

Respiratory system pathology

third year-pathophysiology subject –laboratory science departments
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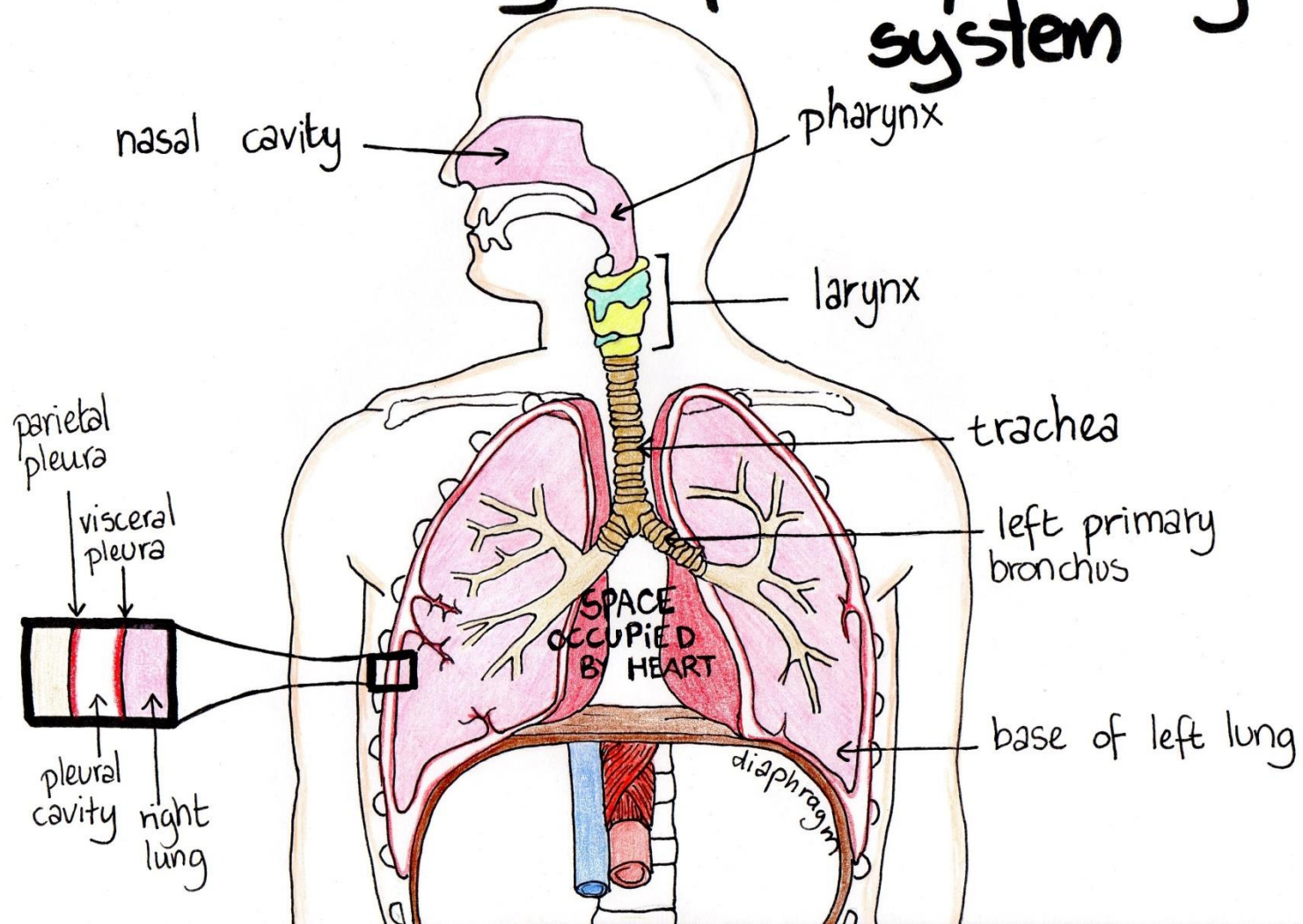
Learning objectives

- 1. Understand the Normal Anatomy and Physiology of the Respiratory System**
- 2. Identify Common Respiratory Diseases and Their Pathogenesis**
- 3. Examine the Histopathology of Respiratory Conditions**
- 4. Recognize Risk Factors and Prevention Strategies for Respiratory Diseases**

Overview of the Respiratory System

- - Anatomy: The respiratory system includes the **upper respiratory tract** (nose, nasal cavity, pharynx, larynx) and the **lower respiratory tract** (trachea, bronchi, bronchioles, lungs).
- Each component plays a crucial role in **conducting air, facilitating gas exchange, and protecting against pathogens.**

Gross anatomy of respiratory system



Functions:

1. - **Gas Exchange:** Oxygen is absorbed into the bloodstream, and carbon dioxide is expelled from the body.
2. - **pH Regulation:** The respiratory system helps maintain acid-base balance by regulating carbon dioxide levels.

Classification of Respiratory Diseases

1. - **Obstructive Diseases:** Conditions that cause narrowing or blockage of airways, leading to difficulty in exhaling air (e.g., **COPD(chronic obstructive pulmonary disease)**)
2. **Restrictive Diseases:** Conditions that restrict lung expansion, leading to reduced lung volumes (e.g. pleural effusion).
3. - **Infectious Diseases:** Diseases caused by pathogens, leading to inflammation and compromised lung function (e.g., pneumonia, tuberculosis).
4. - **Neoplastic Diseases:** Tumors arising in the respiratory system, which can be benign or malignant (e.g., lung cancer).

1. Obstructive Respiratory Diseases

COPD, a major public health problem, is defined as “a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities caused by exposure to noxious particles or gases.” these include

1- Emphysema

2- Chronic bronchitis

3- Asthma

4- Bronchiectasis

COPD has two major clinic pathologic manifestations, •
emphysema and chronic bronchitis, which are often
found together in the same patient

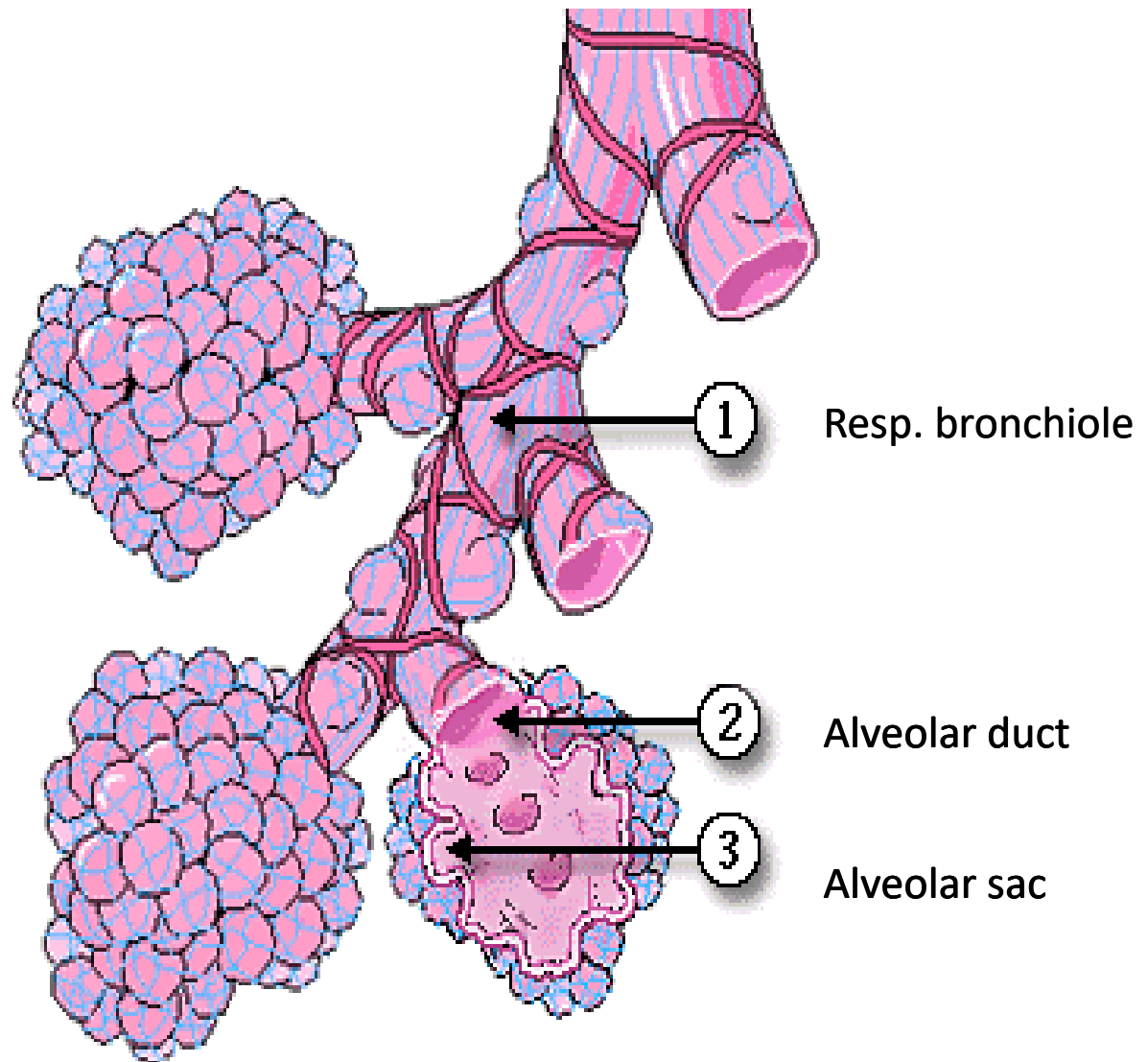
1- Emphysema

It is an abnormal **permanent** enlargement of the air space distal to the terminal bronchiole with **destruction** of their wall , There is **NO** fibrosis.

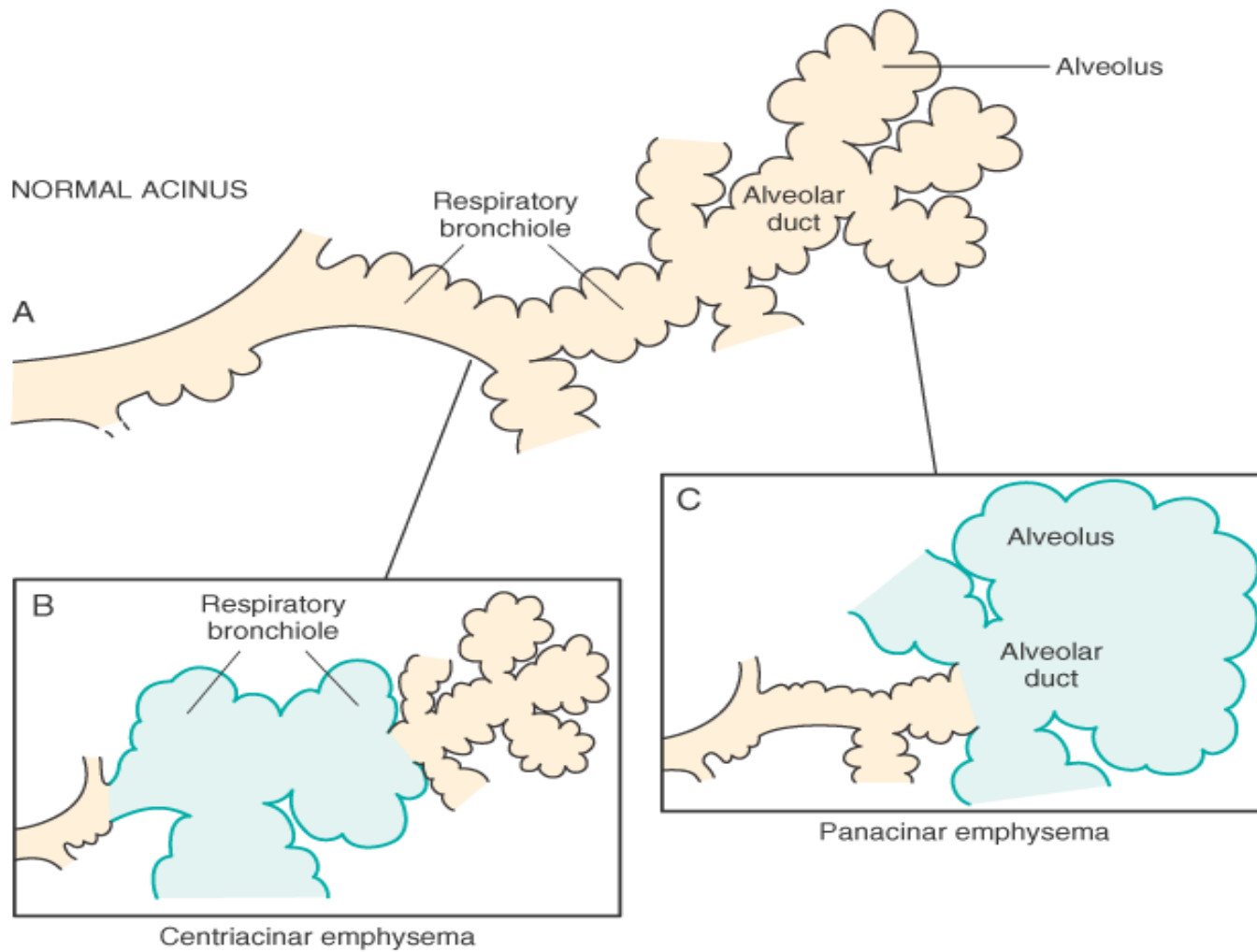
Overinflation: dilatation of the airspace **without destruction** of their walls.

- Based on the segments of the respiratory units that are involved, emphysema is subdivided into four major types:
- **(1) Centriacinar,**
- **(2) Panacinar,**
- **(3) Paraseptal,**
- **(4) Irregular.**
- **Of these, only the first two cause clinically significant airflow obstruction**

Normal respiratory acinus



Emphysema

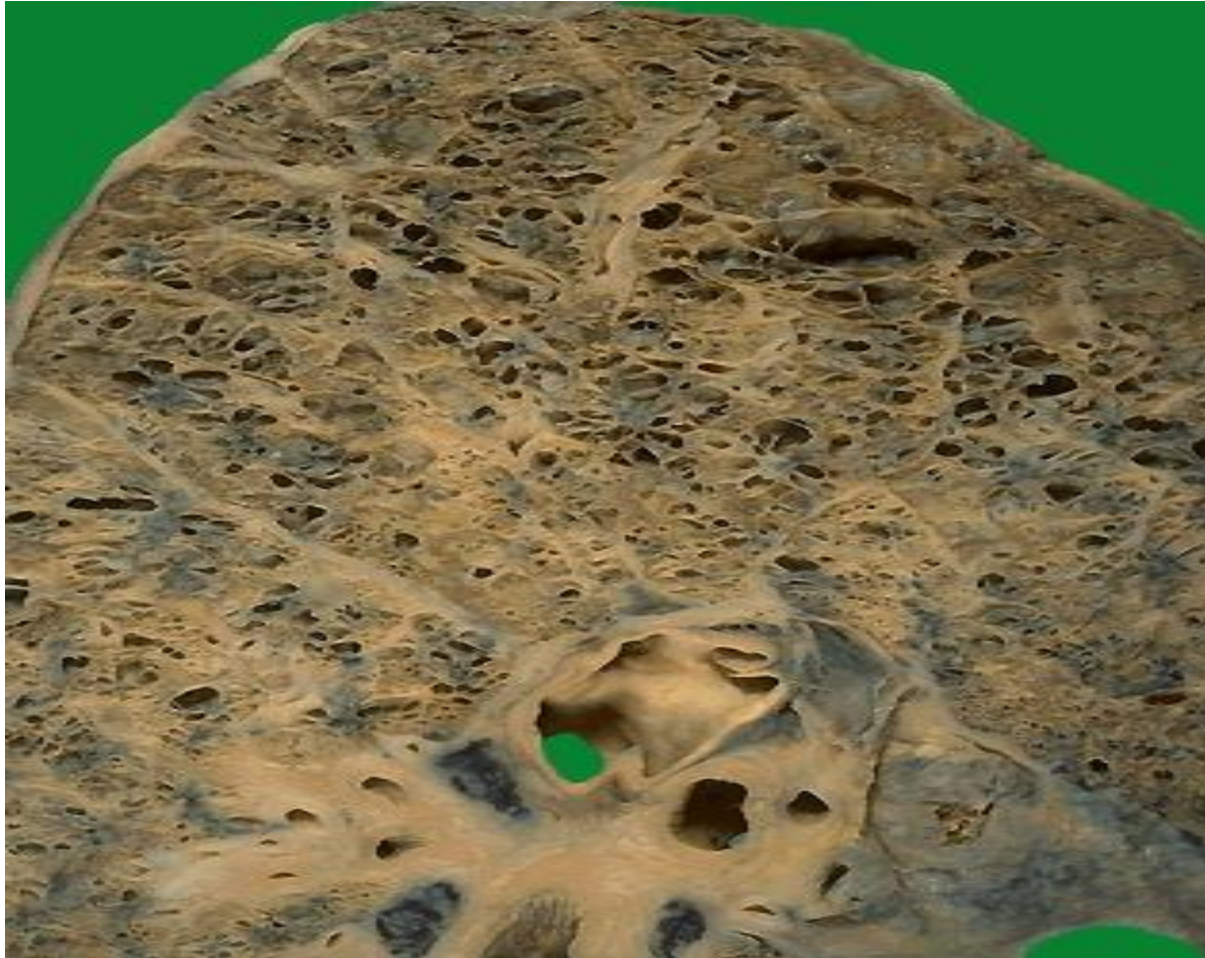


Pathogenesis

- The key role in the whole process is:
- **PROTEASE --- ANTIPROTEASE imbalance.**
- Proteases: are enzymes which digest the tissue.
- Anti-proteases: are the counteracting enzymes that **stop** the action of digestion.
- **Normal persons have a balance between the two enzymes.**
- The main **cellular elastase** (protease) is secreted from the **NEUTROPHILS**, it is capable to digest human lung if not inhibited by the anti-elastase enzyme e.g. (α -1 anti-trypsin).
- The **free radicals** released from the neutrophils can inhibit the release of this α -1 anti trypsin.
- The classic presentation of emphysema in which the patient is dyspneic

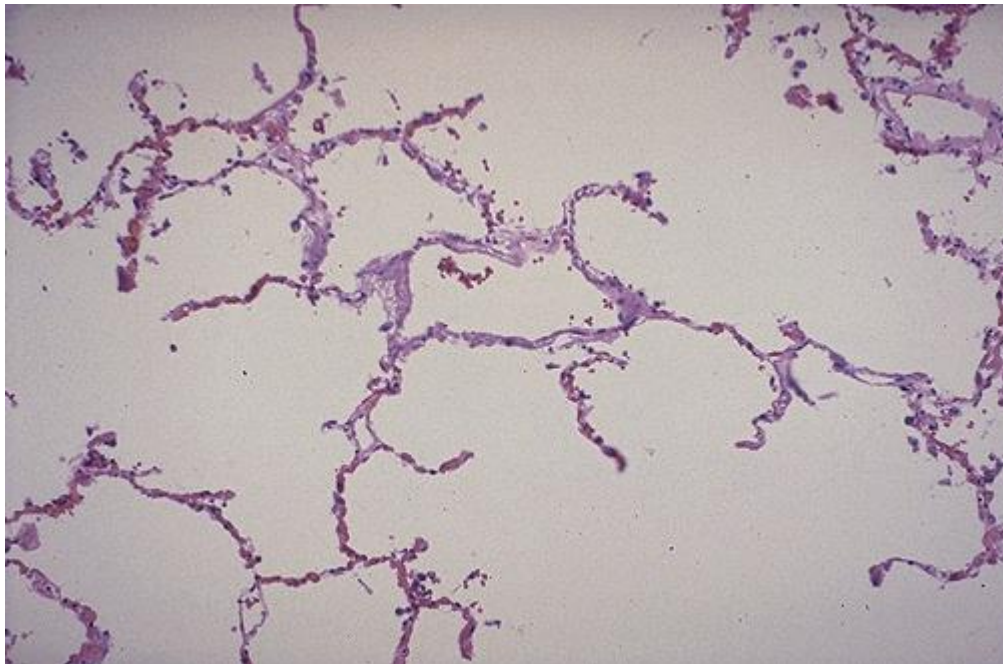
- ***So the Development of emphysema occurs:***
- When there is **↑ elastase activity** as in smoking.
- When there is **↓ anti-elastase activity** as in :
- **-Hereditary** α -1 anti- trypsin deficiency.
- **-Acquired** as in smokers due to the effect of nicotine, O₂ free radicals that inhibit the release of anti-elastase.
- **The effect of smoking in the development of emphysema**
- 1-It **↑** the no. of **neutrophils**, macrophages, in the alveoli.
- 2-Nicotine is a **chemotactic** substance for neutrophils.
- 3-It **stimulates** the elastase activity.
- 4-The oxidants in the smoke and the free radicals from the accompanying neutrophils **→ inhibit** the secretion of anti-elastase.

Gross: Emphysematous lung



Microscopically

Histologic examination reveals destruction of alveolar walls without fibrosis, leading to enlarged air spaces



2- Chronic bronchitis

Clinically :

it is characterized by (cough +sputum) production for at least 3 months in at least 2 consecutive years in the absence of any other identifiable cause.

- . The primary or initiating factor in the genesis of chronic bronchitis is exposure to noxious or irritating inhaled substances such as tobacco smoke (90% of those affected are smokers)dust, cotton

Pathogenesis

- cigarette smoking other air pollutants These environmental irritants induce
 1. hypertrophy of mucous glands in the trachea and bronchi
 2. increase in mucin-secreting goblet cells in the epithelial surfaces
 3. These irritants also cause inflammation marked by the infiltration of macrophages, neutrophils, and lymphocytes
 4. mucous plugging of the bronchiolar lumen this leading to inflammation, and bronchiolar wall fibrosis

BRONCHIAL ASTHMA

Is a chronic relapsing inflammatory disorder characterized by hyper-reactive airways → bronchoconstriction episodic , **reversible**, due to ↑ responsiveness of the trachio-bronchial tree to various stimuli.

produces symptoms such as wheezing, shortness of breath, chest tightness, and cough, which vary over time and in intensity.

- Asthma has several distinct clinical phenotypes, each with different underlying pathogenic mechanisms.
- It may be categorized as atopic (evidence of allergen sensitization and immune activation, often in a patient with allergic rhinitis or eczema) or nonatopic (no evidence of allergen sensitization), of which several subtypes exist

ATOPIC ASTHMA

This type of asthma is a classic example of an IgE-mediated (type I) hypersensitivity reaction. •

The disease usually begins in childhood and is triggered by environmental allergens, such as dusts, pollens

- A positive family history of asthma is common

Diagnosed by

1. positive allergen skin test
2. high total serum IgE levels



NON-ATOPIC ASTHMA

- Individuals with non-atopic asthma do not have evidence of allergen sensitization, and skin test results are usually negative.

A positive family history of asthma is less common in these patients.

- Respiratory infections due to viruses are common triggers in non-atopic asthma.

DRUG-INDUCED ASTHMA

- Several pharmacologic agents provoke asthma.

Aspirin-sensitive asthma is an uncommon type, occurring in individuals with recurrent rhinitis and nasal polyps.

- These individuals are extremely sensitive to small doses of aspirin as well as other non-steroidal anti-inflammatory medications

Pathogenesis

- Aspirin and related drugs trigger asthma in these patients by inhibiting the cyclooxygenase pathway of arachidonic acid metabolism, leading to a rapid decrease in prostaglandin E₂.

Normally prostaglandin E₂ inhibits enzymes that generate proinflammatory mediators such as leukotrienes

which are believed to have central roles in aspirin-induced asthma

PATHOGENESIS

Genetic Predisposition and Environmental Triggers

Environmental Factors: Exposure to allergens (such as dust air pollution, respiratory infections (especially viral), and occupational irritants (e.g., smoke, chemical fumes) can trigger the development or exacerbation of asthma.

Airway Inflammation :- 3 main immune cell take a part in the initiation of airway inflammation

- 1. T-helper (Th) 2 Cells** produce IgE antibodies.
- 2. Eosinophils :** release toxic proteins that contribute to tissue damage and airway hyperresponsiveness (AHR).
- 3. Mast Cells:** releasing histamine and other mediators upon exposure to an allergen. These mediators contribute to bronchoconstriction, mucus production, and vascular leakage.

Morphologically

Grossly:

- Lungs are over inflated.
- There is foci of atelectasis.
- The most striking is the **occlusion** of the airways by thick, mucous plugs .

- **Microscopically**

- repeated episodes of inflammation can lead to permanent changes in the structure of the airways, a process called **airway remodeling**. This involves:
 1. Thickening of airway wall
 2. **Increased smooth muscle mass**
 3. **Mucous gland hyperplasia**

PULMONARY INFECTIONS

- Pulmonary infections in the form of pneumonia are responsible for one sixth of all deaths in the United States
- Pneumonia can be broadly defined as any infection in the lung.
- Pneumonia can result whenever the **local defense mechanisms are impaired or the systemic resistance of the host is lowered**. Factors that impair **resistance include chronic diseases, immunologic deficiencies, treatment with immunosuppressive agents, and leukopenia**.

Local pulmonary defense mechanisms may also be compromised by many factors, including:

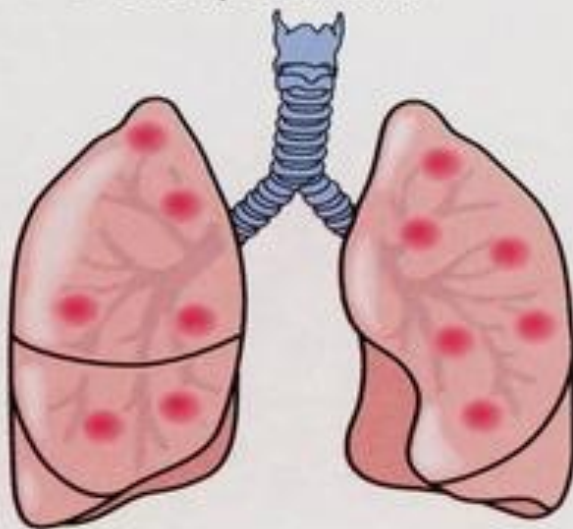
- 1. Loss or suppression of the cough reflex**, as a result of altered consciousness (e.g., coma), infant , any of which may lead to aspiration of gastric contents.
- 2. • Dysfunction of the mucociliary mechanism**, which can be caused by cigarette smoke, viral diseases
- 3. • Accumulation of secretions** in conditions such as cystic fibrosis and bronchial obstruction
- 4. • Pulmonary congestion and edema**

- Pneumonia is classified based on the etiologic agent it could be bacterial or viral
- Often, a **bacterial infection** follows an upper respiratory tract viral infection.
- Bacterial invasion of the lung parenchyma causes the alveoli to be filled with an inflammatory exudate, thus causing consolidation (“solidification”) of the pulmonary tissue

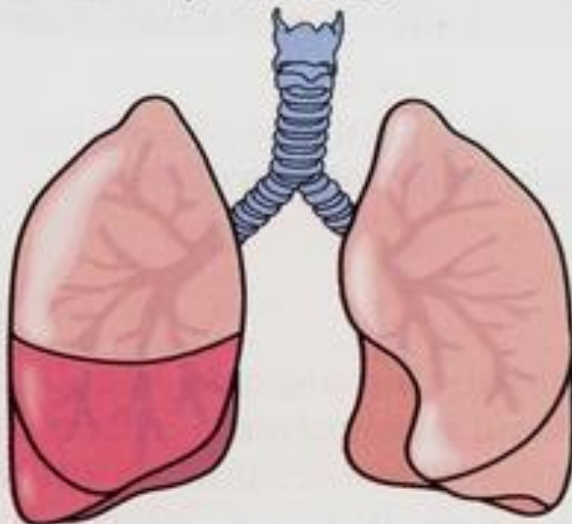
Community-Acquired Bacterial Pneumonia

- Streptococcus pneumoniae is the most common cause of community-acquired acute pneumonia.
- Morphology
- Bacterial pneumonia has two patterns of anatomic distribution:
- **bronchopneumonia and lobar pneumonia.**
- Patchy consolidation of the lung is the dominant characteristic of bronchopneumonia, while consolidation of a large portion of a lobe or of an entire lobe defines lobar pneumonia

A Bronchopneumonia

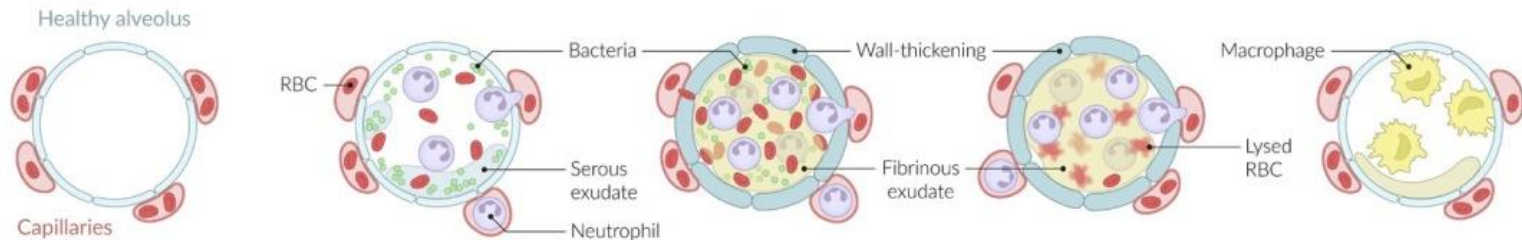
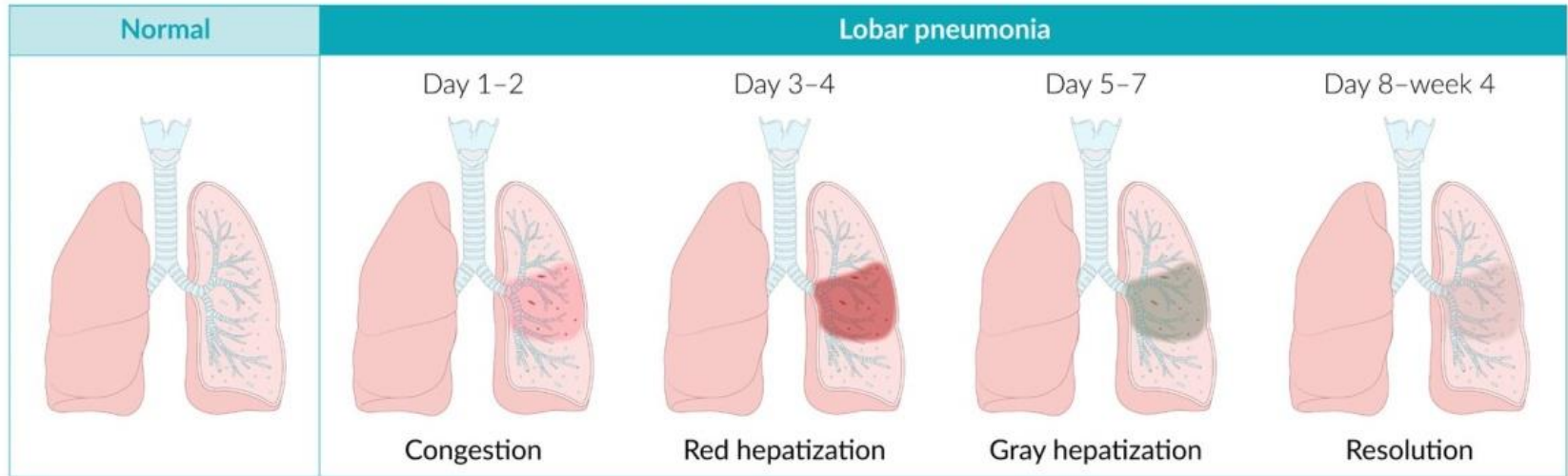


B Lobar pneumonia



- In lobar pneumonia, four stages of the inflammatory response have classically been described: congestion, red hepatization, gray hepatization, and resolution
- **Congestion:** Edema and initial inflammation.
- **Red Hepatization:** Infiltration with blood, neutrophils, and fibrin, causing consolidation.
- **Gray Hepatization:** Red blood cells are cleared, and macrophages appear, leading to a grayish color and further consolidation.
- **Resolution:** The infection clears as the alveolar exudate is removed, and normal lung tissue function returns.

Stages of lobar pneumonia

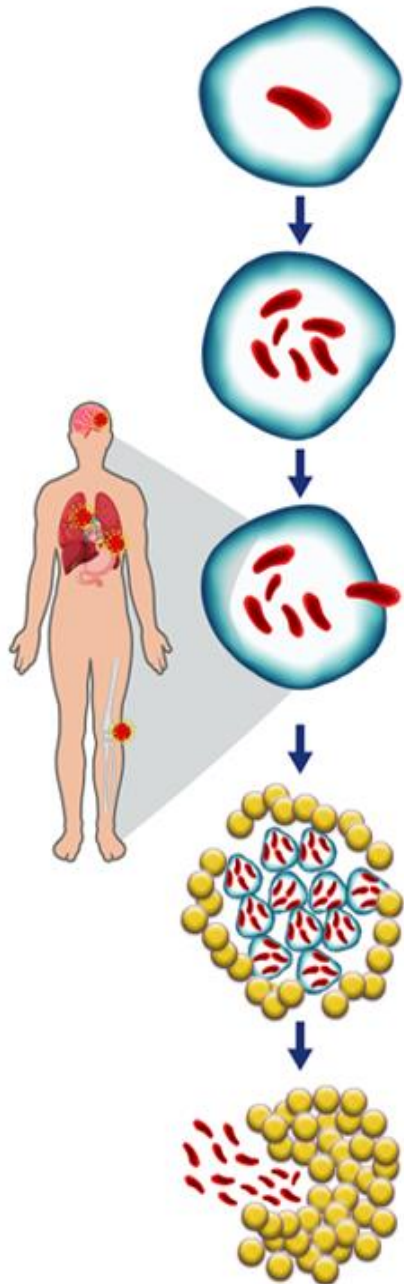


Aspiration Pneumonia

- Aspiration pneumonia occurs in markedly ill patients or those who aspirate gastric contents either while unconscious (e.g., after a stroke) or during repeated vomiting.
- These patients have abnormal gag and swallowing reflexes that predispose to aspiration.
- The resultant pneumonia is **partly chemical due to the irritating effects of gastric acid and partly bacterial (from the oral flora)**.
- This type of pneumonia is often necrotizing, results in a severe clinical course, and is a frequent cause of death.

Tuberculosis

- Tuberculosis is a chronic pulmonary and systemic disease caused most often by (Mycobacterium) M. tuberculosis
- The source of transmission is humans with active tuberculosis who release mycobacteria into the sputum.



1. Entry into macrophages:

Infection occurs when a person inhales droplet nuclei containing tubercle bacilli that reach the alveoli of the lungs. These tubercle bacilli are ingested by alveolar macrophages; the majority of these bacilli are destroyed or inhibited.

2. Replication in macrophages:

Earliest phase of primary tuberculosis (the first 3 weeks); A small number of bacilli may multiply intracellularly and are released when the macrophages die.

3. Bacteriemia and Seeding:

If alive, these bacilli may spread by way of lymphatic channels or through the bloodstream to more distant tissues and organs (for example, regional lymph nodes, apex of the lung, kidneys, brain, and bone, in which TB disease is most likely to develop).

4. Development of cell-mediated immunity:

This occurs approximately 3 weeks after exposure. T-cell mediated macrophage activation and killing of bacteria occurs in this stage.

5. Granulomatous inflammation and tissue damage:

In addition to stimulating macrophages to kill mycobacteria, the T-cell response orchestrates the formation of granulomas and caseous necrosis.

Pathogenesis

1. Entry into the lungs: Once inhaled, the bacteria enter the lungs and are engulfed by macrophages **Mycobacterium tuberculosis has evolved mechanisms to survive and replicate within macrophages.**
2. Development of cell-mediated immunity.
3. T cell–mediated macrophage activation and killing of bacteria. IFN- γ released by the CD4+ T cells of the TH1 subset is crucial in activating macrophages

the TH1 subset is crucial in activating macrophages.

Activated macrophages, in turn, release a variety of mediators , including:

1. TNF, which is responsible for recruitment of monocytes, which in turn undergo activation and differentiation into the “epithelioid histiocytes” that characterize the granulomatous response
2. Formation of nitric oxide (NO) important in killing of mycobacteria
3. anti-microbial peptides that are also toxic to mycobacterial organisms

Pathogenesis continue

- Macrophages activated by IFN- γ differentiate into the “epithelioid histiocytes” that aggregate to form granulomas;
- However, excessive or dysregulated cytokine production can contribute to tissue damage and inflammation seen in TB.
- **Granulomas help contain the infection and prevent the spread of bacteria. However, the bacteria can persist within granulomas, leading to latent TB infection.**
- **Reactivation of latent TB:** Latent TB infection occurs when the immune system is able to control the bacteria but does not completely eliminate it. Factors such as immunosuppression (e.g., HIV infection, malnutrition, or certain medications) can weaken the immune response and allow the bacteria to reactivate, leading to active TB disease.

- **Clinical Features** Clinical tuberculosis is separated into two important types that differ in pathophysiology:
 1. primary tuberculosis, which occurs with the first infection,
 2. secondary tuberculosis, which occurs in an individual who has been previously infected by *M. tuberculosis*.
- **Primary tuberculosis** is the form of disease that develops in a previously unexposed and therefore unsensitized person. With primary tuberculosis, the source of the organism is exogenous. In most people, the primary infection is contained, but in others, primary tuberculosis is progressive and more often resembles an acute bacterial pneumonia with consolidation of the lobe, hilar lymphadenopathy, and pleural effusion.

- **Secondary tuberculosis** is the pattern of disease that arises in a previously sensitized host. It may follow shortly after primary tuberculosis, but more commonly it appears months to years after the initial infection, usually when host resistance is weakened.
- **It most commonly arises from reactivation of a latent infection, but may also result from exogenous reinfection in the case of weakened host immunity.**
- **. Miliary tuberculosis: Type of tuberculosis that occurs when a large number of the bacteria travel through the bloodstream and spread throughout the body**

Morphology

- •Hallmark is necrotizing granulomatous inflammation, composed of central necrotic zone surrounded by epithelioid histiocytes with varied number of multinucleated giant cells and lymphocytes
- •Organisms are usually present within the central zone of necrosis, seen on special stains (in some cases)
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Typical TB granuloma

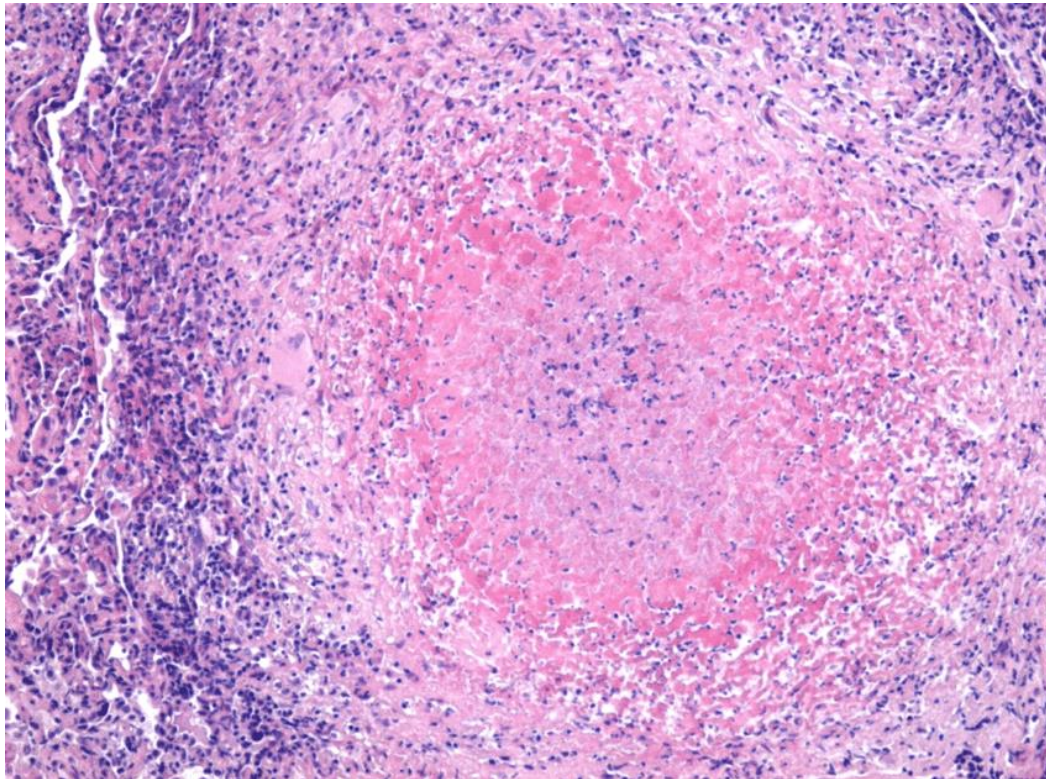
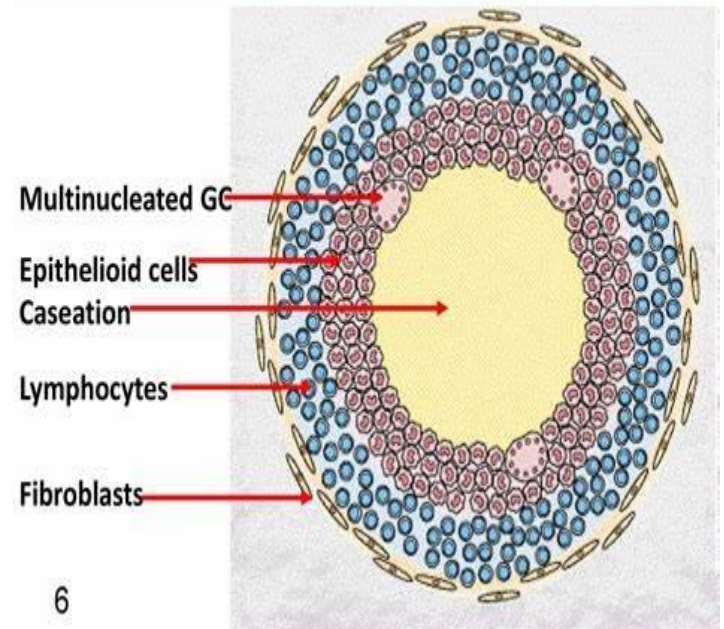


Diagram of typical TB granuloma



SUMMARY

- The respiratory system includes the **upper respiratory tract & lower respiratory tract**

Obstructive Respiratory Diseases includes Emphysema, Chronic bronchitis, Asthma & Bronchiectasis

- Emphysema is a chronic obstructive airway disease characterized by enlargement of air spaces distal to terminal bronchioles
- **Chronic bronchitis** it is characterized by (cough + sputum) production for at least **3** months in at least **2** consecutive years in the absence of any other identifiable cause.
- **Asthma** Is a chronic **relapsing** inflammatory disorder characterized by **hyper-reactive airways → bronchoconstriction** episodic
- **Pneumonia** can be broadly defined as any infection in the lung , it could be viral or bacterial.
- **Tuberculosis** is a chronic pulmonary and systemic disease caused most often by (Mycobacterium) M. tuberculosis



Any questions ?