Objectives

- Describe the pathology of atelectasis, pulmonary oedema and acute lung injury
- Discuss the pathology of common diseases that cause obstructive and restrictive impaired lung function
- Describe the pathophysiology of pulmonary hypertension and pulmonary embolism
- Describe the pathology of common lung infections (pneumonia, lung abscess)
- Name the common tumours arising in the lung and describe the pathology of primary lung cancer
- List the common conditions of the pleura and describe their key pathological features

Note: Thymic lesions will be covered under Study Notes for Lymphoreticular System.

Outline

I. Lung Structure, Function and Congenital Disorders

a. **Normal lung structure and function**
b. **Congenital disorders**: *Pulmonary hypoplasia, Foregut cysts, Pulmonary sequestration*

II. Atelectasis, Pulmonary Oedema and Acute Lung Injury

a. **Atelectasis**: *Resorption, Compression, Contraction*
b. **Pulmonary oedema**: *Haemodynamic oedema, Oedema due to alveolar wall injury*
c. **Acute lung injury (ALI), Acute respiratory distress syndrome (ARDS), Diffuse alveolar damage (DAD)**

III. Obstructive and Restrictive Lung Diseases

a. **Obstructive lung disease**: *COPD (Emphysema, Chronic Bronchitis), Asthma, Bronchiectasis*
b. **Restrictive lung disease**: *UIP, Pneumoconioses (e.g. Asbestosis), Sarcoidosis*

IV. Pulmonary Embolism and Pulmonary Hypertension

a. **Pulmonary embolism**
b. **Pulmonary hypertension**

V. Pulmonary Infections

a. **Pneumonia**: *Bacterial (Bronchopneumonia, Lobar pneumonia), Viral, Fungal*
b. **Lung abscess**

VI. Lung Tumours

a. **Lung carcinoma**: *Adenocarcinoma, Squamous cell carcinoma, Small cell carcinoma*
b. **Carcinoid tumours**
c. **Metastatic tumours to the lung**

VII. Pleura

a. **Pleural effusion**: *Inflammatory vs Non-inflammatory*
b. **Pneumothorax**: *Spontaneous, Traumatic, Tension*
c. **Pleural tumours**: *Malignant mesothelioma*

References

Kumar V, Abbas A, Aster J. *Robbins & Cotran Pathologic Basis of Disease*. 10th ed.

***Note**: Pathweb Study Notes are based on the key topics covered in the lectures in the Yong Loo Lin School of Medicine, as well as additional topics covered in major texts. For more comprehensive discussion on specific pathology topics, readers are advised to refer to the recommended texts in your respective courses.*

I. LUNG STRUCTURE, FUNCTION AND CONGENITAL DISORDERS

Normal lung structure and function

Cardinal function of the lung is the exchange of gases between air and blood

Structure	Components and function
Bronchi	- **Firm cartilaginous walls**: Provide mechanical support - **Columnar ciliated epithelium with mucus-secreting goblet cells and subepithelial glands**: Impede entry of microbes
Bronchiole	- **Lack of cartilage and submucosal glands**: Carry air to alveoli
Acinus	- Composed of **respiratory bronchiole, alveolar ducts and alveolar sacs**: Site of gas exchange
Alveolar wall	- **Anastomosing capillary network**: Bring blood for gas exchange - **Basement membrane +/- interstitium**: Supporting tissue - **Alveolar epithelium**: o Type 1 pneumocytes: Flat; 95% of alveolar surface for gas exchange o Type 2 pneumocytes: Rounded; Synthesize surfactant and can proliferate and differentiate to type 1 pneumocytes to repair alveolar damage - **Alveolar macrophages**: Few, loosely attached to epithelium or lying free with alveolar space

Congenital disorders: overall rare

- **Pulmonary hypoplasia**: Decreased lung size due to defect in lung development, caused by compression / restricted expansion of the lung in utero e.g. congenital diaphragmatic hernia, oligohydramnios
- **Foregut cysts**: From abnormal detachment of the primitive foregut. Incidental or cause symptoms due to compression of adjacent structures or superimposed infection
- **Pulmonary sequestration**: Lung tissue not connected to the airways and has abnormal blood supply arising directly from the aorta or its branches. Can be extralobar or intralobar
- **Miscellaneous**: Tracheal / bronchial anomalies etc.

II. ATELECTASIS, PULMONARY OEDEMA AND ACUTE LUNG INJURY

Atelectasis

Incomplete lung expansion (neonatal atelectasis) or collapse of previously inflated lung; both result in poorly aerated lung tissue, which reduces oxygenation and predisposes to infection. Usually reversible unless caused by fibrosis

- **Resorption atelectasis**: Due to airway obstruction (e.g. from excess mucus secretions / exudates, foreign bodies or tumors), resulting in resorption of air from distal alveoli that then collapse. Mediastinum shifts towards the atelectatic lung due to the reduced volume
- **Compression atelectasis**: Due to accumulation of fluid, air or tumours within the pleural cavity. Mediastinum thus shifts away from the atelectatic lung
- **Contraction atelectasis**: Due to focal or generalized pulmonary or pleural fibrosis preventing full lung expansion

Pulmonary oedema

Excessive interstitial fluid in the alveoli that impairs respiratory function and also predisposes to infection. Can be due to haemodynamic disturbances or increased capillary permeability due to alveolar wall injury

Haemodynamic oedema

- **Increased hydrostatic pressure**: Common; occurs first in the basal regions of the lung lower lobes (dependent oedema). Increased pulmonary venous pressure from left-sided heart failure, volume overload or pulmonary vein obstruction
    - **Histology**: Engorged alveolar capillaries, intra-alveolar finely granular pink transudative material, haemosiderin-laden macrophages ('heart failure cells'). IF long-standing, fibrosis and thickening of the alveolar walls with numerous haemosiderin-laden macrophages result in a grossly firm brown-coloured lung ('brown induration')
- **Decreased oncotic pressure**: Less common e.g. hypoalbuminemia, nephrotic syndrome, liver disease, protein-losing enteropathies
- **Lymphatic obstruction**: Rare

Oedema due to alveolar wall injury

Damage to either alveolar microvasculature or epithelium results in an inflammatory exudate starting in the interstitium and in severe cases, extends into the alveoli. Major component of **acute respiratory distress syndrome**

- **Direct injury**: Damage from infections e.g. bacterial pneumonia, inhaled gases, liquid aspiration, radiation, lung trauma
- **Indirect injury**: Systemic inflammatory response syndrome, drugs/chemicals etc.

Acute lung injury and acute respiratory distress syndrome

- **Acute lung injury (ALI)** = abrupt onset of hypoxemia and bilateral pulmonary oedema, in the absence of cardiac failure (i.e. non-cardiogenic)
- **Acute respiratory distress syndrome (ARDS)** = manifestation of severe ALI (clinical syndrome of progressive respiratory insufficiency)
- **Diffuse alveolar damage (DAD)** = histologic manifestation of ALI

Acute lung injury (ALI)

- **Causes**: Both pulmonary and systemic disorders; more than 50% of cases are caused by **sepsis**, **diffuse pulmonary infections, gastric aspiration and mechanical trauma** including head injuries. Other causes include other forms of physical trauma / injury e.g. near-drowning, inhaled irritants e.g. smoke, chemical injury e.g. barbiturate overdose, hematologic conditions e.g. transfusion-associated lung injury (TRALI), miscellaneous conditions e.g. pancreatitis, uraemia. If idiopathic = **acute interstitial pneumonia**

- **Pathogenesis**: Injury of pneumocytes and pulmonary endothelium initiates a vicious cycle of increasing inflammation and pulmonary damage that impairs alveolar gas exchange. The hypoxemia is exacerbated by ventilation-perfusion mismatch, as the lesions are not evenly distributed:
    - **Endothelial activation**: Early event. Can occur primarily as a response to circulating inflammatory mediators in severe tissue injury or sepsis, or secondarily to pneumocyte injury that is sensed by resident alveolar macrophages which then secrete mediators e.g. TNF that act on the endothelium
    - **Adhesion of neutrophils to activated endothelium and extravasation into interstitium and alveoli**: Neutrophils then degranulate and release inflammatory mediators and neutrophil extracellular traps, setting up the vicious cycle of inflammation and lung damage
    - **Accumulation of intra-alveolar fluid and formation of hyaline membranes**: Occurs as the endothelial activation and injury causes leaky pulmonary capillaries. Surfactant abnormalities also occur due to damaged Type II alveolar pneumocytes. Hyaline membranes then form as a result of organization of the protein-rich oedema fluid and dead alveolar epithelial cells
    - **Resolution of injury**: If the inflammatory stimulus is removed, macrophages remove intra-alveolar debris and secrete fibrogenic cytokines e.g. TGF-β and PDGF, stimulating fibroblast growth and collagen deposition, resulting in fibrosis of alveolar walls. Residual type II pneumocytes proliferate to replace type I pneumocytes, and uninjured capillary endothelium proliferates to restore the endothelium
- **Clinical findings**: Severe dyspnoea and tachypnoea, followed by respiratory failure, hypoxemia and cyanosis. Loss of functional surfactant results in lungs becoming stiff, requiring intubation and high ventilatory pressures. **Radiology**: Diffuse bilateral infiltrates. **Clinical course**: Moderately high mortality rate due to sepsis, multiorgan failure or severe lung injury. Most survivors recover pulmonary function but a minority develop chronic lung disease due to fibrosis.
- **Gross**: Heavy firm red boggy lungs
- **Microscopy**: **Diffuse alveolar damage** - congestion, interstitial and intra-alveolar oedema, inflammation, fibrin deposition and hyaline membranes lining alveolar walls (fibrin-rich oedema fluid mixed with degenerating necrotic epithelial cells). Proliferating or organizing stage – type II pneumocyte hyperplasia and granulation tissue. This can eventually resolve. Late fibrotic stage – if granulation tissue doesn't resolve, fibrosis of alveolar septa occurs

III. OBSTRUCTIVE AND RESTRICTIVE LUNG DISEASES

- **Obstructive lung disease** = diffuse airway disease (at any level of the respiratory tract) resulting in increase in resistance to airflow ($FEV_1/FVC < 0.7$)
- **Restrictive lung disease** = diseases causing reduced expansion of lung parenchyma, resulting in decreased total lung capacity (normal FEV_1/FVC). These include chronic interstitial and infiltrative lung diseases, and chest wall disorders (e.g. neuromuscular disorders, kyphoscoliosis)
- Some diseases can have overlapping features of both obstruction and restriction

Obstructive lung disease

- Includes **chronic obstructive pulmonary disease (COPD)**, **asthma** and **bronchiectasis.** There can be overlap between COPD and asthma in terms of reversibility of bronchospasm

Chronic obstructive pulmonary disease (COPD)

- Characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities caused by exposure to noxious particles or gases.
- **Risk factors**: Strongly associated with cigarette smoking. Other factors include poor lung development early in life, exposure to environmental and occupational pollutants, airway hyperresponsiveness and genetic polymorphisms
- 2 major clinicopathologic manifestations (can be found together in same patient): **emphysema** and **chronic bronchitis**
    - **Emphysema** = irreversible enlargement of airspaces distal to terminal bronchiole, with wall destruction. Also often subtle small airway fibrosis (distinct from chronic bronchitis) that contributes to airflow obstruction
        - Classification according to anatomic distribution: **centriacinar**, **panacinar**, **paraseptal**, **irregular**. Only centriacinar (95%) and panacinar emphysema cause clinically significant airflow obstruction; centriacinar emphysema occurs in **heavy smokers** with COPD and tends to involve the upper lung lobes, while panacinar emphysema occurs in **α1-antritrypsin deficiency** that is exacerbated by smoking and tends to involve the lower zones / lung bases. Paraseptal emphysema probably manifests as spontaneous pneumothorax in young adults, and irregular emphysema is clinically insignificant
        - **Pathogenesis**: Toxic injury from inhaled smoke and other noxious particles damage respiratory epithelium and cause inflammation as well as oxidative stress, resulting in parenchymal destruction. There can also be imbalance in the amount of proteases released from inflammatory and epithelial cells vs protective antiproteases (especially in patients with α1-antitrypsin deficiency – α1-AT is a major inhibitor of proteases especially elastase secreted by neutrophils during inflammation). Superimposed infections can cause acute exacerbations of existing disease
        - **Mechanism**: Airway obstruction results from loss of elastic tissue in the alveolar walls that surround respiratory bronchioles, leading to decreased radial traction and functional collapse of the respiratory bronchioles during expiration. This is exacerbated by small airway changes in smokers
        - **Gross**: Voluminous lungs that may overlap the heart anteriorly, with large air spaces that can form apical blebs or bullae in advanced disease
        - **Microscopy**: Abnormally large alveoli separated by thin septa with focal centriacinar fibrosis. Superimposed changes include small airway inflammation and vascular

changes from secondary pulmonary hypertension due to local hypoxemia and loss of capillary beds
        - **Note**: Emphysema can also occur in other conditions besides COPD e.g. **compensatory hyperinflation** after surgical removal of lung, **obstructive overinflation** due to tumor or foreign bodies in airways, **bullous emphysema** (large subpleural blebs/bullae) or interstitial emphysema (e.g. due to alveolar tears during coughing or thoracic trauma causing air to enter connective tissue of lung, mediastinum or subcutaneous tissue)
    - **Chronic bronchitis** = persistent cough with sputum production for at least 3 months in at least 2 consecutive years, in the absence of any other identifiable cause
        - **Pathogenesis**: Initiated by exposure to noxious /irritating inhaled substances e.g. cigarette smoke (90%), dust from grain, silica, causing mucus hypersecretion in the large and small airways that contributes to airway obstruction. The mucus may also be abnormal and dehydrated due to acquired dysfunction of cystic fibrosis transmembrane conductance regulator (CFTR), and is also ineffectively cleared by dysfunctional respiratory epithelial cilia (both caused by smoke). The cellular damage caused by the inhalants incites both acute and chronic inflammation. Long-standing inflammation and eventual fibrosis involving small airways lead to chronic airway obstruction. Infections may help maintain and acutely exacerbate chronic bronchitis
        - **Gross**: Hyperemia, swelling and edema of mucous membranes, with excessive mucinous or mucopurulent secretions
        - **Microscopy**: Chronic inflammation, smooth muscle hypertrophy in bronchiolar wall, peribronchial fibrosis, goblet cell hyperplasia in small airways and enlargement of submucosal glands in trachea and bronchi (Reid index = ratio of thickness of mucous gland layer to thickness of the wall between epithelium and cartilage). In severe cases, fibrous obliteration of the lumen of the bronchioles occurs (bronchiolitis obliterans). Lining respiratory epithelium may undergo squamous metaplasia and dysplasia due to toxic effects of cigarette smoke
- **Clinical findings**: Usually have smoking history of >40 pack-years. Mostly present with slowly increasing dyspnoea on exertion and chronic productive cough that is worse in the morning; some may present with acute exacerbations causing by superimposed infections, mimicking asthma. Clinical picture depends on disease severity and proportion of emphysematous and bronchitic changes (most patients are a mixture of both):

Chronic bronchitis ("blue bloaters")	**Emphysema ("pink puffers")**
Younger (40-45yo)	Older (50-75 yo)
Cough and sputum+++ with frequent infections, dyspnoea mild and late	Cough and sputum+/- with occasional infections, dyspnoea severe and early
Early respiratory insufficiency due to increased airway resistance >> Cor pulmonale common	Respiratory insufficiency and cor pulmonale usually only end-stage as airway resistance is usually normal / slightly increased

- **Complications**: Progressive lung dysfunction causing pulmonary hypertension, cor pulmonale, death due to heart failure, death due to acute respiratory failure from superimposed infections, fatal pneumothorax from rupture of subpleural blebs (in emphysematous patients)
- **Treatment**: Smoking cessation, oxygen therapy, long-acting bronchodilators with inhaled corticosteroids, antibiotics, physical therapy, bullectomy +/- lung transplant

Asthma

- Characterized by largely reversible bronchoconstriction caused by airway hyperresponsiveness to a variety of stimuli, resulting in chronic airway inflammation and variable expiratory airflow obstruction and producing episodic symptoms of wheezing, shortness of breath, chest tightness and cough. Rarely, an acute attack can be unremitting (acute severe asthma)
- Several distinct clinical phenotypes with different pathogenesis:
    - **Atopic**: IgE-mediated (type I) hypersensitivity reaction. Usually starts in childhood with evidence of allergen sensitization and immune activation (e.g. dust, pollen, dander, food), often associated with allergic rhinitis or eczema and atopic family history
    - **Non-atopic**: No evidence of allergen sensitization (skin prick test usually negative)
    - **Drug-induced**: e.g. aspirin (inhibits cyclooxygenase pathway of arachidonic acid metabolism, leading to rapid decrease in prostaglandin E_2 that usually inhibits enzymes that generate proinflammatory mediators such as leukotrienes)
    - **Occupational**: Repeated exposure to fumes (e.g. epoxy resins), organic and chemical dusts, gases or other chemicals can induce varying mechanisms e.g. type I reactions, direct liberation of bronchoconstrictors and other unknown hypersensitivity reactions
- **Triggers of episodes of bronchospasm**: Respiratory infections (esp. viral), irritants (smoke, fumes), cold air, stress, exercise
- **Pathogenesis of atopic asthma**: Th2-mediated IgE response to environmental allergens in genetically predisposed individuals. The resulting airway inflammation causes release of potent inflammatory mediators (causing largely reversible bronchoconstriction), as well as airway remodeling (which may cause irreversible airway obstruction)
    - **Th2-mediated IgE response**: Exaggerated Th2 response to normally harmless environmental antigens, secreting cytokines (IL-4, IL-5 and IL-13) that promote inflammation (including eosinophil recruitment) and mucus secretion, as well as stimulating B cells to produce IgE antibodies that bind to Fc receptors on submucosal mast cells. Upon repeated allergen exposure, mast cell degranulation and production of cytokines and other mediators occurs, inducing the early-phase (immediate hypersensitivity) and late-phase reactions
        - **Early-phase reaction**: Bronchoconstriction, increased mucus production, vasodilation, increased vascular permeability
        - **Late-phase reaction**: Recruitment of leukocytes (eosinophils, neutrophils, more T cells e.g. Th17 cells that produce IL-17 to recruit neutrophils)
        - **Mediators**: Those that respond to pharmacologic intervention include leukotrienes C_4, D_4, E_4, acetylcholine, IL-5, galectin-10 (forms Charcot-Leyden crystals that induce inflammation and mucus production). Other mediators that are present but may

have only minor contributions / not well-studied include histamine, prostaglandin D_2, platelet-activating factor, IL-4, IL-13, TNF, chemokines etc.
    - **Genetic susceptibility**: Multigenic; often associated with other allergic disorders e.g. eczema
    - **Environmental factors**: Asthma occurs in industrialized societies, hypothesized to be due to airborne pollutants that serve as allergens or limited exposure to microbial antigens ("hygiene hypothesis"). Respiratory viral infections in the young may also be co-factors
- **Clinical findings**: Acute attack usually lasts a few hours – chest tightness, dyspnoea, wheezing, coughing. Rarely, acute severe attack (status asthmaticus) persists for days / weeks that causes marked cyanosis or death. Most patients are asymptomatic between attacks, although some may experience a constant low level of symptoms. **Treatment**: Depends on disease severity - bronchodilators, glucocorticoids, leukotriene antagonists. **Clinical course**: 50% of childhood asthma remits in adolescence; may return in adulthood; other cases have a decline in baseline lung function over time
- **Gross**: Overinflated lungs with small areas of atelectasis, thick mucus plugs occluding bronchi and bronchioles
- **Microscopy**: Mucus plugs that contain shed epithelium, numerous eosinophils, Charcot Leyden crystals, features of airway remodeling (thickened airway wall, sub-basement membrane fibrosis, increased vascularity, submucosal gland hypertrophy and increased numbers of goblet cells, bronchial wall muscle hypertrophy/hyperplasia)

Bronchiectasis

- Characterized by inflammatory destruction of smooth muscle and elastic tissue due to persistent or severe infections, resulting in permanent dilation of bronchi and bronchioles
- **Associations**: Congenital / hereditary conditions that predispose to chronic infections (e.g. cystic fibrosis, immunodeficiencies); Severe necrotizing pneumonia; Bronchial obstruction (e.g. tumour, foreign body, mucus impaction); Immune disorders (e.g. rheumatoid arthritis); Idiopathic (50% of cases; likely due to dysfunctional host immunity to infectious agents, causing chronic inflammation)
- **Pathogenesis**: Two main factors - obstruction interfering with drainage of secretions and infection (the latter is usually the result of a defect in airway clearance e.g. obstruction). Associated conditions:
    - **Cystic fibrosis**: thick viscous secretions lead to airway obstruction, which predisposes to chronic bacterial infections. The infections cause widespread damage to airway walls, resulting in markedly dilated bronchi and progressive fibrous obliteration of smaller bronchioles (bronchiolitis obliterans)
    - **Primary ciliary dyskinesia**: ciliary dysfunction again prevents mucociliary clearance and predisposes to recurrent infections that lead to bronchiectasis
    - **Allergic bronchopulmonary aspergillosis**: hyperimmune response to *Aspergillus fumigatus* that occurs in patients with asthma or cystic fibrosis and results in mucus plug formation, leading to development of bronchiectasis
- **Clinical findings**: Episodes of severe persistent productive cough with foul-smelling +/- bloody sputum, dyspnoea and orthopnoea, and possibly haemoptysis that can be massive; precipitated by

upper respiratory tract infections or introduction of new pathogenic agents. **Complications**: Cor pulmonale, hematogenous spread of infection (brain abscesses), secondary amyloidosis. **Treatment**: Antibiotics and physical therapy

- **Gross**: Dilatation of airways filled with mucopurulent secretions, especially the distal bronchi and bronchioles usually in bilateral lower lobes, up to the pleural surfaces. Can be localized if due to obstruction by tumour / foreign bodies.
- **Microscopy**: Depends on the activity / chronicity of disease – active cases have intense acute and chronic inflammation in the walls of bronchi and bronchioles, associated with ulceration, squamous metaplasia +/- lung abscess formation; chronic cases have fibrosis of the bronchial/bronchiole walls and peribronchiolar fibrosis, leading to subtotal / total lumen obliteration

Chronic diffuse interstitial (restrictive) diseases

- Heterogeneous group of disorders characterized by lung interstitial inflammation and fibrosis, associated with pulmonary function studies indicating restrictive lung disease (decreased diffusion capacity, lung volume and lung compliance)
- **Classification**: Based on histology and clinical features. However, in advanced disease, distinguishing between categories becomes difficult due to diffuse lung scarring (end-stage or "honeycomb" lung)
- **Clinical findings**: Dyspnoea, tachypnoea, end-inspiratory crackles, eventual cyanosis
- **Imaging**: Bilateral disease with small nodules, irregular lines or ground-glass shadows
- **Complications**: secondary pulmonary hypertension and cor pulmonale (right-sided heart failure)

Entity	Key features
Fibrosing diseases	
Usual interstitial pneumonia (UIP) / Idiopathic pulmonary fibrosis (IPF)	• **IPF** = clinicopathologic syndrome marked by progressive interstitial pulmonary fibrosis and respiratory failure o **Cause:** Unknown – likely genetic and environmental factors. Majority are smokers although exact role not known yet • **UIP** = histologic pattern of fibrosis that is seen in IPF, as well as other disease e.g. connective tissue diseases o **Micro**: Patchy interstitial fibrosis with spatial and temporal variation (characteristic early lesion is fibroblastic foci, while late lesion is honeycomb fibrosis). Acute exacerbations can have superimposed DAD
Nonspecific interstitial pneumonia (NSIP)	• Better prognosis than patients with UIP / IPF • Associated with connective tissue diseases but can also be idiopathic
Cryptogenic organizing pneumonia (COP)	• Usually after infection or inflammatory injury to the lung e.g. viral / bacterial pneumonia, inhaled toxins, connective tissue disease
Connective tissue-disease associated	• E.g. SLE, rheumatoid arthritis, systemic sclerosis • **Micro**: Can have different histologic patterns e.g. NSIP, UIP, OP
Pneumoconioses	• Lung disease due to inhalation of mineral dusts during work (occupational e.g. coal dust in coal mining, silica in sandblasting, asbestos in shipyard workers), organic dusts (e.g. mouldy hay during farming) as well as chemical fumes and vapours • Development of disease depends on the amount of dust retention, the size, solubility and cytotoxicity of the dust particle, particle uptake by / transit across epithelial cells and activation of the inflammasome after the

	particles are phagocytosed by macrophages. Tobacco smoking is a major aggravating factor, especially for asbestos. Likely also has a genetic component since only a small percentage of exposed people develop disease • **Coal workers' pneumoconiosis**: lung disease caused by inhalation of coal particles and other admixed forms of dust – can be "simple" (coal macules or nodules in the lung) or "complicated" (progressive massive fibrosis that significantly affects lung function). **Anthracosis** = accumulation of carbon-laden macrophages in the lung, seen in coal miners and, to some extent, in city dwellers and smokers; asymptomatic and usually does not cause dysfunction • **Asbestos-related diseases**: localized fibrous pleural plaques (most common), diffuse pleural fibrosis (rare), recurrent pleural effusions, asbestosis (lung interstitial fibrosis), lung carcinoma, mesothelioma o Asbestos fibres are crystalline hydrated silicates; their different forms (size, shape, solubility) and concentration affect their disease-causing capabilities o Asbestos fibres are phagocytosed by macrophages and activate the inflammasome, stimulating the release of proinflammatory factors and fibrogenic mediators o Asbestos fibres also act as both tumour initiator and promoter o **Micro**: Asbestosis = diffuse interstitial fibrosis with asbestos bodies (golden brown, fusiform or beaded rods with a translucent center). Pleural plaques do not contain asbestos bodies
Drug reactions, radiation pneumonitis	• Medications can cause various acute and chronic lung changes • Radiation pneumonitis is a complication of radiotherapy for thoracic tumours and can have both acute and chronic forms
Granulomatous diseases	
Sarcoidosis	• Systemic granulomatous disease of unknown cause that can involve various tissues and organs, most frequently hilar lymph nodes/lung • **Micro**: Non-necrotizing granulomas, often associated with fibrosis with chronicity (need to exclude other causes e.g. infections, berylliosis)
Hypersensitivity pneumonitis (extrinsic allergic alveolitis)	• Immunologically mediated, predominantly interstitial lung disorders caused by intense and often prolonged exposure to inhaled organic antigens e.g. proteins from bird secretions/feathers (pigeon breeder's lung), thermophilic bacteria in heated water reservoirs (humidifier or air-conditioner lung)
Eosinophilic diseases	
Acute eosinophilic pneumonia	• Unknown cause; rapid onset with respiratory failure; responds to steroids
Secondary eosinophilia	• Various associations e.g. fungal infections, hypersensitivity pneumonitis
Idiopathic chronic eosinophilic pneumonia	• Diagnosed after excluding other causes of pulmonary eosinophilia
Smoking-related diseases	
Desquamative interstitial pneumonia (DIP)	• All patients are cigarette smokers; typically respond to steroids • **Micro**: Numerous pigmented macrophages in alveolar spaces
Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD)	• Histologic findings are common and can be incidental in smokers; the term "RB-ILD" is used only for patients who develop significant pulmonary dysfunction

IV. PULMONARY EMBOLISM AND PULMONARY HYPERTENSION

Pulmonary embolism

- Much more common than large vessel pulmonary thrombosis
- **Pathogenesis**:
    - Thrombi, usually in the deep leg veins (>95%) and sometimes right cardiac atrium, form in patients with increased risk of thrombophilia (primary or secondary hypercoagulable states e.g. antiphospholipid syndrome, cancer, recent surgery (especially leg surgery), immobility, oral contraceptives) and embolise to the lungs. Rarely, pulmonary emboli may also consist of fat, air, bone marrow (from fractures) or tumour
    - Clinical significance of the embolus depends on extent of pulmonary artery occlusion and cardiovascular health of the patient. Emboli can cause (i) respiratory compromise (due to nonperfusion of a ventilated segment i.e. ventilation-perfusion mismatch) and (ii) hemodynamic compromise (due to increased resistance to pulmonary blood flow); the latter can cause sudden death or acute cor pulmonale (right heart failure)
- **Clinical findings**: Large pulmonary emboli can present as sudden death, and is one of the causes of pulseless electrical activity (PEA). If the patient survives, symptoms like chest pain, dyspnoea and shock mimic myocardial infarction. Smaller emboli may be asymptomatic or cause dyspnoea, mild transient chest pain, pleuritic pain, cough. **Clinical course**: Smaller emboli often resolve via contraction and fibrinolysis; multiple small emboli may lead to pulmonary hypertension and cor pulmonale. Most importantly, there is a risk of recurrence, especially in patients with underlying risk factors. **Treatment**: Anticoagulation, supportive measures; prevention e.g. IVC filter
- **Gross**: Large emboli lodge in the main pulmonary artery, its branches or at the bifurcation ('saddle embolus'). Smaller emboli travel more distally (usually lower lung lobes) and can cause a wedge-shaped area of haemorrhage or infarction (the latter is more common if the patient's cardiovascular function is already poor and the bronchial artery supply is insufficient to sustain the lung parenchyma). **Lung infarcts** are classically haemorrhagic, with the pleural surface covered by a fibrinous exudate. Within 48h, the infarct becomes paler and red-brown as the red blood cells lyse and haemosiderin is produced. Eventually, the infarct is replaced by fibrous tissue and forms a scar
- **Micro**: Lines of Zahn distinguish a pulmonary embolus from a postmortem blood clot. Areas of infarct show ischaemic necrosis of alveolar walls, bronchioles and vessels

Pulmonary hypertension

- Mean pulmonary artery pressure ≥ 25mmHg (at rest)
- Can be classified based on **aetiology**:
    (1) **Pulmonary arterial hypertension**: involvement of small pulmonary muscular arteries e.g. in autoimmune diseases like systemic sclerosis. Can also be "idiopathic" although they have a strong genetic component

(2) **Pulmonary hypertension due to congenital or acquired heart disease**: e.g. mitral stenosis causing increase in left atrial pressure and pulmonary venous pressure that is transmitted to the pulmonary arterial vasculature
(3) **Pulmonary hypertension due to lung disease / hypoxia**: e.g. interstitial lung diseases that obliterate alveolar capillaries, causing increased pulmonary resistance to blood flow
(4) **Chronic thromboembolic pulmonary hypertension** and other obstructions: recurrent pulmonary emboli reduce the functional cross-sectional area of the pulmonary vasculature
(5) **Pulmonary hypertension with unclear/multifactorial mechanisms**

- **Morphology**: Medial hypertrophy of pulmonary muscular and elastic arteries, and right ventricular hypertrophy

V. PULMONARY INFECTIONS

Pneumonia = infection of lung parenchyma

- **Pathogenesis**: Microbial organisms overwhelm antimicrobial defence mechanisms
  - **Impaired local defence mechanisms**: Loss/suppression of cough reflex predisposing to aspiration of gastric contents; dysfunctional mucociliary apparatus e.g. due to smoking; accumulation of secretions e.g. bronchiectasis; interference with phagocytic and bactericidal activities of alveolar macrophages e.g. due to alcohol, tobacco smoke; pulmonary congestion and oedema
  - **Lowered systemic host resistance**: Chronic diseases, immunologic deficiencies, immunosuppressive agents, leukopenia
- **Classification**: according to aetiologic agent or clinical setting if no pathogen is isolated (which provides a guide for empiric antimicrobial therapy)

Pneumonia syndrome	Common organisms	Key features
Community-acquired acute pneumonia (CAP)	*Streptococcus pneumoniae* (most common) *Haemophilus influenzae* (children, also acute exacerbation of COPD) *Mycoplasma pneumoniae* (children, young adults) Viruses: influenza, respiratory syncytial virus	• Lung infection in otherwise healthy individuals acquired from the normal environment • **Bacterial infection** often follows upper respiratory tract viral infection; often presents with high fever, chills and productive cough • **Viral pneumonia** is usually mild but can have complications that lead to morbidity and mortality
Health care-associated pneumonia (HCAP)	*Staphylococcus aureus* (methicillin-sensitive (MSSA), methicillin-resistant (MRSA)) *Pseudomonas aeruginosa* *Streptococcus pneumoniae*	• **Risk factors**: hospitalization of at least 2 days within the recent past; nursing home/long term care resident; recent attendance of a hospital/haemodialysis clinic; recent IV antibiotics, chemotherapy or wound care • Higher mortality than CAP
Hospital-acquired pneumonia (HAP)	Gram-negative rods: Enterobacteriaceae (e.g. *Klebsiella* spp.), *Pseudomonas* spp.	• Acquired during a hospital stay

	Gram-positive cocci: *Staphylococcus aureus* (usually MRSA)	• **Risk factors**: severe underlying disease, immunosuppression, prolonged antibiotic therapy, invasive access devices, mechanical ventilation • Often serious and life-threatening
Aspiration pneumonia	Anaerobic oral flora admixed with aerobic bacteria	• **Risk factor**: Abnormal gag and swallowing reflex e.g. in debilitated patients or those who aspirate gastric contents while unconscious or during repeated vomiting • Combination of chemical (gastric acid) and bacterial pneumonia with high mortality or resulting lung abscess
Chronic pneumonia	Nocardia, Actinomyces Granulomatous: *Mycobacterium tuberculosis*, atypical mycobacteria, *Histoplasma capsulatum*	• Usually in immunocompetent patients, with the organism often resulting in a granulomatous reaction
Necrotizing pneumonia and Lung abscess	Anaerobic bacteria *Staphylococcus aureus, Klebsiella pneumoniae*	See section "Lung abscess" below
Immunocompromised host	Cytomegalovirus *Pneumocystis jirovecii* *Mycobacterium avium intracellulare complex (MAC)* Invasive aspergillosis/candidiasis	• Risk of opportunistic infections on top of usual pathogenic organisms, which cause a high mortality

- **Complications**: Abscess formation (especially in pneumococcal or *Klebsiella* infections), spread to pleural cavity (empyema), systemic bacteraemic dissemination (e.g. to heart valves, brain, joints causing septic endocarditis, meningitis, arthritis etc.)
- **Morphology:**
    - Bacterial pneumonia: usually has 2 patterns based on anatomic distribution, but often overlap. The same organisms can produce either pattern, depending on host factors
    - **Bronchopneumonia**: Patchy lung consolidation that is frequently bilateral and often basal. Consolidated areas of acute suppurative inflammation that fills the bronchi, bronchioles and adjacent alveolar spaces
    - **Lobar pneumonia**: Consolidation of a large portion / entire lobe. 4 classic stages of inflammatory response –
        - **Congestion**: Heavy boggy red lung. Engorged vessels and intra-alveolar oedema containing few neutrophils; can have numerous bacteria
        - **Red hepatization**: Red, firm lung (resembles texture of liver). Extensive exudate (neutrophils, red cells, fibrin) in alveolar spaces
        - **Gray hepatization**: Gray-brown colour. Disintegration of red cells but persistence of fibrinopurulent exudate
        - **Resolution**: Breaking down of intra-alveolar exudate that is resorbed, ingested by macrophages, expectorated or organized by fibroblasts
    - Any associated fibrinous pleuritis also resolves or leaves fibrous thickening / adhesions

- Viral pneumonia: Predominantly interstitial inflammation (usually lymphocytic – sometimes referred to as "atypical pneumonia") and interstitial oedema; when complicated by ARDS, may also show changes of diffuse alveolar damage

Lung abscess

- Local suppurative process that causes necrosis of lung tissue, caused by a variety of bacteria
- **Causes**:
  - **Aspiration of infective material**: Most frequent cause; first results in pneumonia then progresses to lung abscess. Occurs in patients with suppressed cough reflexes (e.g. acute alcohol intoxication, seizure), severe dysphagia (e.g. neurologic deficits), protracted vomiting, poor dental hygiene
  - **Post-pneumonia**: Especially in post-transplant or immunosuppressed patients. Organisms are usually *S.aureus, K.pneumoniae*, pneumococcus
  - **Septic embolism**: Infected emboli from thrombophlebitis or infective endocarditis
  - **Post-obstructive pneumonia:** e.g. obstruction from lung tumours
  - **Miscellaneous**: e.g. direct extension of suppurative infections from adjacent structures e.g. oesophagus, traumatic penetration of lungs, haematogenous seeding of lungs
  - **Cryptogenic**
- **Clinical features**: Similar to bronchiectasis – productive purulent cough, fever, chest pain and weight loss. Need to exclude underlying carcinoma (10-15% of cases) in older patients
- **Complications**: Extension into pleural cavity, haemorrhage, production of septic emboli to brain or meninges, secondary amyloidosis (type AA)
- **Gross**: Cavity. Single (more often in aspiration; right-sided) or multiple (more often due to pneumonia or bronchiectasis in which they are basal and diffusely scattered; or any region of the lungs if due to septic emboli)
- **Micro**: Suppurative destruction of lung parenchyma within the central area of cavitation; may have a surrounding fibrous wall in chronic cases

VI. LUNG TUMOURS

Primary lung tumours: Vast majority (90-95%) are carcinomas

Secondary lung tumours: The lung is the most common site of metastatic tumours (both carcinomas and sarcomas arising anywhere in the body)

Lung carcinoma

- Most common cause of cancer mortality worldwide, with different histologic subtypes
- **Risk factors**:
  - **Tobacco smoking**: 80% of lung cancers occur in active smokers or those who smoked recently, although only 10-15% of smokers develop lung cancer, likely due to other factors

that interact with and modify the effects of smoking e.g. P450 enzyme polymorphisms. Exposure to carcinogens in secondhand smoke also contribute to lung cancer
    - **Industrial chemicals**: e.g. asbestos, arsenic, vinyl chloride, high-dose ionizing radiation
    - **Air pollution**: Likely adds to risk in smokers / those exposed to secondhand smoke, e.g. through chronic exposure to air particles in smog that cause lung irritation and chronic inflammation
- **Pathogenesis**: Stepwise accumulation of oncogenic 'driver' mutations resulting in neoplastic transformation of pulmonary epithelial cells. Commonly divided into non-small cell (including adenocarcinoma, squamous cell carcinoma, other types) and small cell carcinoma based on behaviour and prognosis. The molecular features present depend on the histologic tumour type:
    - **Adenocarcinoma**: Most common type in never-smokers, although it is also associated to a lesser extent with smoking. A third of adenocarcinomas have oncogenic gain-of-function mutations involving growth factor receptor signalling pathways that can be targeted by specific inhibitors e.g. tyrosine kinase receptors (EGFR, ALK, ROS1) or their downstream molecules (KRAS – usually in smokers)
    - **Squamous cell carcinoma**: Highly associated with smoking and has diverse genetic aberrations. Most have *TP53* mutations, often as an early event, and may also have *FGFR1* amplification
    - **Small cell carcinoma**: Almost always smoking-related and the highest mutational burden, with inactivation of both *TP53* and *RB*. May also have *MYC* amplification
- **Precursor lesions**: There are morphologic precursor epithelial lesions which do not necessarily all progress to cancer
- **Classification**: Based on histologic type. A small proportion of cancers can have mixed types

Histologic subtype	Key morphologic features
Adenocarcinoma (50%)	• Usually arise in peripheral lung and smaller • **Precursor lesions**: atypical adenomatous hyperplasia, adenocarcinoma in-situ • **Micro**: Invasive malignant epithelial tumour with glandular differentiation or mucin production. Histologic patterns include acinar, lepidic, papillary, micropapillary and solid
Squamous cell carcinoma (20%) M>F, smokers	• Usually arise in the central/hilar region. May be centrally cavitating • **Precursor lesions**: squamous dysplasia, carcinoma in-situ in the bronchial epithelium • **Micro:** Sheets of malignant epithelial cells with keratinisation and/or intercellular bridges
Small cell neuroendocrine carcinoma (15%) Smokers. Most aggressive	• May be central or peripheral in location • **Precursor lesions**: None known • **Micro**: Sheets of round, oval or spindled cells with high N:C ratios, scant cytoplasm, frequent nuclear molding, granular (salt and pepper) chromatin. Prominent mitoses and often necrosis
Large cell neuroendocrine carcinoma	• High grade neuroendocrine carcinoma like small cell NEC but with larger tumour cells

- **Tumour spread**:
  - **Local/regional**: Direct extension to pleural surface, pleural cavity and/or pericardium; Lymphatic spread to bronchial, tracheal and mediastinal lymph nodes
  - **Distant spread**: Through both lymphatic and haematogenous pathways, especially adrenal glands, liver, brain and bone
- **Local effects**:
  - **Bronchial obstruction**: Focal emphysema or atelectasis of the distal lung segment, bronchiectasis, pulmonary abscesses
  - **Superior vena cava syndrome**: The tumour may also compress or invade the superior vena cava causing venous congestion and oedema of the head and arm
  - **Pericarditis / pleuritis**: Extension to pericardium / pleura +/- effusions
  - **Involvement of nerve plexus**: Esp. apical lung cancers that may invade the cervical sympathetic plexus resulting in Horner syndrome (Pancoast tumours)
- **Clinical features:** Usually in patients >50 yo, with cough, weight loss, chest pain, dyspnoea. Other presenting complaints arise from local tumour effects e.g. haemoptysis from tumour haemorrhage in an airway, hoarseness from recurrent laryngeal nerve invasion, dysphagia from oesophageal invasion, infective symptoms from obstructive pneumonia caused by tumour; patients may also present with symptoms from metastases e.g. headache from brain metastases
- **Paraneoplastic syndromes**: Occurs in 1-10% of lung cancer patients

Hormone / hormone-like factor	**Syndrome / manifestation**
Anti-diuretic hormone (ADH)*	Inappropriate ADH secretion (SIADH) → hyponatremia
Adrenocorticotropic hormone (ACTH)*	Cushing syndrome
Parathormone, parathyroid hormone-related peptide, prostaglandin E ^	Hypercalcemia
Calcitonin	Hypocalcaemia
Gonadotropins	Gynaecomastia
Serotonin, bradykinin	Carcinoid syndrome
Other systemic manifestations	
Lambert-Eaton myasthenic syndrome, peripheral neuropathy, acanthosis nigricans, leukemoid reactions, Trousseau syndrome, hypertrophic pulmonary osteoarthropathy (finger clubbing)	

** usually small cell carcinoma; ^ usually squamous cell carcinoma*

- **Prognosis**: Depends on stage, histologic type (adenocarcinoma and squamous cell carcinoma better than small cell carcinoma) and molecular changes present (*KRAS* mutations in adenocarcinomas have poorer prognosis regardless of treatment). **Treatment**: Thoracic surgery, radiation, chemotherapy, tyrosine kinase inhibitors (adenocarcinomas), checkpoint inhibitor therapy. Small cell carcinoma is sensitive to radiation therapy and chemotherapy.

Carcinoid tumours

- Low grade malignant epithelial tumours with neuroendocrine differentiation; classified into **typical** and **atypical** based on mitotic count and presence of necrosis
- **Clinical findings**: Intraluminal growth can cause symptoms such as cough, haemoptysis, obstructive pneumonia, bronchiectasis, emphysema and atelectasis. Functioning lesions (~10% of carcinoids)

can produce carcinoid syndrome (intermittent attacks of diarrhoea, flushing and cyanosis). **Clinical course**: Most do not metastasize but follow a relatively benign course and can be resected

- **Gross**: Central lesions tend to project into the bronchus lumen; peripheral lesions are solid and nodular
- **Microscopy**: Organoid, trabecular, palisading, ribbon or rosette-like arrangements of relatively monomorphic cells and round nuclei with granular 'salt and pepper' chromatin

Metastatic tumours to the lung

- **Gross**: Typically multiple discrete nodules (cannonball lesions) scattered throughout all lobes, especially at the lung periphery. Other patterns of involvement: single nodule; endobronchial or pleural involvement; pneumonic consolidation
- **Microscopy**: Histology of the primary tumour. Some metastatic adenocarcinomas may have foci of lepidic growth pattern mimicking primary lung adenocarcinoma in-situ

VII. PLEURA

Pleural effusion

- Accumulation of fluid in the pleural space (normal <15ml); manifestation of both primary and secondary pleural diseases
- Can occur in various settings due to increased hydrostatic pressure (e.g. congestive heart failure), increased vascular permeability (e.g. pneumonia), decreased osmotic pressure (e.g. nephrotic syndrome), increased intrapleural negative pressure (e.g. atelectasis) or decreased lymphatic drainage (e.g. mediastinal carcinomatosis)

Inflammatory effusions

- **Serous, serofibrinous and fibrinous pleuritis**: usually due to inflammation of the underlying lung e.g. tuberculosis, pneumonia, lung infarction
    - Other causes may be due to systemic conditions e.g. rheumatoid arthritis, uraemia, metastatic pleural involvement, radiotherapy for lung/pleural tumours
    - Usually resolves with resorption of fluid +/- organisation of the fibrinous component
- **Empyema (purulent pleural exudate):** due to bacterial or mycotic seeding of the pleural space (e.g. spread from intrapulmonary infections or more distant sources)
    - Volume is usually small and the pus gets walled off by fibrosis; usually organizes into dense, tough fibrous adhesions that obliterate the pleural space or encases the lung (empyema peel) and can restrict lung expansion
- **Haemorrhagic pleuritis**: Sanguineous inflammatory exudate (different from haemothorax); uncommon and tumour involvement of the pleura must be excluded

Non-inflammatory effusions

- **Hydrothorax (serous fluid)**: Most commonly due to heart failure; also seen in other systemic conditions associated with generalized oedema e.g. renal failure, liver cirrhosis
- **Haemothorax (blood)**: Usually due to trauma, surgery or rupture of aortic aneurysm
- **Chylothorax (lymph fluid)**: Milky white appearance due to finely emulsified fats. Usually due to thoracic duct trauma or obstruction of a major lymphatic duct (usually by malignancy)

Pneumothorax

- Air/gas in pleural cavity, usually associated with emphysema, asthma or tuberculosis
- **Spontaneous pneumothorax**: As a complication of any pulmonary disease that causes emphysematous change, a communicating abscess cavity, or idiopathic (usually in young people due to rupture of small, peripheral usually apical, subpleural blebs)
- **Traumatic pneumothorax**: Usually due to perforating injury to chest wall
- **Tension pneumothorax**: When a pleural defect acts as an air valve allowing air entry during inspiration but does not allow air escape during expiration, resulting in progressively increasing intrapleural pressure that can compress and cause deviation of vital mediastinal structures away and compress the contralateral lung

Pleural tumours

Secondary involvement of the pleura by metastases is more common than primary pleural tumours, usually from lung or breast primary tumours and often producing a serous or serosanguineous pleural effusion

Malignant mesothelioma

- Malignant tumour arising from mesothelial cells lining the serous cavities
- **Risk factors**: Asbestos exposure (long latent period; risk is not magnified by smoking, unlike asbestos-related lung carcinomas)
- **Clinical findings**: Presents with chest pain, dyspnoea, recurrent pleural effusions. Generally poor prognosis
- **Gross**: Diffuse soft greyish-pink tumour arising from either visceral or parietal pleura; usually associated with extensive pleural effusion and direct invasion of thoracic structures
- **Microscopy**: Epithelioid (60-80%), sarcomatoid (10%) or biphasic (10-15%) morphology