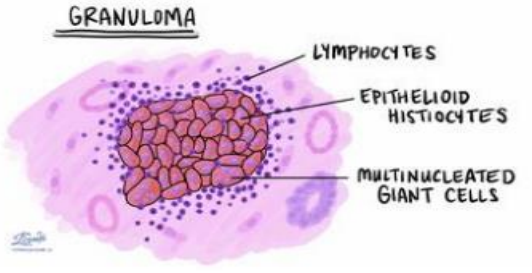
Regarding histology, we lose so much of the alveolar spaces and the residual alveolar spaces which remain are dilated and NOT LINED by pneumocytes (type 1 + type 2 pneumocytes) , but rather they are lined by metaplastic bronchioles epithelium, therefore they are not suitable for gas exchange & walls have extensive fibrosis
In addition, the restrictedly dilated spaces(lumen) are STUFFED with proteinaceous material which further restricts gas exchange. Moreover, lymphocytes and collagen deposition in the interstitium septa (represented in the pic by a star shape), thick band of fibrous connective tissue filled the alveolar septa. This is what we called extensive pulmonary interstitial fibrosis in end stage lung.
When patient reaches end stage (advanced) all lung will be like this pic and can't distinguish the primary cause.

In summary:
Chronic interstitial lung diseases, characterized by reduced lung compliance, diminished capacity, and inflammation, encompass a diverse group with overlapping features. Early differentiation is feasible, but advanced stages pose challenges, leading to common complications like hypoxia and pulmonary hypertension. The nomenclature reflects involvement in the interstitium, restrictive nature, and infiltrative histology. Regular monitoring and early diagnosis are crucial for effective management.

Now, let's start with the first category of restrictive lung diseases:

- GRANULOMATOUS DISEASES:
1- Sarcoidosis
2- Hypersensitivity pneumonia

Granuloma:
type of chronic inflammation made of activated macrophages (epithelioid histocytes) that fused together to form multinucleated giant cells and they are usually cuffed (surrounded) by other inflammatory cells like lymphocytes and plasma cells



1-Sarcoidosis:

Definition:
- Systemic granulomatous disease of unknown etiology.
- Characterized by noncaseating granulomas (no central necrosis) in various tissues and organs.
- Diagnosis of exclusion.

Clinical Presentation:
- Can manifest as acute or chronic illness or restrictive lung disease.
- Named "systemic" due to multi-organ involvement and "inflammatory" as it leads to fibrosis categorizing it among interstitial lung diseases.

Granuloma Characteristics:
- Granulomas are noncaseating, occurring in any tissue or organ.
- There is no large central necrosis; it only contains lymphocytes, macrophages, and multi-nucleated cells.
- Noncaseating indicates that it's either due to sarcoidosis or to infections (fungal, bacterial, etc.), so noncaseating granulomas are not specific to sarcoidosis; diagnosis involves excluding infectious causes first.

Clinical Features:
- Varied clinical picture depending on the affected organ.
- Most common symptoms (90% of cases) in order:
  1. Bilateral hilar lymphadenopathy (enlargement of LYMPH NODES in the hilum area) or lung involvement leading to shortness of breath.
  2. Visual and skin manifestations (nodules).

Presentation Variability:
- Sarcoidosis can present as acute, chronic, or restrictive lung disease.
- Not all sarcoidosis patients exhibit restrictive lung disease.

Etiology and Pathogenesis:
- Etiology remains unknown.
- research evidences suggest that it's a Disordered immune regulation in genetically predisposed persons exposed to certain environmental agents.
- Involves a cell-mediated response to an unidentified antigen, primarily driven by CD4+ helper T cells.

(Growing evidence indicates a disorder in the immune response, particularly T-helper lymphocytes (CD4+), so Genetically predisposed individuals, when exposed to unknown antigens, trigger a cell-mediated immune response.)

Morphology of Sarcoidosis:

Regarding morphology, the important nonspecific characteristic of this disease is the noncaseating epithelioid granuloma.

- Noncaseating Epithelioid Granuloma:

Definition: Discrete, well-circumscribed nodule containing epithelioid cells rimmed by an outer zone rich in CD4+ T cells, including pale cells (abundant light stain cytoplasm) with epithelioid nucleus (elongated and contain euchromatin) which is also named vesicular nucleus (prominent nuclei). These collections of macrophages rimmed by lymphocytes, and we might find multi-nucleated giant cells.

Importance: Non-specific characteristic of sarcoidosis, not sufficient for diagnosis alone. You should roll out other entities in differential diagnosis.

Caseation Necrosis:
- Absent in sarcoidosis granulomas, distinguishing it from tuberculosis.
- Caseation Necrosis (Central necrosis) is not observed in sarcoidosis granulomas.

Chronic Inflammatory Reaction and Scarring:
- Granulomas are part of a chronic inflammatory reaction in response to a stimulus.
- The reaction attempts to heal through fibrosis and scarring.
- Scarring can occur in various tissues, including lymph nodes and lungs, leading to interstitial lung disease.

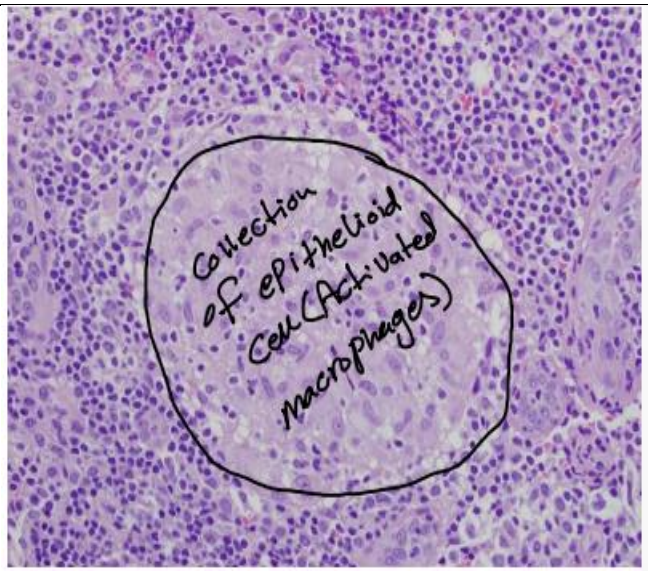
In granuloma, there are two structures, which are considered nonspecific and not important for diagnosis:

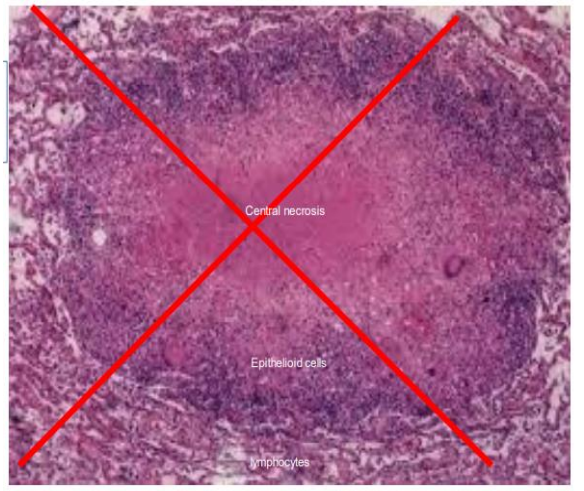
- Schaumann Bodies:
- Laminated concretions composed of calcium and proteins (like onion skin).
- Non-specific and not crucial for diagnosing sarcoidosis.
- Found in multi-nucleated cells within granulomas.

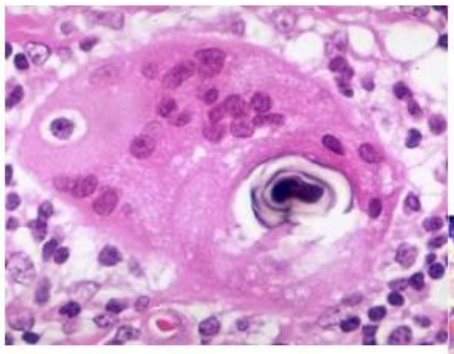
- Asteroid Bodies:
- Star-shaped (stellate) inclusions within giant cells' cytoplasm.
- Non-specific and not required for a sarcoidosis diagnosis.
- May be observed in various forms of granulomas.

Evolution of Granulomas:
- Overtime, granulomas are replaced by hyalinized scars.
- Sarcoidosis granulomas may exhibit Schaumann bodies and Asteroid bodies, which are not necessary for diagnosis and can also appear in granulomas of other origins.

- Summary:
 - Sarcoidosis is characterized by noncaseating epithelioid granulomas with specific morphological features.
 - The absence of caseation necrosis differentiates it from tuberculosis.
 - Presence of Schaumann bodies and Asteroid bodies is not required for a sarcoidosis diagnosis; they are non-specific and can occur in other granulomas.







SHAUMANN BODIES

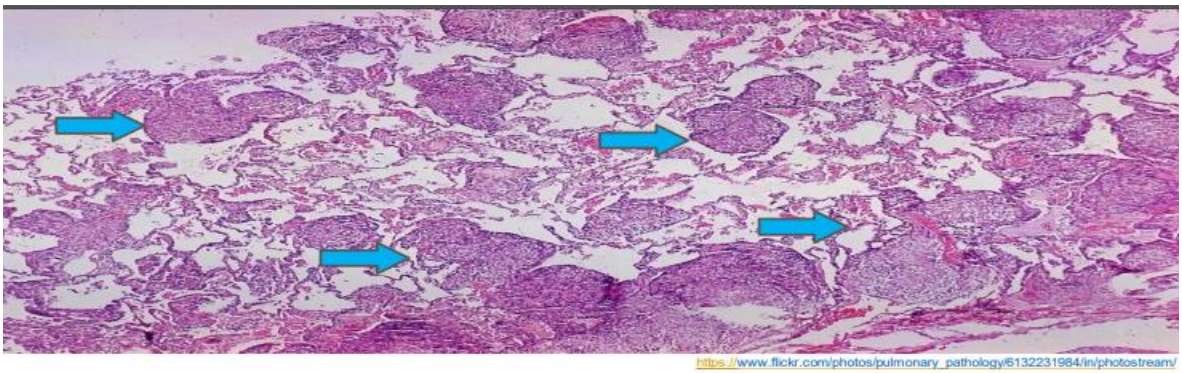
Organ Involvement and Morphology:

MOST COMMONLY INVOLVES: (Lungs - hilar and paratracheal lymph nodes - Skin - eye and lacrimal glands - Spleen, Liver, BM)

1. Lungs:
   - Frequency: 90% of patients.
   - Granulomas Distribution: Involves interstitium, +/- intra-alveolar space and pleura, lymph nodes, blood vessels, and bronchial submucosa.
   - Lesion Characteristics: Accumulation along lymphatics around bronchi and blood vessels. High frequency in bronchial submucosa.
   - Broncho-Alveolar Lavage (BAL): Abundant CD4+ T cells in BAL fluid.
   - Healing Tendency: strong tendency for lesions to heal in the lungs → varying stages of fibrosis and hyalinization are often found (varying According to the age of lesions…)
   - Advanced Stage: 5-15% may progress to honeycomb lung (end-stage) replaced by diffuse interstitial fibrosis (difficult to distinguish primary etiology)

(The earliest stage in fibrosis is formation of fibroblastic foci, But 5-15% of patients will have end stage lung where there is a diffused extensive pulmonary fibrosis leads to sever deterioration in the lung function)

Broncho-alveolar lavage (diagnostic modality to diagnose the diseases of the lower respiratory tract) -we do a bronchoscopy from the nose or mouth and set it to the place that we want to check in the lower respiratory tract, then u introduce a measured amount of fluid inside this space then withdraw it, this fluid is the BAL. Then we do a smear on slide and dye it to see the compartment of this fluid. In BAL we might found cancer or increased in eosinophils or maybe granuloma. In sarcoidosis u will see abundant CD4+ lymphocytes (T-Helper)

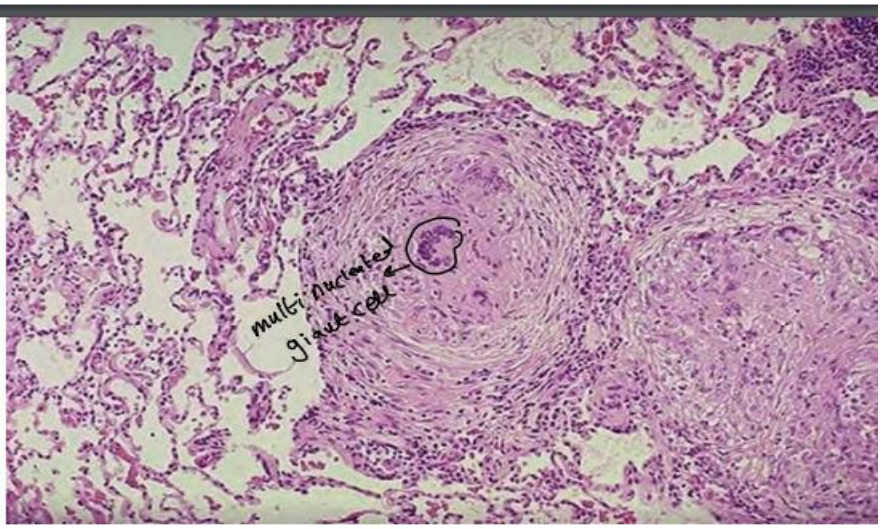


https://www.flickr.com/photos/pulmonary_pathology/6132231984/in/photostream/

This figure shows the changes in the lung in sarcoidosis.
-All alveolar spaces are patent (open) no lesions inside the alveolar spaces but the walls are expanded by nodular proliferation composed of cells which is granuloma (in purple)

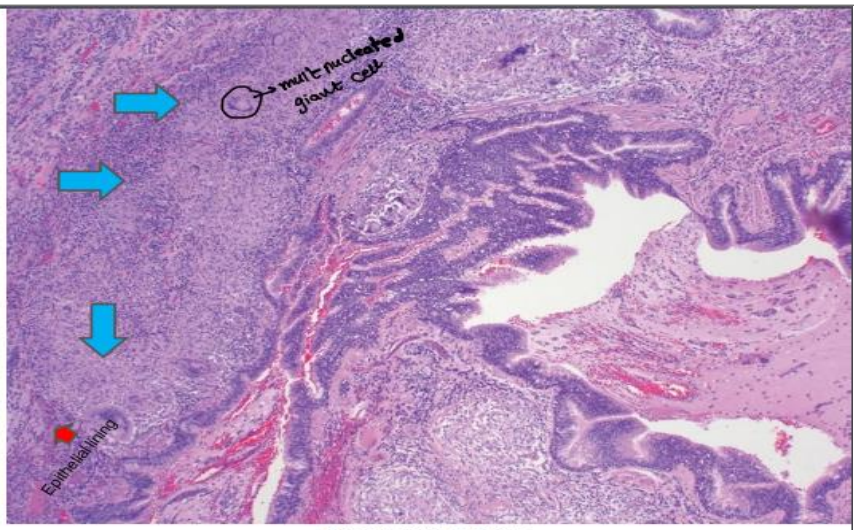
NO NECROSIS

-If u go at higher power in the microscope u will find that this collections which thickening and expanding the wall composed of well circumscribed collection of histiocytes many of them are multi-nucleated which are sprinkled by dark cells (Lymphocytes) all this **in the wall not inside the lumen.**
So we have interstitial non-caseating granuloma formation in the lungs.



Robbin's and Cotran Atlas of pathology, 3rd edition

If u look to a specimen from the bronchial wall They tend to accumulate in the submucosa (under the epithelium)
So we have non-caseating granuloma which is sub mucosal in the bronchial walls.
-note that **it isn't diagnostic**, this just suggest that this patient have sarcoidosis but u have to role out infections.
It tends to be collected in interstitium, intra alveolar, plura, bronchial submucosa and around vessels.

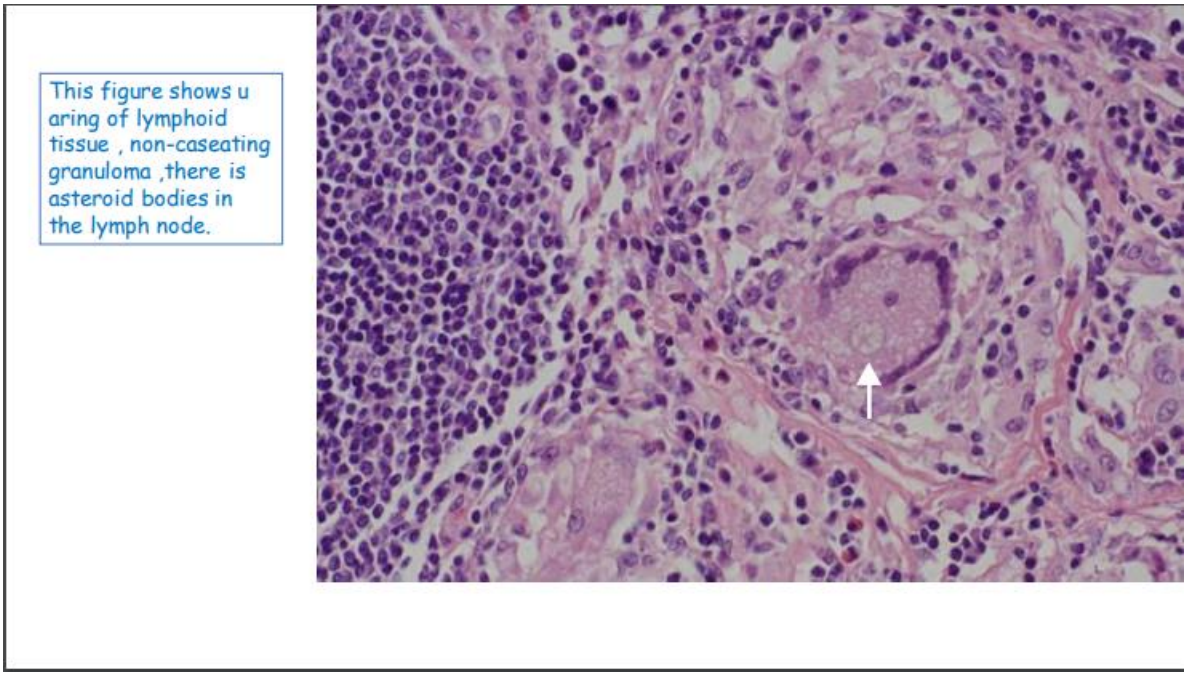


Robbin's basic pathology, 10th edition

2. Lymph Nodes:

- Involvement: Almost all cases, particularly hilar and mediastinal nodes.
- Node Characteristics:

  Enlarged,
  painless,
  firm,
  rubbery,
  discrete “nonmatted” (can mark boundaries),
  nonadherent and do not ulcerate “ unlike TB” (lymph nodes fuse to each other,
  adherent to adjacent structures do ulcerations , extensive necrosis.
  Calcification is sometimes present.
- Granulomas in Nodes: Non-caseating granulomas are found, often showing asteroid bodies. (It not necessary always to find non caseating granuloma because these granulomas tend to heal. Maybe take a biopsy from hilar and find fibrosis.)
- Diagnostic Value: Not essential for diagnosis, as calcification is part of the inflammatory process.



3. Skin:

- Involvement Frequency: 25% of patients.

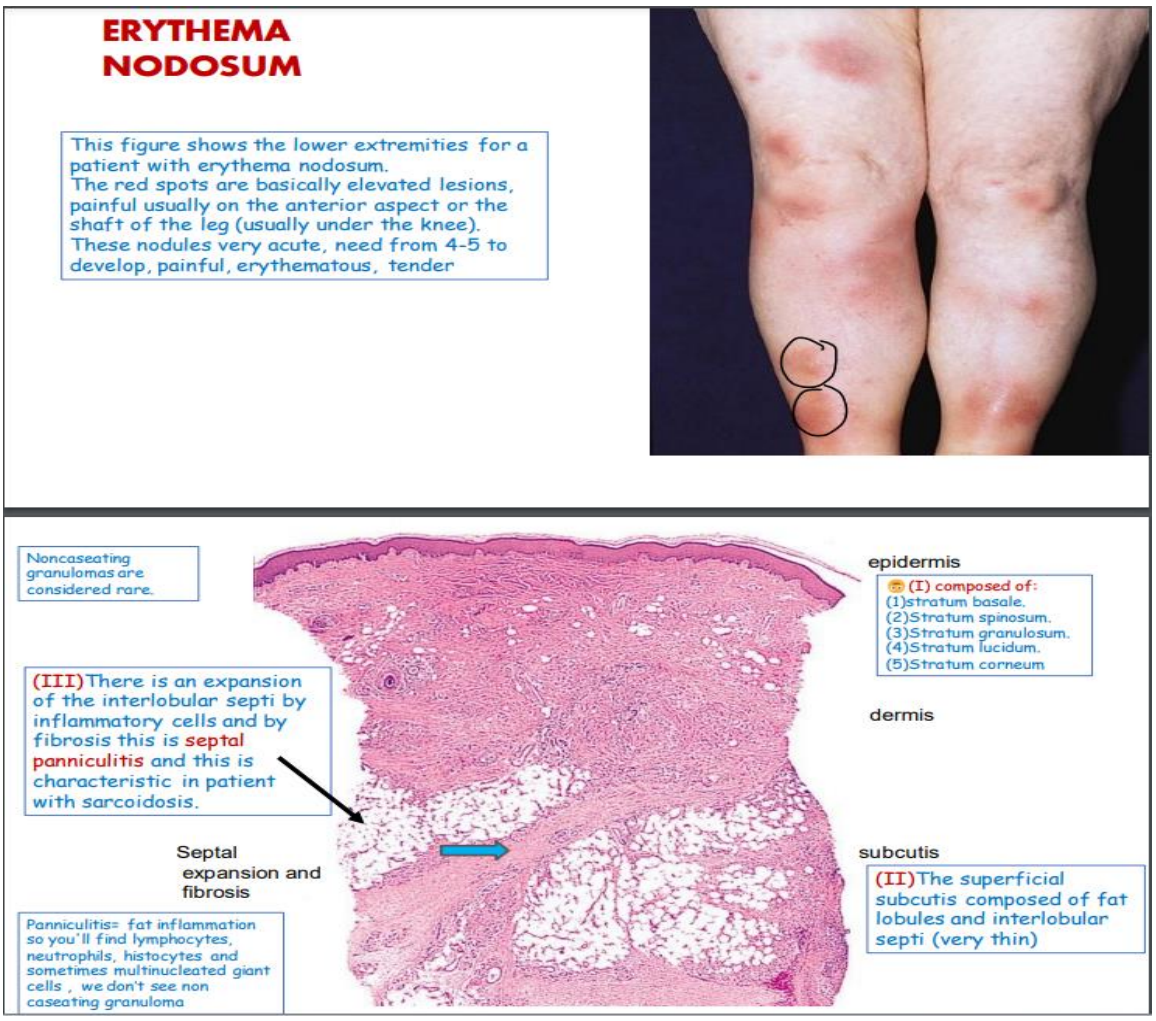
1- Erythema Nodosum (EN): erythema (redness) nodosum (involve nodule)
Hallmark of acute sarcoidosis. (Hallmark of acute attack if you have diagnosed

your patient with sarcoidosis but it can appear in other diseases, so it is not specific for sarcoidosis and not diagnostic.)

Painful, raised, red nodules on anterior aspects of the lower extremities mainly the leg (maybe in the thighs but usually in the anterior aspect of the legs). Sarcoidal granulomas are uncommon in EN (These nodules don't show granuloma, they have pattern of inflammation called septal panniculitis) (Panniculitis: inflammation of the fat in superficial subcutis layer)

2- Subcutaneous Nodules: Painless, discrete, with abundant noncaseating granulomas.

3- Other Skin Manifestations: Erythematous plaques, flat lesions.



4. Eye and Lacrimal Glands: Usually it involves the uveal tract that composed of the iris (the colored part of the eyes) so iritis happen or iridocyclitis if the iris and the ciliary body are involved. Or the posterior part of the uveal tract that in the choroid (the layer between

sclera and retina)
- Involvement Frequency: 20-50% of cases.
1- Uveitis:
Most common eye involvement
iritis or iridocyclitis (unilateral or bilateral).
Choroiditis: Involvement of the posterior uveal tract.
2- cornea can be involved resulting in corneal opacities and the involvement of the optic nerve will lead to glaucoma, and even total loss of vision.
3-Sicca syndrome in lacrimal glands (SICCA SYNDROME: Inflammation in the lacrimal glands, with suppression of lacrimation).

5. Parotid Glands:
- Involvement Frequency: <10% of patients.
- Characteristics: Unilateral or bilateral parotitis with painful enlargement. May lead to xerostomia (dry mouth, No secretions from salivary gland).
Mikulicz syndrome involves combined uveoparotid (Uveal and parotid enlargement) involvement.

6. Spleen, Liver, Bone Marrow:
- Spleen Involvement: In ¾ of cases, contains granulomas, with 10% showing enlargement (Splenomegaly).
- Liver Involvement: Granulomas in portal triads, with 1/3 experiencing hepatomegaly or abnormal liver function.
- Bone Marrow: Involved in 40% of patients, associated with hypercalcemia and hypercalciuria due to increased calcium absorption secondary to production of active vitamin D by the macrophages that form the granulomas. (hypercalcemia and hypercalciuria not related to bone destruction)

Hypercalcemia Mechanism:
- Granulomas contain macrophages producing 1-alpha hydroxylase.
- 1-alpha hydroxylase activates vitamin D.
- Active vitamin D increases calcium absorption in the intestine and resorption in the kidneys.
- Results in hypercalcemia and hypercalciuria (high calcium in the urine), potentially leading to kidney stones.

Clinical Features, Diagnosis, course and outcome of Sarcoidosis:

1. Clinical Features:
- Asymptomatic Majority: Often entirely asymptomatic, leading to random diagnoses during screenings.
- Symptomatic Presentations: Peripheral lymphadenopathy, cutaneous lesions, eye involvement, splenomegaly, or hepatomegaly, depending on organ involvement
- Respiratory and Constitutional Symptoms: In symptomatic cases, 2/3 may experience gradual respiratory symptoms (shortness of breath (most common), dry cough, chest discomfort) or constitutional signs (fever, fatigue, weight loss, anorexia, night sweats).
- Insidious Progression: The disease can manifest acutely or chronically, with an insidious progression of restrictive lung disease.

2. Diagnosis:
- Diagnostic Challenges: Absence of Definitive Test (No definitive diagnostic test for sarcoidosis exists).
- Diagnostic Criteria:
= Clinical Findings
=Radiologic Findings: (Chest X-ray: Commonly reveals bilateral hilar lymphadenopathy // CT scan: Nodular infiltrates in both lungs)
= Histologic Findings: Identification of noncaseating granulomas, suggestive but not diagnostic.
= Exclusion of Other Disorders with Similar presentations, radiology, or histologic findings.
>>Tuberculosis Exclusion: Particularly important to exclude tuberculosis as a cause.
- Noncaseating granulomas are suggestive of sarcoidosis, but exclusion of other causes is a must.

3. Disease Course:
- Unpredictable Course: Varied and unpredictable, with periods of activity and remissions.
- Progressive Chronicity: Some experience a gradual increase in symptoms over time.
- Spontaneous or Steroid-Induced Remissions: Remissions may be spontaneous or induced by steroid therapy.

4. Outcome:
- Diverse Outcomes: Outcomes vary, with some patients experiencing minimal symptoms and complications, while others face permanent dysfunction.
- Recovery Rates: Approximately 65-70% recover with minimal or no residual manifestations.
- Permanent Dysfunction: Around 20% may have permanent lung dysfunction or visual impairment.
- Progressive Pulmonary Fibrosis: 10-15% may face progressive pulmonary fibrosis and cor pulmonale, leading to honeycomb lung and right-sided heart failure.

We are done with **Sarcoidosis**, let's proceed with **Hypersensitivity pneumonitis** (the second disease of **GRANULOMATOUS DISEASES**)

2- Hypersensitivity pneumonitis:

Hypersensitivity Pneumonitis: Overview

Definition:
- Also Known As: Hypersensitivity pneumonia.
- Nature: A spectrum of immunologically mediated, predominantly interstitial lung disorders.
- Cause: Intense, prolonged exposure to inhaled organic antigens, often occupational. (It's not classified as occupational, but many cases are considered occupational (happens at the workplace))
(Briefly, it's a group of antigens or allergens that patients predispose to it in work which leads to hypersensitivity pneumonitis)

Characteristics:
- Alternative Name: Allergic alveolitis.
- Primarily Affects alveoli in response to inhaled organic dust containing antigens (spores of thermophilic bacteria, fungi, animal proteins, bacterial products).
- Comparison with Asthma: Both diseases are caused by known antigens; asthma affects bronchi, hypersensitivity pneumonitis targets alveoli. Asthma is obstructive; hypersensitivity pneumonitis is restrictive.
- Its etiology is known, unlike sarcoidosis.

Syndromes and Antigens: Numerous syndromes are described depending on the occupation or exposure of the individual, examples:

1. Farmer's Lung:
   - Cause: Exposure to dusts generated from humid, warm, newly harvested hay that permits the Rapid proliferation of spores and mold.

2. Humidifier or Air-Conditioner Lung:
   - Cause: Caused by thermophilic bacteria in heated water reservoirs.

3. Hot Tub Lung:
   - Cause: Nontuberculous Mycobacterium.

4. Pigeon Breeder's Lung:
   - Cause: Proteins from serum or feathers (from birds).
   - Occupation: Particularly relevant to individuals involved in pigeon breeding.

General Characteristics:
- Number of Antigens: Over 300 allergens contributing to the development of hypersensitivity pneumonitis.
- Occupational Exposure: Disease development is often associated with consistent daily exposure over extended periods. (Not someone who periodically visits their farm, but rather a person who works on their farm for 8 to 9 hours daily has high prolonged exposure, high dose of this antigens, over time lead to disease.)
- Intensity: High prolonged exposure, high antigen dose over time leads to the manifestation of the disease.

This table shows you examples of the sources of the antigens that can cause hypersensitivity pneumonitis.

Table 13.4 Sources of Antigens Causing Hypersensitivity Pneumonitis

Source of Antigen	Types of Exposures
Mushrooms, fungi, yeasts	Contaminated wood, humidifiers, central hot air heating ducts, peat moss plants
Bacteria	Dairy barns (farmer's lung)
Mycobacteria	Metalworking fluids, sauna, hot tub
Birds	Pigeons, dove feathers, ducks, parakeets
Chemicals	Isocyanates (auto painters), zinc, dyes

From Lacasse Y, Girard M, Cormier Y: Recent advances in hypersensitivity pneumonitis, *Chest* 142:208, 2012.

Immunologic Basis:

- Bronchoalveolar Lavage (BAL): specimens demonstrate Increased CD4+ and CD8+ lymphocytes, with a predominance of cytotoxic T cells (more than T helper cells)
- Specific Antibodies detected in serum against the offending antigen, indicating an immune-mediated process (antigen-antibody complexes).
- Histology (in 2/3 of patients): Noncaseating granulomas in the lungs, signifying an immune reaction.
- Immunofluorescence: Complement and immunoglobulins detected within vessel walls.

Morphology of Hypersensitivity Pneumonitis:

- Histologic Changes Centered on Bronchioles including:

1. Interstitial Pneumonitis: Inflammation in lung parenchyma characterized by lymphocytes, plasma cells, and macrophages. (You'll find lymphocytes around bronchiole or alveoli in interstitium causing interstitial pneumonitis.)
(Eosinophils are Rare in the pulmonary interstitium during inflammation.)

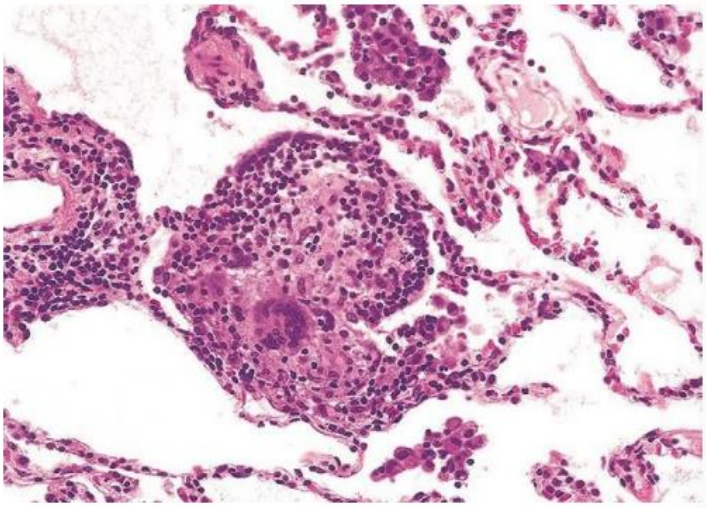
2. Granulomas:
- Nature: "Loose" and poorly formed granulomas without necrosis are present in > 2/3 of cases.
- Location: Peribronchiolar location, not well-defined (not discrete).
- Comparison to Sarcoidosis: Resembles non-caseating granulomas observed in sarcoidosis but with a loosely formed appearance.
- Diagnostic Value: Not strong diagnostic evidence; diagnosis relies on clinical and radiographic findings.

3. Progression to Interstitial Fibrosis: (they may progress to interstitial fibrosis with variable stages of fibrosis and restrictive lung disease)
Some patients may progress to interstitial fibrosis with fibroblastic foci, honeycombing, and obliterative bronchiolitis (in late stages)

4. Intra-Alveolar Infiltration: More than 50% of cases exhibit infiltration within the alveoli.

5. In advanced chronic cases, bilateral, upper-lobe-dominant interstitial fibrosis (UIP pattern) occurs.

- In the advanced stage, the upper part of the lungs tend to be involved more severely and more commonly than the lower lung lobes and it's usually bilateral.
- Pattern of fibrosis is **usual interstitial pattern** which will be discussed in the next lecture.
- So, within the alveolar walls, we have poorly, loosely formed granuloma, no demarcated boundaries , this granuloma is a non-caseating granuloma (loosely formed) seen in hypersensitivity pneumonitis.



In summary, the morphology of hypersensitivity pneumonitis involves initial interstitial pneumonitis around bronchioles, accompanied by loosely formed granulomas. In advanced cases, progression to interstitial fibrosis, honeycombing, and obliterative bronchiolitis may occur, with upper-lobe-dominant distribution. The appearance of poorly demarcated granulomas and fibrotic changes provides histologic insights into the disease's progression.

Clinical Features: (This disease can be acute, subacute (won't be discussed) or chronic.)

- Acute Reaction: Fever, cough, dyspnea, fatigue and constitutional symptoms occurring 4 to 8 hours after exposure to a large amount of allergen. (influenza like)
Resolution: Complete resolution within days (48 hours) if antigenic exposure is terminated after acute attacks.

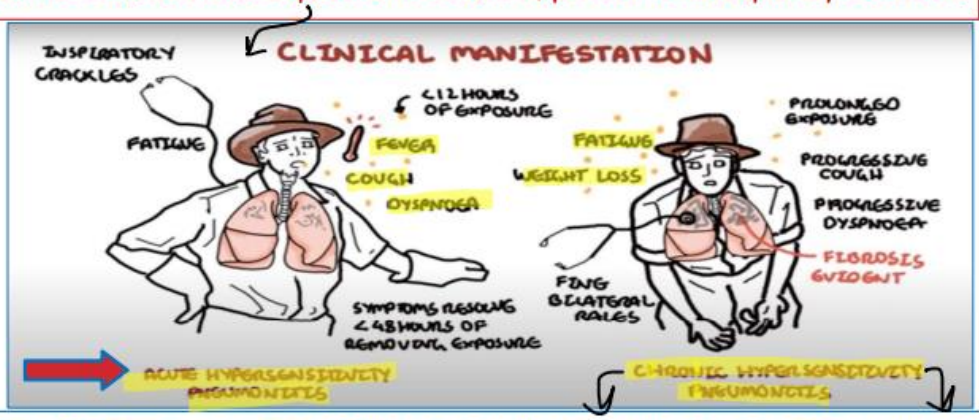
The typical scenario: when the patient was working, he developed fever, cough, dyspnea and his condition got better when he stayed at home.

- Chronic Disease:

Failure to remove the agent from the environment or exposure to this antigen in low dose for a long period of time results in Irreversible chronic interstitial pulmonary disease (Chronic phase)
characterized by Insidious onset of progressive symptoms (cough, dyspnea, malaise, fatigue, weight loss) in the chronic phase.
Restrictive pattern on Pulmonary function test because the patient has interstitial fibrosis. (So, the chronic hypersensitivity pneumonitis linked with interstitial lung disease)

You might hear crackles using stethoscope (صوت خرخشة بصدر المريض)

If we terminate the exposure in 48 hours, patient will completely resolved.



Here the person is exposed daily to small doses of this antigen continuously but these antigens don't enough to induce Acut attacks, it will accumulate and result in chronic hypersensitivity pneumonitis.
Over time patient will develop fatigue, weight loss, progressive dyspnea and cough
If you remove the exposure after 10 years , will the disease completely resolved ?
NO , there will be a partial resolution because there is a prat in lung already permanently affected by interstitial lung disease.

Diagnosis:

- acute form: With the acute form, the diagnosis is obvious because of the temporal relationship of symptom onset and exposure to the antigen
- Chronic Phase Dx: Clinical, radiological (high-resolution CT showing ground glass opacity), and pathological examination.

	sarcoidosis	Hypersensitivity pneu monitis
Workplace related	no	yes
Noncaseating granuloma	Well defined	Poorly defined
Bilateral hilar lymphadenopathy	yes	no
Hypercalcimia and hypercalciuria	yes	no
BAL:	T helper are dominant	Both increased but T cytotoxic are more
Other organs involvement: eye, skin, bone..etc	yes	no

We are done with **Hypersensitivity pneumonitis,** so we are done with the first category of restrictive lung diseases **(GRANULOMATOUS DISEASES).**
let's proceed to the next category **(FIBROSING DISEASES)**

- FIBROSING DISEASES:
1- Idiopathic Pulmonary Fibrosis
2- Nonspecific Interstitial Pneumonia
3- Cryptogenic Organizing Pneumonia
4- Pneumoconiosis: =Coal Worker's Pneumoconiosis (CWP)
=Silicosis
=Asbestosis and Asbestos-Related Diseases

1- Idiopathic Pulmonary Fibrosis:

Idiopathic Pulmonary Fibrosis (IPF) Overview:

- Etiology: Unknown cause, referred to as cryptogenic fibrosing alveolitis.
Cryptogenic it's mean unknown etiology.
Fibrosing because it's interstitial fibrosing.
Alveolitis because the alveolar are the main site for involvement.

- Demographics: Predominantly affects males, typically occurring after the age of 50.

- Pathological Characteristics:
- Pattern of Fibrosis: Usual Interstitial Pneumonia (UIP) pattern.
- Bilateral Involvement: Both lungs are affected, with a patchy and progressive nature.
- characteristic pattern of fibrosis seen in this disease (Fibrotic Lesions Spectrum):
1-Early lesions include fibroblastic foci and extra cellular matrix deposition
2-end-stage lesions involve honeycomb fibrosis
Note that this fibrosis pattern is not specific to IPF and can also be observed in chronic hypersensitivity pneumonitis.
The histologic examination may reveal fibrotic changes, including early fibroblastic foci and end-stage honeycomb fibrosis. However, these findings are not specific to IPF and can also be present in conditions like chronic hypersensitivity pneumonitis.

Diagnostic Approach:

- Radiologic and Histologic Criteria: Diagnosis relies on the identification of radiologic and histologic patterns.
- Exclusion Diagnosis: IPF is diagnosed by excluding other disorders with similar histologic findings, such as asbestosis and collagen vascular diseases.

Pathogenesis of Idiopathic Pulmonary Fibrosis (IPF):

- Unknown Cause: The etiology is unidentified.

• This interstitial fibrosis is believed to result from:
- Environmental Factors: Proposed involvement of repeated cycles of epithelial activation/injury by an unknown environmental agent.
- Genetic Predisposition: Mutations in surfactants, telomerase, or epithelium repair mechanisms
- Defective Epithelial Repair of alveoli

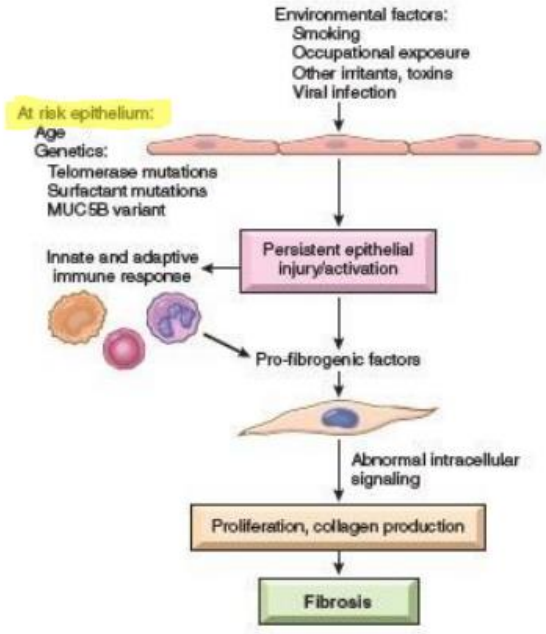


Fig. 13.13 Proposed pathogenic mechanisms in idiopathic pulmonary fibrosis. See text for details.

Robbin's basic pathology, 10th edition

This figure shows the proposed pathogenic mechanism in idiopathic pulmonary fibrosis
The exposure of the epithelium at risk (due to cellular aging & genetic factors) to certain environmental factors such as smoking , occupational exposure , other irritants and viral infections will result in persistent epithelial injury and activation.
This persistent injury in the presence of abnormal epithelial repair at the site of the chronic injury and inflammation will result in exuberant fibroblastic or myofibrobalstic proliferation mediated mainly by the pro-fibrogenic factors, transforming growth factor beta.

Genetic studies showed some which is : the increased risk of IPF in cases of loss of for example telomerase(enzyme maintains ends of chromosomes)due to germ line mutations , so if we have defect in telomerase the telomere going to be shorter→mutations in surfactants

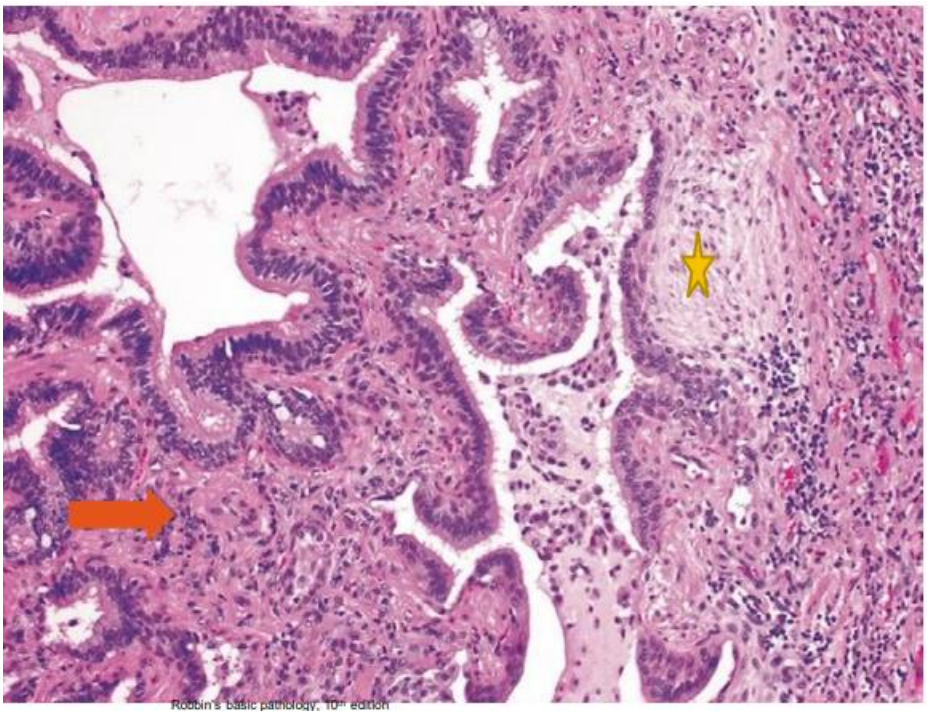
Morphological Characteristics - Macroscopic:

- Pleural Surface Appearance: Cobblestone appearance due to scar retraction along interlobular septa. (the scars retract and the tissue between them remains not retracted especially along the interlobular septa.)
- Usual Interstitial Pneumonia (UIP) pattern of fibrosis
- The cut surface shows fibrosis (firm, rubbery white areas)
- Distribution: Predominantly affects lower lobe and subpleural regions and along the interlobular septa.

Morphological Characteristics - Microscopic:

- Fibrosis Hallmark: Characterized by patchy interstitial fibrosis, which varies in intensity and worsens with time.
- You will see a patchy interstitial inflammation consisting of an alveolar infiltrate of mostly lymphocytes with occasional plasma cells, mast cells and eosinophils is characteristics.
- Temporal Heterogeneity: Presence of early and late lesions simultaneously.
- **Early Lesions - Fibroblastic Foci:** Exuberant fibroblastic proliferations form fibroblastic foci.
- **Late Lesions:** More collagenous, less cellular, potentially exhibiting honeycomb fibrosis.
- Cystic Space Formation: Dense fibrosis leads to the collapse of alveolar walls, forming cystic spaces.
- Lining of Cystic Spaces: Hyperplastic type 2 pneumocytes or bronchiolar epithelium lines the cystic spaces.

- Inflammation Within Fibrotic Areas: Mild to moderate inflammation observed within fibrotic regions, including lymphocytes, plasma cells, neutrophils, eosinophils, and mast cells.
- Additional Features: Foci of squamous metaplasia and smooth muscle hyperplasia may be present.
- Pulmonary Arterial Changes: Hypertensive changes include intimal fibrosis and medial thickening.
(If you reach the stage of the honeycomb lung (extensive fibrosis) so there's a problem in gas exchange that leads to pulmonary hypertension by Spasms of blood vessels)



This histological section shows a case of usual interstitial pneumonia the yellow star points to fibroblastic focus with fibers running parallel to the surface and bluish **myxoid** extracellular matrix honeycombing is presented to the left and in advanced cases you may see secondary pulmonary hypertensive changes such as intimal fibrosis and medial thickening of the pulmonary arteries

Remember as we mentioned: BOTH lesions co-existing

Clinical Features of Idiopathic Pulmonary Fibrosis (IPF):

- Age Range at Presentation: Typically affects individuals aged 55 to 75 years.
- Onset of Symptoms: Gradual onset marked by a nonproductive cough and progressive dyspnea on exertion.
- Physical Examination:
  - Crackles: Characterized by "dry" or "Velcro"-like crackles heard during inspiration, resembling the sound of Velcro being pulled apart.
  - Cyanosis, cor pulmonale, and peripheral edema may develop later.

- Radiologic Findings:
subpleural and basilar fibrosis, reticular abnormalities, and “honeycombing”
(honeycombing is found in radiology and histology)

Diagnostic Value: The combination of clinical features and radiologic findings is often diagnostic for IPF.

Outcome of Idiopathic Pulmonary Fibrosis (IPF):

- Overall Prognosis: The overall prognosis remains poor
- Median Survival: After diagnosis, the median survival is approximately 3 years.
- Definitive Treatment: Lung transplantation stands as the only definitive treatment.

Management of Idiopathic Pulmonary Fibrosis (IPF):

Definitive Treatment: as we mentioned, lung transplantation Treatments for management and slowing down the process.

- Management Approaches:
  • Anti-Inflammatory Therapies, although they have been proven to be of little use since inflammation is of secondary pathogenic importance.
  • Anti-Fibrotic Therapies, are more important and now proved to be used in patient with IPF.

We are done with **Idiopathic Pulmonary Fibrosis**, let’s proceed with **Nonspecific Interstitial Pneumonia (NSIP)** (the second disease of **FIBROSING DISEASES**)

2- Nonspecific Interstitial Pneumonia (NSIP):

The term “nonspecific” implies 2 details:
1. The diagnosis of NSIP is difficult
2. Before NSIP was classified as one of the fibrosing diseases, patients showed a certain presentation that indicates restrictive lung disease. However, this presentation did not meet the criteria of the other fibrosing diseases. Thus, they were grouped into a new entity under the category of fibrosing diseases.

- Despite the term "nonspecific," NSIP exhibits distinct clinical, radiologic, and histologic features.

- Chronic bilateral interstitial lung disease with unknown etiology, often associated with connective tissue diseases like rheumatoid arthritis.

- Clinical Presentation:
  - Typically affects female nonsmokers in their 6th decade of life.
  - Presents with chronic cough and dyspnea over several months.

- Prognosis:
  - Generally has a better prognosis than Idiopathic Pulmonary Fibrosis (IPF).

- Distinguishing Features from IPF:
  - Fibrotic lesions in NSIP are of the same age, unlike the heterogeneous lesions in IPF.

- Radiological Characteristics:
  - Bilateral, symmetric, predominantly lower lobe reticular opacities.

- Histological Patterns:
  - Cellular Pattern: Mild to moderate chronic interstitial inflammation (lymphocytes and a few plasma cells) with minimal, if any, fibrosis.
  - Fibrosing Pattern: Diffuse or uniform patchy interstitial fibrotic lesions (of the same stage), distinguishing it from UIP.

We are done with **Nonspecific Interstitial Pneumonia (NSIP)**, let’s proceed with **Cryptogenic Organizing Pneumonia** (the third disease of **FIBROSING DISEASES**)

3- Cryptogenic Organizing Pneumonia:

- Prevalence and Etiology:
  - Uncommon lung condition with an unknown primary cause.
  - Often observed as a response to various triggers: infections, inflammatory lung injuries (viral and bacterial pneumonia, inhaled toxins, drugs, connective tissue diseases, graft-versus-host disease in BM transplant recipients).

- Clinical Presentation:
  - Manifests with symptoms like cough and dyspnea.

- Radiological Findings:
  - Chest X-ray reveals subpleural or peribronchial patchy airspace consolidation (radiopaque or white areas).

- Microscopic Characteristics:
  - Presence of Masson bodies, which are intraalveolar plugs of loose organizing connective tissue (of the same age).
  - Masson bodies are found within alveolar ducts, alveoli, and often bronchioles.
  - Importantly, these plugs are within the air spaces of the lungs, not in the interstitium.
  - Underlying lung architecture remains normal.
  - No interstitial fibrosis or honeycomb lung, aiding in differentiation from other lung diseases.

- Treatment and Prognosis:
  - Some patients may recover spontaneously, but most require treatment, usually with oral steroids.
  - Prognosis depends on the underlying disorder triggering Cryptogenic Organizing Pneumonia (COP).

We are done with **Cryptogenic Organizing Pneumonia**, let's proceed with **Pneumoconiosis** (the fourth disease of **FIBROSING DISEASES**)

4- Pneumoconiosis:

This disease is caused mainly by inhalants. Thus, it is divided into different entities depending on the inhalant that caused it.
The inhaled dust can reach the distal airways at the bifurcation of the alveolar ducts, and induce inflammation → Fibrosis → Restrictive lung disease

Pneumoconiosis Overview:

- Definition:
  - Lung reactions resulting from the inhalation of various substances such as mineral dusts, organic and inorganic particulates, as well as chemical fumes and vapors.

- The most common mineral dusts are induced by inhalation of
  1. Coal dust
  2. Silica
  3. Asbestos

Different types of pneumoconioses are associated with each of the mentioned dusts.

- Typically related to prolonged exposure in the workplace
(Workers may be continuously exposed to these dusts for extended periods, sometimes up to 30 years, before the onset of the disease. This is true for all 3 dusts)

- Asbestos-Related Risk:
  - For asbestos specifically, the risk of cancer (associated with asbestos pneumoconiosis) is heightened not only for workers but also for:
  1. Family members of asbestos workers.
  2. Individuals exposed to asbestos outside of the workplace.

(Asbestos is found in old building materials…)

Pathogenesis of Pneumoconiosis:

The development of pneumoconiosis is influenced by various factors:

1. Amount of Dust Retained in the lung and airways:

- Depends on:
  - Concentration of the dust in the air.
  - Duration of exposure.
  - Effectiveness of clearance mechanisms, primarily facilitated by cilia within the body.

2. Size and Shape of Particles:
- Determines the particle's ability to reach distal airways.
- Particles <1 μm are usually enter and leave the airways without any significant effect.
- Particles >5 μm are too large to reach distal airways.
- Particles between 1 to 5 μm pose the highest risk, reaching alveolar duct bifurcations. (Phagocytosis of these particles by macrophages in these regions stimulates inflammation and fibrosis)

3. Particle Solubility and Reactivity:
- Solubility, linked to size:
  - Asbestos, Silica, Beryllium (smaller particles) → More soluble → Fast reaction → Acute lung injury.
  - Coal dust (larger, inert) → Less soluble → Reaction takes a longer time → Gradual fibrosis.

4. Other Irritants:
- Concomitant tobacco smoking worsens the effects of inhaled mineral dusts, especially asbestos. (Smoking impairs clearance mechanisms, leading to increased dust accumulation)

5. Role of Pulmonary Alveolar Macrophages:
- Key cellular element in lung injury and fibrosis, so when macrophage phagocyte the particle, It send mediators to initiate the inflammation and cause fibrosis.

Now, let's talk about the pneumoconiosis one by one:

Pneumoconiosis: A. Coal Worker's Pneumoconiosis (CWP)
B. Silicosis
C. Asbestosis and Asbestos-Related Diseases

Here is a general overview on all 3 pneumoconioses:

Table 13.3 Mineral Dust–Induced Lung Disease

Agent	Disease	Exposure
Coal dust	Simple coal worker's pneumoconiosis: macules and nodules Complicated coal worker's pneumoconiosis: PMF	Coal mining
Silica	Silicosis	Sandblasting, quarrying, mining, stone cutting, foundry work, ceramics
Asbestos	Asbestosis, pleural effusions, pleural plaques, or diffuse fibrosis; mesothelioma; carcinoma of the lung and larynx	Mining, milling, and fabrication of ores and materials; installation and removal of insulation

PMF, Progressive massive fibrosis.

(Remember that asbestos is associated with cancer)

(EXTRA) Sandblasting, sometimes known as abrasive blasting, is the operation of forcibly propelling a stream of abrasive material against a surface under high pressure to smooth a rough surface, roughen a smooth surface, shape a surface or remove surface contaminants.

Robbin's basic pathology, 10th edition

A. Coal Worker's Pneumoconiosis (CWP):

- Definition:
  - Lung disease resulting from the inhalation of coal particles and other admixed forms of dust.
  - Coal primarily contains carbon +/- trace metals, inorganic minerals, and crystalline silica.
  - Presence of contaminating silica in coal dust can contribute to disease progression.

- Associated Conditions:
  - Coal workers may also develop centrilobular emphysema and chronic bronchitis independently of smoking, adding an additional layer of complexity to respiratory conditions. (Remember that these 2 diseases are mainly caused by smoking. Now, you know that they are also associated with CWP and not only smoking.)

- Spectrum of Changes:
  1. Asymptomatic Anthracosis:
     - Accumulation of pigment without a cellular reaction.
     - Normal pulmonary function.
     - Detected only through biopsy.

2. Simple Coal Worker's Pneumoconiosis (CWP):

- Accumulations of macrophages with minimal to no pulmonary dysfunction.
- Very minor symptoms.

3. Complicated CWP:

- it can progress to a severe condition known as Progressive Massive Fibrosis (PMF).
- Characterized by extensive fibrosis and compromised lung function.
- Fibrosis may continue progressing even after inhalation exposure stops.
- Less than 10% of cases of simple CWP progress to PMF.

- Progressive Massive Fibrosis (PMF):

- Generic term applicable to any pneumoconiosis.
- Involves a confluent fibrosing reaction in the lungs.
- Can be a complication of any pneumoconiosis, not exclusive to CWP.

- Progression Hierarchy:

- Asymptomatic Anthracosis > Simple CWP > Complicated CWP > PMF.
- This progression hierarchy is not specific to CWP but is a general pattern observed in various pneumoconiosis.

Morphology of Coal Worker's Pneumoconiosis (CWP):

1. Pulmonary Anthracosis:

- Also observed in urban dwellers (exposed to polluted air with coal particles) and tobacco smokers.
- Inhaled carbon pigment is engulfed by alveolar or interstitial macrophages.
- Accumulation in connective tissue along pulmonary and pleural lymphatics, draining lymph nodes, or organized lymphoid tissue along bronchi or in the lung hilus.

Recap:

- Effect on Pulmonary Function Test: No significant effect.

2. Simple CWP:

- Presence of coal macules and nodules, located primarily adjacent to respiratory bronchioles

• Coal Macules (1 to 2 mm in diameter): Dust-laden macrophages and small amounts of collagen fibers arranged in a delicate network.

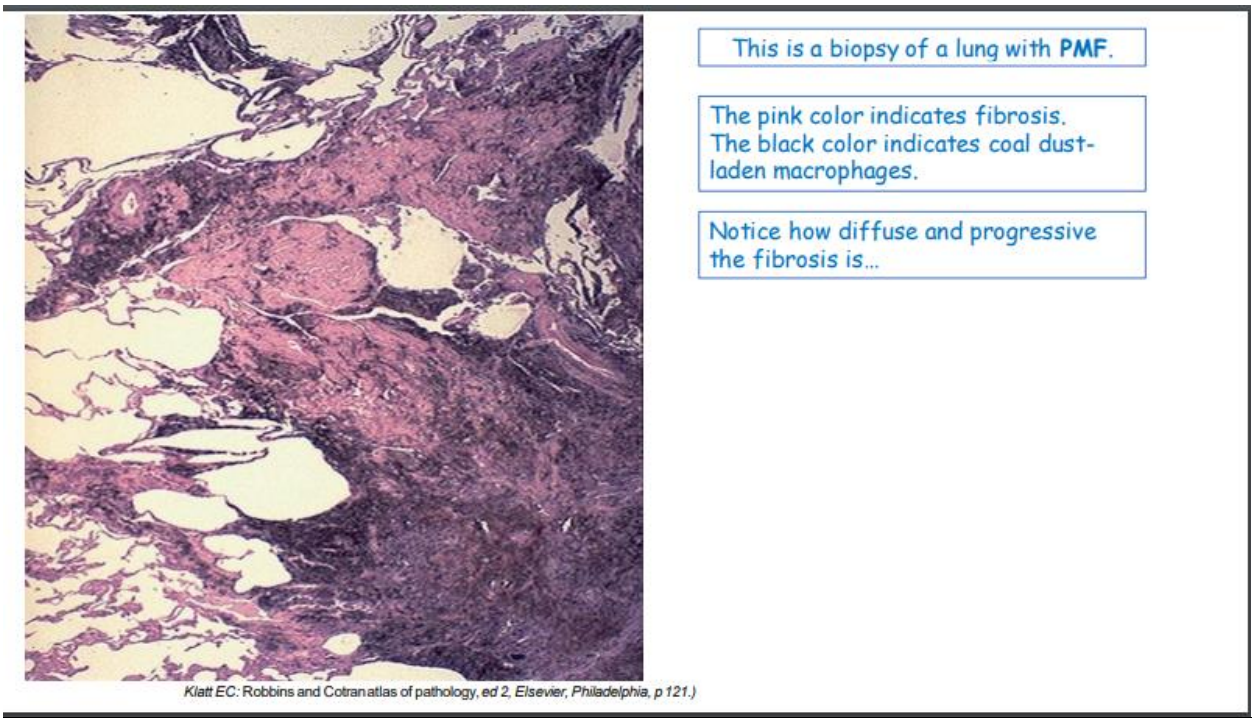
• Coal Nodules (<1 cm): Similar content as macules but larger in size.

- Centrilobular emphysema can occur.
- Involvement is prominent in the upper lobes and upper zones of the lower lobes.

3. Complicated CWP (PMF):

- Coalescence (fusion) of coal nodules occurring over many years.
- Development of multiple dark black scars >2 cm and up to 10 cm consist of dense collagen and pigment.

(Fusion of nodules results in larger, more extensive fibrotic areas.)



Clinical Features of Coal Worker's Pneumoconiosis (CWP):

1. CWP:

- Benign disease with minimal impact on lung function.
- Produces little effect on pulmonary function.

2. Complicated CWP:

- Mild forms generally do not significantly affect lung function.
- Despite being labeled "complicated," it is usually mild in nature.
- Progression to Progressive Massive Fibrosis (PMF):

• About 10% of complicated CWP cases progress to PMF: extensive fibrosis → increasing pulmonary dysfunction → hypoxia → spasm of pulmonary vessels → pulmonary hypertension → cor pulmonale(right side heart failure)

• Factors Influencing Progression:
- Higher coal dust exposure levels.
- Total dust burden.

(Remember we said it's inert so need really long time exposure)

• PMF Progression: Once PMF is established, it tends to progress even in the absence of further dust exposure.

- Distinctive Feature:
No Increased Risk of Lung Carcinoma: Unlike silicosis and asbestosis, coal miners with CWP do not have an increased risk of lung carcinoma.

Pneumoconiosis: A. Coal Worker's Pneumoconiosis (CWP) **done**
B. Silicosis
C. Asbestosis and Asbestos-Related Diseases

B. Silicosis:

SLICA:

- Naturally occurring mineral.
- Accounts for 59% of the earth's crust.
- Two types : crystalline silica (toxic) and amorphous (Amorphous Silica is less toxic).
- Several processes release silica into the air such as:

  Crushing, grinding, and blasting.

Silicosis Overview

- The most prevalent chronic occupational disease in the world.

- Causative Agent:

- Inhalation of crystalline silica mostly in occupational Settings.
- Quartz is the primary crystalline silica implicated in silicosis.
- Quartz is often found in occupational settings.

• Crystalline silica is more fibrogenic and more toxic and is associated with restrictive lung disease. The most important one is Quartz (type of crystalline silica)
• Thankfully, Quartz is not purely found in nature, it is bonded to other chemicals that reduce its fibrogenic effect.

- Amorphous Silica: amorphous silica is less pathogenic compared to crystalline silica.

- Workers in sandblasting and hard-rock mining (occupational settings) are at high risk.

Pathogenesis:

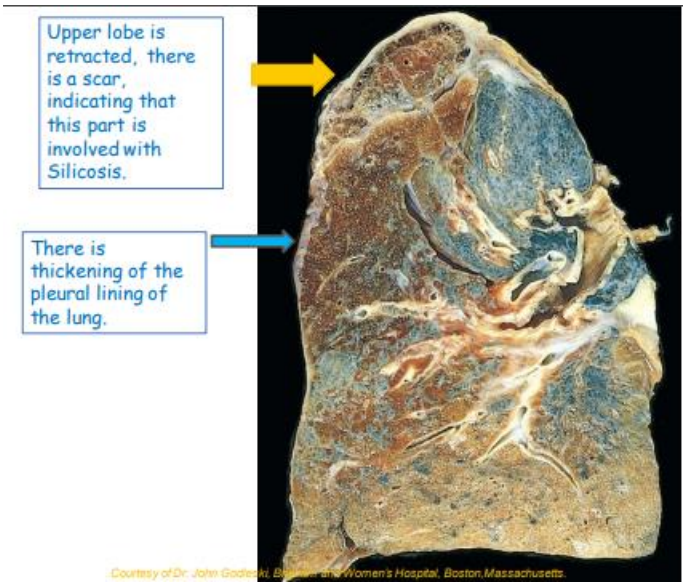
1- After inhalation, silica particles interact with epithelial cells and macrophages.
2- Activation of the inflammasome and the release of inflammatory mediators by pulmonary macrophages.
- Inflammatory mediators include IL-1, TNF, fibronectin, lipid mediators, oxygen-derived free radicals, and fibrogenic cytokines.
(Inhaled particles deposit at the bifurcation of alveolar ducts, phagocytosed by macrophages, leading to inflammation, tissue injury, and fibrosis.)

- When quartz is mixed with other minerals, its fibrogenic effect is reduced, and this fortuitous situation is commonplace, as quartz in the workplace is rarely pure.

Morphology - Silicotic Nodules:

- Macroscopic Features:

Early stages: Tiny, discrete, barely palpable, pale-to-black (if coal dust is present) nodules, typically located in the upper lung zones, can be identified via the gross examination of the lung tissue.



- Microscopic Features:

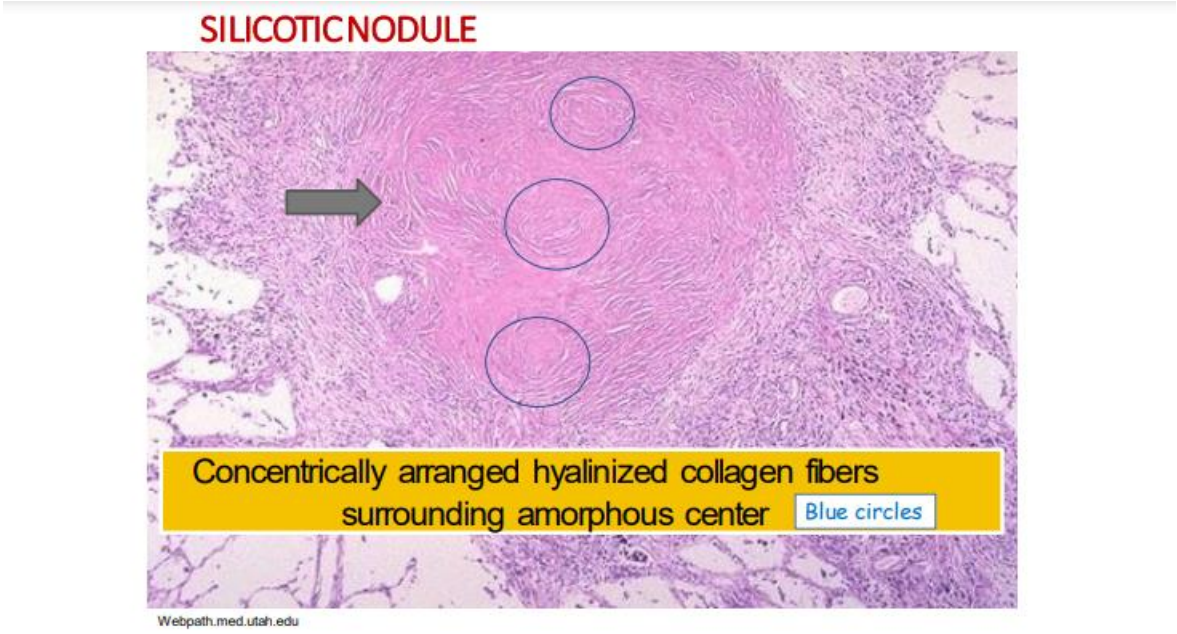
- Silicotic nodules exhibit concentrically arranged hyalinized collagen fibers surrounding an amorphous center with "Whorled" collagen fibers.

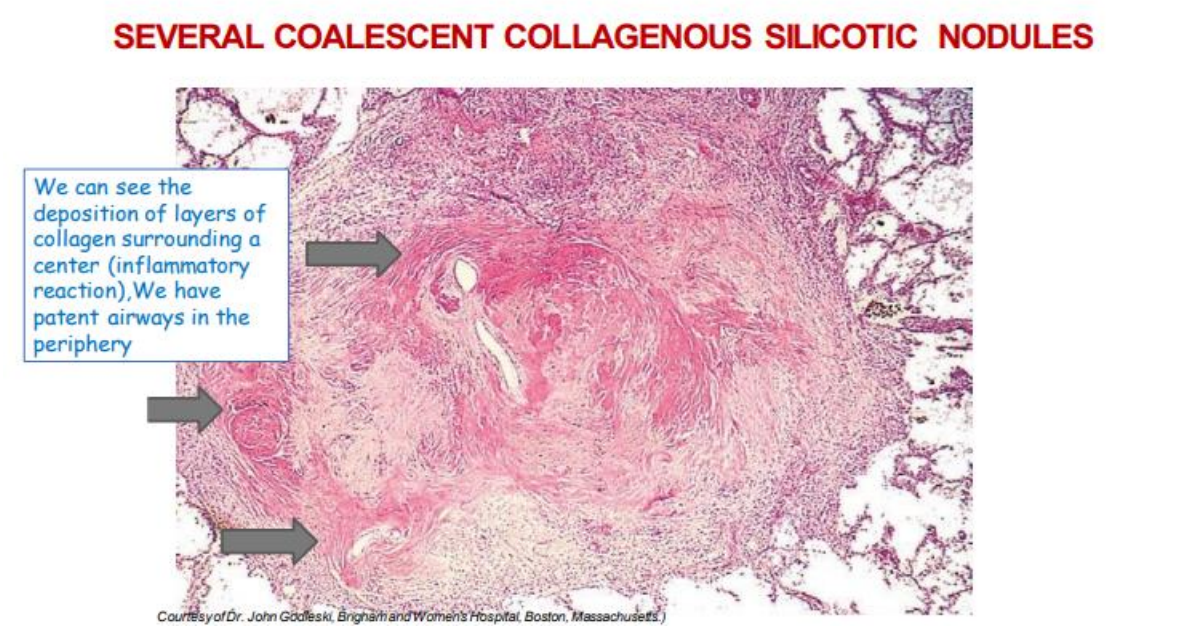
- Since, particles will stimulate the release of fibrogenic cytokines, and thus, the deposition of fibroblastic proliferational collagen.
- Layers and layers of collagen will further be deposited.
- Part of the inorganic matrix of the Silica cannot be digested by macrophages, which will create the amorphous center surrounded by the concentric collagen.

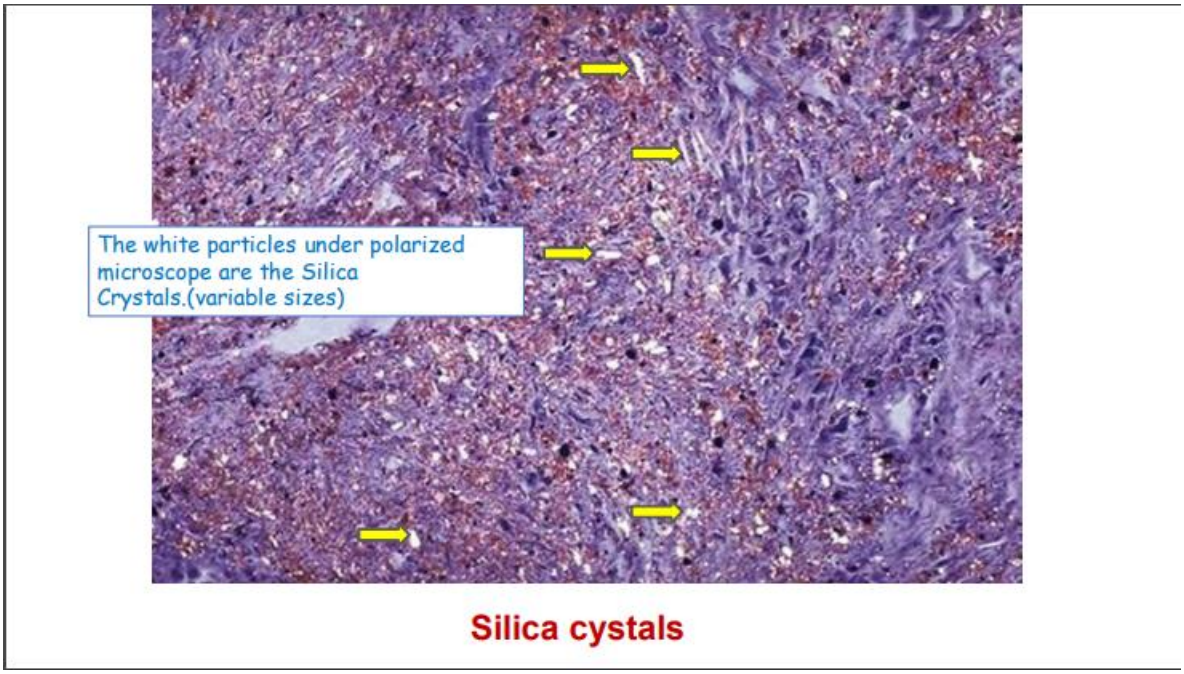
- Polarized microscopy reveals weakly birefringent silica in the center of the nodules

- Progression to PMF: (PMF (Progressive Massive Fibrosis) is a genetic term that may complicate any type of pneumoconiosis.)

- Nodules may coalesce into hard, collagenous scars, progressing to Progressive Massive Fibrosis (PMF) ((if multiple areas of the lung are involved))
- PMF may continue even after exposure cessation.
- Fibrotic lesions can also develop in hilar lymph nodes and pleura.
- Greater exposure and longer duration correlate with increased silicotic nodule formation and severity of restrictive lung disease.
- due to expansion of the nodules and progression to extensive fibrosis, in some cases the intervening lung parenchyma compressed or over expanded ending with honeycomb lung







Clinical Features and Complications

- Asymptomatic Stage:

- Asymptomatic patients are often diagnosed based on routine chest X-rays.
- Fine nodularity is detected in the upper lung zones.
- Most patients remain asymptomatic during this stage.

- Late-Stage (after PMF) (Symptomatic):

- Shortness of breath typically develops late in the course (Most patients do not develop shortness of breath until late in the course).
- Pulmonary hypertension.
- Cor pulmonale and right-sided heart failure.

- Disease Progression:

Worsening continues even after exposure cessation due to undigested silica.

- Silicosis progresses slowly, rarely causing rapid mortality.
- Impaired pulmonary function limits activity, leading to long-term shortness of breath.

- The onset of silicosis can be:
 - Slow and insidious onset (most common, occurring 10 to 30 years after exposure).
 - Accelerated onset (within 10 years of exposure).
 - Rapid onset (in weeks or months after intense exposure to fine dust high in silica; rare).

- Association with Tuberculosis:
 - Silicosis increases susceptibility to tuberculosis (this happen because silicosis associated with depressed cell mediated immunity)
 - Crystalline silica inhibits pulmonary macrophages' ability to kill phagocytosed mycobacteria.

- Silicosis and Lung Cancer:
 Silicosis patients have double the risk of developing lung cancer.

Pneumoconiosis: A. Coal Worker's Pneumoconiosis (CWP) **done**
B. Silicosis **done**
C. Asbestosis and Asbestos-Related Diseases

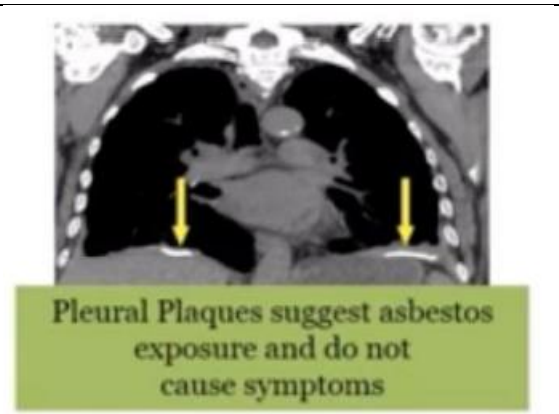
C. Asbestosis and Asbestos-Related Diseases:

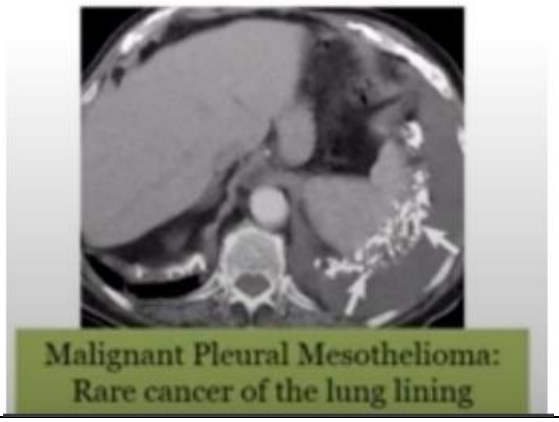
- Asbestos:
 Family of crystalline hydrated silicates with a fibrous structure.

It's one of mineral dust that can cause pneumoconiosis ,other common mineral dusts as we discussed before are the cold dust and silica usually the exposure happens in workplace this is true except for the asbestos as with this mineral the increased risk for cancer extendes to the family members of the asbestos workers and also to the individuals exposed to the asbestos outside the work place so the risk of the asbestos is increased in any patients who is exposed to the asbestos in the work place and outside the work place also to the family members of asbestos workers, further more studies showed an increased incidence of asbestos related cancers in family members of asbestos workers.

- Associated Diseases:

1. Parenchymal Interstitial Fibrosis (Asbestosis)
2. Localized Fibrous Plaques or, rarely, Diffuse Pleural Fibrosis
3. Pleural Effusions
4. Lung Carcinomas
5. Malignant Pleural and Peritoneal Mesotheliomas (after >30 years from the exposure)
6. Laryngeal Carcinoma





- ASBESTOSIS: IS SCARRING OF THE LUNG CAUSED BY ASBESTOS EXPOSURE

Pathogenesis of Asbestosis and Asbestos-Related Diseases:

- Asbestos Fiber Interaction with Macrophages:

Phagocytosis of asbestos fibers by macrophages → Activation of the inflammasome and damage to phagolysosomal membranes → Proinflammatory factors and fibrogenic mediators released (mediators such as IL-1 and other factors)

- Consequences:
1. Cellular and Fibrotic Lung Reactions
2. Tumor Initiator and Promoter:
Mediated by the oncogenic effects of reactive free radicals generated by asbestos fibers in the distal lung near the mesothelial lining

Role in Carcinogenesis:
- Induction of severe inflammation leads to the release of free radicals.
- Asbestos acts as a tumor initiator and promoter, putting individuals at risk of cancer.
- resulting in restrictive lung disease and pleural lesions.

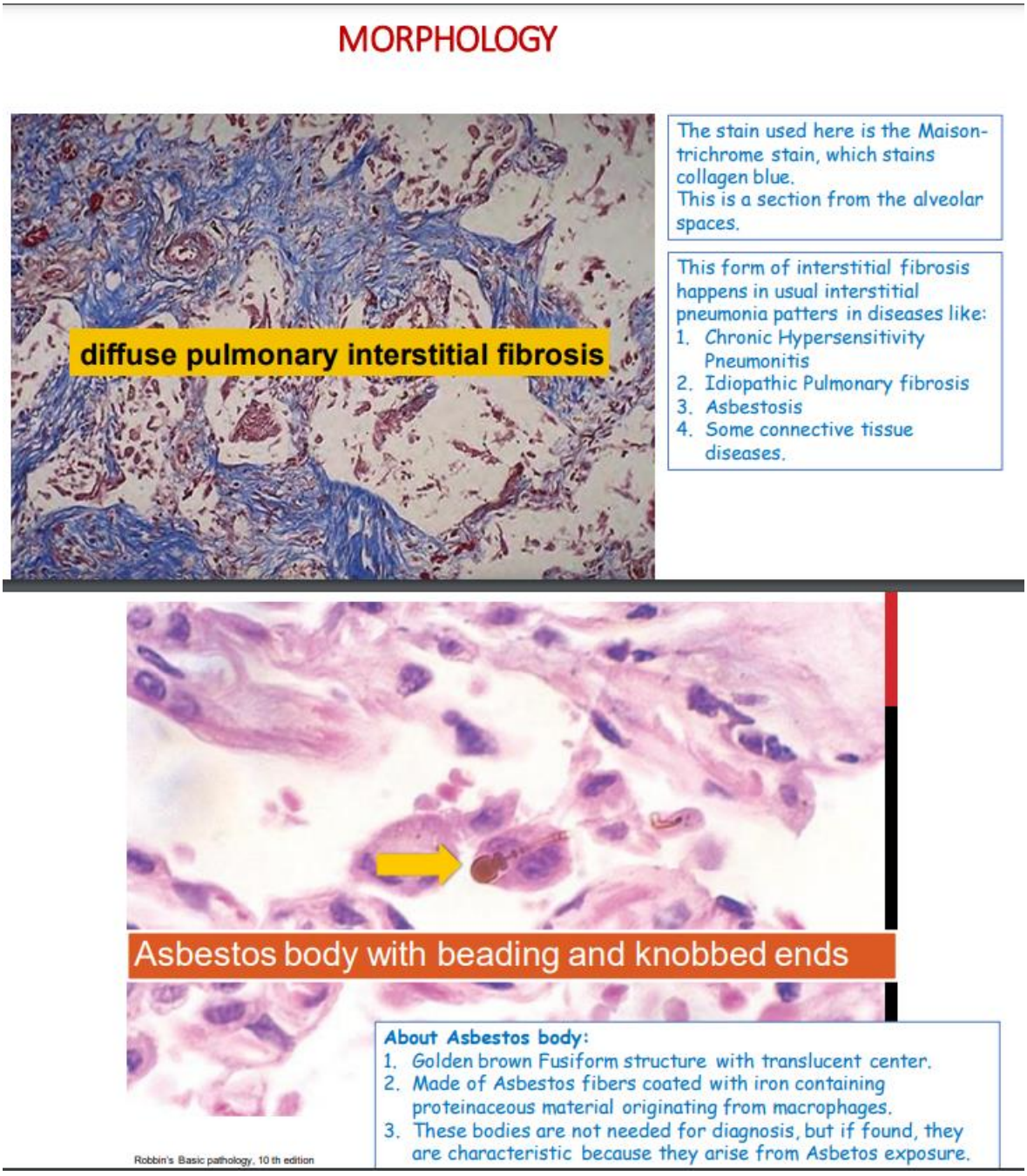
- Asbestos and Tobacco Interaction:
- Reduced muco-ciliary clearance in smokers facilitates asbestos fiber accumulation.
- The adsorption of carcinogens in tobacco smoke onto asbestos fibers results in remarkable synergy between tobacco smoking and the development of lung carcinoma in asbestos workers → Smoking enhances the effect of asbestos by interfering with the mucociliary clearance of fibers.

- Combined Risk:
- Asbestos exposure alone: Fivefold increase in lung carcinoma risk.
- Asbestos exposure combined with smoking: 55-fold increase in the risk of lung carcinoma.
(Exaggeration of effects when both factors are present.)

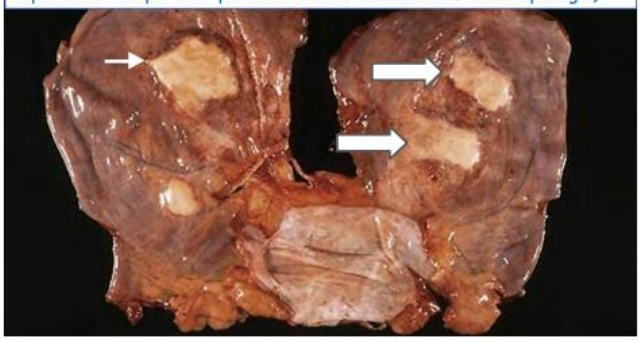
The combined impact of asbestos exposure and smoking significantly amplifies the risk of developing lung carcinoma, highlighting the synergistic relationship between these two factors.

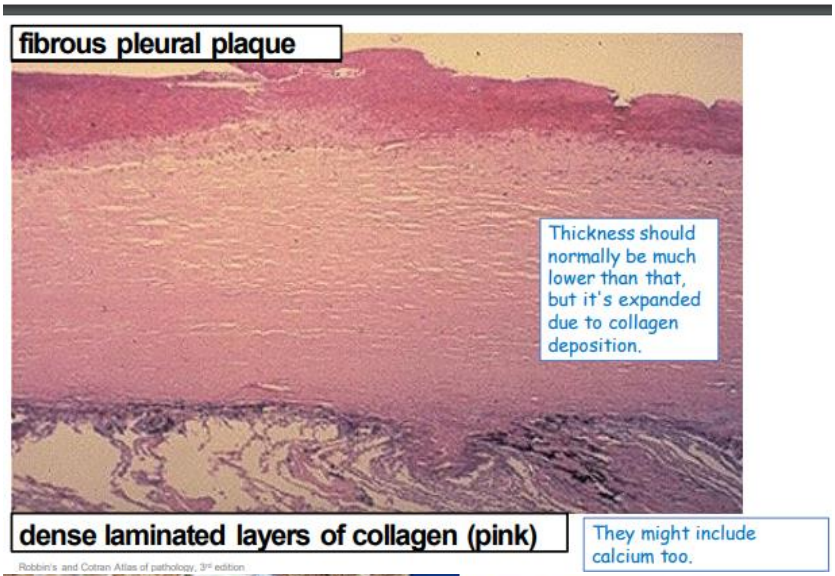
Morphology:
- Diffuse pulmonary interstitial fibrosis (which is usual patchy in distribution with fibroblastic foci and formation of cystic spaces) that cannot be distinguished (indistinguishable) from Usual Interstitial Pneumonia (UIP).
- Asbestos Bodies:
- Golden-brown, fusiform, or beaded rods with a translucent center.
- Composed of asbestos fibers coated with an iron-containing proteinaceous material.
- Begins in the lower lobes and subpleurally, spreading to the middle and upper lobes as fibrosis progresses.

- Pleural Plaques:
  - The most common manifestation of asbestos exposure.
  - Well-circumscribed (well-defined) plaques consisting of dense collagen containing calcium.
  - Located in the anterior and posterolateral aspects of the parietal pleura and over the domes of the diaphragm.



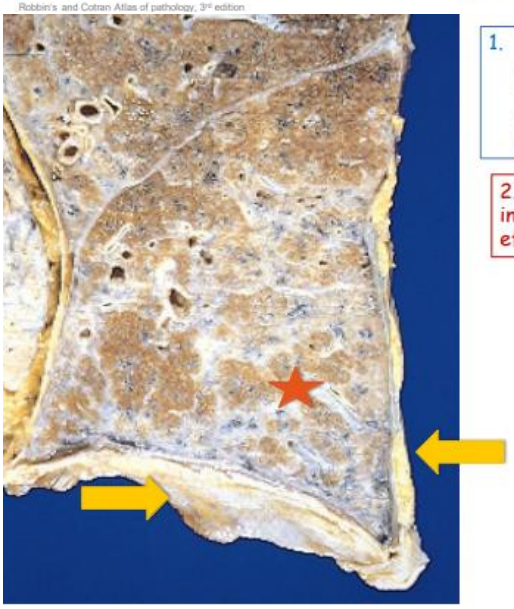
This is a gross examination of the diaphragmatic surface of the lungs. These white lesions are the pleural plaques, which is the most common manifestation of asbestos exposure. (The white arrows points to multiple plural plaques on the pleural aspects of the diaphragm,these plaques develop most frequently on the anterior and posterior lateral aspects of the parietal pleura and over the dome of the diaphragm)





They might include calcium too.

Robbin's and Cotran Atlas of pathology, 3rd edition



1. Yellow arrow: (thick area of visceral pleura covering the lateral and diaphragmatic surface of the lung)

2.Red star :severe interstitial fibrosis effecting the lower lobe

Clinical Features:

Onset and Progression:

- Progressively worsening dyspnea, appearing at least after 10-20 years after initial exposure (typically after 20-30 years after exposure).
- Dyspnea is the first & the most common manifestation (by exertion, but later at rest (it worsens with time)).
- Respiratory Symptoms:
  Cough and sputum production, (due to smoking mainly).

Potential Complications:

- Static or progress to honeycomb lung, congestive heart failure, cor pulmonale (right-sided heart failure), leading to eventual death.
- Asymptomatic Pleural Plaques: (appear in radiograph as circumscribed densities)
  Pleural plaques, a common manifestation, are usually asymptomatic.

Outcomes:

- The risk for developing lung carcinoma is increased 5-fold for asbestos workers
- The relative risk for mesothelioma is more than 1000 times greater than the risk for lung cancer
- Concomitant cigarette smoking increases the risk for lung carcinoma but not for mesothelioma.
- Lung or pleural cancer associated with asbestos exposure carries a poor prognosis.

Pneumoconiosis: A. Coal Worker's Pneumoconiosis (CWP) **done**
B. Silicosis **done**
C. Asbestosis and Asbestos-Related Diseases **done**

We are done with **Pneumoconiosis,** so we are done with the second category of restrictive lung diseases **(FIBROSING DISEASES).**
let's proceed to the next and last category **(SMOKING-RELATED INTERSTITIAL DISEASES)**

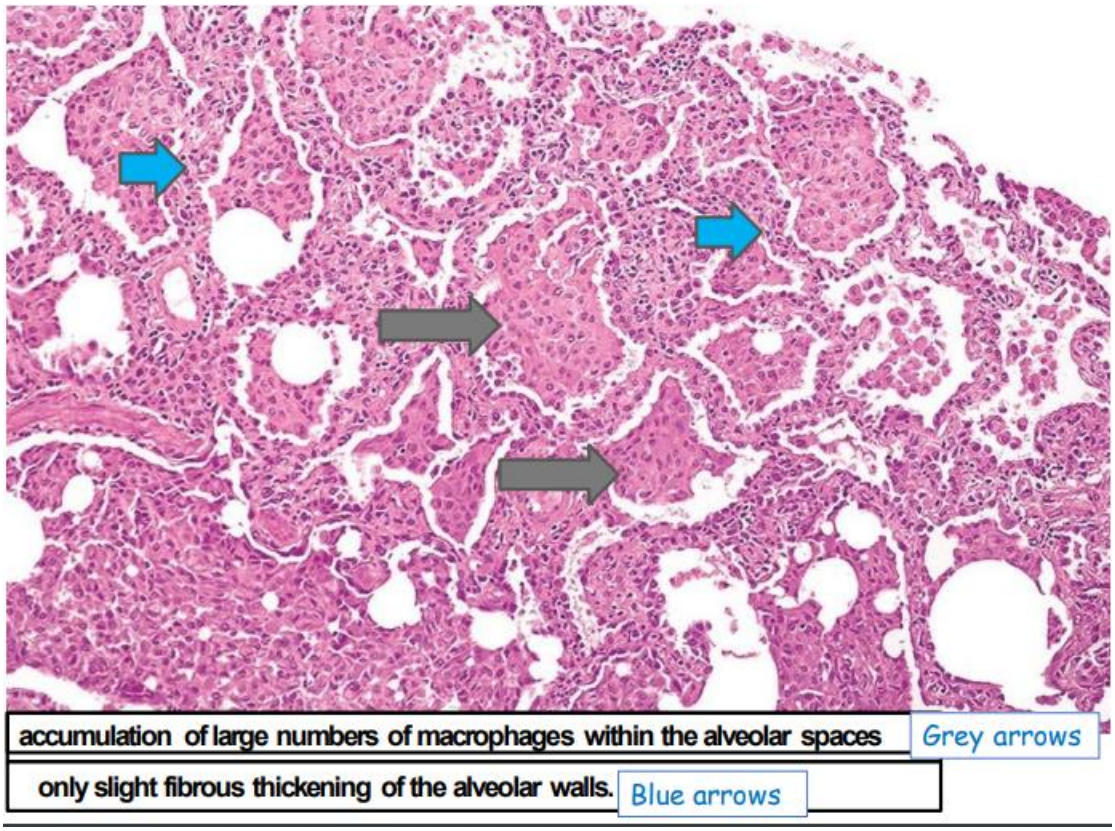
- SMOKING-RELATED INTERSTITIAL DISEASES:
1- Desquamative interstitial pneumonia (DIP)
2- respiratory bronchiolitis- Associated interstitial lung disease

1- Desquamative interstitial pneumonia (DIP):

Histologic Features:

- The most striking histologic feature of DIP is the accumulation of large numbers of macrophages in alveolar air spaces.
- Macrophages contain dusty-brown pigment (smoker's macrophages).
- usually accompanied by inflammation and, possibly, fibrosis of alveolar walls. (when the interstitial fibrosis associate with this disease it considered mild)

• Sparse inflammation in alveolar septa (lymphocytes, plasma cells and eosinophils)
• +/- mild Interstitial fibrosis +/- emphysema



Clinical Presentation and Outcome

- Demographics:
  - Equal prevalence in males and females.
  - Typically affects individuals in their 4th to 5th decade.
  - All affected individuals are smokers.

- Onset and Symptoms:
  - Insidious (gradual) onset of symptoms.
  - Common symptoms include dyspnea and dry cough, developing over weeks or months.

- Pulmonary Function Test (PFT):
  - Reveals a mild restrictive abnormality.
  - Minimal restrictive change in pulmonary function test.

- Prognosis:
  - Generally, a good prognosis is observed.
  - Excellent response to steroids and smoking cessation.
  - However, some patients may progress despite therapy.
    (Rare Progression: In very rare cases, the disease may progress to more fibrosis even after smoking cessation.)

We are done with **Desquamative interstitial pneumonia (DIP)**, let's proceed with **respiratory bronchiolitis- Associated interstitial lung disease** (the second disease of **SMOKING-RELATEDINTERSTITIAL DISEASES**)

2- respiratory bronchiolitis- Associated interstitial lung disease:

- Lesions in Smokers:
  Common lesions observed in smokers, particularly centered in the respiratory bronchioles.

Histology:
  - Presence of smokers' macrophages around the bronchioles.
  - Pigmented intraluminal macrophages similar to those in Desquamative Interstitial Pneumonia (DIP) but in a "bronchiolocentric" distribution (first- and second-order respiratory bronchioles).
  - Aggregates of smokers' macrophages within respiratory bronchioles, alveolar ducts, and peribronchiolar spaces.

- Fibrosis and Emphysema:
  - Fibrosis around respiratory bronchioles can lead to a risk of centrilobular emphysema.
  - Commonly associated with centrilobular emphysema, but not typically severe.

- Mild peribronchiolar fibrosis is possible.

- Coexistence with Desquamative Interstitial Pneumonia (DIP):
  Desquamative interstitial pneumonia is often found in different parts of the same lung, coexisting due to the shared predisposing factor of smoking.

So, macrophages will be present in:
1) Alveolar spaces due to desquamative interstitial pneumonia
2) Bronchioles due to respiratory bronchiolitis

Symptoms and Onset of respiratory bronchiolitis- Associated interstitial lung disease:
  - Symptoms are usually mild with a gradual onset of dyspnea and cough.
  - Typically seen in the 4th to 5th decade in individuals with a history of over 30 pack-years of cigarette smoking.
  - Cessation of smoking often results in improvement.

- Diagnostic Term:
The term "Respiratory Bronchiolitis–Associated Interstitial Lung Disease" is used for patients who exhibit significant pulmonary symptoms, abnormal pulmonary function (affects pulmonary function test), So we need restrictive lung disease/changes to be able to use this term.

We are done with **respiratory bronchiolitis- Associated interstitial lung disease**, so we are done with the third category of restrictive lung diseases **(SMOKING-RELATEDINTERSTITIAL DISEASES),** and finally we are done with **CHRONIC INTERSTITIAL (RESTRICTIVE, INFILTRATIVE) LUNG DISEASES.**

The modified slides files contain some questions, we advise you to read them as follows:
lec2: slides 53-58
lec3: slides 24-25
lec4: slides 42-45

Done by: Adnan Manasra Corrected by: Mohammad Romman