Diffuse lung diseases

- Based on pulmonary function tests, chronic noninfectious diffuse pulmonary diseases can be classified in one of two categories:

1. **Obstructive diseases** (or airway diseases), characterized by an increase in resistance to airflow due to partial or complete obstruction at any level, from the trachea and larger bronchi to the terminal and respiratory bronchioles.
2. **Restrictive diseases,** characterized by reduced expansion of lung parenchyma and decreased total lung capacity.

Pulmonary Function Tests measures:

- **Tidal volume (VT):** This is the amount of air inhaled or exhaled during normal breathing.
- **Residual volume:** This is the amount of air left in the lungs after exhaling as much as you can.
- **Total lung capacity:** This is the total volume of the lungs when filled with as much air as possible.
- **Forced vital capacity (FVC):** This is the amount of air exhaled forcefully and quickly after inhaling as much as you can.
- **Forced expiratory volume (FEV):** This is the amount of air expired during the first, second, and third seconds of the FVC test.
- Normal FEV1/FVC ratio **is 0.8**

OBSTRUCTIVE LUNG (AIRWAY) DISEASES

Under this heading come four entities

1. Asthma
2. Emphysema
3. Chronic bronchitis
4. Bronchiectasis

- The hallmark is a decreased forced expiratory volume at 1 second (FEV_1), Total lung capacity and forced vital capacity are normal. The ratio of FEV_1 \ FVC is characteristically decreased. (Normal FEV1/FVC ratio is 0.8).
- Emphysema and chronic bronchitis are often clinically grouped together under the term chronic obstructive pulmonary disease (COPD), which is one of the leading causes of death.
- The irreversibility of airflow obstruction of COPD distinguishes it from asthma (reversible obstruction).

ASTHMA

- Asthma is a chronic inflammatory disorder of the airways that **is characterized by recurrent reversible episodes of bronchospasm** resulting from an exaggerated bronchoconstrictor response to various stimuli.

Clinical features:

- Wheezing (a soft whistling sound during expiration), dyspnea, chest tightness, and cough**.** Between the attacks, patients may be virtually asymptomatic.

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.
- Initiated by type I (immediate) (IgE–mediated hypersensitivity reaction).
- 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, 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.

- **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: viral infections (e.g., rhinovirus, parainfluenza virus) and inhaled air pollutants, exercise (during or after physical activity), cold dry air and stress.

- **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 that these drugs inhibit cyclooxygenase without affecting lipoxygenase activity and tip the balance of arachidonic acid metabolism toward bronchoconstrictor leukotrienes

- **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:

- Major factors contributing to the development of asthma include;

- Genetic predisposition to type I hypersensitivity (atopy),
- Acute and chronic airway inflammation,
- Bronchial hyper responsiveness to a variety of stimuli.
- **In the classic atopic asthma;**
- Inhaled allergens (antigen) is associated with excessive type 2 helper T (TH2) cell activation, Cytokines produced by TH2 are **IL-4**, **IL-5** and **IL-13,** favoring IgE production and eosinophil recruitment.
- IgE coats submucosal mast cells, which on reexposure to allergen release their granule contents and secrete cytokines and other mediators that directly and via neuronal reflexes induce bronchospasm, increased vascular permeability, mucus production, and recruitment of leukocytes **(The early phase reaction)**
- Bronchospasm is triggered by mediators released from mast cells, including; hist amine, prostaglandin D2, and leukotrienes LTC4, D4, and E4.
- **The late-phase reaction:**
- Inflammatory in nature. Leukocytes recruited to the site of reaction release additional mediators. Characterized by persistent bronchospasm and edema, leukocyte infiltration, and epithelial damage and loss. Several factors released from eosinophils (e.g., major basic protein, eosinophil cationic protein) also cause damage to the epithelium.
- **Repeated bouts of inflammation** lead to structural changes in the bronchial wall (hypertrophy of bronchial smooth muscle and mucus glands and increased vascularity and deposition of subepithelial collagen), that are collectively referred to as ***airway remodeling.***

Morphology:

Gross features:

- In fatal cases, the lungs are over distended because of overinflation.
- The most striking macroscopic finding is: Occlusion of bronchi and bronchioles by thick, mucus plugs contain whorls of shed epithelium **(Curschmann spirals)**, eosinophils and **Charcot-Leyden crystals** (crystalloids made up of the eosinophil protein galectin-10) also are present.

Microscopically:

- 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

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.

EMPHYSEMA

- Emphysema is defined as "**abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls without obvious fibrosis**".

Classification of Emphysema is according to its anatomic distribution within the lobule; the acinus is the structure distal to terminal bronchioles, and a cluster of 3 to 5 acini is called a lobule. There are four major types of emphysema:
1. Centriacinar 2. Panacinar 3. Distal acinar 4. Irregular
Only the first two cause clinically significant airway obstruction, with centriacinar emphysema being about 20 times more common than panacinar disease.

1- **Centriacinar (Centrilobular):** the central or proximal parts of the acini i.e. the respiratory bronchioles are affected, while distal alveoli are spared. The lesions are more common and severe in the upper lobes. This type is most commonly associated with cigarette smoking.
2- **Panacinar (Panlobular) Emphysema:** the acini are uniformly enlarged from the level of the respiratory bronchiole to the terminal blind alveoli. It tends to occur more commonly in the lower lobes and is the type that occurs in α1-antitrypsin deficiency.
3- **Distal Acinar (Paraseptal) Emphysema:** the distal part of the acinus is primarily involved; Typically, near the pleura and adjacent to fibrosis or scars. Characteristically, there are multiple, contiguous, enlarged airspaces up to 2 cm or more in diameter, sometimes forming cystic structures referred to as bullae. This type of emphysema probably underlies many of the cases of spontaneous pneumothorax in young adults due to bullae rupture.
4- **Irregular Emphysema:** the acinus is irregularly involved; it is associated with scarring.

Pathogenesis:
The current theory favors emphysema arising as a consequence of two coexisting imbalances

1. **Proteases—antiproteases imbalance.**
2. **Oxidant------Antioxidant imbalance.**

- Proteases: are enzymes which digest the tissue.
- Normally proteases secreted by neutrophils and macrophages
- Most important one is elastase.
- Anti-proteases: are the counteracting enzymes that stop the action of digestion, important one is antielastase (α -1 anti- trypsin -trypsin), which is normally present in serum, tissue fluids, & macrophages.
- So the development of emphysema occurs:

1. When there is increse in elastase activity as in smoking.
2. When there is decrease in 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:

- Recruiting and activating inflammatory cells (i.e., macrophages and neutrophils) via direct chemoattractive effects of nicotine.
- Inducing neutrophil release of cellular proteases (i.e., elastase)
- Inactivating a1-antitrypsin (via tobacco smoke oxidants or neutrophil derived free radicals)
- Reducing antioxidant (e.g., superoxide dismutase, glutathione) levels via the presence of abundant reactive oxygen species

Gross features

*Panacinar emphysema produces pale, voluminous lungs that obscure the heart at autopsy.

*In centriacinar emphysema the lungs are less voluminous and deeper pink. Generally, in this type the upper two-thirds of the lungs are more severely affected.

Microscopic features

- There is thinning and destruction of alveolar walls**.**
- With advanced disease, adjacent alveoli coalesce, creating large airspaces.
- The capillaries within alveolar walls are reduced in number due to stretching.

Course & prognosis

- Symptoms (e.g., dyspnea, wheezing, cough, wt. loss)
- Patients over ventilate to compensate for loss of parynchyma and well oxygenated at rest so called **pink puffers**
- The eventual outcome of emphysema is the gradual development of secondary pulmonary hypertension.
- Death from emphysema is related to:
- Either respiratory failure or right-sided heart failure (cor- pulmonale).

CHRONIC BRONCHITIS

- Chronic bronchitis is common among cigarette smokers.
- The diagnosis of chronic bronchitis is **clinical**; it is defined **as "a persistent productive cough for at least 3 consecutive months in at least 2 consecutive years." in the absence of any other identifiable cause".**

Pathogenesis

1. Chronic irritation of the airways by cigarette smoking or other air pollutants, such as sulfur dioxide and nitrogen dioxide is the dominant pathogenic mechanism.

- Irritants cause:

I. Hypersecretion of mucus due to hypertrophy of mucous glands & increase in mucin-secreting goblet cells.

- Excess mucin production that contributes to airway obstruction.

II. Inflammation marked by the infiltration of inflammatory cells neutrophils, Macrophages &lymphocytes (In contrast with asthma, eosinophils are not seen in chronic bronchitis).

- Continuous inflammation cause tissue destruction and fibrosis can also lead to chronic airway obstruction

2. Microbial infection

- often is present but has a secondary role by maintaining inflammation and exacerbating symptoms.

Morphological features

Gross features

- The mucosal lining of the larger airways is usually hyperemic and edematous. It is often covered by a layer of mucus or mucopurulent secretions.
- The smaller bronchi and bronchioles may also be filled with similar secretions.

Microscopic features

- The diagnostic feature of chronic bronchitis in the trachea and larger bronchi is;
  - Enlargement of the mucus-secreting glands. This increase can be assessed by the ratio of the thickness of the mucous gland layer to the thickness of the wall between the epithelium and the cartilage (Reid index).
- The Reid index (normally 0.4) is increased in chronic bronchitis.
  - Variable numbers of inflammatory cells, lymphocytes and macrophages but sometimes also admixed neutrophils, are frequently seen in the bronchial mucosa.
- The bronchial epithelium may show squamous metaplasia and dysplasia due to the irritating and mutagenic effects of substances in tobacco smoke.
- Chronic bronchiolitis (small airway disease), characterized by narrowing of bronchioles caused by goblet cell metaplasia, mucus plugging, inflammation, and fibrosis.

Clinical features:

- The cardinal symptom of chronic bronchitis is a **persistent productive cough** and dyspnea on exertion develops.
- In classic cases, patients are hypoxic, cyanotic and hypercapnic so called blue bloaters
- With progression, chronic bronchitis is complicated by pulmonary hypertension and corpulmonale
- Recurrent infections and respiratory failure are constant threats.

BRONCHIECTASIS

- Define as "**the permanent dilation of bronchi and bronchioles caused by destruction of the musclulo- elastic supporting tissues, resulting from or associated with chronic necrotizing infections.**"

Etiology and Pathogenesis.

Two interconnected processes contribute to bronchiectasis: **obstruction and chronic infection.**

1- Bronchial **obstruction**, due to tumor, foreign bodies, and occasionally mucus impaction; providing a favorable substrate for superimposed infection, The resultant inflammatory damage to the bronchial wall

2- Persistent necrotizing infection in the bronchi or bronchioles; may lead to poor clearance of secretions, obstruction, and inflammation

- Congenital or hereditary conditions: that predispose to chronic infections, like :
- ***In cystic fibrosis****:* viscid mucus lead to obstruction & pulmonary infection which end with bronchiectasis.
- ***In immunodeficiency states*** **e.g. immunoglobulin deficiencies result in repeated bacterial infections and bronchiectasis.**
- ***Kartagener syndrome***, an autosomal recessive disorder, develop impair mucociliary clearance in the airways & reduce mobility of spermatozoa leading to persistent infections and bronchiectasis, and sterility in male

Clinical features:

- Severe, persistent **cough;**
- Expectoration of **copious amounts of foul-smelling, mucopurulent sputum.**
- Sometimes bloody sputum; dyspnea and orthopnea in severe cases

Morphology:

Gross features:

- The airways are dilated, up to 4 times their usual diameter.
- On the cut surface of the lung, the transected dilated bronchi appear as cysts filled with mucopurulent secretions

Microscopic features

- Vary with the activity and chronicity of the disease

***Active case**:

1- There is intense **acute and chronic inflammatory exudate** within the walls of the bronchi and bronchioles.

2- **Desquamation** of the lining epithelium and extensive areas of **necrotizing ulceration.** There may be **squamous metaplasia** of the remaining epithelium.

***In chronic cases:**

There is **fibrosis** of the bronchial and bronchiolar walls and peribronchiolar areas.

Complications:

1- 1- In some instances, the necrotizing inflammation destroys the bronchial or bronchiolar walls and forms a **lung abscess**.

2- In cases of severe, widespread bronchiectasis **hypoxemia, hypercapnia, pulmonary hypertension,** and (rarely) **cor pulmonale occur**.

3- **Brain abscesses** and **reactive amyloidosis.**