Common Bronchial and Pulmonary Diseases: lung pathology

• A common approach in the study of lung pathology, is to organize lung diseases into those affecting (1) the airways, (2) the interstitium, and (3) the pulmonary vascular system.

• This division into discrete compartments is deceptively neat. In reality, disease in one compartment is generally accompanied by alterations of morphology and function in another.
OBSTRUCTIVE VERSUS RESTRICTIVE PULMONARY DISEASES

• Diffuse pulmonary diseases can be classified in two categories: (1) obstructive disease (airway disease), characterized by limitation of airflow usually resulting from an increase in resistance caused by partial or complete obstruction at any level, -time.

• and (2) restrictive disease, characterized by reduced expansion of lung parenchyma accompanied by decreased total lung capacity.
LUNG VOLUMES

- Inspiratory Reserve Volume: 3,100 mL (1,900 mL)
- Tidal Volume: 500 mL
- Expiratory Reserve Volume: 1,200 mL (700 mL)
- Residual Volume: 1,200 mL (1,100 mL)

LUNG CAPACITIES

- Inspiratory Capacity: 3,600 mL (2,400 mL)
- VITAL Capacity: 4,800 mL (3,100 mL)
- Total Lung Capacity: 6,000 mL (4,200 mL)

Inhalation:

Exhalation:

End of record:

Start of record:

Functional Residual Capacity: 2,400 mL (1,800 mL)
Remember Physiology

- TLC = 6.0 L = IRV + Vt + ERV + RV
- Forced vital capacity (FVC) = 4.8 L
- The amount of air that can be maximally forced out of the lungs after a maximal inspiration. Emphasis on speed.
First: Obstructive Disorders: Airway Diseases

- The major diffuse obstructive disorders are emphysema, chronic bronchitis, bronchiectasis, and asthma.
- In patients with these diseases, total lung capacity and forced vital capacity (FVC) are either normal or increased.
- Hallmark is a decreased expiratory flow rate, usually measured by forced expiratory volume at 1 second (FEV₁). Thus, the ratio of FEV₁ to FVC is characteristically decreased.
- Expiratory obstruction may result either from anatomic airway narrowing, classically observed in asthma, or from loss of elastic recoil, characteristic of emphysema.
OBSTRUCTIVE PULMONARY DISEASE

1. Emphysema,
2. Chronic Bronchitis,
3. Asthma, And
4. Chronic bronchiectasis

Given the propensity of emphysema and chronic bronchitis to coexist, are often clinically grouped together under the name of chronic obstructive pulmonary disease (COPD).
1-Emphysema

• Is characterized by *abnormal permanent enlargement of the airspaces* distal to the terminal bronchioles, accompanied by *destruction of their walls* without obvious fibrosis.
Pathogenesis

• emphysema arise as a consequence of *two critical imbalances*: The two key pathogenic mechanisms

1. the protease-antiprotease imbalance
2. and oxidant-antioxidant imbalance

Such imbalances almost always **coexist**, and in fact, their effects are additive in producing the end result of tissue damage.
Protease-antiprotease Imbalance Hypothesis

- is based on the observation that patients with a genetic deficiency of the antiprotease $\alpha_1$-antitrypsin have a markedly enhanced tendency to develop pulmonary emphysema, which is compounded by smoking.
- Thus, emphysema is seen to result from the destructive effect of high protease activity in subjects with low antiprotease activity.
Oxidant-antioxidant Imbalance

• Smoking also has a decisive role in perpetuating the oxidant-antioxidant imbalance.

• Normally, the lung contains a healthy antioxidants (superoxide dismutase, glutathione) that keep oxidative damage to a minimum.

• Tobacco smoke contains abundant reactive oxygen species (free radicals), which deplete these antioxidant mechanisms, thereby inciting tissue damage
TOBACCO

Nicotine

Reactive oxygen species ("free radicals")

Inactivation of antiproteases ("functional" α₁AT deficiency)

Neutrophil

Neutrophil elastase

Congenital α₁AT deficiency

Tissue damage

Capillary

IL-8 LTB₄ TNF

Alveolar macrophage

Macrophage elastase and metalloproteinases

EMPHYSEMA

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Anatomic distribution of pure chronic bronchitis and pure emphysema. In chronic bronchitis the small-airway disease (chronic bronchiolitis) results in airflow obstruction, while the large-airway disease is primarily responsible for the mucus hypersecretion.
2-Chronic bronchitis

- Chronic bronchitis is common among cigarette smokers and urban dwellers in smog-ridden cities.
- It is defined as a persistent productive cough for at least 3 consecutive months in at least 2 consecutive years.
Chronic Bronchitis

• It is characterized by inflammation of the bronchial tubes (or bronchi), the air passages that extend from the trachea into the small airways and alveoli.

• Cigarette smoking is the most important underlying risk factor; air pollutants also contribute.

• Chronic obstructive component largely results from small airway disease (chronic bronchiolitis) and coexistent emphysema.

• Histology demonstrates enlargement of mucus-secreting glands, goblet cell metaplasia, and bronchiolar wall fibrosis.
3-Asthma

- Asthma is a chronic inflammatory disorder of the airways that causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and/or early in the morning.
• Because asthma is a heterogeneous disease triggered by a variety of provocative agents, there is no universally accepted classification scheme.

• About 70% of cases are said to be "extrinsic" or "atopic" and are due to IgE and type 2 helper T ($T_{H2}$) cells-mediated immune responses to environmental antigens. Antigen can then enter the mucosa to activate mucosal mast cells and eosinophils, which in turn release additional mediators. Collectively, either directly or through neuronal reflexes, the mediators induce bronchospasm, increased vascular permeability, and mucus production, besides recruiting additional mediator-releasing cells from the blood.

• In the remaining 30% of patients, asthma is said to be "intrinsic" or "non-atopic" and is triggered by non-immune stimuli such as aspirin; pulmonary infections, especially those caused by viruses; cold; psychological stress; exercise; and inhaled irritants.
Airway Remodeling

• atopic asthma is characterized by structural changes in the bronchial wall, referred to as "airway remodeling." These changes include hypertrophy of bronchial smooth muscle and deposition of subepithelial collagen.
Airway remodeling" include:

1. Thickening of the basement membrane of the bronchial epithelium.
2. Edema and an inflammatory infiltrate in the bronchial walls, with a prominence of eosinophils and mast cells.
3. An increase in the size of the submucosal glands.
4. Hypertrophy of the bronchial muscle walls.
• direct stimulation by (parasympathetic) provokes bronchoconstriction reflex.
• This occurs within minutes after stimulation and is therefore called the acute, or immediate, response, which consists of bronchoconstriction, edema (due to increased vascular permeability), and mucus secretion.
2- Non-Atopic Asthma

• *Viral infections of the respiratory tract* (most common) and *inhaled air pollutants* such as sulfur dioxide, ozone, and nitrogen dioxide agents increase airway hyper-reactivity in both normal and asthmatic subjects.

• In the asthmatic subjects the bronchial response, manifested as spasm, is much more severe and sustained.
3- Drug-Induced Asthma: Several pharmacologic agents provoke asthma, *aspirin* being the most striking example.

4- Occupational Asthma: This form of asthma is stimulated by fumes (plastics), organic and chemical dusts (wood, cotton, platinum), gases, and other chemicals. Asthma attacks usually develop after repeated exposure to the inciting antigen(s).
Bronchiectasis

- Bronchiectasis is the permanent dilation of bronchi and bronchioles caused by destruction of the muscle and elastic supporting tissue, resulting from or associated with chronic necrotizing infections.
Bronchiectasis

• symptom: cough and expectoration of copious amounts of purulent (containing pus) sputum.
• Clubbing of the fingers may develop.
• In cases of severe, widespread bronchiectasis, significant obstructive ventilatory defects develop, with hypoxemia, hypercapnia, pulmonary hypertension, and (rarely) cor pulmonale.
Bronchiectasis. Cross-section of lung demonstrating dilated bronchi extending almost to the pleura.
Second: Restrictive Diseases

- FVC is reduced
- the expiratory flow rate is normal or reduced proportionately.
- Hence, the ratio of $FEV_1$ to FVC is near normal.
- The restrictive defect occurs in two general conditions:
  1. Chest wall disorders in the presence of normal lungs (e.g., severe obesity, diseases of the pleura, and neuromuscular disorders, (that affect the respiratory muscles).
  2. Acute or chronic interstitial lung diseases.

The classic acute restrictive disease is ARDS.

Chronic restrictive diseases include the pneumoconioses, interstitial fibrosis, and sarcoidosis.
**Interstitial lung diseases (ILD)**

- ILD is a group of lung diseases affecting the interstitium.
- The interstitium is the tissue between the air sacs of the lungs - the tissue is affected by fibrosis (scarring).
- The pulmonary interstitium is composed of the basement membrane of the endothelial and epithelial cells (fused in the thinnest portions), collagen fibers, elastic tissue, fibroblasts, a few mast cells, and occasional mononuclear cells.
ILD

• The symptoms and course of these diseases may vary from person to person, but the common link between the many forms of ILD is that they all begin with an inflammation.

• bronchiolitis - inflammation that involves the bronchioles (small airways)

• alveolitis - inflammation that involves the alveoli (air sacs)

• vasculitis - inflammation that involves the small blood vessels (capillaries)
Diffuse Interstitial (Restrictive, Infiltrative) Lung Diseases

1- Fibrosing Diseases
   a- Idiopathic Pulmonary Fibrosis
   b- Nonspecific Interstitial Pneumonia
   c- Cryptogenic Organizing Pneumonia
   d- Pulmonary Involvement in Collagen Vascular Diseases
   e- Pneumoconioses
   f- Drug- and Radiation-Induced Pulmonary Diseases

2- Granulomatous Diseases
   Sarcoidosis
   Hypersensitivity Pneumonitis

3- Pulmonary Eosinophilia

4- Smoking-Related Interstitial Diseases
ILD

• The hallmark of these disorders is reduced compliance (i.e., more pressure is required to expand the lungs because they are stiff), which in turn necessitates increased effort of breathing (dyspnea).

• Furthermore, damage to the alveolar epithelium and interstitial vasculature produces hypoxia.
ILD may be classified according to the cause as follows:

- Inhaled substances
  1. Inorganic inhalation of silica as in pneumoconiosis
  2. Organic Hypersensitivity as in alveolitis
- Drug-induced
  - Statins
- Autoimmune diseases
  - Rheumatoid arthritis
- Infection
  - Tuberculosis: is an infectious disease caused by the bacterium Mycobacterium tuberculosis
- Idiopathic
  - Sarcoidosis
  - Idiopathict pulmonary fibrosis
- Malignancy
Regardless of the type of interstitial disease or specific cause, the earliest common manifestation of most of the interstitial diseases is **alveolitis**, that is, accumulation of inflammatory and immune effector cells within the alveolar walls and spaces.

If the injury is mild and self-limited, resolution with restoration of normal architecture follows. However, with persistence of the injurious agent, *cellular interactions involving lymphocytes, macrophages, and neutrophils lead to parenchymal injury, proliferation of fibroblasts, and progressive interstitial fibrosis.*
• 1-Idiopathic pulmonary fibrosis (interstitial pneumonia) is one form of "interstitial lung disease".

• It is characterized histologically by diffuse interstitial fibrosis, which in advanced cases results in severe hypoxemia and cyanosis.

• With progression, ILD individuals can develop respiratory failure, often in association with pulmonary hypertension and cor pulmonale.
2-Pneumoconiooses

- **Pneumoconiosis** is a group of chronic fibrosing diseases of the lung resulting from exposure to organic and inorganic particulates, most commonly mineral dust and from agriculture.
- The dust particles remain in the lung where they can cause inflammation or fibrosis (scarring).
- If the inflammation or fibrosis is severe enough or involves a large enough area of lung tissue, breathing will be affected. Dry cough and shortness of breath are common symptoms of fibrosis.
- The effects of damage from inhaled mineral dusts may not show up for many years, so patients may not develop symptoms until long after they are no longer exposed to these dusts. The most common causes of pneumoconiosis are inhalation of asbestos, silica (sand or rock dust) or coal dust.

Pneumo= air  /Konis = dust
Silica, Coal, Asbestos

Macrophages
Silicosis / CWP
- nodules

Mitochondria damage
- ROS production
- DNA damage

Epithelial Cells

Apoptosis

Treg: TGF-β, PDGF, etc.
Teff: IL-1β, IL-4, IFNγ, etc.
Other: TNFα, Gremlin

Myofibroblast

Collagen

Fibrotic Response
3-sarcoidosis

- Sarcoidosis is a disease in which abnormal collections of chronic inflammatory cells (granulomas) form as nodules in multiple organs.
- Granulomas most often appear in the lungs or the lymph nodes, but virtually any organ can be affected.
- When it affects the lungs there may be wheezing, cough, shortness of breath, or chest pain.
Pulmonary Infections

Community-Acquired Acute Pneumonias
Community-Acquired Atypical Pneumonias
Influenza Infections
Severe Acute Respiratory Syndrome (SARS)

Nosocomial Pneumonia
Aspiration Pneumonia
Lung Abscess
Chronic Pneumonia

- **Tuberculosis**
  Nontuberculous Mycobacterial Disease
  Histoplasmosis, Coccidioidomycosis, and Blastomycosis

Pneumonia in the Immunocompromised Host
Cytomegalovirus Infections
*Pneumocystis* Pneumonia

Opportunistic Fungal Infection
Candidiasis
Cryptococcosis
The Opportunistic Molds

Pulmonary Disease in HIV Infection
4-Pulmonary Infections: Tuberculosis

- **MTB**, or **TB** (short for *tubercle bacillus*) is a common and in many cases lethal infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis*.

- Tuberculosis usually attacks the lungs but can also affect other parts of the body. It is spread through the air when people who have an active MTB infection cough, sneeze, or otherwise transmit their saliva through the air.

- Most infections in humans result in an asymptomatic, latent infection, and about one in ten latent infections eventually progresses to active disease, which, if left untreated, kills more than 50% of those infected.
• The histopathologic hallmark of host reaction to tuberculosis in immunocompetent persons is the presence of granulomas, usually with central caseating necrosis.

• Secondary (reactivation) tuberculosis arises in previously exposed persons when host immune defenses are compromised.
• Symptoms include chest pain, coughing up blood, and a productive, prolonged cough for more than three weeks. Systemic symptoms include fever, chills, night sweats, appetite loss, weight loss, pallor, and fatigue.
Symptoms of Tuberculosis

(Established) pulmonary tuberculosis
- Poor appetite
- Miliary tuberculosis
- Productive cough

Primary pulmonary tuberculosis
- Night sweats
- Weakness
- Return of dormant tuberculosis
- Fever
- Cough with increasing mucus
- Coughing up blood

Structural abnormalities
- Dry cough
- Weight loss

Tuberculous pleuritis
- Gastrointestinal symptoms
- Chest pain

Extrapulmonary tuberculosis
- Common sites:
  - Meninges
  - Lymph nodes
  - Bone and joint sites
  - Genitourinary tract
5-Pulmonary Infections/ Pneumonia

• **Pneumonia** is an inflammatory condition of the lung affecting primarily the microscopic air sacs known as alveoli.

• Typical signs and symptoms include a varying severity and combination of productive or dry cough, chest pain, fever, and trouble breathing, depending on the underlying cause.

• Pneumonia is usually caused by infection with viruses or bacteria (*Streptococcus pneumoniae*) and less commonly by other microorganisms, certain medications and conditions such as autoimmune diseases.
6-Acute Respiratory Distress Syndrome

- ARDS is a clinical syndrome of progressive respiratory insufficiency caused by diffuse alveolar damage in the setting of sepsis, severe trauma, and diffuse pulmonary infections.
- There is an imbalance of pro- and anti-inflammatory mediators causing acute inflammatory injury to the alveolar epithelium and capillary endothelium.
- Neutrophils and their products have a crucial role in the pathogenesis of ARDS.
- Alveolar edema, epithelial necrosis, and accumulation of neutrophils.
• The alveolar capillary membrane is formed by two separate barriers: the microvascular endothelium and the alveolar epithelium.

• In ARDS the integrity of this barrier is compromised by either endothelial or epithelial injury, or, more commonly, both.

• The acute consequences of damage to the alveolar capillary membrane include: increased vascular permeability and alveolar flooding, loss of diffusion capacity, and widespread surfactant abnormalities caused by damage to type II pneumocytes.
Acute Lung Injury and ARDS
Clinically, acute lung injury manifests as

- (1) dyspnea,
- (2) There is usually rapid onset of life-threatening respiratory insufficiency, cyanosis, and *severe arterial hypoxemia that may progress to multisystem organ failure.*
- (3) pulmonary (edema)
Carcinoma of Bronchus