Anatomy and Histology

- The major function of the lung is to replenish oxygen and excrete carbon dioxide from blood. The anatomy and the intricate histology of the lung a uniquely designed to facilitate this function.
- Right and left lungs are invested in visceral pleura and weigh approximately 300-450 gm.
- Developmentally, the respiratory system is an outgrowth from the ventral wall of the foregut. The midline trachea develops two lateral outpouchings, the lung buds. The right lung bud eventually divides into three main bronchi, and the left into two main bronchi, thus giving rise to three lobes on the right and two on the left. The lingula represents the anterior inferior division of the upper lobe and is a counter part of the middle lobe.
- The right main bronchus deviates only 20-30 degrees off the main bronchus as against the left that deviates 40-60 degrees off the main. In an upright position, this predisposes to aspiration into the right main bronchus more often.
- Connective tissue, smooth muscle and cartilage provide the basic structural framework. The main bronchi branch dichotomously, giving rise to progressively smaller airways, termed bronchioles, which are distinguished from bronchi by the lack of cartilage and sub-mucosal glands within their walls. With progressive branching of bronchi, the cartilaginous mass within the airway decreases while the smooth muscle progressively increases.
- The trachea and the bronchi are lined by pseudostratified ciliated columnar epithelium that comprise of 4 major types of cells a) ciliated cells b) goblet cells c) basal cells and neuroendocrine cells. The ciliated cells are key components of the mucociliary escalator. The airway epithelium is surfaced by a thin film of mucus. The ratio of the ciliated to goblet cells is about 7: to 25:1. In case of acute bronchial irritation, the number of goblet cells increases drastically. The basal cells are pluripotent reserve cells that differentiate into ciliated and non-ciliated cells and repopulate the epithelium after a bronchial injury.
- Difference between bronchiole and bronchus:
  - Bronchiole has no cartilage, no submucosal glands and no goblet cells.
- The part distal to the terminal bronchiole is called acinus and it comprises of respiratory bronchioles, alveolar ducts, alveolar sacs and ultimately alveoli.
- The ultimate site of gas exchange is in the alveolus. The microscopic structure of the alveolar walls (or alveolar septa) consists of the following components,
  - The capillary endothelium and basement membrane.
  - The pulmonary interstitium is composed of fine elastic fibers, small bundles of collagen, a few fibroblast-like cells, smooth muscle cells, mast cells, and rare mononuclear cells. It is most prominent in thicker portions of the alveolar septum.
Lung Pathology Part I

- Alveolar epithelium contains a continuous layer of two principal cell types: flattened plate-like type I pneumocytes covering 95% of the alveolar surface and rounded type II pneumocytes. The latter synthesize pulmonary surfactant and are the main cell type involved in repair of alveolar epithelium after damage to type I pneumocytes.
- The alveolar walls are not solid but are perforated by numerous pores of Kohn, which permit passage of air, bacteria, and exudates between adjacent alveoli.
- A few alveolar macrophages usually lie free within the alveolar space. In the adult, these macrophages often contain phagocytosed carbon particles.

Development of lung

- The development of the respiratory system during the fetal period is traditionally divided into several stages.
- The pseudoglandular stage (7-17 weeks). During this period, an important process of growth and branching allows the setup of all pulmonary structures with the exception of the elements needed for gas exchange.
- The canalicular stage (17-27 weeks). The terminal bronchioles give rise to the canaliculi, or tubes that make up the proper respiratory part of the lung. All of the airsapces that derive from a terminal bronchiole form an acinus. The acinus includes an alveolar duct which buds and later gives rise to alveolar sacs. An essential characteristic of this stage is the differentiation of the epithelium into cuboidal secretory cells (Type II pneumocytes) which will synthesize the surfactant, and flat cells (Type I pneumocytes). The vascularization also develops considerably.
- The saccular-alveolar stage (27-40 weeks). The respiratory part of the bronchopulmonary tree develops with the formation of alveolar sacs separated by primary septa. The alveolar sacs will be progressively divided into smaller subunits by secondary septa, leading to the formation of alveoli.

Congenital anomalies

- Agenesis: Complete absence of lung tissue beyond the trachea or mainstem bronchus. Agenesis can be unilateral, bilateral or lobar. Bilateral agenesis is incompatible with life. Unilateral agenesis is frequently associated with cardiovascular anomalies including ASD, PDA and anomalous pulmonary venous return.
- Hypoplasia: Incomplete or defective development of the lung resulting in diminished size. In majority of the cases, the deformity is readily attributable to an associated malformation that directly or indirectly compromises the thoracic space available for lung growth. Examples of common associations include diaphragmatic hernia, causes of oligohydranmios (renal agenesis or dysgenesis, polycystic renal disease) and large abdominal wall defects.
- Tracheoesophageal fistula (TOF) and Esophageal atresia: Frequently go hand in hand. Suspect esophageal atresia with or without TOF if there is maternal polyhydramnios, or if infant has
excessive oral or pharyngeal secretion or if there is choking, cyanosis or coughing at feeding. Most common variety is esophageal atresia with TOF to the distal esophageal segment

- Bronchogenic cyst: Foregut buds that become separated and disconnected from the tracheobronchial tree progressively enlarge and form a cystic mass. These can be seen in children, young adults with no sex predilection. CXR shows spherical, well-marginated masses, usually located in the mid mediastinum. Typically tends to be a unilocular cyst filled with clear fluid lined by cuboidal to columnar ciliated epithelium, may contain cartilage and glands (like submucosal glands). Can get infected.

- Congenital Pulmonary Airway Malformation (CPAM)/ Congenital Cystic Adenomatoid Malformation (CCAM): relatively common “hamartomatous conditions”, separated into five types based on clinical, radiographic and pathologic features. Hamartoma is defined as a common benign tumor in an organ composed of tissue elements normally found at that site but that are growing in a disorganized mass. The lesion comprises of multiple, irregular varying sized acinar structures lined by cuboidal, ciliated pseudostratified columnar or alveolar epithelium. The entity shows a slight male predominance and is most commonly seen in newborns and up to first 2 years of life. The infants may present with signs of infection (cough, fever) or with respiratory distress, depending on the size of the lesion.

- Sequestration: Discrete mass of lung tissue that is not connected to the tracheobronchial tree. Extralobar sequestration arises due to an abnormal budding from the foregut, lies outside the normal lung, completely surrounded by its own visceral pleura, most frequently presenting within 6 months of life, with a male predominance. May present with dyspnea, cyanosis, feeding difficulties and frequently found between the lower lobe and the diaphragm. Typically receives and drains into the systemic circulation rather than pulmonary circulation. Histologically, sections look normal or show dilated bronchioles or inflammation or a co-existing CPAM. Intralobar sequestration on the other hand is acquired as a result of obstruction of the bronchial tree and vascular supply to the affected segment of lung and 98% of the cases occur in the lower lobe. Intralobar sequestrations frequently show evidence of chronic infection, including lymphoid hyperplasia, accumulation of foamy macrophages, and fibrosis.

**Acute lung injury (ALI)/ Acute respiratory distress syndrome (ARDS)/ Neonatal respiratory distress syndrome (NRDS)**

- The term *acute lung injury* encompasses a spectrum of bilateral pulmonary damage (endothelial and epithelial), which can be initiated by numerous conditions. Clinically, acute lung injury manifests as (1) acute onset of dyspnea, (2) decreased arterial oxygen pressure (hypoxemia), and (3) development of bilateral pulmonary infiltrates on the chest radiograph, all in the absence of clinical evidence of primary left-sided heart failure. Since the pulmonary infiltrates in
acute lung injury are usually caused by damage to the alveolar capillary membrane, rather than by left-sided heart failure, such accumulations constitute an example of noncardiogenic pulmonary edema. **Acute lung injury can progress to the more severe acute respiratory distress syndrome**

- Acute respiratory distress syndrome (ARDS) is a clinical syndrome caused by diffuse alveolar capillary and epithelial damage. The usual course is characterized by rapid onset of life-threatening respiratory insufficiency, cyanosis, and severe arterial hypoxemia that is refractory to oxygen therapy and may progress to multisystem organ failure.

- The histologic manifestation of ARDS in the lungs is known as diffuse alveolar damage (DAD). ARDS can occur in a multitude of clinical settings and is associated with either direct injury to the lung or indirect injury in the setting of a systemic process (see PowerPoint).

- Pathogenesis: In ARDS, the integrity of alveolar-capillary membrane 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. Lung injury is caused by an imbalance of pro-inflammatory and anti-inflammatory mediators (see PowerPoint). After an acute insult, there is increased synthesis of interleukin 8 (IL-8), a potent neutrophil chemotactic and activating agent, by pulmonary macrophages. Release of this and similar mediators, such as IL-1 and tumor necrosis factor (TNF), leads to endothelial activation as well as sequestration and activation of neutrophils in pulmonary capillaries. Neutrophils are thought to have an important role in the pathogenesis of ARDS. Activated neutrophils release a variety of products (e.g., oxidants, proteases, leukotrienes and platelet-activating factor,) that damage the alveolar epithelium and endothelium. Continuous assault worsens endothelial leakiness and the impairment of production of surfactant because of epithelial damage. The damage can be counteracted by endogenous antiproteases, antioxidants, and anti-inflammatory cytokines (e.g., IL-10). Balance between the destructive and protective factors that determines the degree of tissue injury and clinical severity of ARDS.

- In the acute phase of ARDS, the lungs are dark red, firm, airless, and heavy. Microscopic examination reveals capillary congestion, necrosis of alveolar epithelial cells, interstitial and intra-alveolar 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. In the organizing stage, vigorous proliferation of type II pneumocytes occurs in an attempt to regenerate the alveolar lining. Resolution is unusual; more commonly, there is organization of the fibrin exudates, with resultant intra-alveolar fibrosis. Marked thickening of the alveolar septa ensues, caused by proliferation of interstitial cells and deposition of collagen.
What about neonates and infants? There are many causes of respiratory distress in the newborn, including excessive sedation of the mother, fetal head injury during delivery, aspiration of blood or amniotic fluid, and intrauterine hypoxia secondary to compression from coiling of the umbilical cord about the neck. The most common cause, however, is respiratory distress syndrome (RDS), also known as hyaline membrane disease. It is so called because of the formation of “membranes” in the peripheral air spaces observed in autopsied lungs of infants succumbing to this condition. In the early days, it was thought that the membranes caused the disease. Only subsequent studies demonstrated that the “membranes” are not a cause but an effect of the disease.

The key problem is insufficient pulmonary surfactant production by immature lungs resulting in failure of lungs to inflate after birth. Lung surfactant is a complex mixture of phospholipids, neutral lipids and proteins. The main constituent is dipalmitoyl phosphatidylcholine (DPPC) and is responsible for achieving low surface tensions. Presence of surfactant specific proteins SP-A, SP-B, SP-C and SP-D, unsaturated phosphatidyl cholines (PC) and phosphatidylglycerol (PG) help in the adsorption of lung surfactant to the interface. Surfactant can be secreted as early as 20 weeks but is not produced in sufficient amounts till 34 weeks. Deficiency leads to increased surface tension and increased resistance to inflation and collapse. This leads to ventilation perfusion mismatch, hypoxia, endothelial and epithelial injury, increased capillary permeability and epithelial necrosis and hyaline membranes.

Corticosteroids stimulate the formation of surfactant lipids and associated proteins. Therefore, conditions associated with intrauterine stress and fetal growth restriction that increase corticosteroid release lower the risk of developing RDS. Surfactant synthesis can be suppressed by the compensatory high blood levels of insulin in infants of diabetic mothers, which counteracts the effects of steroids. This may explain, in part, why infants of diabetic mothers are at higher risk for developing RDS. Labor is known to increase surfactant synthesis; accordingly, cesarean section performed before the onset of labor may be associated with increased risk for RDS.

Delaying labor (if permissible) to permit fetal maturity can help prevent RDS. Fetal lung maturity can be assayed using Lecithin: sphingomyelin ratio and lamellar body counts. Prophylactic administration of exogenous surfactant has greatly reduced the incidence and complications of RDS.

Complications from the use of high concentrations of ventilator administered oxygen in the treatment of neonatal RDS could result in retinopathy of prematurity (ROP) which is abnormal blood vessel proliferation in the retina of the eye in a premature infant and bronchopulmonary dysplasia. BPD is a chronic lung disorder that is most common among children who were born prematurely, with low birth weights and who received prolonged mechanical ventilation to treat respiratory distress syndrome. BPD is characterized by decrease in alveolar septation and manifested as large, simplified alveolar spaces.
Mechanical Dysfunction

- **Atelectasis**, also known as collapse, is loss of lung volume caused by inadequate expansion of air spaces. It results in shunting of inadequately oxygenated blood from pulmonary arteries into veins, thus giving rise to a ventilation-perfusion imbalance and hypoxia. On the basis of the underlying mechanism or the distribution of alveolar collapse, atelectasis is classified into three forms (Fig. 12–2).
  - Resorption atelectasis. Resorption atelectasis occurs when an obstruction prevents air from reaching distal airways. The air already present gradually becomes absorbed, and alveolar collapse follows. Depending on the level of airway obstruction, an entire lung, a complete lobe, or one or more segments may be involved. The most common cause of resorption collapse is obstruction of a bronchus by a mucus or mucopurulent plug. This frequently occurs postoperatively but also may complicate bronchial asthma, bronchiectasis, chronic bronchitis, tumor, or foreign body aspiration, particularly in children.
  - Compression atelectasis. Compression atelectasis (sometimes called passive or relaxation atelectasis) is usually associated with accumulation of fluid, blood, or air within the pleural cavity, which mechanically collapses the adjacent lung. This is a frequent occurrence with pleural effusion, caused most commonly by congestive heart failure (CHF). Leakage of air into the pleural cavity (pneumothorax) also leads to compression atelectasis. Basal atelectasis resulting from the elevated position of the diaphragm commonly occurs in bedridden patients, in patients with ascites, and during and after surgery.
  - Contraction atelectasis. Contraction (or cicatriziation) atelectasis occurs when either local or generalized fibrotic changes in the lung or pleura hamper expansion and increase elastic recoil during expiration. Atelectasis (except when caused by contraction) is potentially reversible and should be treated promptly to prevent hypoxemia and superimposed infection of the collapsed lung
- **Pulmonary edema**

Most common cause is hemodynamic or cardiogenic edema because of left heart failure or volume overload. Other causes include microvascular injury from infections, liquid aspirations, drugs, radiation, high altitude or neurogenic edema. In cases of hemodynamic edema, rising pressure in the pulmonary veins cause back pressure changes resulting in congestion and edema. There is increase in the hydrostatic pressure of the venules of the visceral pleura resulting in pleural effusion. Lungs become boggy and heavy. There is perivasculcar and interstitial transudates, alveolar septal edema and edema fluid within alveolar spaces on microscopy. Varying number of red cells extravasate from the leaky capillaries which are then phagocytosed by macrophages. The
hemoglobin from the red cells is broken down resulting in hemosiderin laden macrophages/heart failure cells that is a reflection of previous episodes of pulmonary edema.

References:

Robbins Basic Pathology: Ninth edition: Chapters 6 and 12

Dail and Hammar's Pulmonary Pathology: Volume I: Non Neoplastic Lung Diseases: Pulmonary sequestration