DISEASE OF THE RESPIRATORY SYSTEM
Pathology of lung diseases

- Very important in clinical medicine
- Obstructive and Restrictive Pulmonary Diseases
- Complication of air pollution
- Primary lung infection
- Malignancy
Atelectasis (collapse)

- Incomplete expansion of the lungs or collapse of previously inflated lung substance.
- Significant atelectasis reduce oxygenation and predispose to infection.
Types of Atelectasis

1. Resorption atelectasis.
2. Compression atelectasis.
3. Microatelectasis (patchy atelectasis).
4. Contraction atelectasis.
Types of Atelectasis

1. **Resorption atelectasis.**

   - Result from complete obstruction of an airway and absorption of entrapped air. Obstruction can be caused by:
     
     a. Mucous plug (postoperatively or exudates within small bronchi seen in bronchial asthma and chronic bronchitis).
     
     b. Aspiration of foreign body.
     
     c. Neoplasm.
     
     d. Enlarged lymph node

   - The involvement of lung depend on the level of airway obstruction.
   - Lung volume is diminished and the mediastinum may shift toward the atelectatic lung.
2. **Compression atelectasis**

Results whenever the pleural cavity is partially or completely filled by fluid, blood, tumor or air, e.g.
- patient with cardiac failure
- patient with neoplastic effusion
- patient with abnormal elevation of diaphragm in peritonitis or subdiaphragmatic abscess.
Types of atelectasis

3. **Microatelectasis (patchy atelectasis).**

- Develops when there is loss of pulmonary surfactant.
- Occur in neonatal or adult respiratory distress syndrome.
Types of atelectasis

4. **Contraction atelectasis.**

- Local or generalized fibrotic changes in pleura or lung preventing full expansion of the lung.
Atelectasis

- Atelectatic lung is prone to develop superimposed infection.

- It is reversible disorder except for contraction atelectasis.
Obstructive and Restrictive Pulmonary Diseases

• Diffuse pulmonary diseases are divided into:

1] Obstructive disease: characterized by limitation of airflow owing to partial or complete obstruction at any level from tracheae to respiratory bronchioles.

2] Restrictive disease: characterized by reduced expansion of lung parenchyma with decreased total lung capacity.
Obstructive Pulmonary Diseases

• Include bronchial asthma, emphysema, chronic bronchitis, bronchieactasis, cystic fibrosis and brochiolitis.

• Pulmonary function test: limitation of maximal airflow rate during forced expiration (FEVI).
Restrictive Lung Diseases

- Reduced total lung capacity, while the expiratory flow rate is near normal.
- Occur in two general conditions:
  1. Chest wall disorder.
  2. Acute or chronic, interstitial and infiltrative diseases, e.g. ARDS, pneumoconiosis.
Chronic obstructive pulmonary diseases

**Bronchial asthma**

- Chronic relapsing inflammatory disorder characterized by hyperactive airways leading to episodic, reversible bronchoconstriction owing to increased responsiveness of the tracheobronchial free to various stimuli.
- It has been divided into two basic types:
  1. Extrinsic asthma.
  2. Intrinsic asthma.
- Clinical features: attacks of dyspnea, cough and wheezing
CLASSIFICATION OF ASTHMA

**Extrinsic Asthma**
- Initiated by type 1 hypersensitivity reaction induced by exposure to extrinsic antigen.
- Subtypes include:
  a. atopic (allergic) asthma.
  b. occupational asthma.
  c. allergic bronchopulmonary aspergillosis.
- Develop early in life

**Intrinsic Asthma**
- Initiated by diverse, non-immune mechanisms, including ingestion of aspirin, pulmonary infections, cold, inhaled irritant, stress and exercise.
- Develop later in life
Extrinsic Asthma

- Atopic (allergic) asthma is the most common form
- Other allergic manifestation
- Other family member is also affected
- Serum IgE and eosinophil are increased
- immune related, TH2 subset of CD4+ T cells
Macrophage

CD4 cell

IL-12

IFN-γ

IL-4

T_H1 cell

Defense against intracellular organisms

T_H2 cell

Allergic inflammation; induction of antibody production by B cells
Pathogenesis of Bronchial Asthma

EXAGGERATED BROCHOCONTRICTION

• Two components:
  1. Chronic airway inflammation.
  2. Bronchial hyperresponsiveness.
• The mechanisms have been best studied in atopic asthma.
Pathogenesis of Extrinsic Asthma

• Begins in childhood.
• Triggered by environmental antigens, e.g. dusts, pollen, animal dander or food.
• Positive family history of atopy.
• Preceded by allergic rhinitis, urticaria, eczema.
• Skin test with antigen result in an immediate wheel and flare reaction.
Pathogenesis of Atopic Asthma

• A classic example of type 1 IgE-mediated hypersensitivity reaction.

• In the airway – initial sensitization to antigen (allergen) with stimulation of $T_\text{H}2$ type T cells and production of cytokines (IL-4, 5, and IL-13).

• Cytokines promote:
  1. IgE production by B cell.
  2. Growth of mast cells.
  3. Growth and activation of eosinophils.
• IgE-mediated reaction to inhaled allergens elicits acute response (within minutes) and a late phase reaction (after 4-8 hours)
• Mediators induce bronchospasm, vascular permeability & mucous production.
Pathogenesis of Atopic Asthma

• Mediator produced during acute-phase response are:
  - Leukotrienes C4, D4 & E4
  - Prostaglandins D2, E2, F2
  - Histamine
  - Platelet-activating factor
  - Mast cell tryptase.

• In the late phase reaction, recruitment of leukocytes mediated by product of mast cells including:
  1. Eosinophil and neutrophil chemotactic factors
  2. IL-4 & IL-5 and induce TH2 subset of CD4+ T cells
  3. Platelet-activating factor
  4. Tumor necrosis factor.

• Other cell types are involved: activated epithelial cells, macrophages and smooth muscle (eotaxin)
Pathogenesis of Atopic Asthma

Late phase reaction:

• The arrival of leukocytes at the site of mast cell degranulation lead to:

  1. Release of more mediators to activate more mast cells
  2. Cause epithelial cell damage.

Eosinophils produce major basic protein, eosinophilic cationic protein and eosinophil peroxidase. These amplify and sustains injury without additional antigen.
Non-Atopic Asthma

- Triggered by respiratory tract infection including viruses and inhaled air pollutants e.g. sulfur dioxide, ozone.
- Positive family history is uncommon.
- Serum IgE – normal.
- No other associated allergies.
- Skin test – negative.
- Hyperirritability of bronchial tree.
- Subtypes:
  1. Drug-induced asthma.
  2. Occupational asthma.
Morphology of Asthma

- **Grossly:** Lung overdistended (over inflation), occlusion of bronchi and bronchioles by thick mucous.

- **Histologic finding:** Mucous contain Curschmann spirals, eosinophil and Charcot-Leyden crystals.
  - Thick BM.
  - Edema and inflammatory infiltrate in bronchial wall.
  - Submucosal glands increased.
  - Hypertrophy of the bronchial wall muscle.
Clinical Coarse

• Classic asthmatic attack – dyspnea, cough.
• Status asthmaticus – severe cyanosis and death.
• May progress to emphysema.
• Superimposed bacterial infection may occur.
Chronic Obstructive Pulmonary Disease (COPD)

- A group of conditions that share a major symptom: dyspnea with chronic or recurrent obstruction to airflow within the lung.
- The incidence of COPD has increased dramatically in the past few decades.
- Include chronic bronchitis, bronchieactasis, asthma and emphysema.
- Emphysema and chronic bronchitis often co-exist.
**Emphysema**

- Is characterized by permanent enlargement of the airspaces distal to the terminal bronchioles accompanied by destruction of their walls, without obvious fibrosis.
- Over inflation.
- Types of emphysema:
  1. Centriacinar > 95%
  2. Panacinar
  3. Paraseptal
  4. Irregular
Emphysema

Incidence

• Emphysema is present in approximately 50% of adults who come to autopsy.
• Pulmonary disease was considered to be responsible for death in 6.5% of these patients.
Centriacinar (centrilobular) emphysema

- Occur in heavy smoker in association with chronic bronchitis.
- The central or proximal parts of the acini are affected, while distal alveoli are spared.
- More common and severe in upper lobes (apical segments)
- The walls of the emphysematous space contain black pigment.
- Inflammation around bronchi & bronchioles.
Panacinar (panlobular) emphysema

- Acini are uniformly enlarged from the level of the respiratory bronchiole to the terminal blind alveoli.
- More commonly in the lower lung zones.
- Occurs in $\alpha_1$-antitrypsin deficiency.
Distal acinar (paraseptal) emphysema

- The proximal portion of the acinus is normal but the distal part is dominantly involved.
-Occurs adjacent to areas of fibrosis, scarring or atelectasis.
- More severe in the upper half of the lungs.
- Sometimes forming cyst-like structures with spontaneous pneumothorax.
Irregular Emphysema

• The acinus is irregularly involved, associated with scarring.
• Most common form found in autopsy.
• Asymptomatic.
Pathogenesis of Emphysema

• Is not completely understood.
• Alveolar wall destruction and airspace enlargement invokes excess protease or elastase activity unopposed by appropriate antiprotease regulation (protease-antiprotease hypothesis)

• Protease-antiprotease imbalance occur in 1% of emphysema
• $\alpha_1$-antitrypsin, normally present in serum, tissue fluids and macrophages, is a major inhibitor of proteases secreted by neutrophils during inflammation.
• Encoded by codominantly expressed genes on the proteinase inhibitor (Pi) locus on chromosome 14.
• Any stimulus that increase neutrophil or macrophages in the lung with release of protease lead to elastic tissue damage.
Pathogenesis of Emphysema

- The protease-antiprotease hypothesis explains the effect of cigarette smoking in the production of centriacinar emphysema.
  - Smokers have accumulation of neutrophils in their alveoli.
  - Smoking stimulates release of elastase.
  - Smoking enhances elastase activity in macrophages, macrophage elastase is not inhibited by $\alpha_1$-antitrypsin.
  - Tobacco smoke contains reactive oxygen species with inactivation of proteases.
Emphysema

Morphology

• The diagnosis depend largely on the macroscopic appearance of the lung.

• The lungs are pale, voluminous.

• Histologically, thinning and destruction of alveolar walls creating large airspaces.
  * Loss of elastic tissue.
  * Reduced radial traction on the small airways.
  * Alveolar capillaries is diminished.
  * Fibrosis of respiratory bronchioles.
  * Accompanying bronchitis and bronchiolitis.
Emphysema

Clinical course

- Cough and wheezing.
- Weight loss.
- Pulmonary function tests reveal reduced FEV1.

Death from emphysema is related to:

1. Pulmonary failure with respiratory acidosis, hypoxia and coma.
2. Right-sided heart failure.
Other types of emphysema

- Compensatory emphysema.
- Senile emphysema.
- Obstructive overinflation.
- Bullous emphysema.
- Mediastinal (interstitial) emphysema.
Chronic Bronchitis

• Common among cigarette smokers and urban dwellers.
• The diagnosis of chronic bronchitis is made on clinical grounds.
• Persistent productive cough for at least 3 consecutive months in at least 2 consecutive years.
• Can occur in several forms:
  1. Simple chronic bronchitis.
  2. Chronic mucopurulent bronchitis.
  3. Chronic asthmatic bronchitis.
  4. Chronic obstructive bronchitis.
Chronic bronchitis

Pathogenesis
• Hypersecretion of mucus that starts in the large airways.
• Causative factor are cigarette smoking and pollutants.

Morphology
• Enlargement of the mucus-secreting glands, increased number of goblet cells, loss of ciliated epithelial cells, squamous metaplasia, dysplastic changes and bronchogenic carcinoma.
• Inflammation, fibrosis and resultant narrowing of bronchioles.
• Coexistent emphysema.

Clinical Course
• Prominent cough and the production of sputum.
• COPD with hypercapnia, hypoxemia and cyanosis.
• Cardiac failure.
# Emphysema and Chronic Bronchitis

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Predominant Bronchitis</th>
<th>Predominant Emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>“Blue bloaters”</td>
<td>“Pink Puffers”</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>40-45</td>
<td>50-75</td>
</tr>
<tr>
<td>Cough</td>
<td>Mild, late</td>
<td>Severe, early</td>
</tr>
<tr>
<td>Infection</td>
<td>Early, copious sputum</td>
<td>Late, scanty sputum</td>
</tr>
<tr>
<td>Respiratory Insufficiency</td>
<td>Common</td>
<td>Occasional</td>
</tr>
<tr>
<td>Cor pulmonale</td>
<td>Common</td>
<td>Terminal</td>
</tr>
<tr>
<td>Airway resistance</td>
<td>Increased</td>
<td>Rare, terminal</td>
</tr>
<tr>
<td>Elastic recoil</td>
<td>Normal</td>
<td>Normal or slightly increased</td>
</tr>
<tr>
<td>Chest radiography</td>
<td>Prominent vessels, large heart</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperinflation, small heart</td>
</tr>
</tbody>
</table>
Bronchiolar and bronchial injury

 Bronchospasm
 Hypersecretion of mucus

 Reversible obstruction in bronchioles and small bronchi

 Continued and repeated injury (smoking) Continued and repeated infection

 Chronic bronchitis

 Destruction of alveolar walls

 Occasional respiratory infection

 Emphysema

 Continued and repeated injury (smoking) Continued and repeated infection

 Chronic bronchitis and emphysema
Bronchiactasis

- Chronic necrotizing infection of the bronchi and bronchioles leading to or associated with abnormal dilatation of these airways.
- Bronchial dilatation should be permanent.
Conditions associated with Bronchiactasis

1. **Bronchial obstruction**
   - **Localized:**
     - tumor, foreign bodies or mucous impaction
   - **Generalized:**
     - bronchial asthma
     - chronic bronchitis

2. **Congenital or hereditary conditions:**
   - Congenital bronchiactasis
   - Cystic fibrosis.
   - Intralobar sequestration of the lung.
   - Immunodeficiency status.
   - Immotile cilia and kartagner syndrome.

3. **Necrotizing pneumonia.**
   Caused by TB, staphylococci or mixed infection.
Bronchiactasis

Etiology and pathogenesis

• Obstruction and infection.
  Bronchial obstruction (atelectasis of airway distal to obstruction) – bronchial wall inflammation.

• These changes become irreversible:
  1. If obstruction persist.
  2. If there is added infection.
Kartagener Syndrome

• Inherited as autosomal recessive trait.
• Patient develop bronchiactasis, sinusitis and situs inversus.
• Defect in ciliary motility due to absent or irregular dynein arms.
• Lack of ciliary activity interferes with bronchial clearance.
• Males have infertility.
Morphology of Bronchiactasis

- Usually affects lower lobes bilaterally (vertical airways).
- Dilated airways up to four times of normal, reaching the pleura.
- Tube-like enlargement (cylindroid) or fusiform (saccular).
- Acute and chronic inflammation, extensive ulceration of lining epithelium with fibrosis.
Lung abscess