Pathology of respiratory system

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ASTHMA:

- It is a COPD characterized :
- **recurrent reversible episodes of bronchoconstriction**
- **Clinical features:**
- **wheezing:** a soft whistling sound **during expiration**, dyspnea,
- chest tightness, and
- cough,
- caused by **airway hyper responsiveness to a variety of stimuli.**
- Between the attacks, patients may be virtually asymptomatic.

- **The hallmarks of asthma are:**

- 1- Intermittent, reversible airway obstruction either spontaneously or with treatment.

- 2- **Chronic** bronchial **inflammation**

- Many cells play a role in the inflammatory response, in particular **eosinophils, mast cells**, macrophages, lymphocytes, neutrophils.
  3- **Bronchial smooth muscle cell hypertrophy** and **hyper reactivity.**

- Sometimes trivial stimuli are sufficient to trigger attacks in patients, because of airway hyperreactivity.

- 4-I**ncreased** **mucus secretion**

- **Types (classification):**
- asthma can be subclassified based on **its triggers** into the following types:
- **Atopic asthma(Allergic) (or previously extrinsic)** :
- This is **the most common** type of asthma.
- It is a **type I (immediate)** IgE–mediated hypersensitivity reaction.
- is caused by a Th2 and IgE-mediated immunologic reaction to **environmental (extrinsic)allergens**
- is characterized by **acute-phase (immediate)** and **late-phase reactions.** The Th2 cytokines IL-4, IL-5, and IL-13 are important mediators
- It usually begins **in childhood**.
- A **positive family history of atopy** and/or **asthma** is common

- the onset of asthmatic attacks is often **preceded** by allergic rhinitis, urticaria, or eczema.

- Attacks may be **triggered by allergens** in:

dust, pollen, molds, animal dander (dried skin flakes), or food, cigarette smoke, perfumes or by infection.

- A **skin test** with the offending antigen results in an immediate wheal-and-flare reaction.

- Serum IgE levels and **eosinophil** count are usually elevated .

2- Non atopic asthma(Non allergic) or (previously intrinsic):

- Patients **DO NOT have evidence of allergen sensitization**,
- **skin test** results usually are **negative.**
- **Negative family history** of asthma.
- **Triggers** for non-atopic asthma are less clear but include:

1-viral infections (e.g., rhinovirus, parainfluenza virus) and

2- inhaled air pollutants,

3-exercise(during or after physical activity)

4- cold dry air

5- stress.

- Although the connections are not well understood, eosinophils are common to both atopic and nonatopic variants of asthma, so they are treated in a similar way.

- **mixed asthma** : combination of both allergic and non allergic asthma which is the most common form of asthma.

Drug-Induced asthma:

- Several pharmacologic agents provoke asthma.
- **aspirin** and **other NSAID** are the most common drugs.
- Patients with aspirin sensitivity present with recurrent rhinitis, nasal polyps, urticaria, and bronchospasm.
- The precise pathogenesis is unknown but is likely to involve some **abnormality in prostaglandin metabolism** results from **inhibition of cyclooxygenase by aspirin.**

Occupational asthma:

- Occupational asthma may be triggered by **fumes**, **organic and chemical dusts (wood, cotton, platinum),** and other chemicals like **formaldehyde .**
- Asthma attacks usually develop after **repeated exposure** to the inciting antigen(s).
- **Underlying mechanisms** :vary according to stimulus and include:
- type I hypersensitivity reactions or direct liberation of bronchoconstrictor substances

Pathogenesis : The major etiologic factors of asthma are

- 1. **Genetic predisposition** to type I hypersensitivity ("atopy") lead to release of histamine,
- 2. Airway **inflammation**
- 3. Bronchial **hyper-responsiveness** to a variety of stimuli.

Pathogenesis.

- The main underlying pathogenetic feature of asthma (all forms of asthma) is airway **hyperresponsiveness** to a variety stimuli …..bronchconstriction.
- Hyperresponsiveness is mainly **due to bronchial inflammation**

Manifested by the **presence of inflammatory cells** (particularly eosinophils, lymphocytes, and mast cells), and by **damage to the bronchial epithelium.**

Details of Pathogenesis of asthma as following:

Bronchial inflammation…….. Airways hyperresponsiveness (bronchoconstriction) by followings reactions:

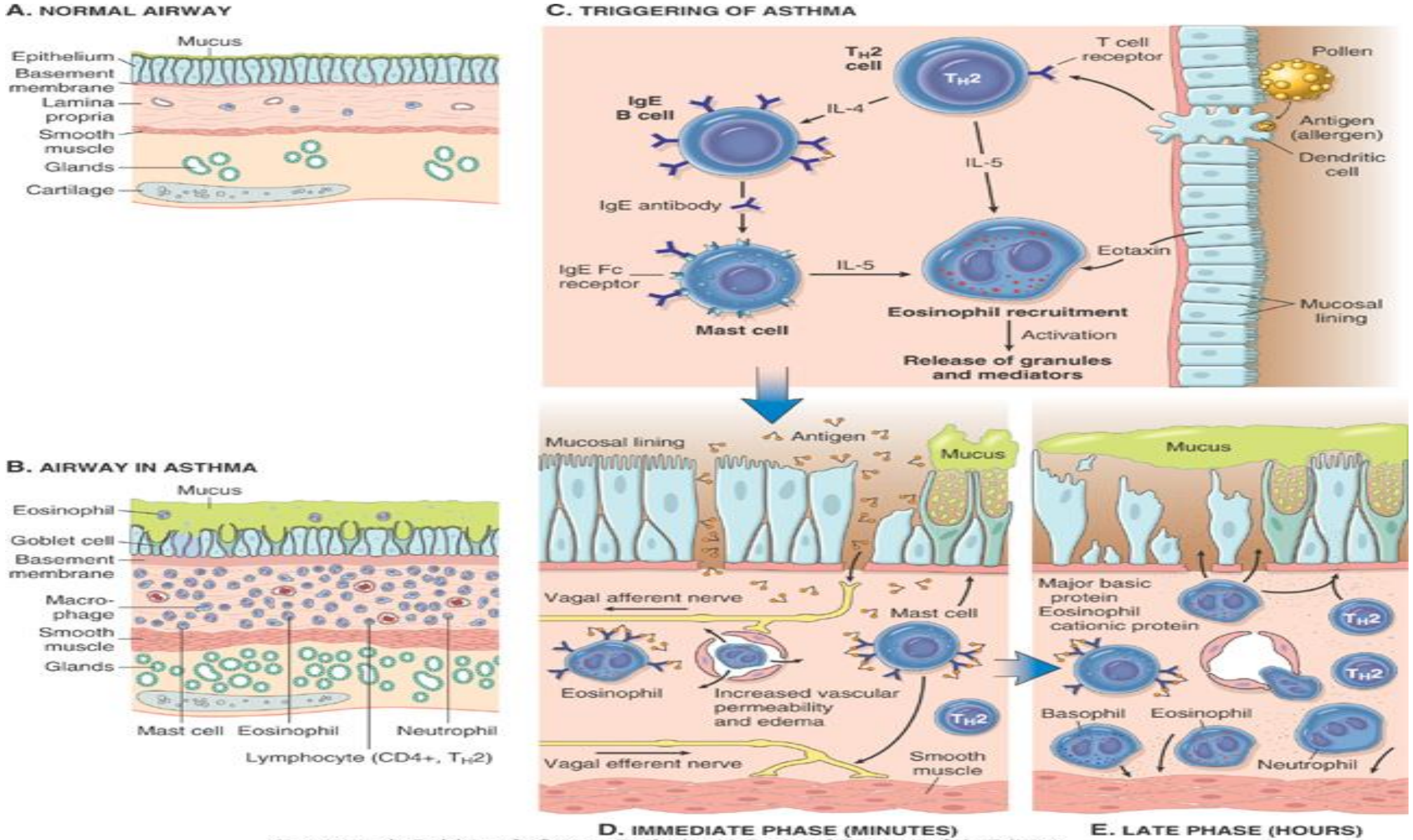
1. Sensitization: exposure to allergens ……..binding of IgE to IgE receptors on mast cells, less on eosinophils in the airways.

2. Re-exposure to the allergens ……..degranulation of mast cells……. these cells release preformed mediators that open tight junctions between epithelial cells.

3. ***Then Antigen*** **can enter the mucosa** to activate mucosal mast cells and eosinophils, which, in turn, release additional mediators.

4. These mediators, either directly or via neuronal reflexes, induce bronchospasm, increased vascular permeability, and mucus production or also recruit additional mediator-releasing cells from the blood (within minutes).

5. **Late phase**: occur after hours, initiated by the accumulated leucocytes from the previous stage



***Intrinsic Asthma*.**

The mechanism of bronchial inflammation and hyperresponsiveness is much less clear in patients with intrinsic (nonatopic) asthma.

Possible causes :viral infections of the respiratory tract and inhaled air pollutants such as sulfur dioxide, ozone, and nitrogen dioxide.

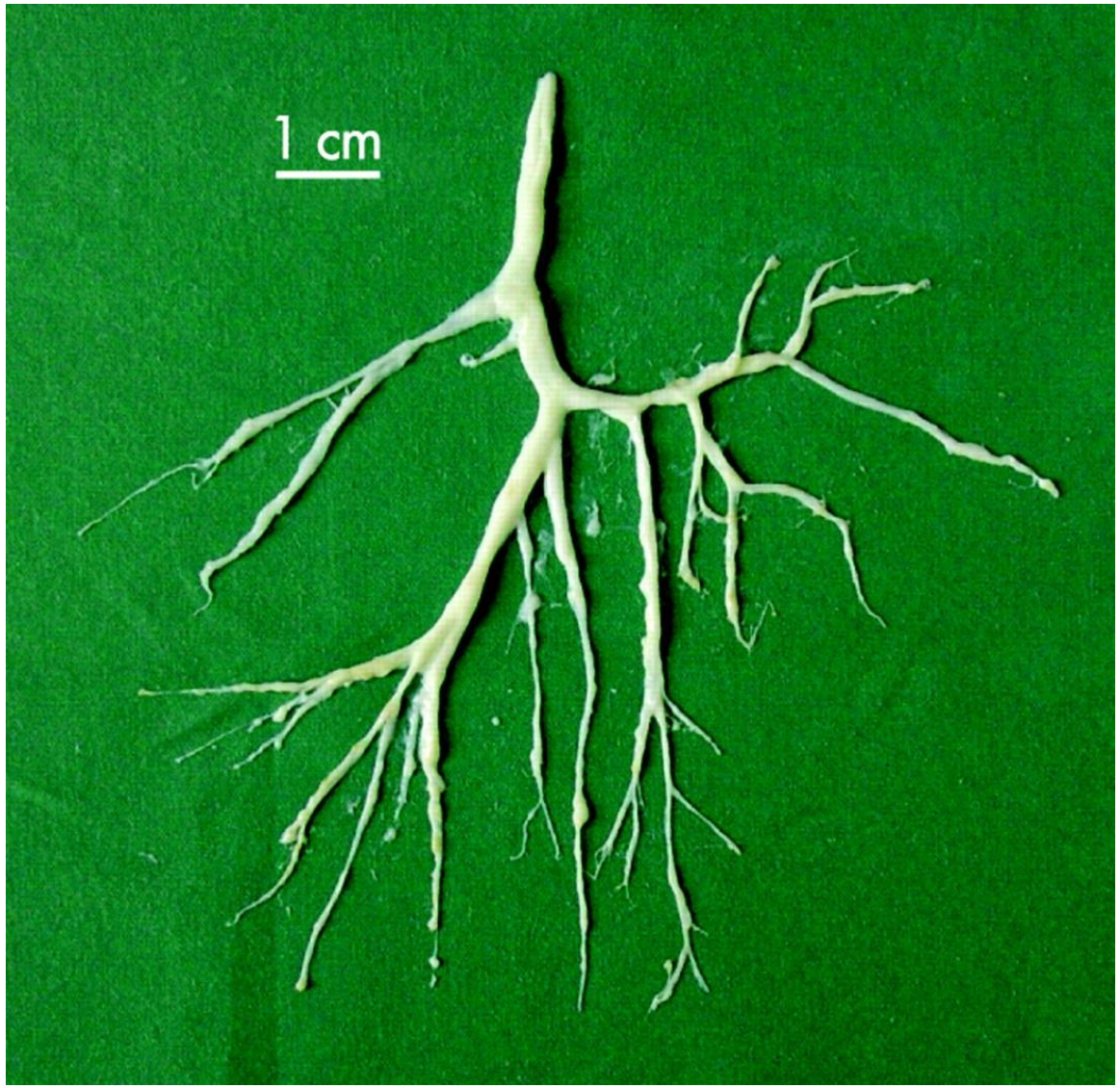
- It is thought that **virus-induced inflammation** of the respiratory mucosa **decrease the threshold of the subepithelial parasympathetic vagal receptors** to irritants in the airways causing **bronchoconstriction and inflammation**.

Morphology:

- **Gross features:**
- **in fatal cases, the lungs are** overdistended because of overinflation.

- The most striking macroscopic finding is:
- occlusion of bronchi and bronchioles by thick, mucus plugs and shed epithelium and eosinophils

Bronchial Asthma Mucus Plug



bronchi and bronchioles are occluded by thick tenacious mucous plug that are shed epithelium and eosinophils

MIC:

characteristic histologic findings include the followings:

1. Edema, hyperemia, and an **inflammatory infiltrate** in the bronchial walls, with prominent eosinophils and mast cells.

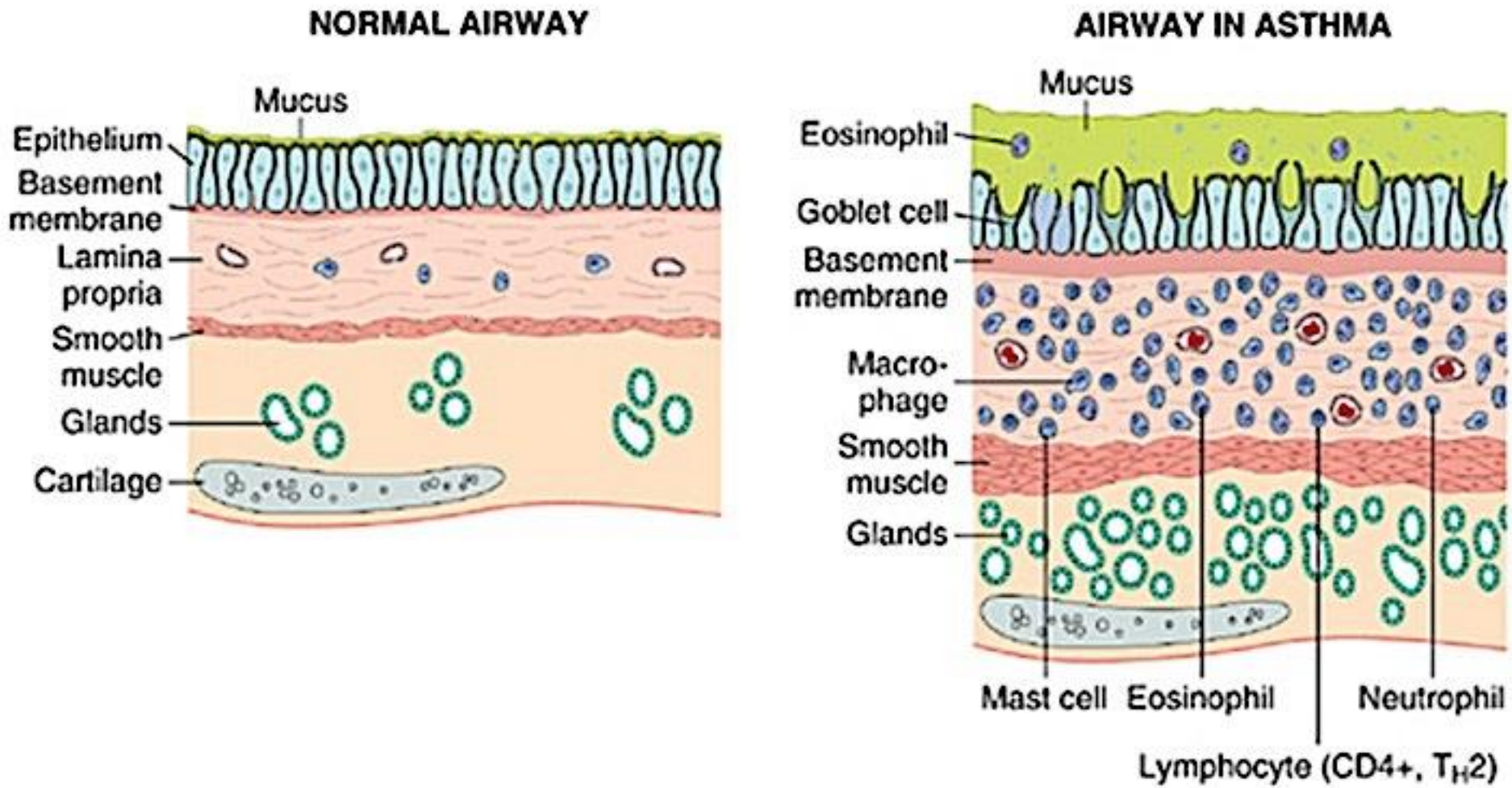
2. An increase in size of the submucosal mucous glands.

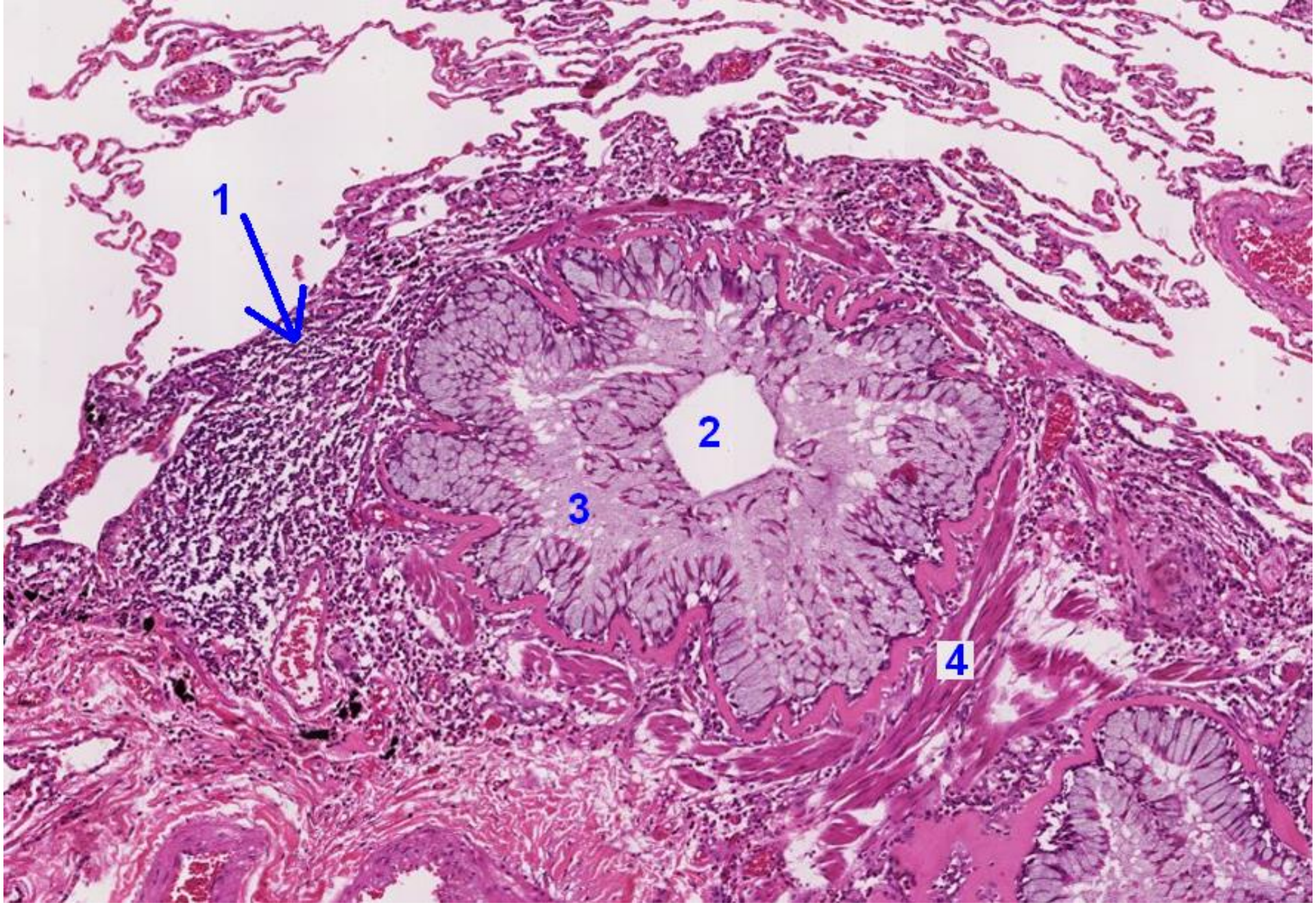
3. **Patchy necrosis** and **shedding of epithelial cells**.

4. **thickened basement membrane**.

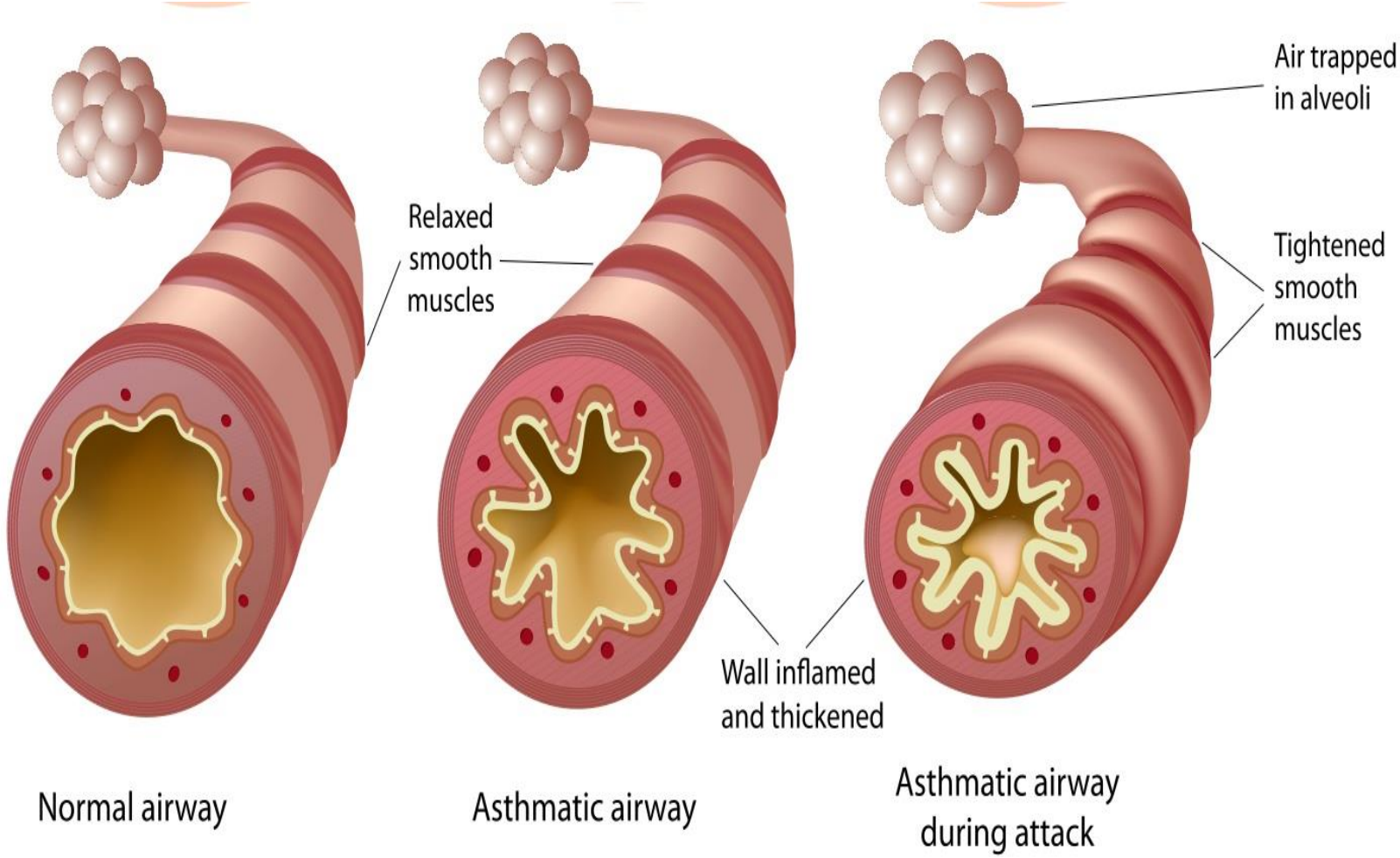
5. **Hypertrophy and hyperplasia of the smooth muscle** in the bronchial wall.

6. the mucus plugs contain **whorls of shed epithelium** and **eosinophils**


NORMAL AIRWAY
Mucus
Epithelium
Basement membrane
Lamina propria
Smooth muscle
Glands
Cartilage
AIRWAY IN ASTHMA
Mucus
Eosinophil
Goblet cell
Basement membrane
Macro-phage
Smooth muscle
Glands
Mast cell
Eosinophil
Neutrophil
Lymphocyte (CD4+, T_H2)



What are the 4 classical histologic findings in bronchial asthma?


Relaxed
smooth
muscles
Air trapped
in alveoli
Tightened
smooth
muscles
Wall inflamed
and thickened
Normal airway
Asthmatic airway
Asthmatic airway
during attack

- **Clinical features & prognosis:**
- an attack of asthma is characterized by severe dyspnea ,cough with wheezing; the chief difficulty lies in expiration.
- The patient struggles to get air into the lungs and then cannot get it out, so that there is **progressive hyperinflation of the lungs** with air trapped distal to the bronchi, which are constricted and filled with mucus and debris.
- In the usual case, attacks last from 1 to several hours and subside either spontaneously or with therapy.
- Occasionally a severe attack occurs that does not respond to therapy and persists for days and even weeks called acute severe asthma (formerly known as status asthmaticus). The associated hypercapnia, acidosis, and severe hypoxia may be fatal.
- **Treatment:** bronchodilators, glucocorticoids, and leukotriene antagonists.

Respiratory Pathology Outline

- Congenital anomalies
- Atelectises
- Obstructive lung diseases
- **Restrictive lung diseases**
- Infections
- Carcinoma

Restrictive Lung Diseases:

Are characterized by **reduced compliance** (i.e., more pressure is required to expand the lungs because they are stiff).

Two general features of restrictive pulmonary diseases

1. **Initiating injury** affects either **endothelial or alveolar epithelium or both**; **with chronicity,** injurious changes are **restricted to Interstitium (**interstitial lung disease).

2. **Interstitial fibrosis produces a "stiff lung**," which in turn reduces lung compliance…….(dyspnea)……. Hypoxia.

Restrictive Lung Diseases

- Reduced expansion of lung parenchyma so
- total lung capacity (**TLC)is reduced** (while in obstructive lung diseases FEV1 is reduced)
- Include:
- **Chest wall disease :** the defect outside the lung e.g. polio, obesity, pleural diseases.
- **Chronic interstitial and infiltrative lung diseases** e.g. pneumoconiosis, interstitial fibrosis , sarcoidosis ,connective tissue diseases

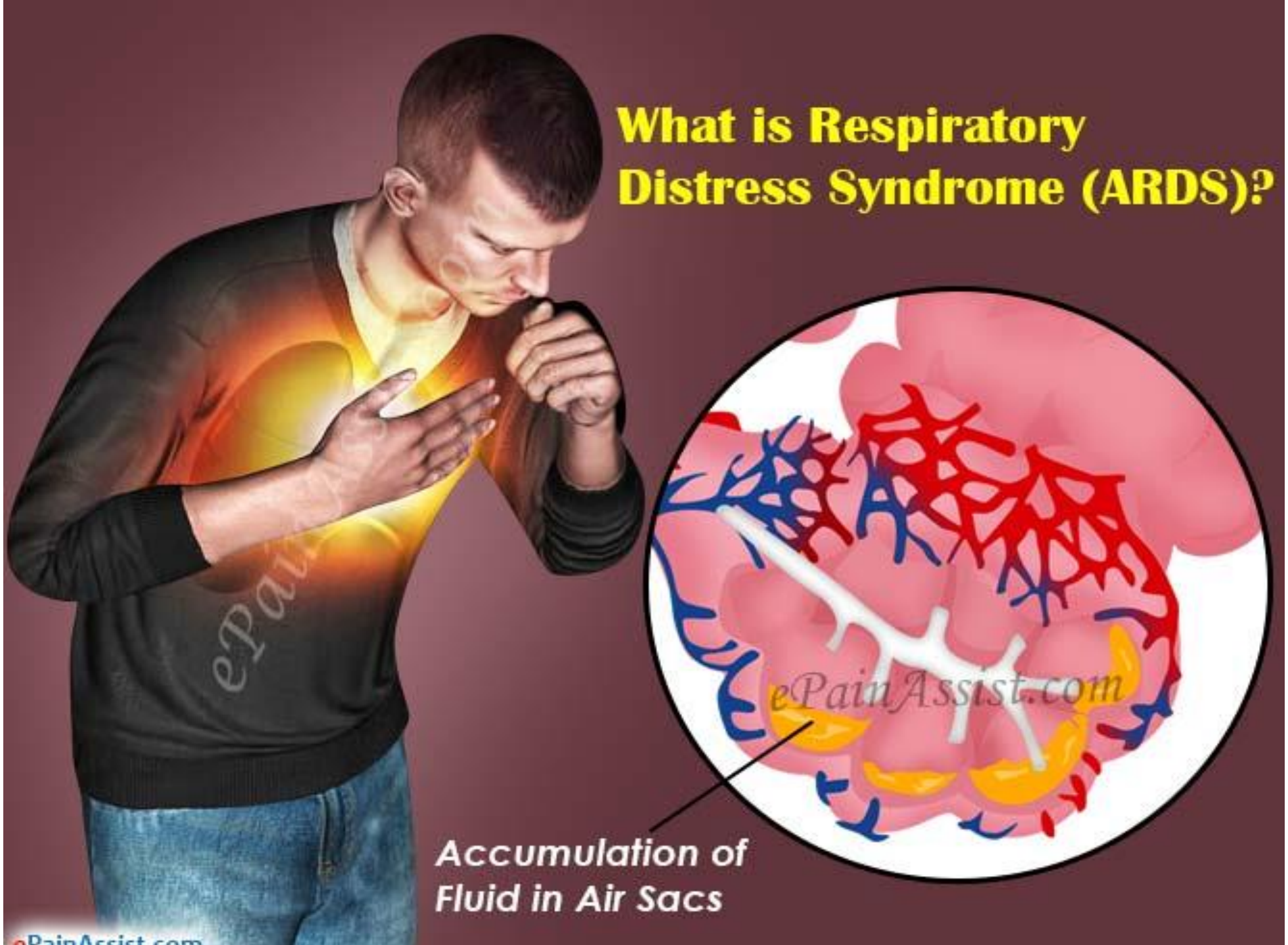
Types of Restrictive lung disease

can be either:

(1) Acute, (pulmonary edema, often with accompanying inflammation).

(2) Chronic (chronic inflammation and fibrosis)

What is Respiratory Distress Syndrome (ARDS)?



Acute Lung Injury(ALI) and Acute Respiratory Distress Syndrome (ARDS):

- **"Def.: A clinical syndrome which can be initiated by numerous conditions leading to diffuse alveolar capillary endothelial and epithelial cell damage. Increased permeability result in exudation of fluid leading to Progressive respiratory insufficiency**
- **Clinically: It is Characterized by**

1. Acute onset of ***dyspnea*.**
2. ***Hypoxemia***.
3. Development ***of bilateral pulmonary infiltrates on radiographs***.
4. ***Absence of clinical evidence of primary left-sided heart failure***.

- Represent the most common cause of *noncardiogenic pulmonary edema.*

- **Acute lung injury (ALI)** :
- bilateral pulmonary edema
- **Other organs NOT affected.**

- **Acute respiratory distress syndrome (ARDS):**
- is a manifestation of **severe fulminant form of ALI**.
- Often **with multiorgan involvement**.
- The condition may progress to multisystem organ failure.
- Both ARDS and ALI are associated with inflammation lead to increases in pulmonary vascular permeability, edema, and epithelial cell death.
- The microscopic manifestation of these diseases is called: **diffuse alveolar damage (DAD).**
- ALI is a well-recognized complication of diverse conditions including both pulmonary and systemic disorders.

Causes are diverse; all lead to extensive bilateral injury to alveoli.

A. Respiratory

- 1. Diffuse infections (viral, bacterial pneumonia)
- 2. gastric Aspiration
- 3. Inhalation of toxic gases
- 4. Inhaled Irritants: Oxygen toxicity, Smoke, Irritant gases and chemicals

B. Non-respiratory

- 1. Sepsis (septic shock)
- 2. Trauma (head injury)
- 3. Burns
- 4. Pancreatitis
- 5. Ingested toxins
- 6-Uremia

There is an acute onset of dyspnea, hypoxemia (refractory to O2 therapy), and radiographic bilateral pulmonary infiltrates (noncardiogenic pulmonary edema).

The condition may progress to multisystem organ failure.

▪ In many cases, several predisposing conditions are present (e.g., shock, oxygen therapy, and sepsis).

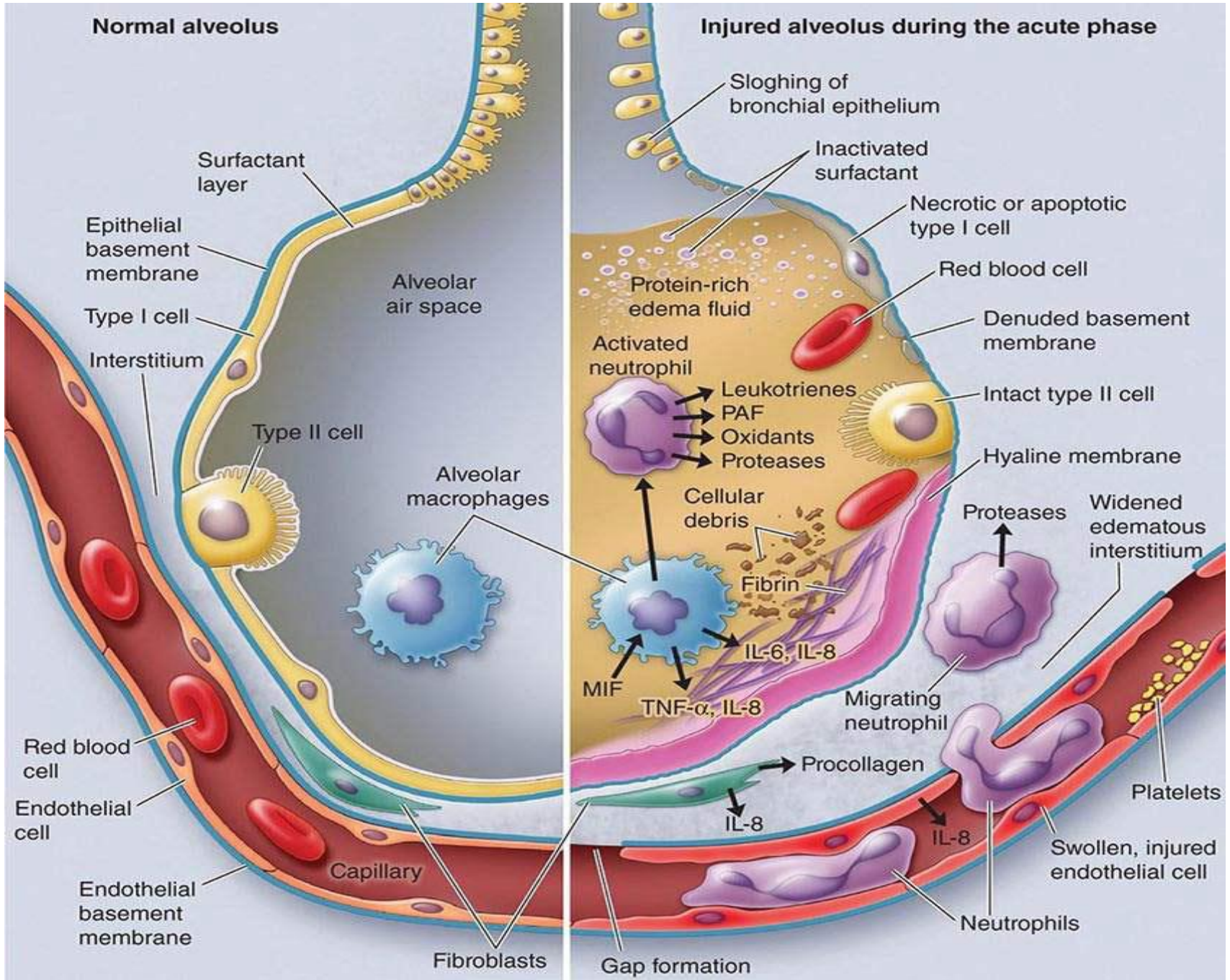
▪ ARDS should not be confused with **respiratory distress syndrome of the newborn;** which is caused by a deficiency of surfactant caused by prematurity.

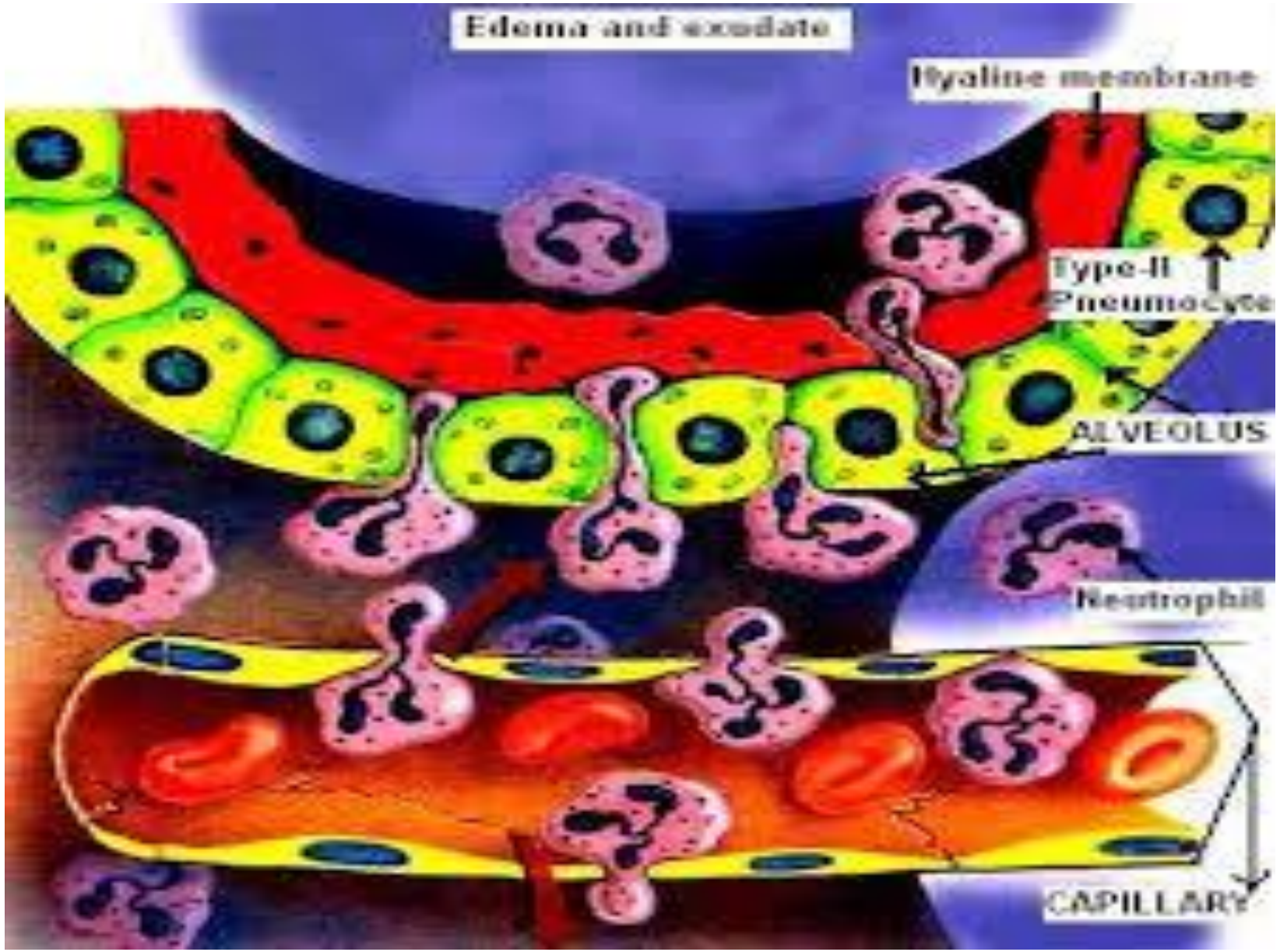
▪ *Pathogenesis*

- The ***alveolar capillary membrane*** is formed by *two separate barriers -* ***the microvascular endothelium and the alveolar epithelium.***
- ***In ALI and ARDS*** the integrity of this *barrier is compromised by either* ***endothelial or epithelial injury, or, more commonly, both****.*
- Alveolar capillary membrane injury result in widespread surfactant abnormalities caused by damage to type II pneumocytes.

▪

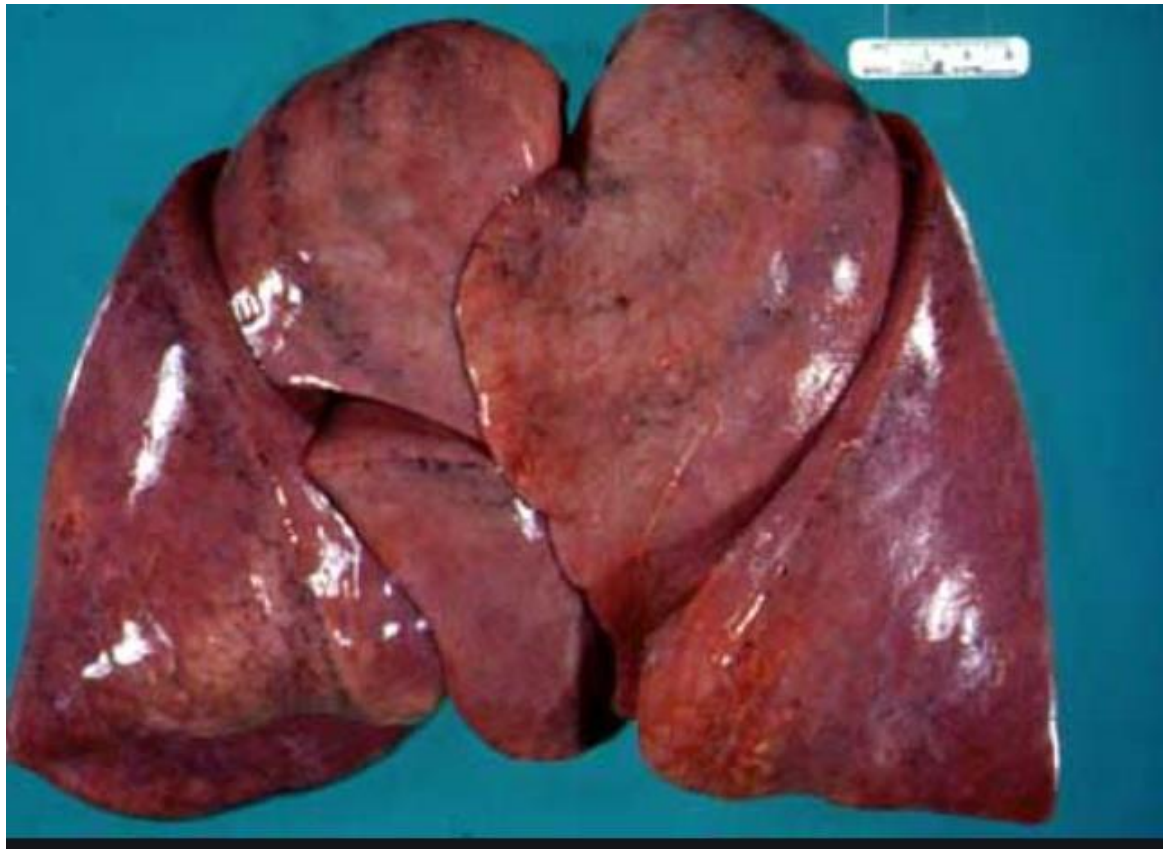
- activation of macrophage..release of inflammatory mediators….endothelial cells damage.. Extravasation of neutrophils to the interstitium and alveolar lumen.
- Increase in vascular permeability and endothelial activation and injury make pulmonary capillaries leaky…interstitial and intra-alveolar edema ... . Ultimately the inspissated protein-rich edema fluid and debris from dead alveolar epithelial cells organize into hyaline membranes, a characteristic feature of ALI/ARDS.
- Resolution of injury: if the inflammatory stimulus decrease , macrophages remove intra-alveolar debris and release fibrogenic cytokines such as transforming growth factor β (TGF-β) and platelet-derived growth factor. These factors stimulate fibroblast growth and collagen deposition, leading to fibrosis of alveolar walls. Residual type II pneumocytes proliferate to replace type I pneumocytes, reconstituting the alveolar lining. Endothelial restoration occurs through proliferation of uninjured capillary endothelium.

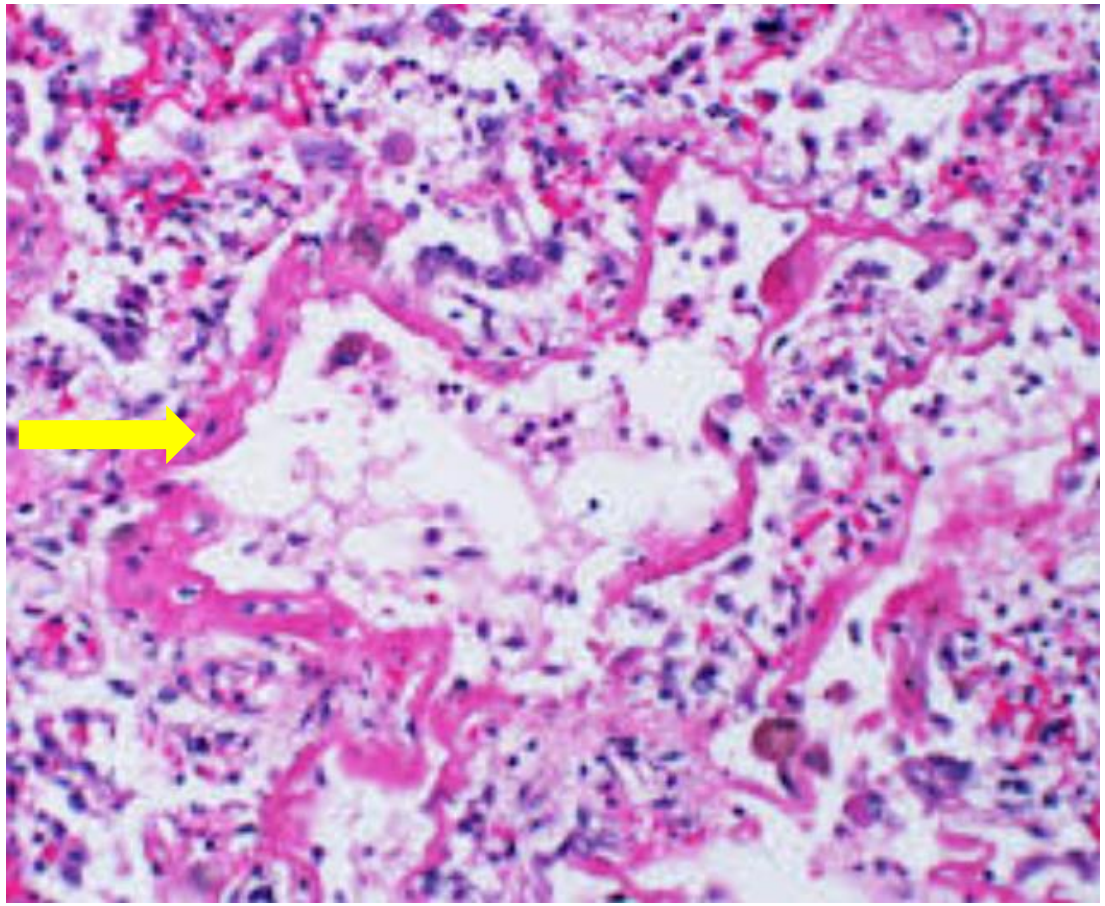

Normal alveolus
Surfactant layer
Epithelial basement membrane
Type I cell
Interstitium
Alveolar air space
Type II cell
Alveolar macrophages
Red blood cell
Endothelial cell
Capillary
Endothelial basement membrane
Fibroblasts
Injured alveolus during the acute phase
Sloghing of bronchial epithelium
Inactivated surfactant
Necrotic or apoptotic type I cell
Protein-rich edema fluid
Red blood cell
Denuded basement membrane
Activated neutrophil
Leukotrienes
PAF
Oxidants
Proteases
Intact type II cell
Hyaline membrane
Cellular debris
Proteases
Widened edematous interstitium
Fibrin
IL-6, IL-8
MIF
TNF-α, IL-8
Migrating neutrophil
Procollagen
IL-8
IL-8
Platelets
Swollen, injured endothelial cell
Neutrophils
Gap formation


Edema and exudate
Hyaline membrane
Type-II Pneumocyte
ALVEOLUS
Neutrophil
CAPILLARY

- ***MORPHOLOGY:***
- ***Gross***: In the **acute exudative stage,** the lungs resemble the **liver**; they are **dark red, firm, airless and heavy**.
- **Microscopiclly:**
- **In acute exudative phase:**
- capillary **congestion**,
- **necrosis** of alveolar epithelial cells,
- interstitial and intraalveolar **edema** and hemorrhage,
- and (particularly with sepsis) collections of neutrophils in capillaries.
- The most characteristic finding is the presence of **hyaline membranes**, particularly lining the distended alveolar ducts.
- Such membranes consist of **fibrin-rich edema fluid** admixed with remnants of **necrotic epithelial cells**.

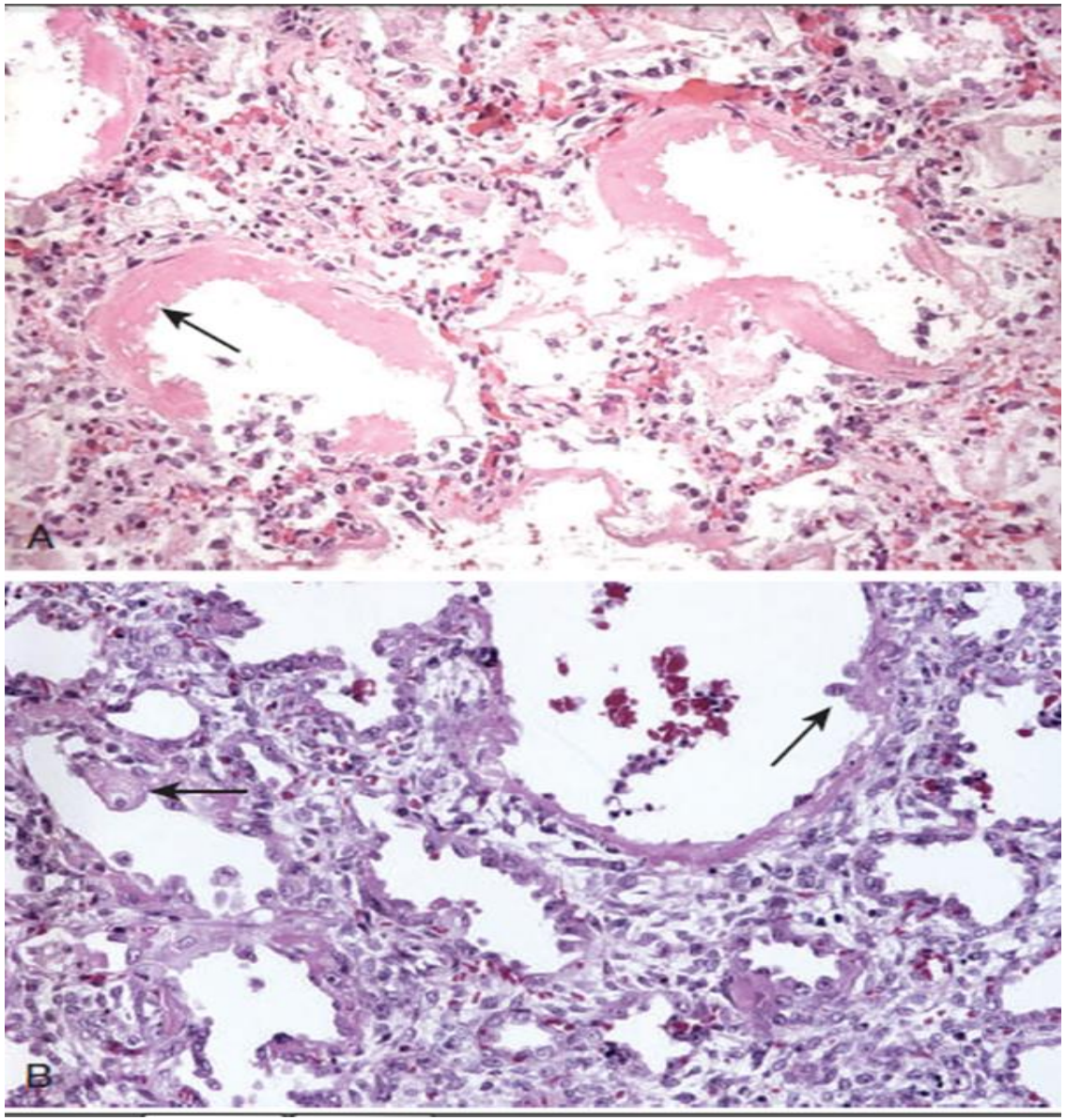
Acute Respiratory Distress Syndrome (ARDS):





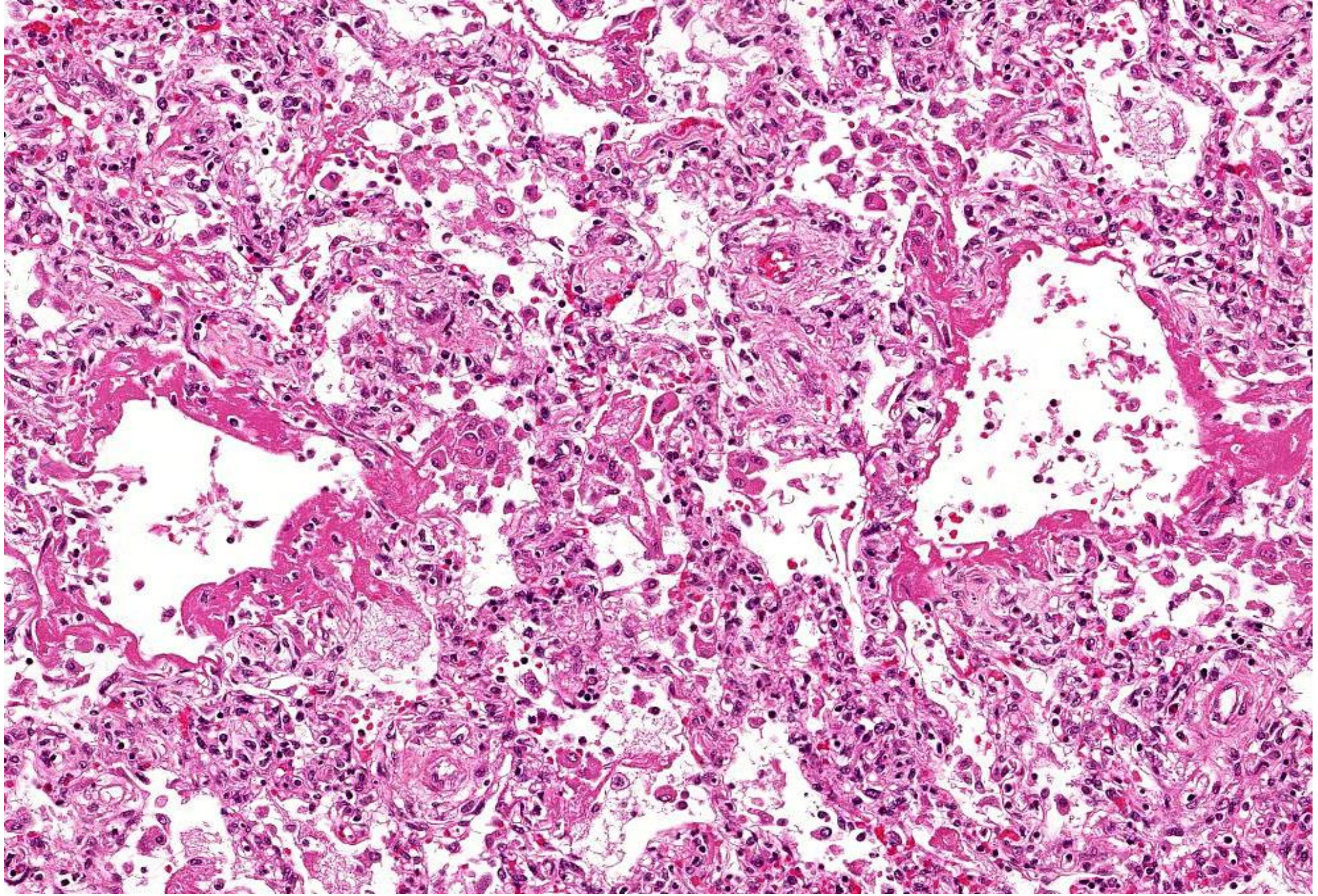
Gross appearance of lungs resemble the liver; they are dark red, firm, airless.

Microscopical appearance of lung showing hyaline membranes formation consist of protein-rich edema fluid admixed with remnants of necrotic epithelial cells

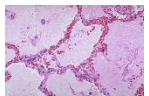


Acute lung injury and acute respiratory distress syndrome. (A) Diffuse alveolar damage in the acute phase. Some alveoli are collapsed, while others are distended; many are lined by bright pink hyaline membranes *(arrow).*

(B) The healing stage is marked by resorption of hyaline membranes and thickening of alveolar septa by inflammatory cells, fibroblasts, and collagen. Numerous reactive type II pneumocytes also are seen at this stage *(arrows),* associated with regeneration and repair.

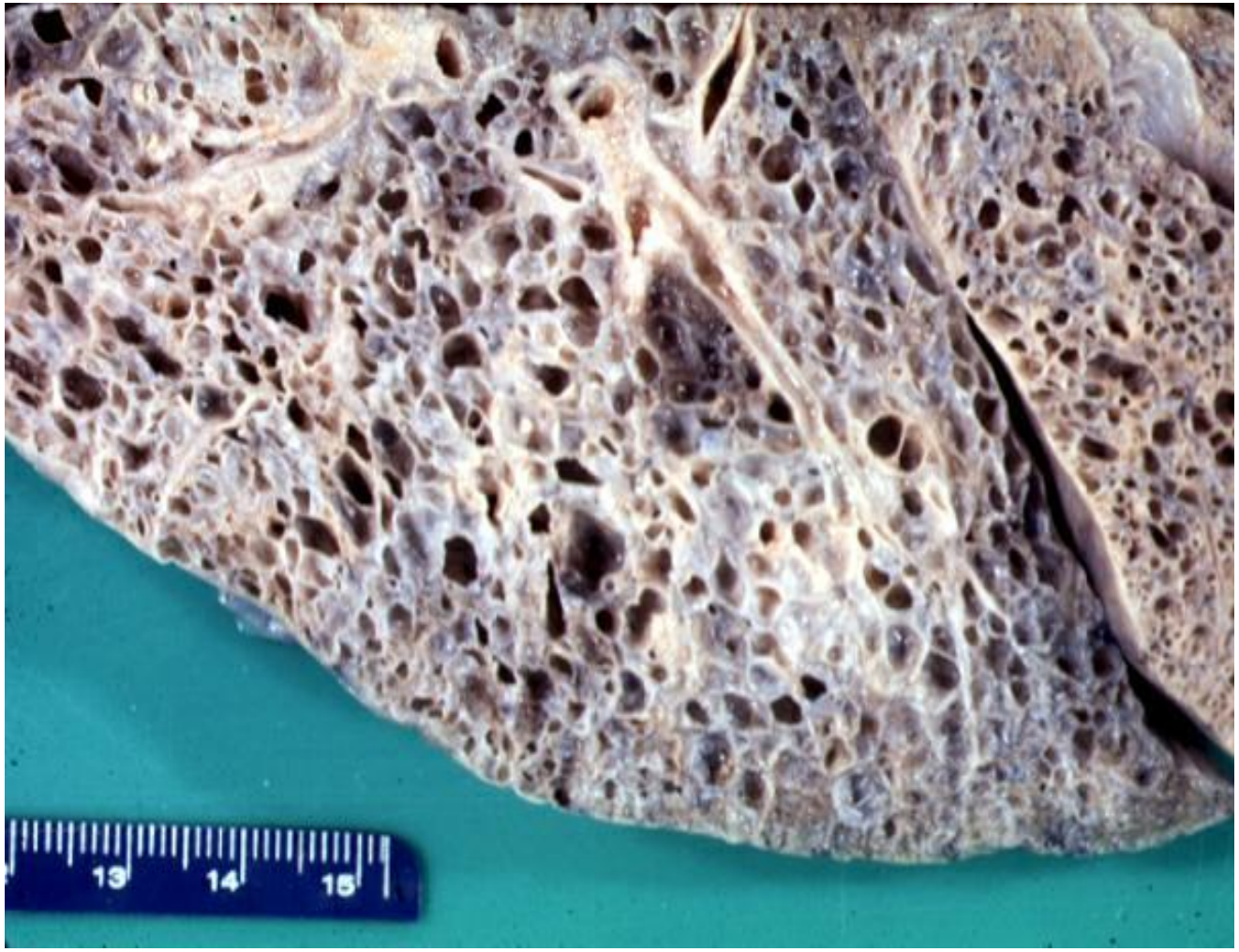


ARDS



- **In the proliferative (organizing stage)**
- **type II pneumocytes proliferate** in an attempt to regenerate the alveolar lining and
- granulation tissue forms in the alveolar walls and spaces.
- In most cases the granulation tissue resolves, leaving minimal functional impairment.
- Sometimes, however, fibrotic thickening (scarring) of the alveolar septa ensues (late fibrotic stage).

- Resolution is unusual; more commonly, the fibrin-rich exudates organize into intraalveolar fibrosis.
- Marked thickening of the alveolar septa occur due to proliferation of interstitial cells and deposition of collagen.
- **Reparative process leads to:**
- **Proliferation of fibroblasts & hyperplasia of pneumocytes type II** result in **diffuse interstitial fibrosis** interspersed with **dilated and distorted airspaces (honeycomb lung).**



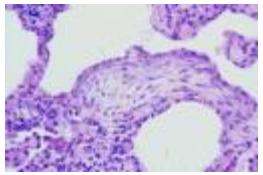
Honey comb lung : gross appearance showing multiple cysts like structures resulting from interstitial fibrosis

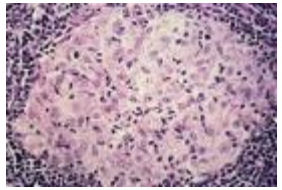
Chronic diffuse interstitial (Restrictive) disease:

- These are a heterogeneous group of disorders characterized predominantly by:
- 1-inflammation and fibrosis of the **lung interstitium** associated with
- 2-pulmonary function studies indicative of restrictive lung disease (reduced FVC, The ratio of FEV1 to FVC is normal)
- 3-The hallmark of these disorders is **reduced compliance** (because of stiff lungs).
- **Restrictive defects occur in two general conditions:**
- (1) **chest wall disorders** (e.g., neuromuscular diseases such as poliomyelitis, pleural diseases, and kyphoscoliosis)
- (2) **chronic interstitial and infiltrative diseases**, such as pneumoconioses and interstitial fibrosis of unknown etiology.

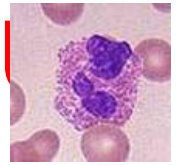
RESTRICTIVE (INFILTRATIVE)

- REDUCED COMPLIANCE, reduced gas exchange)
- Are also DIFFUSE, ↑ density, ↓ crepitance
- HETEROGENEOUS ETIOLOGIES





- FIBROSING
- GRANULOMATO



- EOSINOPHILIC

- SMOKING RELATED

Clinical features:

- dyspnea, tachypnea, cyanosis, without wheezing or other evidence of airway obstruction.
- **Pulmonary function test (PFT):** reductions in diffusion capacity, lung volume, and lung compliance.
- **Chest radiographs**: bilateral lesions appear as small nodules, irregular lines, or ground-glass shadows, all corresponding to areas of interstitial fibrosis.
- Although the entities can often be distinguished in their early stages, **advanced forms** are hard to differentiate because all result in diffuse scarring of the lung, often referred to as **end-stage lung or honeycomb lung.**
- **Complications**:
- 1- secondary pulmonary hypertension
- 2- right sided heart failure (cor pulmonale) may result.

Idiopathic Pulmonary Fibrosis (IPF)

- It is a clinicopathologic syndrome characterized histologically by **progressive diffuse interstitial fibrosis** which in advanced cases results in **respiratory failure** (**severe hypoxemia and cy**anosis).
- **Asbestosis** & **the connective tissue** diseases SHOULD BE EXCLUDED
- **Males** (usually **over 60 years**) are more often affected.
-

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

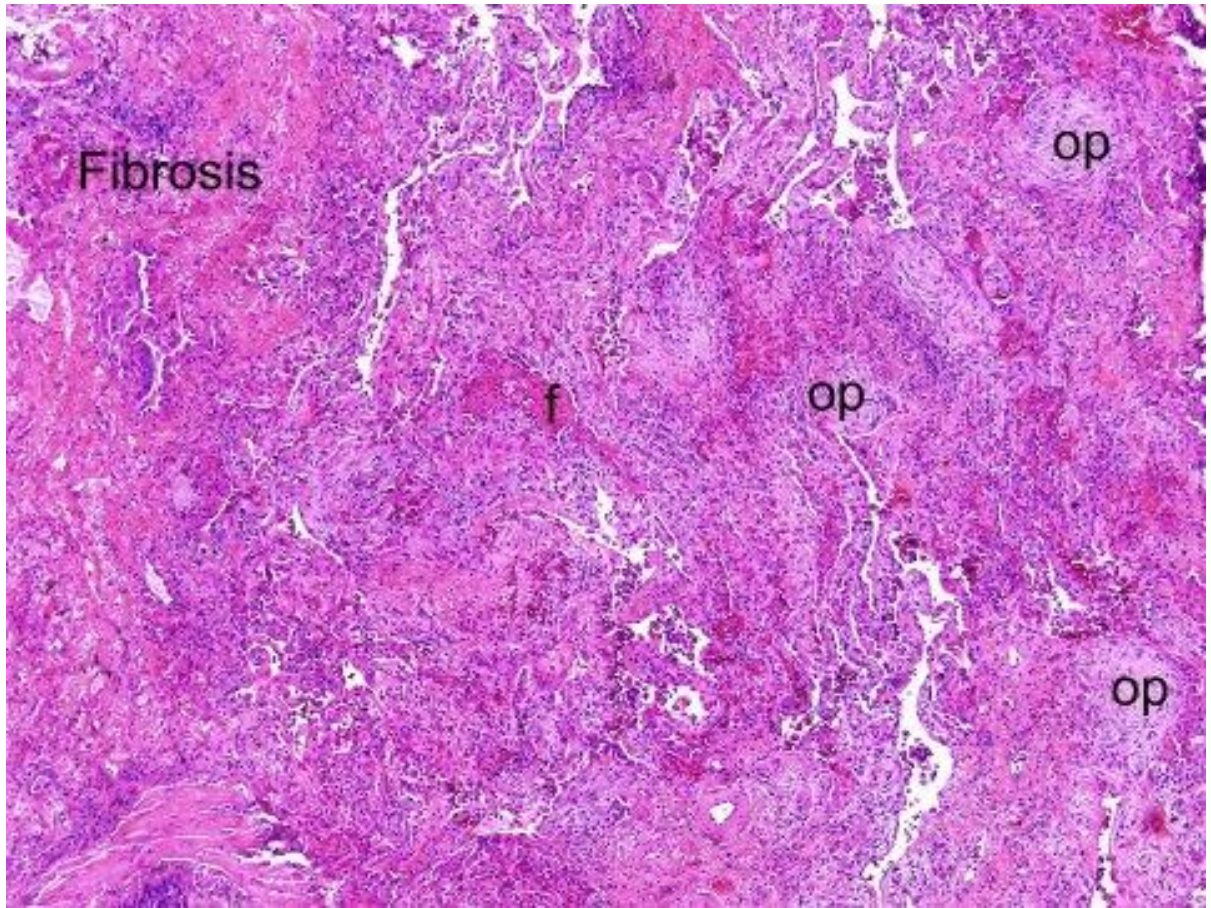
The histologic hallmark is :

patchy interstitial fibrosis, which varies in intensity.

- The dense fibrosis causes collapse of alveolar walls and formation of cystic spaces lined by hyperplastic type II pneumocytes (**honeycomb lung**).

IPF (UIP)

- **IDIOPATHIC, i.e., not from any usual caused, like lupus, scleroderma**
- **FIBROSIS**



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

Clinical Features

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

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

- **Treatment:** Lung transplantation is the only definitive therapy; however, two drugs, a **tyrosine kinase inhibitor** and a **TGF-β antagonist**, have both been shown to slow disease progression and represent the first effective targeted therapies for IPF.

- Sarcoidosis: is a **systemic granulomatous disease** of **unknown etiology** characterized by **noncaseating granulomas** in many tissues and organs.

- Other diseases, including **mycobacterial** or **fungal infections** also produce noncaseating granulomas; therefore, the histologic diagnosis of sarcoidosis is one of exclusion.

Bilateral hilar lymphadenopathy &/or **parenchymal lung involvement** is the major presenting manifestations in 90% of cases.

Eye and skin involvement are also frequent and may occasionally be the presenting feature of the disease.

Sarcoidosis occurs throughout the world, affecting both sexes and all races and ages. There is a predilection for **adults younger than 40 years of age**.

Sarcoidosis is one of the few pulmonary diseases with a **higher prevalence among nonsmokers.**

- Although the etiology of sarcoidosis **remains unknown**, it is probably a disease of **disordered immune regulation** in **genetically predisposed individuals** exposed to **certain environmental agents**.

- **Pathologic features**

- **Noncaseating epithelioid granulomas** are the histopathologic marker of sarcoidosis . composed of aggregates of tightly clustered epithelioid macrophages, often with giant cells.

- Two other microscopic features are sometimes seen in the granulomas:

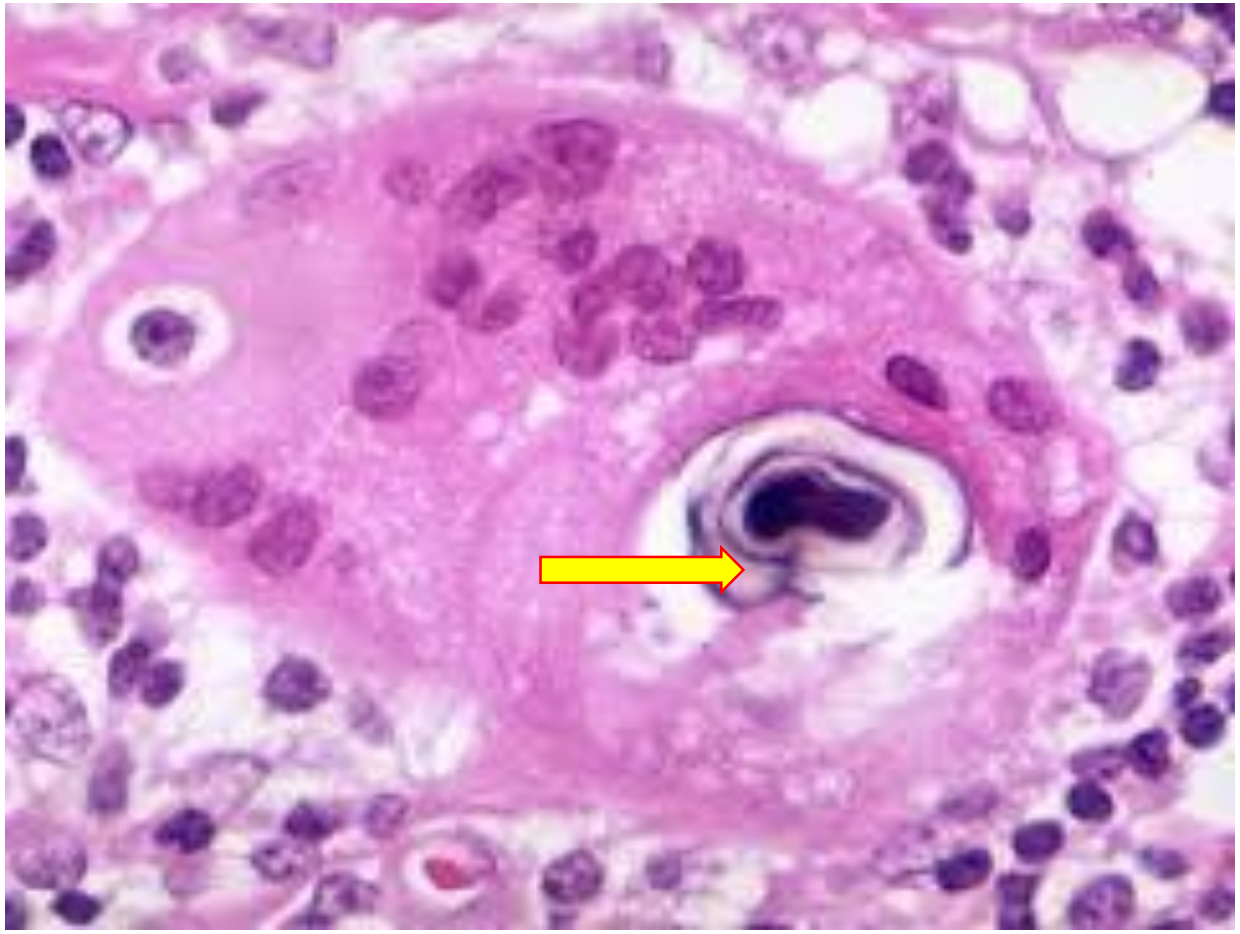
- 1**. Schaumann bodies**, laminated concretions composed of calcium and proteins;

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

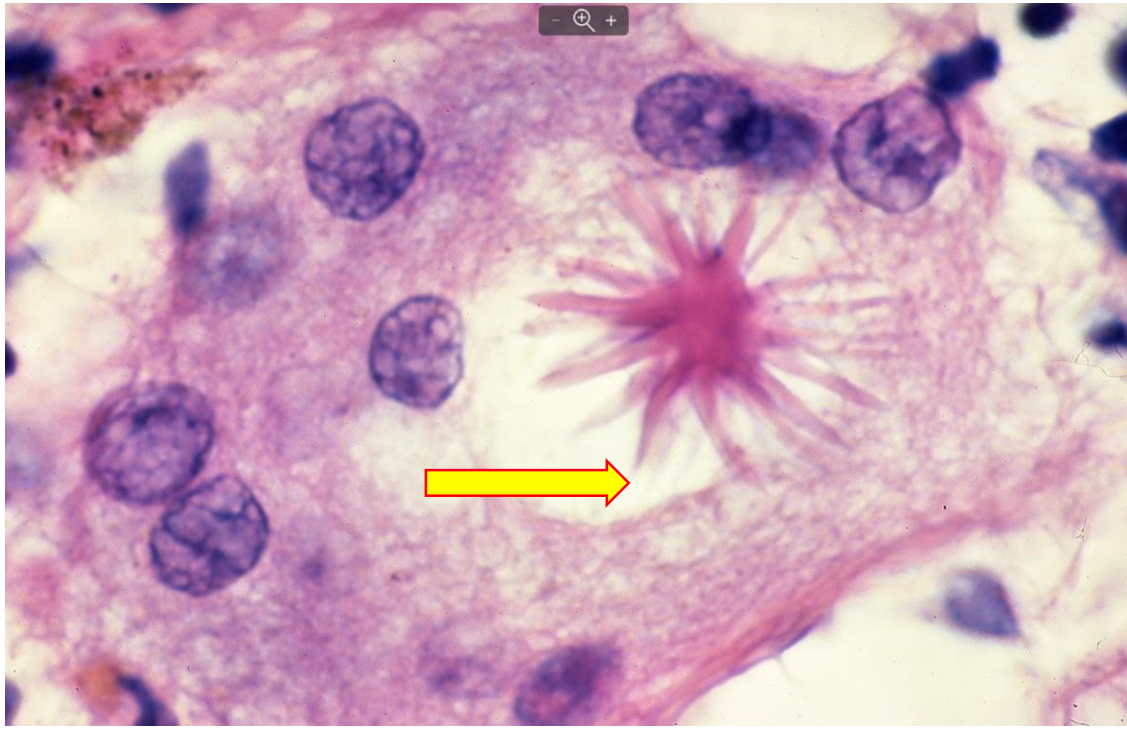
- **Caseation necrosis (typical of tuberculosis) is absent**.

- The lungs are involved in 90% of patients. The granulomas predominantly involve the i**nterstitium** rather than airspaces. later result in **honeycomb lung** which may lead to **pulmonary hypertension & cor pulomanle**.

- Intrathoracic hilar and paratracheal lymph nodes are enlarged in the majority of patients.



Schaumann bodies are calcium and protein inclusions inside of Langhans giant cells as part of a granuloma



Asteroid bodies**,** stellate inclusions enclosed within giant cells