THE LUNG

ATELECTASIS (COLLAPSE) is loss of lung volume caused by inadequate expansion of airspaces; this leads to shunting of inadequately oxygenated blood from pulmonary arteries into veins, thus giving rise to hypoxia.

Pathogenetically atelectasis is classified into three forms
1. **Resorption atelectasis complicating obstruction.** The air already present distally gradually becomes absorbed, and alveolar collapse follows. Depending on the level of airway obstruction, an entire lung, a complete lobe, or a segment may be involved. A mucous or muco-purulent plug is the most common cause of such obstruction for e.g. following surgical operations or bronchial asthma, bronchiectasis, chronic bronchitis, or the aspiration of foreign bodies, particularly in children.
2. **Compression atelectasis** is usually due to mechanical compression of the lung by pleural distension as in pleural effusion (congestive heart failure) or pneumothorax. Basal atelectasis is another example & is due to elevated diaphragm as that occurs in bedridden patients, in those with ascites, and during and after surgery.
3. **Contraction atelectasis** occurs in the presence of focal or generalized pulmonary fibrosis or pleural fibrosis; in these situations there is interference with expansion and an increase in elastic recoil during expiration.

Atelectasis (except contraction type) is reversible and should be treated quickly to prevent hypoxemia and infection of the collapsed lung.

ADULT RESPIRATORY DISTRESS SYNDROME (ARDS) (previously “Shock lung”) is “progressive respiratory insufficiency caused by diffuse alveolar damage”

The clinical setting associated with ARDS include
A. **Respiratory**
   1. Diffuse infections (viral, bacterial)
   2. Aspiration
   3. Inhalation (toxic gases, near drowning)
   4. O₂ therapy
B. **Non-respiratory**
   1. Sepsis (septic shock)
   2. Trauma (with hypotension)
   3. Burns
   4. Pancreatitis
   5. Ingested toxins (e.g. paraquat)

There is an acute onset of dyspnea, hypoxemia (refractory to O₂ therapy), and radiographic bilateral pulmonary infiltrates (noncardiogenic pulmonary edema). The condition may progress to multisystem organ failure.

Pathogenesis
In ARDS there is damage to alveolar capillary membrane by endothelial &/or epithelial injury. This leads to three consequences
1. Increased vascular permeability (endothelial damage)
2. Loss of diffusion capacity of the gases
3. Widespread surfactant deficiency (damage to type II pneumocytes).

**Nuclear factor κB**, is suspected of tilting the balance in favor of pro-inflammatory rather than anti-inflammatory mediators, which causes the endothelial damage. This leads to fluid accumulation. Following the insult, there is increased synthesis of a potent neutrophil chemotactic and activating agent **IL-8 & TNF** by pulmonary macrophages. The recruited, activated neutrophils release oxidants, proteases, etc. that cause damage to the alveolar epithelium leading to loss of surfactant that interferes with alveolar expansion.

**Gross features:** in the acute phase the lungs are dark red, airless, and heavy.
Microscopic features:
The histologic reflection of ARDS in the lungs is known as **diffuse alveolar damage.**

**Early stage** is characterized by
- Capillary congestion and stuffing by neutrophils
- Necrosis of alveolar epithelial cells
- Interstitial and intra-alveolar edema and sometimes hemorrhage
- The presence of hyaline membranes is characteristic. They particularly line the distended alveolar ducts & consist of fibrin admixed with necrotic epithelial cells.
- Overall, the picture is very similar to that seen in respiratory distress syndrome in the newborn.

**Organizing stage** is characterized by
- Marked regenerative proliferation of type II pneumocytes
- Organization of the fibrin exudates. This eventuates in intra-alveolar fibrosis.
- Marked fibrotic thickening of the alveolar septa.

*The prognosis of ARDS* is gloomy and mortality rates are around 60% despite improvements in supportive therapy. However, in most patients who survive the acute insult normal respiratory function returns. Alternatively, diffuse interstitial fibrosis occurs with permanent impairment of respiratory function.

**OBSTRUCTIVE PULMONARY DISEASE**
Under this heading come four entities
1. Emphysema
2. Chronic bronchitis
3. Asthma
4. Bronchiectasis
Although chronic bronchitis may exist without emphysema, and pure emphysema may occur (with inherited α₁-antitrypsin deficiency), the two diseases usually coexist. This is because long-term cigarette smoking is a common underlying agent in both disorders. 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)

**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.

**Centriacinar (Centrilobular) Emphysema:** the central 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.*
**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.

**Distal Acinar (Paraseptal) Emphysema**: the distal part of the acinus is primarily involved especially adjacent to the pleura and the lobular connective tissue septa. Characteristically, there are multiple, adjacent, 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.

**Irregular Emphysema**: the acinus is irregularly involved; it is associated with scarring.

**Pathogenesis of centriacinar & panacinar forms of emphysema**

These are thought to arise as a result of imbalances of protease-antiprotease and oxidant-antioxidant. The protease-antiprotease imbalance hypothesis is supported by the enhanced tendency of emphysema development in patients with genetic α₁-antitrypsin deficiency, which is aggravated by smoking. α₁-Antitrypsin, is a major inhibitor of proteases (particularly elastase) secreted by neutrophils during inflammation. Emphysema seems to result from the destructive effect of high protease activity in subjects with low antiprotease action. Smokings seems to play a decisive role in the pathogenesis of emphysema

1. It causes accumulation of neutrophils & macrophages within the alveoli through its direct chemoattractant effects and through the reactive oxygen species contained in it. These activate the transcription factor NF-κB, which switches on genes that encode TNF and IL-8. These, in turn, attract and activate more neutrophils. Accumulated active neutrophils release their granules, which are rich in a variety of proteases (elastase, proteinase, etc.) that result in tissue damage.
2. Smoking also enhances elastase activity in macrophages; this elastase is not inhibited by α₁-antitrypsin; additionally, it can digest this antiprotease.
3. Tobacco smoke contains abundant reactive oxygen free radicals, which deplete the antioxidant mechanisms, thereby inciting tissue damage. A secondary consequence of oxidative injury is inactivation of native antiproteases, resulting in "functional" α₁-antitrypsin deficiency even in patients without enzyme deficiency.

**Gross features**

- The diagnosis and classification of emphysema depend on the gross appearance of the lung.
- 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**

With the loss of elastic tissue in the surrounding alveolar septa, there is reduced radial traction on the small airways. As a result, they tend to collapse during expiration-an important cause of chronic airflow obstruction in severe emphysema. The patient is barrel-chested and dyspneic, with obviously prolonged expiration. Hyperventilation is prominent thus gas exchange is adequate and blood gas values are relatively normal i.e. there is no cyanosis. Patients with emphysema and chronic bronchitis usually
have less prominent dyspnea and respiratory drive, so they retain carbon dioxide, become hypoxic, and are often cyanotic. The eventual outcome of emphysema is the gradual development of secondary pulmonary hypertension, arising from both hypoxia-induced pulmonary vascular spasm and loss of pulmonary capillary surface area from alveolar destruction and stretching. Death from emphysema is related to either pulmonary failure, or right-sided heart failure (cor pulmonale).

Conditions Related to Emphysema
Several conditions resemble but are not really emphysema, these include
a. **Compensatory emphysema** refers to dilation of alveoli in response to loss of lung substance elsewhere, as in residual lung tissue after surgical removal of a diseased lung or lobe.
b. **Obstructive overinflation**: the lung expands because air is trapped within it. A common cause is subtotal obstruction by a tumor or foreign object, & mucous plugs in asthmatic patients. It can be a life-threatening emergency if the affected portion extends sufficiently to compress the remaining normal lung.
c. **Bullous emphysema** refers to any form of emphysema that produces bullae (spaces >1 cm in diameter). They represent localized accentuations of one of the four forms of emphysema, are most often subpleural that with rupture leads to pneumothorax.
d. **Mediastinal (interstitial) emphysema** signifies the entrance of air into the connective tissue of the lung, mediastinum, and subcutaneous tissue. It may spontaneous as with a sudden increase in intra-alveolar pressure (associated with vomiting or violent coughing) that causes a tear, with dissection of air into the connective tissue. It is also likely to occur in patients on respirators who have partial bronchiolar obstruction or in persons who suffer a perforating injury (e.g., a fractured rib). When the interstitial air enters the subcutaneous tissue, the patient may blow up like a balloon, with marked swelling of the head and neck.

**CHRONIC BRONCHITIS** is common among cigarette smokers and in smog-ridden cities. 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."

Pathogenesis
The distinctive feature of this disease is **hypersecretion of mucus**, beginning in the large airways. Although the single most important cause is **cigarette smoking**, other air pollutants, such as sulfur dioxide and nitrogen dioxide, may contribute. These environmental irritants induce hypertrophy of mucous glands in the trachea and main bronchi and a marked increase in mucin-secreting goblet cells in the surface epithelium of smaller bronchi and bronchioles. In addition, these irritants cause inflammation with infiltration of CD8+ T cells, macrophages, and neutrophils. Microbial infection is often present but has a secondary role, chiefly by maintaining the inflammation.

Airflow obstruction in chronic bronchitis results from
1. **Small airway disease**, (chronic bronchiolitis) induced by goblet cell metaplasia with mucus plugging of the bronchiolar lumen, inflammation, and bronchiolar wall fibrosis
2. **Coexistent emphysema**: while small airway disease is important in the early and mild airflow obstruction, chronic bronchitis with significant airflow obstruction is almost always complicated by emphysema.

**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.
- A variable density of inflammatory cells, largely mononuclear but sometimes admixed with neutrophils, is frequently present in the bronchial mucosa. Neutrophils increased markedly during superimposed acute exacerbations.
- Chronic bronchiolitis (small airway disease), characterized by goblet cell metaplasia, mucus plugging, inflammation, and fibrosis. In severe cases, there may be complete obliteration of the lumen due to fibrosis (bronchiolitis obliterans).

Patients with chronic bronchitis presents with a prominent productive cough that may persist indefinitely without ventilatory dysfunction. However, some may develop significant COPD with outflow obstruction. This is accompanied by hypercapnia, hypoxemia, and (in severe cases) cyanosis. *With progression, chronic bronchitis is complicated by pulmonary hypertension and cardiac failure. Recurrent infections and respiratory failure are constant threats.*

**ASTHMA** is "a chronic inflammatory disorder of the airways that causes recurrent attacks of breathlessness". The inflammation seems to cause an *increase in airway responsiveness* (bronchospasm) to a variety of stimuli, which would cause no such ill effects in nonasthmatic individuals. In two-thirds of the cases, the disease is *"extrinsic" (atopic)* due to IgE and T\textsubscript{H}2-mediated immune responses to environmental antigens. In the remaining one-third, asthma is *"intrinsic" (non-atopic)* and is triggered by non-immune stimuli such as aspirin; pulmonary infections, especially viral (common cold); psychological stress, etc.

**Pathogenesis**
The major etiologic factors of asthma are

1. Genetic predisposition to type I hypersensitivity ("atopy"),
2. Airway inflammation
3. Bronchial hyper-responsiveness to a variety of stimuli.

**The role of \textsubscript{T}{H}2**: the "atopic" form of asthma is associated with an excessive T\textsubscript{H}2 reaction against environmental antigens. *Three cytokines produced by T_{H2} cells are, in particular, responsible for most of the features of asthma;*

1. **IL-4** stimulates IgE production
2. **IL-5** activates eosinophils
3. **IL-13** stimulates mucus production

In addition, epithelial cells are activated to produce chemokines that recruit more T\textsubscript{H}2 cells, eosinophils, & other leukocytes, thus amplifying the inflammatory reaction.

**The role of genetics**: in asthma the bronchial smooth muscle hypertrophy and the deposition of subepithelial collagen may be the result of a genetically inherited predisposition. ADAM33 is one of the genes implicated.

**The role of mast cells**: these are part of the inflammatory infiltrate & contribute by secreting growth factors that stimulate smooth muscle proliferation. Atopic asthma, which usually begins in childhood, is triggered by environmental antigens (dusts, pollen, animal dander, and foods). In the airways the inhaled antigens stimulates induction of T\textsubscript{H}2-type cells and release of interleukins **IL-4 and IL-5**. This leads to synthesis of IgE that binds to mucosal mast cells. Subsequent exposure of IgE-coated mast cells to the same antigen causes the release of chemical mediators. In addition, direct stimulation of subepithelial vagal receptors provokes reflex bronchospasm. These occur within minutes after stimulation thus called *acute,* or
immediate, response. Mast cells release other cytokines that cause the influx of other leukocytes, including eosinophils. These inflammatory cells set the stage for the late-phase reaction, which starts 4 to 8 hours later.

The role of eosinophils: these cells are particularly important in the late phase. Their effects are mediated by
1. **Major basic protein and eosinophil cationic protein**, which directly damage airway epithelial cells.
2. **Eosinophil peroxidase** causes tissue damage through oxidative stress.
3. **Leukotriene C4**, which contribute to bronchospasm.

Viral infections of the respiratory tract and inhaled air pollutants such as sulfur dioxide increase airway hyper-reactivity in both normal & non-atopic asthmatics. In the latter, however, the bronchial spasm is much more severe and sustained. It is thought that virus-induced inflammation of the respiratory mucosa renders the subepithelial vagal receptors more sensitive to irritants.

The ultimate humoral and cellular mediators of airway obstruction are common to both atopic and non-atopic variants of asthma, and hence they are treated in a similar way.

Drug-Induced Asthma: several drugs provoke asthma, aspirin being the most striking example. Presumably, aspirin inhibits the cyclooxygenase pathway of arachidonic acid metabolism without affecting the lipoxygenase route, thereby shifting the balance toward bronchocoonstrictor leukotrienes.

Occupational Asthma: this form is stimulated by fumes (epoxy resins, plastics), organic and chemical dusts (wood, cotton, platinum), gases (toluene), and other chemicals. Asthma attacks usually develop after repeated exposure to the inciting antigen(s).

Pathologic features
Gross features: in fatal cases, the lungs are overdistended because of overinflation.

Microscopic features:
- There is occlusion of bronchi and bronchioles by thick, tenacious mucous plugs, which contain numerous eosinophils.
- Structural changes of airways include
  - Thickening of the basement membrane of the bronchial epithelium
  - Edema and an inflammatory infiltrate in the bronchial walls, with a prominence of eosinophils and mast cells.
  - An increase in the size of the submucosal glands.
  - Hypertrophy of the bronchial muscle cells.

Course & prognosis
An attack of asthma is characterized by severe dyspnea with wheezing; the chief difficulty lies in expiration. The victim 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 paroxysm occurs that does not respond to therapy and persists for days and even weeks (*status asthmaticus*). The associated hypercapnia, acidosis, and severe hypoxia may be fatal.

BRONCHIECTASIS refers to "the permanent dilation of bronchi and bronchioles caused by destruction of the musculo-elastic supporting tissues, resulting from or associated with chronic necrotizing infections." The disease is secondary to persisting infection or obstruction caused by a variety of conditions. Once developed, it gives
rise to symptoms dominated by cough and expectoration of copious amounts of purulent, foul sputum. Diagnosis depends on an appropriate history along with radiographic demonstration of bronchial dilation. The conditions that most commonly predispose to bronchiectasis include the following:

1. **Bronchial obstruction** e.g. by tumors, foreign bodies. Under these conditions, the bronchiectasis is localized to the obstructed segment. Bronchiectasis can also complicate **atopic asthma and chronic bronchitis** through mucus impaction. In **cystic fibrosis**, widespread severe bronchiectasis results from obstruction and infection caused by the secretion of abnormally viscid mucus. **Kartagener syndrome**, an autosomal recessive disorder, is frequently associated with bronchiectasis and sterility in males. Structural abnormalities of the cilia impair mucociliary clearance in the airways, leading to persistent infections, and reduce the mobility of spermatozoa.

2. **Necrotizing, or suppurative, pneumonia**, particularly with virulent organisms such as Staphylococcus aureus or Klebsiella spp., may predispose to bronchiectasis. In the past, postinfective bronchiectasis was sometimes a sequel to the childhood pneumonias that complicated measles, whooping cough, and influenza, but this has substantially decreased with the advent of successful immunization. Post-tuberculosis bronchiectasis continues to be a significant cause in endemic areas.

**Pathogenesis**

- Two processes are crucial and tangled in the pathogenesis of bronchiectasis: **obstruction and chronic persistent infection**. Either of these two processes may come first.
- Normal clearance mechanisms are impaired by obstruction, so secondary infection soon follows; conversely, chronic infection in time causes damage to bronchial walls, leading to weakening and dilation. For example, obstruction caused by a bronchogenic carcinoma or a foreign body impairs clearance of secretions, providing a fertile soil for superimposed infection. The resultant inflammatory damage to the bronchial wall and the accumulating exudate further distend the airways, leading to irreversible dilation.
- A persistent necrotizing inflammation in the bronchi or bronchioles may cause obstructive secretions, inflammation throughout the wall (with peribronchial fibrosis and traction on the walls), and eventually dilation.

**Gross features**

- Usually there is bilateral involvement of the lower lobes
- When tumors or aspiration of foreign bodies lead to bronchiectasis, involvement may be sharply localized to a single segment of the lungs.
- The airways may be dilated up to 4 times their usual diameter and can be followed almost to the pleural surfaces

**Microscopic features**

- There is intense acute and chronic inflammatory exudate within the walls of the bronchi and bronchioles.
- The desquamation of lining epithelium causes extensive areas of ulceration. When healing occurs, the lining epithelium may regenerate completely.
- In chronic cases there is fibrosis of the bronchial and bronchiolar walls and peribronchiolar areas.
- In some instances, the necrotizing inflammation destroys the bronchial or bronchiolar walls and forms a lung abscess.
In cases of severe, widespread bronchiectasis hypoxemia, hypercapnia, pulmonary hypertension, and (rarely) cor pulmonale occur. Metastatic brain abscesses and reactive amyloidosis are other, less frequent complications.

**DIFFUSE INTERSTITIAL (RESTRICTIVE) LUNG DISEASES**

These are a heterogeneous group of disorders characterized by diffuse and usually chronic involvement of the pulmonary connective tissue, principally the delicate alveolar walls. The hallmark of these disorders is reduced compliance (because of stiff lungs), which necessitates increased effort of breathing. There are, in addition, abnormalities in the ventilation-perfusion ratio, leading to hypoxia. Chest radiographs show diffuse infiltration by small nodules or "ground-glass shadows." With progression respiratory failure may develop, often in association with pulmonary hypertension and cor pulmonale. The end stage of most of these diseases, irrespective of etiology, is diffuse interstitial pulmonary fibrosis with or without honeycombing.

**Idiopathic Pulmonary Fibrosis (IPF) (cryptogenic fibrosing alveolitis)** is characterized histologically by diffuse interstitial fibrosis, which in advanced cases results in severe hypoxemia and cyanosis. Males (usually over 60 years) are more often affected. Grossly, the pleural surfaces of the lung have cobblestone appearance because of the retraction of scars along the interlobular septa. The histologic hallmark is patchy interstitial fibrosis, which varies in intensity. The dense fibrosis causes collapse of alveolar walls and formation of cystic spaces lined by hyperplastic type II pneumocytes (honeycomb fibrosis). The interstitial inflammation is usually patchy and consists of lymphocytes. Secondary pulmonary hypertensive changes are often present.

**Pulmonary Involvement in Collagen Vascular Diseases**

Many collagen vascular diseases (e.g., SLE, rheumatoid arthritis, systemic sclerosis) are associated with pulmonary manifestations. The histologic changes are in part similar to that of IPF, vascular sclerosis, organizing pneumonia, and bronchiolitis. Pleural involvement may also be present. Pulmonary involvement in these diseases is usually associated with a poor prognosis.

**Pneumoconioses** refer to the non-neoplastic lung reactions to inhalation of mineral dusts (Organic and inorganic). The three most common of these result from exposure to coal dust, silica, and asbestos; nearly always due to exposure in the workplace. However, the increased risk of cancer as a result of asbestos exposure extends to family members of asbestos workers and to other individuals exposed to asbestos outside the workplace.

**Pathogenesis**

The reaction of the lung to mineral dusts depends on the size, shape, solubility, and reactivity of the particles; particles that are 1 to 5 μm are the most dangerous, because they lodge at the bifurcation of the distal airways. Coal dust is relatively inert, and large amounts must be deposited in the lungs before the disease is clinically apparent. Silica, asbestos, and beryllium are more reactive than coal dust, resulting in fibrotic reactions at lower concentrations. The pulmonary alveolar macrophage play central role in the initiation and progression of lung injury and fibrosis. The more reactive particles stimulate the macrophages to release mediators of inflammation and fibroblast proliferation with collagen deposition. Some of the inhaled particles may reach the lymphatics. This leads to an amplification and extension of the local reaction. Tobacco smoking worsens the effects of all inhaled mineral dusts, but particularly asbestos particle.

1. **Coal Workers’ Pneumoconiosis**
The spectrum of lung findings in coal workers includes
a. Asymptomatic anthracosis, in which pigment accumulates without cellular reaction. It is also commonly seen in all urban dwellers and tobacco smokers. Inhaled carbon pigment is engulfed by alveolar or interstitial macrophages, which then accumulate in the connective tissue along the lymphatics, including the pleural lymphatics, or in lymph nodes.
b. Simple coal workers' pneumoconiosis is characterized by nodules that consist of dust-laden macrophages with small delicate network of collagen fibers.
c. Progressive massive fibrosis develops in 10% of those with the above; it occurs through the coalescence of the fibrotic nodules. The fibrosis is extensive and lung function is impaired with subsequent pulmonary hypertension, and cor pulmonale. There is no increased frequency of bronchogenic carcinoma (cf. silicosis & asbestosis).

2. Silicosis is the most common chronic occupational disease in the world. It is caused by inhalation of silica crystals mostly quartz, usually in occupational settings. The condition is characterized by the formation of silicotic nodules, at first tiny, discrete, pale or black (when mixed with carbon) involving the upper zones of the lungs. Microscopically, the silicotic nodule consists of concentrically arranged hyalinized collagen fibers surrounding an amorphous center. Polarized microscopy reveals weakly birefringent silica particles, primarily in the center of the nodules. With progression, the individual nodules coalesce into large collagenous scars, and eventually progressive massive fibrosis. Silicosis is associated with an increased susceptibility to tuberculosis presumably due depression of cell-mediated immunity. Silica from occupational sources is carcinogenic in humans. However, this subject continues to be controversial.

3. Asbestos and Asbestos-Related Diseases
Asbestos is a family of silicate crystals with a fibrous spatial arrangement. Occupational exposure to asbestos is associated with
1. Interstitial pulmonary fibrosis (asbestosis) 2. Localized fibrous pleural plaques
5. Malignant mesotheliomas (pleural, peritoneal) 6. Laryngeal carcinoma
An increased incidence of asbestos-related cancers is noted in family members of asbestos workers.
Asbestosis signifies diffuse pulmonary interstitial fibrosis & characteristically shows the presence of asbestos bodies, which are seen as golden brown, beaded rods. They consist of asbestos fibers coated with an iron-protein material. In contrast to coal workers pneumoconiosis and silicosis, asbestosis begins in the lower lobes and subpleural regions, but the entire lungs become affected as fibrosis progresses. Simultaneously, the visceral pleura undergoes fibrous thickening.
Pleural plaques are the most common manifestation of asbestos exposure and are well-circumscribed patches of dense collagen that develop most frequently on the parietal pleura and over the domes of the diaphragm.
The risk of bronchogenic carcinoma is increased about five times for asbestos workers. The risk for mesotheliomas, normally a very rare tumor, is more than 1000 times greater. Both pleural and peritoneal mesotheliomas have an association with asbestos exposure. Concomitant cigarette smoking greatly increases the risk of
bronchogenic carcinoma but not that of mesothelioma. The carcinoma & mesothelioma associated with asbestos exposure have a particularly poor prognosis.

**Drug and Radiation-Induced Pulmonary Diseases**

Drugs can cause both acute and chronic changes in the lungs. For example, *bleomycin* (an anticancer agent) & *amiodarone* (an anti-arrhythmic agent) causes pneumonitis and interstitial fibrosis. *Radiation pneumonitis* is a well-known complication of *therapeutic radiation* of pulmonary and other thoracic tumors.

**Granulomatous Diseases**

*Sarcoidosis* is a *systemic granulomatous disease of unknown etiology characterized by noncaseating granulomas in many tissues and organs*. Other diseases, including mycobacterial or fungal infections and berylliosis, sometimes also produce noncaseating granulomas; therefore, the histologic diagnosis of sarcoidosis is one of exclusion. Bilateral hilar lymphadenopathy &/or lung involvement is the major presenting manifestations in most cases. Eye and skin involvement are also frequent and may occasionally be the presenting feature of the disease. Sarcoidosis occurs throughout the world, affecting both sexes and all races and ages. There is a predilection for adults younger than 40 years of age. Sarcoidosis is one of the few pulmonary diseases with a *higher prevalence among nonsmokers*. Although the etiology of sarcoidosis remains unknown, it is probably a disease of disordered immune regulation in genetically predisposed individuals exposed to certain environmental agents.

**Pathologic features**

- **Noncaseating epithelioid granulomas are the histopathologic marker of sarcoidosis.** A thin layer of fibroblasts is present peripheral to the granuloma; over time, these proliferate and lay down collagen that replaces the entire granuloma with a hyalinized scar.
- Two other microscopic features are sometimes seen in the granulomas: 1. *Schaumann bodies*, laminated concretions composed of calcium and proteins; and 2. *Asteroid bodies*, stellate inclusions enclosed within giant cells. They are neither specific nor required to make the diagnosis. *Caseation necrosis (typical of tuberculosis)* is absent.
- The lungs are involved in 90% of patients. The granulomas predominantly involve the interstitium rather than airspaces. In up to 15% of patients, the granulomas are eventually replaced by diffuse interstitial fibrosis resulting in a honeycomb lung.
- Intrathoracic hilar and paratracheal lymph nodes are enlarged in the majority of patients. Unlike in tuberculosis, lymph nodes in sarcoidosis are "nonmatted" (nonadherent) and do not ulcerate.

**Course & prognosis:** in about two-thirds of symptomatic cases there is a gradual appearance of dyspnea with or without fever, fatigue, weight loss, etc. Because of the variable and nondiagnostic clinical features, frequently lung or lymph node biopsy is performed. The presence of noncaseating granulomas is suggestive of sarcoidosis, but other identifiable causes of granulomatous inflammation must be excluded. Sarcoidosis follows an unpredictable course. Overall, 70% of affected individuals recover with minimal or no residual manifestations; 20% develop permanent lung dysfunction or visual impairment. Of the remaining 10%, most die of progressive pulmonary fibrosis and cor pulmonale.

Other granulomatous lung diseases including infectious e.g. TB, fungal, etc. will be covered below.
Pulmonary Eosinophilia
A number of pulmonary entities are characterized by an infiltration and activation of eosinophils. These diverse diseases are generally of immunologic origin, but are incompletely understood. Pulmonary eosinophilia is divided into the following categories:

Smoking-Related Interstitial Lung Diseases
Smoking is a definite cause of COPD (emphysema and chronic bronchitis). However, smoking is also associated with restrictive interstitial lung diseases. Desquamative interstitial pneumonia (DIP) and respiratory bronchiolitis are the two related examples. The most striking histologic feature of DIP is the accumulation of large numbers of macrophages containing dusty brown pigment (smoker's macrophages) in the airspaces. The alveolar septa are thickened by a sparse lymphocytic infiltration, and interstitial fibrosis, when present, is mild. Patients with DIP typically have a good prognosis with excellent response to steroid therapy and smoking cessation. Respiratory bronchiolitis is a common histologic lesion found in smokers, characterized by the presence of pigmented intraluminal macrophages similar to DIP, but within respiratory bronchioles. Mild peribronchiolar fibrosis is also seen. As with DIP, individuals present with gradual onset of dyspnea and dry cough, and the symptoms recede with cessation of smoking.

DISEASES OF VASCULAR ORIGIN
Pulmonary Embolism, Hemorrhage, and Infarction
More than 95% of all pulmonary emboli arise from thrombi within the large deep veins of the lower legs, typically the popliteal and larger veins above it. Autopsy data on the incidence of pulmonary emboli vary widely, ranging from 1% in the general hospitalized population, to 30% in individuals dying after severe burns, trauma, or fractures. The influences that predispose to venous thrombosis in the legs were discussed in the chapter of hemodynamic disturbances.

The consequences of thromboembolism in the lung depend largely on
1. The size of the embolus, which defines the size of the occluded pulmonary artery
2. The cardiopulmonary status

There are two important consequences of embolic pulmonary arterial occlusion:
A. An increase in pulmonary artery pressure primarily from blockage of flow.
B. Ischemia of the down-stream pulmonary parenchyma.

Thus, occlusion of a major vessel results in a sudden increase in pulmonary artery pressure, diminished cardiac output, right-sided heart failure (acute cor pulmonale), or even death. If smaller vessels are occluded, the result is less catastrophic, and the event may even be clinically silent. The lung is oxygenated not only by the pulmonary arteries but also by bronchial arteries and directly from air in the alveoli. If the bronchial circulation is normal and adequate ventilation is maintained, the resultant decrease in blood flow does not cause infarction. Indeed, infarction resulting from pulmonary thromboembolism is the exception rather than the rule, occurring in as few as 10% of cases. It occurs only if there impairment of cardiac function or bronchial circulation, or if the region of the lung at risk is underventilated as a result of underlying pulmonary disease.

Pulmonary Hypertension
Pulmonary blood pressures are only about 1/8 of systemic pressure. Pulmonary hypertension (pressures reach 1/4 or more of systemic levels) is most often secondary to a decrease in the cross-sectional area of the pulmonary vascular bed, or to increased pulmonary vascular blood flow. The causes of pulmonary hypertension include:

1. **Chronic obstructive or interstitial lung disease**, due to destruction of lung parenchyma and consequent reduction in alveolar capillaries.
2. **Recurrent pulmonary emboli** leading to a reduction in the functional cross-sectional area of the pulmonary vascular bed
3. **Antecedent heart disease** e.g., mitral stenosis, which increases left atrial pressure, leading to higher pulmonary venous pressures, and ultimately pulmonary arterial hypertension. Congenital left-to-right shunts are another cause of secondary pulmonary hypertension.
4. **Primary (idiopathic) pulmonary hypertension** an uncommon cause.

Pathologic features

Vascular alterations in all forms of pulmonary hypertension (primary and secondary) involve the entire arterial tree and include:

1. Large elastic arteries show atheromas
2. Medium-sized muscular arteries show proliferation of smooth muscle cells in the intima & media, causing thickening of the wall with luminal narrowing
3. In smaller arteries and arterioles there is medial hypertrophy, and reduplication of the internal and external elastic membranes. Individuals with severe, long-standing primary pulmonary hypertension may develop **plexogenic pulmonary arteriopathy** i.e. a tuft of capillary formations producing a network that occupy the lumens of dilated thin-walled, small arteries.

Course & prognosis

Secondary pulmonary hypertension may develop (depending on the cause) at any age. Primary pulmonary hypertension, on the other hand, is almost always encountered in young persons, more commonly women. These persons eventually develop severe respiratory insufficiency and cyanosis, and death usually results from right-sided heart failure (cor pulmonale) within 2 to 5 years of the diagnosis. Without lung transplantation the prognosis is very poor.

Diffuse Alveolar Hemorrhage Syndromes

This may be secondary, complicating for e.g. necrotizing bacterial pneumonia, passive venous congestion, bleeding diathesis. The primary form is represented by a group of “primary” immune-mediated diseases that present as hemoptysis, anemia, and radiographic diffuse pulmonary infiltrates. **Goodpasture syndrome** is the classical member. It is characterized by rapidly progressive, glomerulonephritis and hemorrhagic interstitial pneumonitis. Both the renal and the pulmonary lesions are caused by antibodies targeted against collagen IV (basement membrane). The characteristic linear pattern of immunoglobulin deposition (usually IgG) is diagnostic in renal biopsy specimens & is also seen along the alveolar septa. These antibodies can be detected in the serum of the patients. The lungs are heavy, with areas of red-brown consolidation.

**Idiopathic Pulmonary Hemosiderosis** is a disease of uncertain etiology that has pulmonary manifestations and histology similar to those of Goodpasture syndrome, but there is no associated renal disease or circulating anti-basement membrane antibody.

**Pulmonary Angiitis and Granulomatosis (Wegener Granulomatosis; WG):** the majority of WG patients develop upper respiratory or pulmonary manifestations the
result of necrotizing vasculitis ("angiitis") and parenchymal necrotizing granulomatous inflammation.

PULMONARY INFECTIONS
Pneumonias are common cause of death. Defects in natural immunity and humoral immunodeficiency lead to an increased incidence of infections with pyogenic bacteria whereas cell-mediated immune defects lead to increased infections with intracellular microbes (as mycobacteria and herpes viruses) as well as with microorganisms of very low virulence (as Pneumocystis jiroveci). Cigarette smoke impairs mucociliary clearance and pulmonary macrophage activity, while alcohol impairs cough and epiglottic reflexes, thereby increasing the risk of aspiration, and also interferes with neutrophil mobilization and chemotaxis. Pneumonia may be acute or as chronic disease. The histologic spectrum of pneumonia may vary from a fibrinopurulent alveolar exudate seen in acute bacterial pneumonias, to mononuclear interstitial infiltrates in viral and other atypical pneumonias, to granulomas and cavitation seen in many of the chronic pneumonias (e.g. tuberculous).

Acute bacterial pneumonias can present as one of two anatomic (and radiographic) patterns:
1. Bronchopneumonia showing a patchy distribution of inflammation that generally involves more than one lobe. The initial infection is of the bronchi and bronchioles with extension into the adjacent alveoli.
2. Lobar pneumonia, which is by contrast, affecting the contiguous airspaces of part or all of a lobe; these are homogeneously filled with an exudate that can be visualized on radiographs as a lobar or segmental consolidation. Streptococcus pneumoniae is responsible for more than 90% of lobar pneumonias. The anatomic distinction between lobar pneumonia and bronchopneumonia is often become blurred because (a) many organisms can produce either of the two patterns of distribution and (b) confluent bronchopneumonia can be hard to distinguish radiologically from lobar pneumonia.

Classifying pneumonias by the setting in which they arise considerably narrows the list of suspected pathogens and hence help choosing the suitable empirical antibiotic for treatment. Pneumonia can arise in seven distinct clinical settings ("pneumonia syndromes"), and the causative pathogens are reasonably specific to each category.

1. Community-Acquired Acute Pneumonias are mostly bacterial in origin. Frequently it follows a viral upper respiratory tract infection. There is usually abrupt high fever, pleuritic chest pain, and a productive mucopurulent cough and occasionally hemoptyisis. S. pneumoniae (pneumococcus) is the most common cause.

Streptococcus (Pneumococcal) pneumoniae occur with increased frequency in those with underlying chronic diseases (CHF, COPD, or diabetes), humoral immunodeficiencies & impaired splenic function (e.g., sickle cell disease or splenectomy).

Either lobar or bronchopneumonia, may occur; the latter is much more prevalent at the extremes of age. Because pneumococcal lung infections usually originate by aspiration of pharyngeal flora (20% of adults harbor S. pneumoniae in their throats), the lower lobes or the right middle lobe are most frequently involved. In the era before antibiotics, pneumococcal pneumonia involved entire or almost entire lobes (lobar pneumonia) and evolved through four stages: congestion, red hepatization, gray hepatization, and resolution. Early antibiotic therapy alters or stops this typical progression, so if the person dies, the anatomic changes seen at autopsy may not match the classic stages. During the first stage, that of congestion, the affected lobe(s)
is (are) heavy, red, and wet; histologically, vascular congestion can be seen, with proteinaceous fluid, scattered neutrophils, and many bacteria in the alveoli. Within a few days, the stage of **red hepatization** follows, in which the lung lobe has a liver-like consistency; the alveolar spaces are packed with neutrophils, red cells, and fibrin. In the next stage, **gray hepatization**, the lung is dry, gray, and firm, because the red cells are lysed, while the fibrinosuppurative exudate persists within the alveoli. **Resolution** follows in uncomplicated cases; the exudates within the alveoli are enzymatically digested to produce semifluid debris that is resorbed, ingested by macrophages, coughed up, or organized by fibroblasts. The pleural reaction (**fibrinous or fibrinopurulent pleuritis**) may similarly resolve or undergo organization, leaving fibrous thickening or permanent adhesions.

In the **bronchopneumonia**, gray-red to yellow patches of consolidation, up to 4 cm in diameter are distributed throughout one or several lobes, most frequently bilateral and basal. Confluence of these foci may occur in severe cases, producing the appearance of a lobar consolidation. The large intervening areas are generally normal. Histologically, the reaction consists of focal suppurative exudate that fills the bronchi, bronchioles, and adjacent alveolar spaces. With appropriate therapy, complete resolution of the inflammation is the rule for both forms. **Occasional complications especially with serotype 3 pneumococci may occur:**

1. Abscess
2. Empyema
3. Solid areas of fibrosis complicating organization
4. Bacteremic dissemination may lead to meningitis, arthritis, or infective endocarditis.

Examination of Gram-stained sputum is an important step in the diagnosis of acute pneumonia. The presence of numerous neutrophils containing the typical gram-positive, lancet-shaped diplococci is good evidence of pneumococcal pneumonia, however, *S. pneumoniae* is a part of the endogenous flora and therefore false-positive results may be obtained. Isolation of pneumococci from blood cultures is more specific.

**Other organisms commonly implicated in community-acquired acute pneumonias include Haemophilus influenzae**, which is the most common bacterial cause of acute exacerbation of COPD. *Moraxella catarrhalis*, which is the second most common bacterial cause of acute exacerbation of COPD in adults. *Staphylococcus aureus* is an important cause of secondary bacterial pneumonia after viral respiratory illnesses (e.g., measles in children and influenza in both children and adults). It is associated with a high incidence of complications, such as lung abscess and empyema. **Klebsiella pneumoniae** is the most frequent cause of gram-negative bacterial pneumonia. It frequently afflicts debilitated and malnourished persons, particularly **chronic alcoholics**. Thick and gelatinous sputum is characteristic; because the organism produces an abundant viscid capsular polysaccharide, which the individual may have difficulty coughing up. **Pseudomonas aeruginosa** is associated with infections in cystic fibrosis & in hospitalized patients. It is also common in neutropenic persons, usually secondary to chemotherapy; in victims of extensive burns; and in those requiring mechanical ventilation. *P. aeruginosa* has a propensity to invade blood vessels at the site of infection with consequent extrapulmonary spread; Pseudomonas bacteremia is a fulminant disease, with death occurring within a matter of days. **Legionella pneumophila** (the agent of legionnaire disease) is common with some predisposing condition such as cardiac, renal, immunologic, or hematologic disease. Organ transplant recipients are particularly susceptible. Legionella pneumonia can be
quite severe and immunosuppressed individuals may have a fatality rate of 30% to 50%.

2. Community-Acquired Atypical Pneumonias denotes absence of physical findings of consolidation (due to lack of alveolar exudates), & only moderate elevation of WBC count. *Mycoplasma pneumoniae* is the most common offender. It is particularly common among children and young adults. Other etiologic agents are viruses (including influenza types A and B), *Chlamydia pneumoniae* and *Coxiella burnetti* (Q fever). Atypical pneumonias may be complicated by secondary bacterial infection due to denudation of the respiratory epithelium that interferes with mucociliary clearance. Viral infections of the respiratory tract are well known for this complication.

**Pathologic features of atypical pneumonias**

Regardless of cause, the morphologic patterns are similar. The process may be patchy, or it may involve whole lobes bilaterally or unilaterally. Grossly, there are red-blue, congested areas. **Microscopically**, the inflammatory reaction is largely confined within the alveolar walls, which are widened by edema & mononuclear inflammatory infiltrate of lymphocytes, histiocytes, and, occasionally, plasma cells. *In contrast to bacterial pneumonias, alveolar spaces are free of cellular exudates.* In severe cases ARDS may develop. Identifying the causative agent can be difficult. Tests for *Mycoplasma* antigens and polymerase chain reaction (PCR) testing for *Mycoplasma* DNA are available. Patients with community-acquired pneumonia for which a bacterial agent seems unlikely are treated with a macrolide antibiotic effective against *Mycoplasma* and *Chlamydia pneumoniae*, because these are the most common treatable pathogens.

**Influenza Infections**

The influenza virus is RNA virus, bound by a nucleoprotein that determines the virus type (A, B, or C). The spherical surface of the virus is a lipid bilayer containing the viral hemagglutinin and neuraminidase, which determine the subtype (e.g., H1N1, H3N2, etc.). Host antibodies to the hemagglutinin and neuraminidase prevent and ameliorate, respectively, future infection with the influenza virus. The type A viruses are the major cause of *pandemic* and *epidemic* influenza infections. Epidemics of influenza occur through mutations of the hemagglutinin and neuraminidase antigens that allow the virus to escape most host antibodies (*antigenic drift*). Pandemics, which last longer and are more widespread than epidemics, may occur when both the hemagglutinin and neuraminidase are replaced through recombination of RNA segments with those of animal viruses, making all animals susceptible to the new influenza virus (*antigenic shift*). Commercially available influenza vaccines provide reasonable protection against the disease, especially in vulnerable infants and elderly individuals. A particular subtype of avian influenza (*"bird flu,"* H5N1) has caused massive outbreaks in domesticated poultry in parts of Southeast Asia in the last few years; this strain is particularly dangerous, since it has the potential to "jump" to humans and thereby cause an unprecedented, worldwide influenza pandemic.

The 2009 outbreak of *influenza A virus subtype H1N1* is an epidemic of a new strain of influenza virus identified in April 2009, commonly referred to as "*Swine flu.*" It is thought to be a mutation of four known strains of influenza A virus subtype H1N1: one endemic in humans, one endemic in birds, and two endemic in pigs (swine). **The signs of infection with swine flu are similar to influenza.** People at higher risk of serious complications include people age 65 years and older, children younger than 5 years old, pregnant women, people of any age with chronic medical conditions (such as asthma, diabetes, or heart disease), and people who are immunosuppressed.
Transmission is through Sneezes or coughs, and contaminated objects (touching something with flu viruses on it and then touching your mouth or nose). Influenza viruses are not known to be transmissible to people through eating processed pork or other food products derived from pigs."

**Severe Acute Respiratory Syndrome (SARS)**
This first appeared in the end of 2002 in China, and subsequently spread to several neighboring countries (Hong Kong, Taiwan etc.), where large outbreaks also occurred. Between 2002 and 2003, when the outbreak ended, over 8,000 cases and about 750 deaths had been ascribed to SARS. The cause is a previously undiscovered coronavirus (SARS-CoV), which has the ability to infect the lower respiratory tract and induce viremia. The lungs of patients dying of SARS, usually shows ARDS changes with multinucleated giant cells.

3. **Nosocomial Pneumonia (hospital-acquired)** defined as "pulmonary infections acquired in the course of a hospital stay". They are common in hospitalized persons with severe illness, immune suppression, or prolonged antibiotic therapy. Those on mechanical ventilation are also susceptible; infections acquired in this setting are designated ventilator-associated pneumonia. Gram-negative rods and S. aureus are the most common offenders.

4. **Aspiration Pneumonia** occurs in markedly debilitated patients or those who aspirate gastric contents either while unconscious (e.g., after a stroke) or during repeated vomiting. The resultant pneumonia is partly chemical, resulting from the extremely irritating effects of the gastric acid, and partly bacterial. Recent studies implicate aerobes (S. pneumoniae, S. aureus, H. influenzae, and Pseudomonas aeruginosa) more commonly than anaerobes (such as Bacteroides). This type of pneumonia is often necrotizing with a fulminant clinical course. In those who survive, abscess formation is a common complication.

5. **Necrotizing pneumonia & Lung Abscess**
Lung Abscess refers to "a localized area of suppurative necrosis within the pulmonary parenchyma, resulting in the formation of one or more large cavities". Necrotizing pneumonia often coexists or evolves into lung abscess, making the distinction between the two somewhat subjective. The causative organism may be introduced into the lung by any of the following mechanisms:

a. **Aspiration of infective material** from carious teeth or infected sinuses or tonsils, as during oral surgery, anesthesia, coma, or alcoholic intoxication and in debilitated patients with depressed cough reflexes.

b. **Aspiration of gastric contents**, usually accompanied by infectious organisms from the oropharynx.

c. **As a complication of necrotizing bacterial pneumonias**, particularly those caused by S. aureus, Streptococcus pyogenes, K. pneumoniae, Pseudomonas spp. etc.

d. **Mycotic infections and bronchiectasis**

e. **Bronchial obstruction**, particularly with bronchogenic carcinoma.

f. **within a necrotic portion of a tumor**

g. **Septic embolism**, from septic thrombophlebitis or from infective endocarditis of the right side of the heart.

h. **hematogenous spread of bacteria** in disseminated pyogenic infection as with staphylococcal bacteremia.
Anaerobic bacteria are present in almost all lung abscesses, sometimes in vast numbers, and they are the exclusive isolates in one-third to two-thirds of cases.

**Pathological Features**

- Abscesses vary in diameter from very small lesions to large cavities of 5 cm or more.
- The localization and number depend on the mode of development. Pulmonary abscesses resulting from aspiration are much more common on the right side (more vertical airways), and are mostly single. In this location, they tend to occur in the posterior segment of the upper lobe and in the apical segments of the lower lobe. Abscesses that develop in the course of pneumonia or bronchiectasis are commonly multiple, basal, and diffusely scattered. Septic emboli and abscesses arising from hematogenous seeding are commonly multiple and may affect any region of the lungs.
- As the focus of suppuration enlarges, it usually ruptures into airways. Thus, the contained exudate may be partially drained, producing an air-fluid level on radiographic examination.

**Microscopic features**

- There is suppurative liquefactive necrosis
- Depending on the chronicity, the above may be surrounded by variably thickened fibrous tissue and mononuclear infiltration by variable amounts of (lymphocytes, plasma cells, macrophages).

**Complications**

1. **Rupture into the pleural cavity** producing bronchopleural fistulas, the consequence of which is pneumothorax or empyema.
2. **Embolization** of septic material to the brain, gives rise to meningitis or brain abscess.
3. **Secondary amyloidosis** may develop in chronic cases

**Course & prognosis**

The manifestations of a lung abscess are similar to those of bronchiectasis (productive cough of copious, foul sputum). Abscesses occur in up to 15% of persons with bronchogenic carcinoma; thus, when a lung abscess is suspected in an older person, underlying carcinoma must be considered. Overall, the mortality rate is in the range of 10%.

6. **Chronic Pneumonia** is mostly a localized lesion in an immunocompetent person, with or without regional lymph node involvement. There is typically granulomatous inflammation, which may be due to bacteria (e.g., *M. tuberculosis*) or fungi. In the immunocompromised, there is usually systemic dissemination of the causative organism, accompanied by widespread disease.

**Tuberculosis**

Tuberculosis is by far the most important of the chronic pneumonia; it causes 6% of all deaths worldwide. Tuberculosis is "a communicable chronic granulomatous disease caused by *Mycobacterium tuberculosis*". It usually involves the lungs but may affect any organ or tissue. Tuberculosis thrives wherever there is poverty, crowding, and chronic debilitating illness; elderly, with their weakened defenses, are also susceptible. **Certain disease states also increase the risk:**

1. Diabetes mellitus
2. Hodgkin lymphoma
3. Chronic lung disease (particularly silicosis)
4. Chronic renal failure
5. Malnutrition & Alcoholism
6. Immunosuppression including HIV infection.

Most of these predisposing conditions are related to impairment of T cell-mediated immunity against the Mycobacteria. The latter are slender rods that are acid fast, thus stained positively with ZN stain. *M. tuberculosis hominis* is responsible for most cases of tuberculosis. Oropharyngeal and intestinal tuberculosis contracted by drinking milk contaminated with *Mycobacterium bovis* is now rare in developed nations. Other mycobacteria, particularly *M. avium-intracellulare*, are much less virulent than *M. tuberculosis* and rarely cause disease. However, it complicates up to 30% of patients with AIDS.

**Pathogenesis**

**Primary TB**

- In the previously unexposed immunocompetent individual, the source of the organism is exogenous; this leads to the development of cell mediated immunity; primarily mediated by T\_H\_1 cells, which stimulate macrophages to kill bacteria but this is associated simultaneously with the development of destructive tissue hypersensitivity in the form of caseation necrosis.
- The virulent organisms once inside macrophages impair effective phagolysosomal digestion, which in turn leads to unrestricted mycobacterial proliferation. Thus, the earliest phase of primary tuberculosis is characterized by bacillary proliferation within alveolar macrophages, with resulting bacteremia and seeding of multiple sites. Nevertheless, most persons at this stage are asymptomatic; only about 5% of the infected develop significant disease.
- The activated macrophages release a variety of mediators including secretion of TNF, which is responsible for recruitment of monocytes, which in turn undergo activation and differentiation into the "epithelioid histiocytes" that characterize the granulomatous response.
- About 3 weeks are needed for the development of the hypersensitivity reaction.

**Pathological features of primary TB**

- The inhaled bacilli are embedded in the distal airspaces of the lower part of the upper lobe or the upper part of the lower lobe, usually close to the pleura.
- As sensitization develops, a bout1 cm area of gray-white inflammatory consolidation develops (the Ghon focus). The center of this focus undergoes caseous necrosis.
- Tubercle bacilli, either free or within phagocytes, drain to the regional nodes, which also often caseate. *This combination of Ghon focus and nodal involvement is referred to as the Ghon complex.*
- During the first few weeks, there is also lymphatic and hematogenous dissemination to other parts of the body.
- In approximately 95% of cases, development of cell-mediated immunity controls the infection. Hence, the Ghon complex undergoes progressive fibrosis, often followed by radiologically detectable calcification, and, despite seeding of other organs, no lesions develop.
- **Microscopically**, there is the characteristic granulomatous inflammatory reaction that forms both caseating and noncaseating tubercles. Individual tubercles are microscopic; it is only when multiple granulomas coalesce that they become macroscopically visible. The granulomas are usually enclosed within a fibroblastic rim with lymphocytes. Multinucleate giant cells are present in the granulomas.

*The chief potential harmful outcomes of primary tuberculosis are*
1. Induction of destructive tissue hypersensitivity, which is more damaging on subsequent infection (secondary TB)
2. Healed foci of scarring may harbor viable bacilli for years, and thus be a potential nidus for reactivation when host defenses are compromised
3. The disease progresses relentlessly into **progressive primary tuberculosis** (uncommon). This occurs in immunocompromised individuals e.g. AIDS patients or in those with nonspecific impairment of host defenses (malnourished children or elderly). Immunosuppression results in the absence of a tissue hypersensitivity reaction and thus there are no granulomas but only sheets of foamy histiocytes packed with the bacilli (**nonreactive tuberculosis**). Progressive primary tuberculosis often resembles acute bacterial pneumonia, with lower and middle lobe consolidation, hilar lymphadenopathy, and pleural effusion; caviation is rare. Lympho-hematogenous dissemination may result in the development of tuberculous meningitis and miliary tuberculosis.

**Secondary Tuberculosis (Postprimary) (Reactivation Tuberculosis)**

Secondary tuberculosis is the pattern of disease that arises in a previously sensitized host.

**Pathogenesis**

- Reactivation of the dormant primary infection (as in nonendemic, low-prevalence areas) or re-exposure to the bacilli in a previously sensitized host (as in endemic areas) results in rapid recruitment of defensive reactions but also tissue necrosis (caseation). This occurs when the protection (immunity) offered by the primary infection is weakened.
- Whatever the source, only less than 5% with primary disease subsequently develop secondary tuberculosis.
- **Secondary pulmonary tuberculosis is classically localized to the apex of one or both upper lobes.** This may relate to high oxygen tension in the apices.
- Because of the **preexistence of hypersensitivity**, the bacilli excite a marked tissue response that tends to wall off the focus. As a result of this localization, the regional lymph nodes involvement is less prominently than they are in primary tuberculosis.
- **Cavitation occurs readily in the secondary form, & is almost inevitable in neglected cases.** As a result erosion of airways occurs; this converts the patient into a source of infection to others; he now raises sputum containing bacilli.

**Gross features of secondary TB**

- The initial lesion is usually a small focus of consolidation, less than 2 cm in diameter, near the apical pleura. Such foci are sharply circumscribed, firm, and gray-white to yellow areas that have a variable amount of central caseation and peripheral fibrosis. This, if neglected progresses to caviations.

**Microscopic features**

- The active lesions show characteristic coalescent tubercles with central caseation. TB bacilli can be demonstrated by specific staining methods.

**Progression of secondary TB**

In favorable cases, the initial localized apical parenchymal damage undergoes progressive healing by fibrosis & eventually represented by fibrocalcific scars. This happy outcome occurs either spontaneously or after therapy. Alternatively, the disease may progress and extend along several different pathways:

**A. Progressive pulmonary tuberculosis:** the apical lesion enlarges with expansion of the area of caseation. Erosion into a bronchus evacuates the caseous center, creating a ragged, irregular cavity lined by caseous material; whereas erosion of blood vessels
results in hemoptysis. The pleural cavity is always involved and serous pleural effusions, tuberculous empyema, or fibrous obliteration may develop.

**B. Miliary pulmonary disease** occurs when organisms drain through lymphatics into the lymphatic ducts, which empty into the venous return to the right side of the heart and thence into the pulmonary arteries. Individual lesions are either microscopic or small (2-mm) foci of yellow-white; these scatter diffusely through the lungs (*miliary is derived from the resemblance of these foci to millet seeds*). Miliary lesions may expand and coalesce to yield almost total consolidation of large regions or even whole lobes of the lung.

**C. Endobronchial, endotracheal, and laryngeal tuberculosis** may develop when infective material is spread either through lymphatic channels or from expectorated infectious material. The mucosal lining may be studded with minute granulomatous lesions.

**D. Systemic miliary tuberculosis** occurs when infective foci in the lungs invade the pulmonary venous return to the heart; the organisms subsequently disseminate through the systemic arterial system. Almost every organ in the body may be seeded. The appearances are similar to miliary pulmonary disease. Miliary tuberculosis is most prominent in the liver, bone marrow, spleen, adrenals, meninges, kidneys, fallopian tubes, and epididymis.

**E. Isolated-organ tuberculosis** may appear in any one of the organs or tissues seeded hematogenously and may be the presenting manifestation of tuberculosis. Organs typically involved include the meninges (tuberculous meningitis), kidneys (renal tuberculosis), adrenals (formerly an important cause of Addison disease), bones (tuberculous osteomyelitis), and fallopian tubes (tuberculous salpingitis). When the vertebrae are affected, the disease is referred to as Pott disease. Paraspinal "cold" abscesses in persons with this disorder may track along the tissue planes to present as an abdominal or pelvic mass.

**F. Tuberculous Lymphadenitis** is the most frequent form of extrapulmonary tuberculosis, usually occurring in the cervical region ("scrofula"). It tends to be unifocal, and most individuals do not have evidence of ongoing extranodal disease.

**H. Intestinal tuberculosis** was fairly common as a primary focus of tuberculosis contracted by the drinking of contaminated milk. In developed countries today, intestinal tuberculosis is more often a complication of protracted advanced secondary tuberculosis, secondary to the swallowing of coughed-up infective material. Typically, the organisms are trapped in mucosal lymphoid aggregates of the small and large bowel, which then undergo inflammatory enlargement with ulceration of the overlying mucosa, particularly in the ileum.

**The diagnosis of pulmonary disease** is based in part on the history and on physical and radiographic findings of consolidation or cavitation in the apices of the lungs. However, *tubercle bacilli must be identified to establish the diagnosis*.

The most common method for diagnosis of tuberculosis remains demonstration of acid-fast organisms in sputum by special stains e.g. acid-fast stained; most protocols require at least two sputum examinations before labeling the case as sputum negative. Conventional cultures for mycobacteria require up to 10 weeks. **PCR amplification of M. tuberculosis DNA allows for even greater rapidity of diagnosis** and is currently approved for use. PCR assays can detect as few as 10 organisms in clinical specimens, compared with greater than 10,000 organisms required for smear positivity. **However, culture remains the gold standard because it also allows testing of drug susceptibility.**
Prognosis is generally favorable if infections are localized to the lungs, but it worsens significantly when the disease occurs in the setting of aged, debilitated, or immunosuppressed persons, who are at high risk for developing miliary tuberculosis, and in those with multi-drug resistant-TB. Amyloidosis may appear in persistent cases.

Nontuberculous Mycobacterial Disease is mostly in the form of chronic but clinically localized pulmonary disease in immunocompetent individuals. Strains implicated most frequently include *M. avium-intracellulare*. Nontuberculous mycobacteriosis may present as upper lobe cavitary disease, mimicking tuberculosis, especially in individuals with a long-standing history of smoking or alcoholism. The presence of concomitant chronic pulmonary disease e.g. COPD, is an important risk factor. In immunosuppressed individuals (primarily, HIV-positive patients), M. avium-intracellulare presents as disseminated disease, associated with systemic symptoms.

Histoplasmosis, Coccidioidomycosis, and Blastomycosis
Fungal infections of the lung are due mainly to *Histoplasma capsulatum, Coccidioides immitis,* and *Blastomyces dermatitidis.* Infections present either as isolated pulmonary involvement as in immunocompetent individuals, or as disseminated disease in immunocompromised persons. T cell-mediated immune responses are critical for containing the infection, and therefore, persons with compromised cell-mediated immunity, such as those with HIV, are more prone to systemic disease. Clinical manifestations may take the form of (1) acute (primary) pulmonary infection, (2) chronic (cavitary) pulmonary disease, or (3) disseminated miliary disease. The primary pulmonary nodules, composed of aggregates of macrophages studded with organisms, are associated with similar lesions in the regional lymph nodes. These lesions develop into small granulomas complete with giant cells, and may develop central necrosis and later fibrosis and calcification. The similarity to primary tuberculosis is striking, and differentiation requires identification of the yeast forms (best seen with periodic acid-Schiff or silver stains).

7. Pneumonia in the Immunocompromised Host
The appearance of a pulmonary infiltrate and signs of infection (e.g., fever) are some of the most common and serious complications in immunocompromised persons whose immune and defense systems are suppressed by disease, immunosuppression for organ transplants, malignancy, or irradiation. A wide variety of opportunistic microorganisms, many of which rarely cause infection in normal hosts, can cause these pneumonias.

*Examples of pulmonary opportunistic pathogens include*

1. **Bacteria** (*P. aeruginosa, Mycobacterium spp., etc*)
2. **Viruses** (cytomegalo and herpesvirus viruses)
3. **Fungi** (*P. jiroveci, Candida spp., Aspergillus spp., and Cryptococcus neoformans*).

**Cytomegalovirus Infections**
Cytomegalovirus (CMV), a member of the herpesvirus family, may produce a variety of disease manifestations, depending partly on the age of the infected host but even more on the host's immune status. In immunosuppressed adults, **CMV pneumonia** is a serious problem. Histologically, affected cells (alveolar macrophages, epithelial and endothelial cells) are characteristically enlarged, often to a diameter of 40 μm, and they show cellular and nuclear polymorphism. Prominent intranuclear basophilic inclusions occupying half the nuclear diameter are usually separated from the nuclear membrane by a clear halo. **CMV in immunosuppressed individuals occurs most**
commonly in recipients of organ & allogeneic bone marrow transplants as well as patients with AIDS. CMV is the most common opportunistic viral pathogen in AIDS. In all the above settings, serious, life-threatening disseminated CMV infections occur; primarily pneumonitis, colitis, and retinitis. The pneumonia is interstitial in type & can progress to full-blown ARDS. Diagnosis of CMV infections is made by demonstration of characteristic morphologic alterations in tissue sections, viral culture, rising antiviral antibody titer, and PCR-based detection of CMV DNA.

**Pneumocystis Pneumonia**

*P. jiroveci* (formerly *P. carinii*), an opportunistic infectious agent long considered to be a protozoan, is now believed to be more closely related to fungi. Virtually all persons are exposed to *Pneumocystis* during early childhood, but in most the infection remains latent. Reactivation and clinical disease occurs almost exclusively in those who are immunocompromised (very commonly in AIDS patients but also in the severely malnourished infants). *Pneumocystis* produce an interstitial pneumonitis with a characteristic intra-alveolar foamy, pink-staining exudate with H&E stains ("cotton candy" exudate). Silver stains of tissue sections reveal *cup-shaped cyst* in the alveolar exudates. The most sensitive and effective method of diagnosis is to identify the organism in bronchoalveolar lavage fluids or in a transbronchial biopsy specimen. Immunofluorescence antibody kits and PCR-based assays have also become available for use on clinical specimens.

**Opportunistic Fungal Infection**

1. **Candidiasis**

*Candida albicans* is the most frequent disease-causing fungus. It is a normal inhabitant of the oral cavity. Systemic candidiasis (with associated pneumonia) is a disease that is restricted to immunocompromised patients. In tissue sections, *C. albicans* demonstrates yeastlike forms, pseudohyphae, and true hyphae. The organisms may be visible with routine hematoxylin and eosin stains, but a variety of special "fungal" stains (methenamine-silver, periodic acid-Schiff) are commonly used to highlight the pathogens. *Candida pneumonia* usually presents radiographically as bilateral nodular infiltrates, resembling *Pneumocystis pneumonia*.

2. **Cryptococcosis** is caused by *C. neoformans* & is almost exclusively presents as an opportunistic infection in immunocompromised hosts, particularly those with AIDS or hematolymphoid malignancies. The fungus, 5- to 10-μm yeast, has a thick, gelatinous capsule, which is invaluable for the diagnosis. The capsular antigen is the substrate for latex agglutination assay, which is positive in more than 95% of patients infected with the organism. Human cryptococcosis usually manifests as pulmonary, central nervous system, or disseminated disease.

3. **The Opportunistic Molds:** Mucormycosis and invasive aspergillosis are uncommon infections almost always limited to immunocompromised hosts. The hyphae of Mucormycosis are nonseptate and branch at right angles; in contrast, the hyphae of Aspergillus species are septate and branch at more acute angles. Pulmonary mucormycosis can cause cavitory lung lesions or may present radiologically with diffuse "miliary" involvement. Invasive aspergillosis is associated with necrotizing pneumonia, the fungus tends to invade blood vessels, and thus systemic dissemination, especially to the brain, is often a fatal complication. Allergic pulmonary aspergillosis occurs in patients with asthma who develop an exacerbation of symptoms due to reaction to the fungus growing in the bronchi. Aspergilloma ("fungus ball") occurs by colonization of preexisting pulmonary cavities (e.g., ectatic bronchi or lung cysts, post-tuberculous cavitory lesions) by the fungus.
LUNG TUMORS
Bronchial carcinomas constitute 95% of primary lung tumors; the remaining 5% includes bronchial carcinoids, sarcomas, lymphomas, and a few benign lesions.
Pulmonary Hamartoma is the most common benign lesion; it is rounded, small (3-4 cm), discrete mass that often displayed as "coin" lesion on chest radiographs. They consist mainly of mature cartilage with a scattered of bronchial glands that are often admixed with fat, fibrous tissue, and blood vessels in varying proportions.

Carcinomas
Carcinoma of the lung is the commonest cause of cancer-related deaths in industrialized countries. The rate of increase among males is slowing down, but it continues to accelerate among females; it has overrun breast cancer as a cause of death since 1987. This is undoubtedly related to the strong relationship of cigarette smoking and lung cancer. Most patients are in the age group of 50-60 years. The prognosis of lung cancer is very poor: the 5-year survival rate for all stages combined is about 15%.

There are four major histologic types of lung carcinomas
1. Squamous cell carcinoma
2. Adenocarcinoma
3. Small-cell carcinoma
4. Large-cell carcinoma.
Adenocarcinomas are the most common primary tumors arising in women, in lifetime nonsmokers, and in persons younger than 45 years. For therapeutic purposes, carcinomas of the lung are divided into two groups: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). The latter category includes squamous cell, adenocarcinomas, and large-cell carcinomas. The reason for this division is that virtually all SCLCs have metastasized by the time of diagnosis and hence are not curable by surgery. Therefore, they are best treated by chemotherapy, with or without radiation. In contrast, NSCLCs usually respond poorly to chemotherapy and are better treated by surgery. In addition, these two groups show genetic differences. SCLCs are characterized by a high frequency of RB gene mutations, while the p16 gene is commonly inactivated in NSCLCs.

Etiology and Pathogenesis
It seems that large areas of the respiratory mucosa have undergone mutation after exposure to carcinogens ("field effect"). On this fertile soil, those cells that accumulate additional mutations ultimately develop into cancer.
The role of Cigarette smoking is the main agent responsible for the genetic changes that give rise to lung cancers. About 90% of lung cancers occur in active smokers (or those who stopped recently). The increased risk is 60 times greater among habitual heavy smokers (two packs a day for 20 years) compared with nonsmokers. Women have a higher susceptibility to carcinogens in tobacco than men. Although cessation of smoking decreases the risk of developing lung cancer over time, genetic changes that predate lung cancer can persist for many years in the bronchial epithelium of ex-smokers. Passive smoking (proximity to cigarette smokers) increases the risk to twice that of nonsmokers. There is a linear correlation between the intensity of smoking and the appearance of squamous metaplasia that progresses to squamous dysplasia and carcinoma in situ, before culminating in invasive cancer. Squamous and small-cell carcinomas show the strongest association with tobacco exposure.
The role of occupation-related environmental agents; these may act alone or synergistically with smoking to be pathogenitically related to some lung cancers, for
e.g. radioactive ores; dusts containing arsenic, chromium, uranium, nickel, vinyl chloride, and mustard gas. Exposure to asbestos increases the risk of lung cancer 5 times in nonsmokers. However, heavy smoking with asbestos exposure increases the risk to 50 times.

The role of hereditary (genetic) factors: not all persons exposed to tobacco smoke develop cancer. It seems that the effect of carcinogens is modulated by hereditary (genetic) factors. Many procarcinogens require metabolic activation via the P-450 enzyme system for conversion into carcinogens. Evidences support this scenario in that persons with specific genetic abnormalities of P-450 genes have an increased capacity to metabolize procarcinogens derived from cigarette smoke and thus sustain the greatest risk of developing lung cancer.

The role of bronchioalveolar stem cells (BASCs) in the development of peripheral adenocarcinoma: the "cell of origin" for peripheral adenocarcinomas is the BASCs. Following peripheral lung injury, the multipotent BASCs undergo expansion to replenish the normal cell types found in this location, thereby facilitating epithelial regeneration. BASCs are considered the tumor initiating cells i.e. the first to acquire the somatic K-RAS mutation that enables their daughter cells to escape normal "checkpoint" mechanisms and result in pulmonary adenocarcinomas.

Gross Features
- Carcinomas of the lung begin as small mucosal lesions that are usually firm and gray-white. Further enlargement result in either intraluminal masses, or invasion of the bronchial wall to form large bulky masses pushing into adjacent lung parenchyma. Obstruction of the bronchial lumen often produces distal atelectasis and infection.
- Some tumors tend to a rise centrally near the hilum i.e. in major brochi, these are exemplified by squamous cell & small cell carcinomas. Adenocarcinomas may occur centrally but are usually more peripherally located, many arising in relation to peripheral lung scars ("scar carcinomas").
- Large tumors may undergo cavitation; this is caused by central necrosis
- These tumors may extend to the pleura, invade the pleural cavity and chest wall, and spread to adjacent intrathoracic structures.
- Metastasis occurs first to peribronchial, hilar and mediastinal lymph nodes
- More distant spread can occur via the lymphatics or the hematogenous route.

Microscopic features

Squamous cell carcinomas are often preceded for years by squamous metaplasia or dysplasia in the bronchial epithelium, which then transforms to carcinoma in situ, a phase that may last for several years. These tumors range from well-differentiated showing keratin pearls and intercellular bridges to poorly differentiated neoplasms having only minimal residual squamous cell features.

Adenocarcinomas assume a variety of forms, including gland forming (acinar), papillary, and solid types. The solid variant often requires demonstration of intracellular mucin production by special stains to establish its adenocarcinomatous nature.

Bronchioloalveolar carcinomas (BACs) are a subtype of adenocarcinomas. They involve peripheral parts of the lung, either as a single nodule or, more often, as multiple diffuse nodules that may coalesce to produce pneumonia-like consolidation. The key feature of BACs is their growth along preexisting structures and preservation of alveolar architecture.
Large-cell carcinomas are undifferentiated malignant epithelial tumors that lack the cytologic features of glandular or squamous differentiation. The cells have large nuclei, prominent nucleoli. Large-cell carcinomas probably represent undifferentiated examples of squamous cell or adenocarcinomas at the light microscopic level. Ultrastructurally, however, minimal glandular or squamous differentiation is common.

Small-cell lung carcinomas are composed of small tumor cells with a round to fusiform nuclei with finely granular chromatin, and scant cytoplasm. Mitotic figures are frequently seen (Fig. 2-45). Despite the term of "small," the neoplastic cells are usually twice the size of resting lymphocytes. Necrosis is invariably present and may be extensive. These tumors are derived from neuroendocrine cells of the lung, and hence they express a variety of neuroendocrine markers in addition to many polypeptide hormones that may result in paraneoplastic syndromes (see below).

Combined tumors: a minority of bronchogenic carcinomas reveal more than one line of differentiation, sometimes several, suggesting that all are derived from a multipotential progenitor cell.

All subtypes of lung cancer show involvement of successive chains of nodes about the carina, in the mediastinum, and in the neck (scalene nodes) and clavicular regions and, sooner or later, distant metastases. Involvement of the left supraclavicular node (Virchow node) is particularly characteristic and sometimes calls attention to an occult primary tumor. These cancers, when advanced, often extend into the pericardial or pleural spaces, leading to inflammation and effusions. They may compress or infiltrate the superior vena cava to cause either venous congestion or the full-blown vena caval syndrome. Apical neoplasms may invade the brachial or cervical sympathetic plexus to cause severe pain in the distribution of the ulnar nerve or to produce Horner syndrome (ipsilateral enophthalmos, ptosis, miosis, and anhidrosis). Such apical neoplasms are sometimes called Pancoast tumors, and the combination of clinical findings is known as Pancoast syndrome. Pancoast tumor is often accompanied by destruction of the first and second ribs and sometimes thoracic vertebrae. As with other cancers, tumor-node-metastasis (TNM) categories have been established to indicate the size and spread of the primary neoplasm.

Course & prognosis
Carcinomas of the lung are silent lesions that more often than not have spread beyond curable resection at the time of diagnosis. Too often, the tumor presents with symptoms related to metastatic spread to the brain (mental or neurologic changes), liver (hepatomegaly), or bones (pain). Overall, NSCLCs have a better prognosis than SCLCs. When NSCLCs (squamous cell carcinomas or adenocarcinomas) are detected before metastasis or local spread, cure is possible by lobectomy or pneumonectomy. SCLCs, on the other hand, is almost always have spread by the time of the diagnosis, even if the primary tumor appears small and localized. Thus, surgical resection is not a practical treatment. They are very sensitive to chemotherapy but invariably recur. Median survival even with treatment is 1 year.

Paraneoplastic syndromes
Up to10% of all patients with lung cancer develop clinically overt paraneoplastic syndromes. These include

1. Hypercalcemia caused by secretion of a parathyroid hormone-related peptide.
2. Cushing syndrome (from increased production of ACTH);
3. Inappropriate secretion of ADH
4. Neuromuscular syndromes, including a myasthenic syndrome, peripheral neuropathy, and polymyositis
5. Clubbing of the fingers and hypertrophic pulmonary osteoarthropathy
6. Hematologic manifestations, including migratory thrombophlebitis, nonbacterial endocarditis, and disseminated intravascular coagulation.

Hypercalcemia is most often encountered with squamous cell carcinomas, the hematologic syndromes with adenocarcinomas. The remaining syndromes are much more common with small-cell neoplasms, but exceptions occur.

Bronchial Carcinoids are thought to arise from the Kulchitsky cells (neuroendocrine cells) of the bronchial mucosa and represent about 5% of all pulmonary neoplasms. The mean age of occurrence is 40 years. Ultrastructurally, the neoplastic cells contain cytoplasmic dense-core neurosecretory granules and may secrete hormonally active polypeptides. In contrast to the more ominous small-cell carcinomas, carcinoids are often resectable and curable.

**Gross features**
Most bronchial carcinoids originate in main bronchi and grow in one of two patterns
1. An Obstructing spherical, intraluminal mass
2. A mucosal plaque penetrating the bronchial wall to fan out in the peribronchial tissue.

Some tumors, (about 10%) metastasize to hilar nodes but distant metastasis is rare.

**Microscopic features**
- They are composed of nests of uniform cells that have regular round nuclei with "salt-and pepper" chromatin, absent or rare mitoses.
- A subset designated atypical carcinoid that differ from the typical by
  1. Having higher mitotic rate, cytologic pleomorphism, and focal necrosis
  2. Having a higher incidence of lymph node and distant metastasis.

Typical carcinoid, atypical carcinoid, and small-cell carcinoma can be considered to represent a continuum of increasing histologic aggressiveness and malignant potential within the spectrum of pulmonary neuroendocrine neoplasms.

**Course & prognosis**
Most clinical features are related to their intraluminal growth (cough, hemoptysis, and recurrent bronchial and pulmonary infections). Some are asymptomatic and discovered by chance on imaging studies. Only rarely do they induce the carcinoid syndrome, characterized by intermittent attacks of diarrhea, flushing, and cyanosis. The reported 10-year survival rates for typical carcinoids are 85%, but these drop to 35% for atypical carcinoids. Only 5% of patients with SCLC are alive at 10 years.