Atelectasis
- either incomplete expansion of the lungs (neonatal) or collapse of previously inflated lung, producing areas of relatively airless pulmonary parenchyma
- reduces oxygenation, predisposes to infection
- reversible except if caused by contraction
  - acquired either:
    - resorption atelectasis (obstruction airway, resorption trapped oxygen)
      - mucus plugging eg asthma, bronchitis, bronchiectasis, post op, FBs
    - mediastinum shifts towards affected lung
    - compression atelectasis
      - effusion, pneumothorax, haemothorax, peritonitis – basal atelectasis
      - mediastinum shift away from affected lung
    - contraction atelectasis
      - when local or general fibrotic changes in lung prevent full expansion

Acute Lung Injury
- a spectrum of pulmonary lesions (endothelial and epithelial)
- initiated by many factors
- susceptibility my be heritable
- mediators include cytokines, oxidants, growth factors (incl TNF, IL1, IL6, IL10, TGFβ)
- may manifest as congestion, oedema, surfactant disruption, atelectasis
- may progress to ARDS or acute interstitial pneumonia

Pulmonary Oedema
- most common haemodynamic mechanism: ↑ hydrostatic pressure in LVF
- heavy, wet lungs – initially basal due to greater hydrostatic pressure
- alveolar capillaries engorged, intra-alveolar granular pink precipitate, alveolar microhaemorrhages and haemosiderin-laden macrophages (“heart failure” cells)
- longstanding LVF – many haemosiderin-laden macrophages, fibrosis, thickening alveolar walls – lungs firm and brown (brown induration)

Oedema caused by microvascular injury
- injury to capillaries of alveolar septa
- usually normal hydrostatic pressure
- oedema due to primary injury to vascular endothelium or damage to alveolar epithelial cells, with secondary microvascular injury
- results in leakage of fluids and proteins into interstitial space, and if severe also into alveoli
- can be localised (as in pneumonia) or diffuse (contributing to ARDS)

Classification/causes pulmonary oedema

Haemodynamic oedema
- ↑ hydrostatic pressure (↑ pulm venous pressure)
  - LVF (common)
  - volume overload
  - pulm vein obstruction
- ↓ oncotic pressure (less common)
  - hypoalbuminaemia
  - nephritic syndrome
  - liver disease
  - protein-losing enteropathies

Lymphatic obstruction (rare)

Oedema due to microvascular injury (alveolar injury)
- infections (pneumonia, septicaemia)
- inhaled gases (oxygen, smoke)
- liquid aspiration (gastric contents, near-drowning)
- drugs and chemicals (chemo – bleomycin, amphotericin B, heroin, kerosene, paraquat)
- shock, trauma
- radiation
- transfusion related
Oedema of undetermined origin
- high altitude
- neurogenic (CNS trauma)

Acute respiratory distress syndrome (diffuse alveolar damage)
- caused by diffuse alveolar capillary damage (DAD)
- rapid onset life threatening respiratory insufficiency, cyanosis and severe arterial hypoxaemia refractory to oxygen therapy, may progress to multiorgan failure
- complication of may conditions, often a combination of predisposing factors (eg shock, O2 therapy, sepsis)

Conditions associated with development of ARDS
**Infection**
- sepsis, diffuse pulmonary infections (viral, mycoplasma, PCP, military TB), aspiration

**Physical injury**
- trauma incl head injuries, pulmonary contusion, near-drowning, fat emboli with fractures, burns, ionizing radiation

**Inhaled irritants**
- oxygen toxicity, smoke, irritant gases/chemicals

**Chemical injury**
- overdose heroin, methadone, aspirin, barbiturate, paraquat

**Haematological conditions**
- multiple transfusions, DIC

**Pancreatitis**

**Uraemia**

**Cardiopulmonary bypass**

**Hypersensitivity reactions**

(>50% cases due to sepsis, pulmonary infections, aspiration or head injuries)

Pathogenesis ARDS
- central to causation: diffuse damage to alveolar capillary walls, with a number of steps leading to resp failure
- cf. respiratory distress of newborns due to lack of surfactant

1. result of cascade of cellular events initiated by infectious or non-infectious inflammatory stimuli
2. initial injury to either capillary endothelium (most frequently) or alveolar epithelium
3. as early as 30 minutes following acute insult (e.g., acid aspiration, trauma, exposure to bacterial LPS), ↑ synthesis IL-8 by pulmonary macrophages (potent neutrophil chemotactic and activating agent)
4. along with other cytokines eg IL1 and TNF, leads to pulmonary microvascular sequestration of neutrophils then margination into alveolar space where they are activated
5. activated neutrophils release variety of products incl oxidants, proteases, platelet-activating factor, and leukotrienes that cause active tissue damage
6. cause ↑ vascular permeability and alveolar oedema, loss of diffusion capacity, and surfactant inactivation caused by damage to type II pneumocytes, and hyaline membrane formation
7. release of macrophage inhibitory factor (MIF) sustains the ongoing inflammatory response
8. release of macrophage-derived fibrogenic cytokines such as transforming growth factor β (TGF-β) and platelet-derived growth factor (PDGF) stimulate fibroblast growth and collagen deposition associated with the healing phase of injury

![Image of ARDS pathogenesis](image-url)
Morphology ARDS
- acutely lungs heavy, red, firm, boggy. Congestion, interstitial and intra-alveolar oedema, inflammation, fibrin deposits. Alveolar walls lined with waxy hyaline membrane
- organising stage: type II epithelial cells proliferate to regenerate alveolar lining. Organisation and fibrosis of exudate – resolution unusual. +/- superimposed infection

Clinical course ARDS
- marked dyspnoea and tachypnoea but CXR initially normal
- ↑ cyanosis, hypoxemia, respiratory failure, appearance diffuse bilateral infiltrates on CXR.
- hypoxemia can become unresponsive to oxygen therapy, respiratory acidosis can develop
Poorly aerated regions still perfused, so V-Q mismatch and hypoxemia. Mortality ~60%.

Acute Interstitial Pneumonia
- clinicopathologic term used to describe widespread acute lung injury with a rapidly progressive clinical course similar to that seen in ARDS
- ARDS associated with known causes eg sepsis, pulmonary infection, gastric aspiration, and trauma, acute interstitial pneumonia is of unknown aetiology
- present with acute respiratory failure often following ~3/52 URTI-like illness ; mortality rate ~ 50%

Obstructive vs Restrictive Lung Diseases
2 categories diffuse pulmonary disease:

1. obstructive (or airway disease): ↑ resistance to airflow due to partial or complete obstruction
   - PFTs show limitation max airflow rates during forced expiration (measured FEV1)
   - exp flow obstruction due to airway narrowing (asthma), or loss elastic recoil (emphysema)
     - emphysema, chronic bronchitis, bronchiectasis, asthma
2. restrictive ↓ expansion lung parenchyma, with ↓ TLC
   - normal or proportionately ↓ flow rate
     - 1. chest wall disorders with normal lungs (e.g., neuromuscular diseases -polio, severe obesity, pleural diseases, kyphoscoliosis)
     - 2. acute or chronic interstitial and infiltrative diseases. (acute – ARDS; chronic - pneumoconioses, interstitial fibrosis of unknown aetiology, and most infiltrative conditions)

Obstructive Pulmonary Diseases
- emphysema, chronic bronchitis, asthma, bronchiectasis → common trigger (smoking)

Emphysema
abnormal permanent enlargement airspaces distal to terminal bronchiole, with destruction of walls and without fibrosis

<table>
<thead>
<tr>
<th>Disorders Associated with Airflow Obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Term</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
</tr>
<tr>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Emphysema</td>
</tr>
<tr>
<td>Small airway disease, bronchiolitis</td>
</tr>
</tbody>
</table>

Types of Emphysema
Classified according to anatomic distribution within the lobule (cluster of acini).
(1) centriacinar (centrilobular) – 95% cases
(2) panacinar
(3) paraseptal (distal acinar)
(4) irregular
Centriacinar (centrilobular) Emphysema
- central or proximal parts of acini, formed by respiratory bronchioles affected, distal alveoli spared
- more common and more severe in upper lobes
- walls of emphysematous spaces often contain large amounts of black pigment
- inflammation around bronchi and bronchioles is common
- in severe centriacinar emphysema, the distal acinus may be involved
- predominantly in heavy smokers, often in association with chronic bronchitis

Panacinar (panlobular) Emphysema
- acini uniformly enlarged from respiratory bronchiole to terminal blind alveoli
- occur more commonly in the lower zones and anterior margins of the lung
- associated with α₁-antitrypsin (α₁-AT) deficiency

Distal Acinar (Paraseptal) Emphysema
- proximal portion of acinus normal, but distal part is predominantly involved
- more severe in upper half of lungs
- multiple, continuous, enlarged airspaces from less than 0.5 cm to more than 2.0 cm in diameter, sometimes forming cystlike structures
- probably underlies many cases of spontaneous pneumothorax in young adults

Airspace Enlargement with Fibrosis (Irregular Emphysema)
- associated with scarring
- most common form of emphysema because most lungs at autopsy shows one or more scars from a healed inflammatory process - these foci of irregular emphysema are asymptomatic

Incidence
- fourth leading cause of morbidity and mortality in the US
- association with smoking

Pathogenesis
- mild chronic inflammation of airways, parenchyma, and pulmonary vasculature
- ↑ macrophages, CD8+ T lymphocytes, and neutrophils
- activated inflammatory cells release mediators, including leukotriene B4, IL-8, TNF that damage lung structures or sustain neutrophilic inflammation
- destruction of alveolar walls hypothesis protease-antiprotease mechanism (alveolar wall destruction from imbalance between proteases (mainly elastase) and antiproteases)
  - homozygous patients with genetic deficiency of protease inhibitor α1-AT have a ↑↑ risk of emphysema, compounded by smoking
- principal antielastase is α1-AT (others are secretory leukoprotease inhibitor in bronchial mucus and serum α1-macroglobulin)
- principal elastase activity derived from neutrophils (other elastases formed by macrophages, mast cells, pancreas, and bacteria)
- neutrophil elastase capable of digesting human lung, inhibited by α1-AT
α1-AT deficiency and emphysema (panacinar)
- reflects lack of antiprotease throughout acinus and susceptibility to chronic low-level proteolysis from neutrophils in transit through lung circulation
- any stimulus that ↑ number leukocytes in lung or release of elastase-containing granules ↑ elastolytic activity
- emphysema from destructive effect of high protease activity in low antiprotease activity
- in smokers, neutrophils and macrophages accumulate in alveoli (?possibly involves direct chemoattractant effects of nicotine as well as effects of reactive oxygen species in smoke)
- accumulated neutrophils activated and release granules, rich in cellular proteases (neutrophil elastase, proteinase 3, and cathepsin G), resulting in tissue damage
- smoking also enhances elastase activity in macrophages; macrophage elastase is not inhibited by α1-antitrypsin and can proteolytically digest this antiprotease
- neutrophils most important in α1-AT deficiency, but in more common smoking-related emphysema, both neutrophil and macrophage proteases play a role

Smoking and emphysema (centriacinar)
- smoking important in perpetuating oxidant-antioxidant imbalance
- normally lung contains healthy complement of antioxidants (superoxide dismutase, glutathione) that keep oxidative damage to minimum
- secondary consequence of oxidative injury is inactivation of native antiproteases, resulting in "functional" α1-antitrypsin deficiency even in patients without enzyme deficiency
- impaction of smoke particles, predominantly at bifurcation of respiratory bronchioles, results in influx of neutrophils and macrophages, both which secrete proteases
- a increase in protease activity localized in centriacinar region, together with the smoke-induced oxidative damage, causes centriacinar pattern of emphysema seen in smokers

Morphology
Panacinar emphysema
- large lungs, often overlapping the heart

Centriacinar emphysema
- lungs not particularly pale or large unless disease advanced
- upper two thirds of lungs are more severely affected

Large apical blebs or bullae characteristic of irregular emphysema secondary to scarring and distal acinar emphysema.

Microscopically:
- abnormally large alveoli separated by thin septa with only focal centriacinar fibrosis
- loss of attachments of alveoli to outer wall of small airways
- pores of Kohn so large that septa appear floating or protrude blindly into alveolar spaces with club-shaped end
- with advance of disease possibly blebs or bullae

Clinical Course
- no symptoms until >1/3 pulmonary parenchyma damaged
- dyspnoea first symptom; begins insidiously, steadily progressive
- cough or wheezing, expectoration variable, depend on extent of associated bronchitis
- weight loss common
- barrel-chested, prolonged expiration, sits forward, pursed lip breathing
- expiratory airflow limitation measured by spirometry

Severe illness:
- overdistention severe, diffusion capacity is low, blood gas relatively normal at rest
- such patients may overventilate and remain well oxygenated (pink puffers)
patients with chronic bronchitis have a history of recurrent infection, abundant purulent sputum, hypercapnia, and severe hypoxemia (blue bloaters)
cor pulmonale and eventual CHF, related to secondary pulmonary vascular HTN - poor prognosis
death due to (1) respiratory acidosis and coma, (2) right-sided heart failure, and (3) massive collapse of the lungs secondary to pneumothorax

Emphysema and Chronic Bronchitis

<table>
<thead>
<tr>
<th></th>
<th>Predominant Bronchitis</th>
<th>Predominant Emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>40-45</td>
<td>50-75</td>
</tr>
<tr>
<td><strong>Dyspnea</strong></td>
<td>Mild; late</td>
<td>Severe; early</td>
</tr>
<tr>
<td><strong>Cough</strong></td>
<td>Early; copious sputum</td>
<td>Late; scanty sputum</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td>Common</td>
<td>Occasional</td>
</tr>
<tr>
<td><strong>Respiratory insufficiency</strong></td>
<td>Repeated</td>
<td>Terminal</td>
</tr>
<tr>
<td><strong>Cor pulmonale</strong></td>
<td>Common</td>
<td>Rare; terminal</td>
</tr>
<tr>
<td><strong>Airway resistance</strong></td>
<td>Increased</td>
<td>Normal or slightly increased</td>
</tr>
<tr>
<td><strong>Elastic recoil</strong></td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Chest radiograph</strong></td>
<td>Prominent vessels; large heart</td>
<td>Hyperinflation; small heart</td>
</tr>
<tr>
<td><strong>Appearance</strong></td>
<td>Blue bloater</td>
<td>Pink puffer</td>
</tr>
</tbody>
</table>

Other Types of Emphysema

Compensatory Hyperinflation (Emphysema)
- dilation alveoli but not destruction septal walls, response to loss of lung substance elsewhere
- hyperexpansion of residual lung parenchyma following removal of diseased lung or lobe

Obstructive Overinflation
- lung expands because air is trapped in it
- common cause: subtotal obstruction by tumour or FB
- overinflation in obstructive lesions occurs either because:
  1. ball-valve action - air enters on inspiration but can’t leave on expiration
  2. bronchus obstructed but ventilation through collaterals brings air in
- can be a life-threatening because affected portion distends sufficiently to compress normal lung

Bullous Emphysema
- any form of emphysema that produces large subpleural blebs or bullae (spaces > 1 cm diameter)
- most often subpleural, and occur near the apex, sometimes in relation to old Tb scarring
- rupture of bullae may cause pneumothorax

Interstitial Emphysema
- entrance of air into connective tissue of lung, mediastinum, or subcutaneous tissue
- usually due to alveolar tears in pulmonary emphysema providing entrance of air into c.t. of lung
- rarely due to a wound or a fractured rib, also whooping cough, bronchitis, obstruction to airways (blood clots, tissue, FBs), artificially ventilated, inhale irritant gases

Chronic Bronchitis
- common in smokers and inhabitants of smog-laden cities
- when persistent for years, it may:
  1. progress to chronic obstructive airway disease
  2. lead to cor pulmonale and heart failure
  3. cause atypical metaplasia and dysplasia of the respiratory epithelium
- persistent cough with sputum production for at least 3 months in at least 2 consecutive years, in the absence of any other identifiable cause
- simple bronchitis: productive cough, no physiologic evidence airflow obstruction (some have hyperreactive airways with intermittent bronchospasm and wheezing - chronic asthmatic bronchitis)
- heavy smokers may develop chronic airflow obstruction, usually with evidence of associated emphysema, classified as showing obstructive chronic bronchitis

Pathogenesis
- initiating factor: chronic irritation by inhaled - tobacco smoke, grain, cotton, silica
bacterial and viral infections may trigger acute exacerbations
- earliest feature: hypersecretion mucus in large airways, with hypertrophy submucosal glands in trachea/bronchi
- proteases released from neutrophils, such as neutrophil elastase and cathepsin, and matrix metalloproteinases, stimulate this mucus hypersecretion
- as chronic bronchitis persists, also marked increase in goblet cells of small airways leading to excessive mucus production that contributes to airway obstruction
- submucosal gland hypertrophy and increase in goblet cells a protective metaplastic reaction
- resp epithelial effects of environmental irritants mediated through epidermal growth factor (EGF) receptor
- smoke/other irritants, cause hypertrophy of mucous glands, also cause bronchiolitis/small airway disease
- role of infection appears to be secondary - not responsible for initiation of chronic bronchitis but significant in maintaining it and may be critical in producing acute exacerbations
- cigarette smoke predisposes to infection in more than one way.
  - interferes with ciliary action of the respiratory epithelium
  - may cause direct damage to airway epithelium
  - inhibits ability of bronchial and alveolar leukocytes to clear bacteria

Morphology
- characteristic histologic features: chronic inflammation of airways (predominantly lymphocytes) and enlargement of the mucus-secreting glands of trachea and bronchi
- numbers of goblet cells increase slightly, major increase in size of mucous glands.
- measured by Reid index (ratio of thickness of mucous gland layer to thickness of wall between epithelium and cartilage) – normal 0.4, increases in chronic bronchitis
- bronchial epithelium may exhibit squamous metaplasia and dysplasia
- narrowing bronchioles by goblet cell metaplasia, mucus plugging, inflammation, fibrosis
- most severe cases, may be obliteration of lumen due to fibrosis (bronchiolitis obliterans)

Clinical Features
- persistent cough productive of sputum, SOBOE
- elements of COPD may appear, including hypercapnia, hypoxaemia, and mild cyanosis
- many patients with COPD have both bronchitis and emphysema
- long-standing severe - cor pulmonale with cardiac failure
- death due to acute intercurrent bacterial infections

Asthma
- chronic inflammatory disorder of airways that causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and/or in early morning
- widespread bronchoconstriction and airflow limitation at least partly reversible
- inflam causes increase in airway responsiveness (bronchospasm) to a variety of stimuli
- many cells incl eosinophils, mast cells, macrophages, T lymphocytes, neutrophils, epithelial
- may be triggered by exercise, cold or exposure to allergen previously been sensitized
- mild intermittent, mild, moderate, and severe persistent asthma
- steroid-dependent, steroid-resistant, difficult, and brittle asthma
- extrinsic (initiated by a type I hypersensitivity reaction induced by exposure to an extrinsic antigen) and intrinsic (initiated by nonimmune mechanisms, including ingestion of aspirin; pulmonary infections, esp viral; cold; inhaled irritants; stress; exercise)
- other informal categories: seasonal, exercise-induced, drug-induced, occupational, bronchitis in smokers
- allergic bronchopulmonary aspergillosis may complicate asthma, allergic reaction to fungus

Pathogenesis
Major aetiologic factors:
- genetic predisposition to type I hypersensitivity ("atopy")
- acute and chronic airway inflammation
- bronchial hyperresponsiveness
Type 2 helper T (TH2) cells, a type of CD4+ helper T cell, are prominent components of the bronchial inflammation. TH2 cells secrete interleukins that promote allergic inflammation and stimulate B cells to produce IgE and other antibodies. Type 1 helper T (TH1) cells produce IFN-γ and IL2, which initiate killing of viruses and other intracellular organisms by activating macrophages and cytotoxic T cells.

These two subgroups of helper T cells constitute an immunoregulatory loop: cytokines from TH1 cells inhibit TH2 cells, and vice versa. An imbalance in this reciprocal arrangement may be the key to asthma. In patients with allergic asthma, T cell differentiation is skewed in the direction of TH2. A transcription factor called T-bet is required for TH1 cell differentiation, and studies on lung tissues from asthmatics reveal absence of T-bet in lung lymphocytes.

In addition to inflammatory responses, asthma is characterized by structural changes in bronchial wall, referred to as "airway remodeling." Hypertrophy of bronchial smooth muscles and deposition of subepithelial collagen, heavy infiltration of smooth muscle cells by mast cells, and release of vasoactive mediators and cytokines such as PDGF and proteases that can trigger smooth muscle proliferation.

**Atopic Asthma**

- Most common type of asthma usually begins in childhood.
- Triggered by environmental antigens - dusts, pollens, animal dander, foods.
- Positive family history of atopy common, attacks are often preceded by allergic rhinitis, urticaria, or eczema.
- Initial sensitization to inhaled antigens (allergens) (priming or sensitization).
- Stimulates induction of TH2-type cells that release cytokines such as IL-4 and IL-5.
- These cytokines promote IgE production by B cells, growth of mast cells (IL-4), and growth and activation of eosinophils (IL-5).
- Within minutes of re-exposure to antigen immediate (acute) reaction is triggered by Ag-induced cross-linking of IgE bound to IgE receptors on mast cells in airways.
- These cells release preformed mediators that open tight junctions between epithelial cells.
- Antigen can then enter mucosa to activate mucosal mast cells and eosinophils, which release additional mediators.
- Either directly or via neuronal reflexes, mediators induce bronchospasm, increased vascular permeability (oedema), and mucus production.
- These cells also release cytokines that cause influx of other leukocytes (neutrophils, eosinophils, and basophils; also lymphocytes and monocytes) signals initiation of late phase of asthma (starts 4 to 8 hours later and may persist for 12 to 24 hours or more) and a fresh round of mediator release from leukocytes, endothelium, and epithelial cells. Factors, particularly from eosinophils (e.g., major basic protein, eosinophil cationic protein), also cause damage to the epithelium.

Epithelial cells produce a large variety of cytokines:
- Eotaxin, made by epithelial cells, potent chemoattractant, activator of eosinophils.
- Major basic protein of eosinophils causes epithelial damage and airway constriction.

**Nonatopic Asthma**

- Nonatopic, or nonreaginic asthma, frequently triggered by respiratory tract infection.
- Viruses (e.g., rhinovirus, parainfluenza virus) most common provokers.
- Positive family history is uncommon.
- Serum IgE levels are normal.
- No other associated allergies.
- Skin test results are usually negative.
- hyperirritability of the bronchial tree - virus-induced inflammation of the respiratory mucosa lowers threshold of subepithelial vagal receptors to irritants

**Drug-Induced Asthma**
- aspirin-sensitive asthma uncommon, occurs with recurrent rhinitis and nasal polyps
- exquisitely sensitive to small doses of aspirin
- aspirin inhibits cyclooxygenase pathway of arachidonic acid metabolism without affecting lipoxygenase route, tipping balance toward elaboration of bronchoconstrictor leukotrienes

**Occupational Asthma**
- stimulated by fumes (epoxy resins, plastics), organic and chemical dusts (wood, cotton, platinum), gases (toluene), and other chemicals (formaldehyde, penicillin products)

**Morbidity**
- grossly: lungs overdistended due to overinflation, and may be small areas of atelectasis
- occlusion of bronchi and bronchioles by thick, tenacious mucous plugs
- histo: mucous plugs contain whorls of shed epithelium, give rise to Curschmann spirals, eosinophils and Charcot-Leyden crystals present (collections of crystalloid)
- "airway remodeling"
  - o thickening BM of bronchial epithelium
  - o oedema + inflam infiltrate bronchial walls, prominence of eosinophils and mast cells
  - o increase in size of submucosal glands
  - o hypertrophy of bronchial wall muscle

**Clinical Course**
- classic asthmatic attack lasts up to several hours, followed by prolonged coughing
- raising of copious mucous secretions provides
- in some patients, these symptoms persist at a low level all the time
- status asthmaticus, severe acute paroxysm for days or weeks, may cause cyanosis and death
- elevated eosinophil count in the peripheral blood and finding of eosinophils, Curschmann spirals, and Charcot-Leyden crystals in the sputum

**Bronchiectasis**
- permanent dilation of bronchi and bronchioles caused by destruction of muscle and elastic tissue, resulting from or associated with chronic necrotizing infections
- dilation permanent; reversible dilation often accompanies viral and bacterial pneumonia
- cough, fever, and expectoration of copious amounts of foul-smelling, purulent sputum
- develops in association with a variety of conditions:
  - o congenital/hereditary conditions: cystic fibrosis, intralobar sequestration of lung, immunodeficiency states, primary ciliary dyskinesia and Kartagener syndromes
  - o postinfectious: necrotizing pneumonia caused by bacteria (Tb, S aureus, H influenzae, Pseudomonas), viruses (adenovirus, influenza, HIV), fungi (Aspergillus)
  - o bronchial obstruction: tumour, FBs, mucus impaction
  - o other conditions: RA, SLE, IBD, post-transplantation (chronic lung rejection, and chronic graft-versus-host disease after bone marrow transplantation)

**Aetiology and Pathogenesis**
- obstruction and infection
- after bronchial obstruction normal clearing mechanisms are impaired, pooling of secretions distal to obstruction, and inflammation of airway
- severe infections of bronchi lead to inflammation, often with necrosis, fibrosis, and eventually dilatation of airways

**Cystic fibrosis**
- primary defect in chloride transport leads to impaired secretion of chloride ions into mucus, low sodium and water content, defective mucociliary action, and accumulation of thick viscid secretions that obstruct airways
- leads to marked susceptibility to bacterial infections, which further damage airways
- with repeated infections, widespread damage to airway walls, with destruction of supporting smooth muscle and elastic tissue, fibrosis, and further dilatation of bronchi
- smaller bronchioles progressively obliterated owing to fibrosis (bronchiolitis obliterans)

**Primary ciliary dyskinesia**
- autosomal-recessive syndrome
- poorly functioning cilia - retention secretions and recurrent infections cause bronchiectasis
- absence or shortening of dynein arms that are responsible for coordinated bending of cilia
- half patients have Kartagener syndrome (bronchiectasis, sinusitis, situs inversus)

**Allergic bronchopulmonary aspergillosis (ABPA)**
- results from hypersensitivity reaction to fungus Aspergillus fumigatus
- complication of asthma and cystic fibrosis
- intense airway inflammation with eosinophils and formation of mucus plugs
- periods of exacerbation and remission may lead to proximal bronchiectasis and fibrotic lung

**Morphology**
- usually affects lower lobes bilaterally, most severe in more distal bronchi and bronchioles
- may be localized to a single segment of lung (FB/tumour)
- airways are dilated, filled with mucopurulent secretions
- histological: intense acute and chronic inflammatory exudation within walls of bronchi and bronchioles, assoc with desquamation of the lining epithelium and necrotizing ulceration
- may be pseudostratification of columnar cells or squamous metaplasia of epithelium
- necrosis may destroy bronchial walls and form lung abscess
- chronic - fibrosis bronchiolar walls and peribronchiolar fibrosis lead to obliteration of lumen
- mixed flora: staph, strep, pneumococci, enteric organisms, anaerobes, H infl, Pseudomonas

**Clinical Course**
- severe, persistent cough; expectoration foul-smelling, sometimes bloody sputum
- dyspnoea and orthopnoea in severe cases; and occasional life-threatening hemoptysis
- systemic febrile reaction may occur when powerful pathogens are present.
- symptoms episodic and precipitated by URTIs
- cough paroxysmal, frequent in the morning, and changes in position
- obstructive ventilatory insufficiency can lead to marked dyspnoea and cyanosis
- cor pulmonale, metastatic brain abscesses, and amyloidosis complications

**Diffuse Interstitial (Infiltrative, Restrictive) Diseases**
Heterogeneous group of disorders characterized by diffuse and usually chronic involvement of pulmonary connective tissue, principally most peripheral and delicate interstitium in alveolar walls.

- dyspnoea, tachypnoea, end-insp crackles, eventual cyanosis, without wheeze or obstruction
- classic features: reduction carbon monoxide diffusing capacity, lung volume, compliance
- CXRs show diffuse infiltration by small nodules, irregular lines, or ground glass shadows
- secondary pulmonary hypertension and RHF with cor pulmonale may result
- advanced forms - scarring and gross destruction of lung - honeycomb lung
- most common associations are environmental diseases (25%), sarcoidosis (20%), idiopathic pulmonary fibrosis (15%), and collagen vascular diseases (10%)

**Pathogenesis**
- earliest common manifestation of most interstitial diseases is alveolitis - accumulation of inflammatory and immune effector cells within alveolar walls and spaces
- accumulation of leukocytes:
  - distorts normal alveolar structures
  - results in release mediators that can injure parenchymal cells and stimulate fibrosis
  - give rise to an end-stage fibrotic lung in which alveoli are replaced by cystic spaces separated by thick bands of connective tissue interspersed with inflammatory cells

**Major Categories of Chronic Interstitial Lung Disease**

<table>
<thead>
<tr>
<th>Fibrosing</th>
<th>Usual interstitial pneumonia (idiopathic pulmonary fibrosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonspecific interstitial pneumonia</td>
<td></td>
</tr>
<tr>
<td>Cryptogenic organizing pneumonia</td>
<td></td>
</tr>
<tr>
<td>Associated with collagen vascular diseases</td>
<td></td>
</tr>
<tr>
<td>Pneumoconiosis</td>
<td></td>
</tr>
<tr>
<td>Drug reactions</td>
<td></td>
</tr>
<tr>
<td>Radiation pneumonitis</td>
<td></td>
</tr>
</tbody>
</table>
Granulomatous Sarcoidosis
Hypersensitivity pneumonitis
Eosinophilic
Smoking-Related
Desquamative interstitial pneumonia
Respiratory bronchiolitis-associated interstitial lung disease
Other
Pulmonary alveolar proteinosis

- interactions among lymphocytes and macrophages and release of lymphokines and monokines are responsible for slowly progressive pulmonary fibrosis
- alveolar macrophage, in particular, plays a central role in the development of fibrosis

Fibrosing diseases

Idiopathic Pulmonary Fibrosis
- "cryptogenic fibrosing alveolitis"
- histologic pattern of fibrosis referred to as usual interstitial pneumonia (UIP), also seen in other diseases - collagen vascular disorders and asbestosis

Pathogenesis
- causative agent(s) unknown
- caused by repeated cycles of acute lung injury (alveolitis) by unidentified agent
- "wound healing" gives rise to fibroblastic proliferation, and "fibroblastic foci"
- mediators of wound healing such as TGF-β are expressed at these sites
- inflammatory response may be modified by genetic or environmental factors, are TH2 type
- eosinophils, mast cells, and IL-4 and IL-13 found in the lesions

Morphology
- pleural surfaces of lung cobblestoned owing to retraction of scars along interlobular septa
- fibrosis (firm, rubbery white areas) of lung parenchyma with lower-lobe predominance
- microscopically - patchy interstitial fibrosis
- dense fibrosis causes collapse of alveolar walls and formation of cystic spaces lined by hyperplastic type II pneumocytes or bronchiolar epithelium (honeycomb fibrosis)
- foci of squamous metaplasia and smooth muscle hyperplasia may be present
- secondary pulm HTN changes (intimal fibrosis and medial thickening of pulmonary arteries)

Clinical Course
- begins insidiously, gradually increasing dyspnoea on exertion and dry cough, 40-70 yrs
- hypoxemia, cyanosis, and clubbing late
- gradual deterioration despite treatment (steroids, cyclophosphamide, azathioprine)
- mean survival 3 years or less
- lung transplantation only definitive therapy
Nonspecific Interstitial Pneumonia (NSIP)  
- diffuse interstitial lung disease, unknown aetiology, biopsies fail to show diagnostic features  
- divided into cellular and fibrosing patterns  
- dyspnoea and cough of several months' duration; 46 to 55 yrs

Cryptogenic Organizing Pneumonia (COP)  
- aka "bronchiolitis obliterans organizing pneumonia"  
- unknown etiology  
- cough and dyspnoea, subpleural or peribronchial patchy areas of airspace consolidation  
- no interstitial fibrosis or honeycomb lung

Pulmonary Involvement in Collagen Vascular Diseases  
- SLE, RA, scleroderma, dermatomyositis-polymyositis, and mixed connective tissue disease  
- different patterns: NSIP, UIP, vascular sclerosis, organizing pneumonia, bronchiolitis  
- diffuse interstitial fibrosis (NSIP pattern) classically in progressive systemic sclerosis  
- patchy, transient parenchymal infiltrates noted in SLE, and severe pneumonitis may occur  
- RA - pulmonary involvement common and may occur in one of four forms  
  o (1) chronic pleuritis, with or without effusion  
  o (2) diffuse interstitial pneumonitis and fibrosis  
  o (3) intrapulmonary rheumatoid nodules  
  o (4) pulmonary hypertension

Pneumoconioses  
- non-neoplastic lung reaction to inhalation of mineral dusts encountered in the workplace, includes organic as well as inorganic particulates and chemical fumes and vapours

General Pathogenesis  
- cigarette smoking, that affects integrity of mucociliary apparatus significantly predisposes to accumulation of dust  
- most dangerous particles range from 1 to 5 μm in diameter because they may reach the terminal small airways and air sacs and settle in their linings  
- protection provided by phagocytosis of particles can be overwhelmed by large dust burden deposited with occupational exposures and by specific chemical interactions of particles with cells  
- smaller particles tend to cause acute lung injury  
- larger particles may persist within the lung parenchyma for years - evoke fibrosing collagenous pneumoconioses, such as is characteristic of silicosis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Disease</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mineral Dusts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coal dust</td>
<td>Anthracosis,</td>
<td>Coal mining (particularly hard coal)</td>
</tr>
<tr>
<td>Silica</td>
<td>Silicosis, Caplan syndrome</td>
<td>Foundry work, sandblasting, hardrock mining, stone cutting, others</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Asbestosis, pleural plaques, mesothelioma</td>
<td>Mining, milling, and fabrication; insulation</td>
</tr>
<tr>
<td></td>
<td>Caplan syndrome</td>
<td></td>
</tr>
<tr>
<td>Beryllium</td>
<td>Acute berylliosis</td>
<td>Mining, fabrication</td>
</tr>
<tr>
<td><strong>Organic Dusts That Induce Hypersensitivity Pneumonitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouldy hay</td>
<td>Farmer's lung</td>
<td>Farming</td>
</tr>
<tr>
<td>Bagasse</td>
<td>Bagassosis</td>
<td>Manufacturing wallboard, paper</td>
</tr>
<tr>
<td>Bird droppings</td>
<td>Bird-breeder's lung</td>
<td>Bird handling</td>
</tr>
<tr>
<td><strong>Chemical Fumes and Vapors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrous oxide, sulfur dioxide, ammonia, benzene, insecticides</td>
<td>Bronchitis, asthma, pulmonary oedema, ARDS</td>
<td>Occupational and accidental exposure</td>
</tr>
</tbody>
</table>

Coal Workers’ pneumoconiosis (CWP)  
- spectrum of lung findings in coal workers
(1) asymptomatic anthracosis
(2) simple coal workers' pneumoconiosis (CWP) - little to no pulmonary dysfunction
(3) complicated CWP, or progressive massive fibrosis (PMF) - lung function is compromised

Morphology
- anthracosis coal-induced pulmonary lesion in coal miners
- inhaled carbon pigment engulfed by alveolar or interstitial macrophages, then accumulate in c.t. along lymphatics or in organized lymphoid tissue along bronchi or hilum
- simple CWP: coal macules (1 to 2 mm diameter) and larger coal nodules
  o coal macule - carbon-laden macrophages; nodule also contains small amounts of delicate network of collagen fibers
  o later, dilation of adjacent alveoli, sometimes referred to as centrilobular emphysema
- complicated CWP (PMF): on a background of simple CWP, requires many years to develop
  o intensely blackened scars larger than 2 cm, up to 10 cm
  o center of lesion often necrotic, likely from local ischemia

Clinical Course
- usually benign
- mild forms of complicated CWP show no abnormalities of lung function
- <10% cases PMF develops, leading to pulm dysfunction, pulm HTN, and cor pulmonale
- once PMF develops, may become progressive
- unlike silicosis, no convincing evidence that coal dust increases susceptibility to Tb
- some evidence that exposure to coal dust increases incidence of chronic bronchitis and emphysema, independent of smoking
- no evidence that CWP in absence of smoking predisposes to cancer

Silicosis
- inhalation crystalline silicon dioxide (silica)
- most prevalent chronic occupational disease in the world
- presents after decades of exposure as slowly progressing, nodular, fibrosing pneumoconiosis
- large number of occupations at risk, especially sandblasters and many mine workers
- heavy exposure over months to a few years can result in acute silicosis

Pathogenesis
- silica occurs crystalline and amorphous forms, crystalline forms much more fibrogenic
- quartz most commonly implicated in silicosis
- particles interact with epithelial cells and macrophages
- although lung macrophages that ingest silica particles may succumb to its toxic effects, silica causes activation and release of mediators by viable macrophages
- mediators include IL-1, TNF, fibronectin, lipid mediators, oxygen-derived free radicals, and fibrogenic cytokines (TNF most important)

Morphology
- grossly in early stages: tiny, barely palpable, discrete pale to blackened (if coal dust is also present) nodules in upper zones
- as progresses, these nodules may coalesce into hard, collagenous scars
- some nodules may undergo central softening and cavitation (may be due to superimposed tuberculosis or to ischemia)
- fibrotic lesions may also occur in hilar lymph nodes and pleura
- thin sheets of calcification may occur in lymph nodes, seen radiographically as eggshell calcification (i.e., calcium surrounding a zone lacking calcification)
- if continues to progress, expansion and coalescence of lesions produce PMF

Clinical Course
- usually detected on routine CXR on asymptomatic worker
- do not develop shortness of breath until late in course, after PMF is present
- disease may be progressive, even if patient no longer exposed
- associated with increased susceptibility to tuberculosis
  o silicosis results in depression of cell-mediated immunity, and crystalline silica may inhibit the ability of pulmonary macrophages to kill phagocytosed mycobacteria

Asbestos-Related Diseases
- a family of crystalline hydrated silicates that form fibers
- is linked to:
  - localized fibrous plaques or, rarely, diffuse pleural fibrosis
  - pleural effusions
  - parenchymal interstitial fibrosis (asbestosis)
  - lung carcinoma
  - mesotheliomas (1000x risk)
  - laryngeal and perhaps other extrapulmonary neoplasms, including colon carcinomas

**Pathogenesis**
- two distinct geometric forms of asbestos: serpentine (curly and flexible fibers) and amphibole (straight, stiff, and brittle fibers)
- amphiboles, less prevalent, more pathogenic than chrysotiles
- asbestos can also act as a tumor initiator and a tumor promoter
- some oncogenic effects are mediated by reactive free radicals generated by asbestos fibers
- potentially toxic chemicals adsorbed onto asbestos fibers contribute to oncogenicity
- synergy between tobacco smoking and development of lung carcinoma in asbestos workers
- macrophages attempt to ingest and clear fibers and are activated to release chemotactic factors and fibrogenic mediators that amplify the response
- chronic deposition of fibers and persistent release of mediators lead to generalized interstitial pulmonary inflammation and interstitial fibrosis

**Morphology**
- diffuse pulmonary interstitial fibrosis indistinguishable from diffuse interstitial fibrosis from other causes, except for presence of asbestos bodies
  - golden brown, fusiform or beaded rods with translucent center and consist of asbestos fibers coated with an iron-containing proteinaceous material
  - arise when macrophages attempt to phagocytose asbestos fibers; iron presumably derived from phagocyte ferritin
  - other inorganic particulates may become coated with similar iron protein complexes and are called ferruginous bodies
- begins as fibrosis around respiratory bronchioles and alveolar ducts, extends to involve adjacent alveolar sacs and alveoli
- enlarged airspaces in thick fibrous walls, eventually affected regions become honeycombed
- scarring may narrow pulm arteries/arterioles, causing pulmonary HTN and cor pulmonale
- pleural plaques, most common manifestation of asbestos exposure - well-circumscribed plaques of dense collagen often containing calcium

**Clinical Course**
- clinical findings very similar to those caused by other diffuse interstitial lung disease
- dyspnoea first manifestation; at first, SOBOE, later SOBAR
- cough associated with production of sputum
- manifestations more common after 20 years or more
- disease may remain static or progress to respiratory failure, cor pulmonale, and death

**Drug-Induced Lung Diseases**
- acute and chronic alterations in respiratory structure and function

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pulmonary Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxic drugs</td>
<td></td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Pneumonitis and fibrosis</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Pneumonitis and fibrosis</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td>β-Antagonists</td>
<td>Bronchospasm</td>
</tr>
</tbody>
</table>

**Drug-Induced Pulmonary Disease**

**Radiation-Induced Lung Diseases**
- radiation pneumonitis: complication of radiation of pulmonary/thoracic tumours (oesophl, breast, mediastinal)
- acute and chronic forms
- acute radiation pneumonitis occurs in 10% to 20% 1 to 6 months after therapy
  - fever, dyspnoea out of proportion to volume of lung irradiated, pleural effusion, and radiologic infiltrates that usually correspond to an area of previous radiation
  - steroid therapy - symptoms may resolve completely in some patients without long-term effects, in others there is progression to chronic radiation pneumonitis
- initially causes a lymphocytic alveolitis or hypersensitivity pneumonitis that can lead to pulmonary fibrosis (chronic radiation pneumonitis)

Granulomatous Diseases

Sarcoidosis
- systemic disease unknown cause with noncaseating granulomas in many tissues and organs
- bilateral hilar lymphadenopathy or lung involvement on CXRs in 90%
- eye and skin lesions next in frequency
- diagnosis of exclusion (TB, fungal, berylliosis also produce noncaseating granulomas)
- F>M

Aetiology and Pathogenesis
- aetiology unknown ? disordered immune regulation in genetically predisposed individuals exposed to certain environmental agents

Immunologic Factors:
- development cell-mediated response to unidentified antigen, driven by CD4+ helper T cells
- TNF released at high levels by activated alveolar macrophages, and TNF level in bronchoalveolar fluid a marker of disease activity
- polyclonal hypergammaglobulinemia, another manifestation of helper T-cell dysregulation

Genetic Factors:
- familial and racial clustering of cases
- association with certain HLA genotypes (e.g., class I HLA-A1 and HLA-B8)

Environmental Factors:
- mycobacteria, Propionibacterium acnes, and Rickettsia species

Morphology
- noncaseating granulomas, composed of aggregate of tightly clustered epithelioid cells, often with Langhans or foreign body type giant cells, with time may become enclosed within fibrous rims or may eventually be replaced by hyaline fibrous scars
- laminated concretions composed of calcium and proteins known as Schaumann bodies
- stellate inclusions known as asteroid bodies enclosed within giant cells found in approximately 60% of granulomas
  - 2nd two not pathognomonic of sarcoidosis because asteroid and Schaumann bodies also in other granulomatous diseases (e.g., tuberculosis)
- lymph nodes involved in most cases, sometimes calcified
- spleen affected microscopically in three quarters of cases
- liver affected slightly less often than spleen, may also be moderately enlarged
- bone marrow may be affected: phalangeal bones of hands and feet, creating small circumscribed areas of bone resorption within the marrow cavity and diffuse reticulated pattern throughout cavity, with widening bony shafts or new bone formation outer surfaces

Clinical Course
- varying severity and inconstant distribution of lesions
- may be discovered unexpectedly on routine CXRs as bilateral hilar adenopathy or may present with peripheral lymphadenopathy, cutaneous lesions, eye involvement, splenomegaly, or hepatomegaly
- insidious onset of respiratory abnormalities (shortness of breath, cough, chest pain, haemoptysis) or fever, fatigue, weight loss, anorexia, night sweats
- unpredictable course: chronicity or periods of activity interspersed with remissions

Hypersensitivity Pneumonitis
- spectrum of immunologically mediated, predominantly interstitial, lung disorders caused by intense, prolonged exposure to inhaled organic dusts and related occupational antigens
- an immunologically mediated response to an extrinsic antigen that involves both immune complex and delayed type hypersensitivity reactions
- progression to serious chronic fibrotic lung disease can be prevented by removal of environmental agent
- commonly results from inhalation of organic dust containing antigens made up of spores of thermophilic bacteria, true fungi, animal proteins, or bacterial products
- Farmer's lung results from exposure to dusts generated from harvested humid, warm hay that permits rapid proliferation of spores of thermophilic actinomycetes
- Pigeon breeder's lung (bird fancier's disease) provoked by proteins from excreta or feathers
- humidifier or air-conditioner lung caused by thermophilic bacteria in heated water reservoirs
- BAL show increased levels of proinflammatory chemokines such as MIP-1α and IL-8m and increased numbers of T lymphocytes - both CD4+ and CD8+
- most patients have specific antibodies in their serum, suggestive of type III (immune complex) hypersensitivity
- noncaseating granulomas in two thirds suggests the development of a T cell-mediated (type IV) delayed-type hypersensitivity against antigen

**Morphology**
- histologic changes in subacute and chronic forms characteristically centered on bronchioles
  - (1) interstitial pneumonitis with lymphocytes, plasma cells, and macrophages
  - (2) noncaseating granulomas
  - (3) interstitial fibrosis and obliterative bronchiolitis (in late stages)
  - (4) intra-alveolar infiltrate

**Clinical Features**
- acute attacks: 4-6 hrs post-exposure recurring episodes fever, dyspnoea, cough, leukocytosis
- diffuse and nodular infiltrates on CXR, PFTS show acute restrictive disorder
- exposure continuous and protracted - chronic form: signs of progressive respiratory failure, dyspnoea, and cyanosis and a decrease in TLC and compliance

**Pulmonary eosinophilia**
- a number of diseases show infiltration of eosinophils, recruited by elevated alveolar levels of eosinophil attractants such as IL-5
- divided into following categories:
  - acute eosinophilic pneumonia with respiratory failure
  - simple pulmonary eosinophilia, or Löffler syndrome
  - tropical eosinophilia, caused by infection with microfilariae
  - secondary eosinophilia (in a number of parasitic, fungal, and bacterial infections; in hypersensitivity pneumonitis; in drug allergies; in asthma, allergic bronchopulmonary aspergillosis, or vasculitis)
  - so-called idiopathic chronic eosinophilic pneumonia

**Smoking-related Interstitial diseases**
- grouped into obstructive (emphysema, bronchitis) and restrictive or interstitial diseases
- majority of patients with idiopathic interstitial fibrosis (IPF) are smokers
- desquamative interstitial pneumonia (DIP) and respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) probably represent two ends of a spectrum of smoking-associated interstitial lung diseases

**Desquamative Interstitial Pneumonia (DIP)**
- large collections of airspace macrophages
- minimal if any fibrosis and is nonprogressive in vast majority of cases

**Morphology**
- accumulation of large number of macrophages with abundant cytoplasm containing dusty brown pigment (smokers' macrophages) in airspaces
- finely granular iron may be seen in macrophage cytoplasm
- macrophages contain lamellar bodies within vacuoles, from necrotic type II pneumocytes
- alveolar septa thickened by sparse inflammatory infiltrate of lymphocytes including plasma cells and occasional eosinophils
- emphysema often present
- insidious onset of dyspnoea and dry cough over weeks or months, with clubbing
- mild restrictive abnormality with moderate reduction of diffusing capacity
- good prognosis with excellent response to steroid therapy and cessation of smoking
Pulmonary Alveolar Proteinosis (PAP)
- rare, CXR - bilateral patchy asymmetric pulmonary opacification; histo - accumulation of acellular surfactant in intra-alveolar and bronchiolar spaces
- acquired, congenital, or secondary PAP
  o acquired PAP: unknown etiology, 90% cases of PAP, GM-CSF-neutralizing autoantibody?
  o congenital PAP rare cause of immediate-onset neonatal respiratory distress (fatal)
  o secondary PAP uncommon underlying causes include lysterin protein intolerance, acute silicosis and other inhalational syndromes, immunodeficiency disorders, malignancies, and hematopoietic disorders

Morphology
- peculiar homogeneous, granular precipitate within alveoli, causing focal-to-confluent consolidation of large areas of the lungs with minimal inflammatory reaction
- nonspecific respiratory difficulty of insidious onset, cough, and abundant sputum
- symptoms lasting for years, often with febrile illnesses
- risk for developing secondary infections
- benign course or progressive dyspnoea, cyanosis, and respiratory insufficiency may occur

Pulmonary Embolism
- clots that occlude large pulmonary arteries almost always embolic
- thromboses develop only in presence of pulm HTN, pulm atherosclerosis, and heart failure
- 95% emboli from deep veins
- risk factors: immobile, hypercoagulable states, primary (factor V Leiden, antiphos synd) or secondary (obesity, surgery, cancer, OCP, pregnancy)
- clinical significance depends on extent to which pulmonary artery blood flow is obstructed
- results in V-Q mismatch and hemodynamic compromise due increased resistance to pulmonary blood flow - acute right-sided heart failure

Morphology
- depend on size of embolic mass and general state of the circulation
- large emboli/saddle embolus - sudden death, due to blockage of blood flow through lungs or acute RHF (acute cor pulmonale)
- with adequate cardiovascular function, bronchial arterial supply can often sustain lung parenchyma despite obstruction to pulmonary arterial system - haemorrhages may occur, but no infarction
- PE causes infarction only when circulation already inadequate, in heart or lung disease
- extend to periphery of lung substance as a wedge with the apex pointing toward hilum
- pulmonary infarct classically hemorrhagic
- apposed pleural surface covered by a fibrinous exudate
- eventually converts into a contracted scar
- histologically, ischemic necrosis of lung substance within area of haemorrhage
- can have septic infarcts, and some convert to abscesses

Clinical Course
- large PE – sudden death (electromechanical dissociation); shock
- dyspnoea, tachypnoea, fever, chest pain, cough, and haemoptysis +/- pleural friction rub
- CXR - wedge-shaped infiltrate, D-dimer, CTPA, pulmonary angiography
- emboli often resolve via contraction and fibrinolysis
- multiple small emboli may cause pulm HTN, pulm vascular sclerosis, and cor pulmonale
- prevention; early ambulation, graduated compression stockings for bedridden patients, preventive anticoagulation in high-risk individuals, insertion of filter into inferior vena cava
- treatment: anticoagulation +/- thrombolysis
- nonthrombotic forms: air (iatrogenic), bone marrow (trauma, bone marrow necrosis in sickle cell patients), fat (trauma and surgery), amniotic fluid (during parturition), and FBs (IVDU)

Pulmonary Hypertension
- pulmonary circulation normally low resistance, pulmonary BP is ~1/8th of systemic BP
- most frequently secondary to structural cardiopulmonary conditions that increase pulmonary blood flow or pressure (or both), pulmonary vascular resistance, or left heart resistance to blood flow. These include the following:
  o chronic obstructive or interstitial lung diseases: hypoxia as well as destruction of lung parenchyma and have fewer alveolar capillaries - increased pulm art resistance
congenital/acquired heart disease: mitral stenosis, because of increase in atrial pressure leads to increase in pulmonary venous pressure and increase in pulmonary artery pressure. 
- recurrent thromboemboli: reduction in functional cross-sectional area of pulmonary vascular bed brought about by obstructing emboli, which leads to increase in pulmonary vascular resistance.
- autoimmune disorders: systemic sclerosis, involve pulmonary vasculature, leading to inflammation, intimal fibrosis, medial hypertrophy, and pulmonary hypertension. 
  - primary, or idiopathic, pulmonary hypertension

**Pathogenesis**
- associated with obstruction to vasculature caused by proliferation of endothelial, smooth muscle, and intimal cells accompanied by concentric laminar intimal fibrosis.
- BMPR2 is a cell-surface protein belonging to the TGF-β receptor superfamily implicated.
- in secondary forms of pulmonary hypertension, endothelial cell dysfunction is produced by process that initiates the disorder, such as increased shear and mechanical injury associated with left-to-right shunts or biochemical injury produced by fibrin in thromboembolism.
- some patients with pulmonary hypertension have a vasospastic component.

**Morphology**
- arterioles/small arteries - medial hypertrophy and intimal fibrosis, narrowing lumina.

**Clinical Course**
- primary pulmonary hypertension most common in women 20 to 40 years.
- dyspnoea and fatigue, some patients have chest pain of anginal type.
- later severe respiratory distress, cyanosis, and RVH, and death from cor pulmonale.
- therapy with vasodilators (e.g., calcium channel blockers or inhaled nitric oxide) and antithrombotic medications (e.g., warfarin, prostacyclin, and TXA receptor blockers).

**Diffuse Pulmonary Haemorrhage Syndromes**
- complication of some interstitial lung disorders.
- pulmonary haemorrhage syndromes: Goodpasture syndrome, idiopathic pulmonary haemosiderosis, and vasculitis-associated haemorrhage, found in conditions such as hypersensitivity angiitis, Wegener granulomatosis, and lupus erythematosus.

**Goodpasture Syndrome**
- uncommon autoimmune disease.
- presence of circulating autoantibodies targeted against collagen IV.
- giving rise to proliferative, usually rapidly progressive glomerulonephritis and a necrotizing haemorrhagic interstitial pneumonitis.
- teens or twenties, M>F.
- Ab mediated injury to glomerular and pulmonary basement membranes; trigger unknown.
- respiratory symptoms: haemoptysis, and CXR - focal pulmonary consolidations.
- manifestations of glomerulonephritis - progressive renal failure.
- common cause of death is uraemia.
- trmt: plasma exchange and immunosuppressives.

**Idiopathic Pulmonary Haemosiderosis**
- rare disorder, intermittent, diffuse alveolar haemorrhage.
- insidious onset productive cough, haemoptysis, anaemia, weight loss with pulm infiltrations.
- haemorrhage into alveolar spaces, and haemosiderosis, within alveolar septa and in macrophages lying within alveoli.
- cause and pathogenesis unknown.

**Wegener Granulomatosis**
- autoimmune disease often involves upper respiratory tract and/or lungs.
- haemoptysis.

**Pulmonary Infections**
- pneumonia = any infection of lung parenchyma.
- can result whenever defense mechanisms impaired or whenever resistance of host is lowered.
  - factors that affect resistance include:
    - chronic diseases.
    - immunologic deficiency.
- treatment with immunosuppressive agents
- leukopenia
- unusually virulent infections
  - clearing mechanisms can be interfered with by:
    - loss or suppression of cough reflex (coma, anaesthesia, neuromuscular disorders, drugs, chest pain)
    - injury to mucociliary apparatus, by impairment of ciliary function or destruction ciliated epithelium from cigarette smoke, inhalation of hot gases, viral diseases, or genetic disturbances (immotile cilia syndrome)
    - interference with phagocytic or bactericidal action of alveolar macrophages by alcohol, tobacco smoke, anoxia, or oxygen intoxication
    - pulmonary congestion and oedema
    - accumulation of secretions in cystic fibrosis and bronchial obstruction
- defects in innate immunity (including neutrophil and complement defects) and humoral immunodeficiency typically lead to an increased incidence of infections with bacteria
- cell-mediated immune defects lead to increased infections with intracellular microbes (Tb, HSV) as well as with microorganisms of very low virulence, such as PCP
- viral pneumonia may predispose to bacterial pneumonia
- pneumonia can arise in seven distinct clinical settings ("pneumonia syndromes"), and implicated pathogens specific to each category:

**The Pneumonia Syndromes**

<table>
<thead>
<tr>
<th>Community-Acquired</th>
<th>Strept pneumo, H infl, Morax cat, Staph aureus, Legionella, Klebsiella</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-Acquired Atypical</td>
<td>Mycoplasma, Chlamydia, viruses (RSV, parainfl, flu A, B, adeno)</td>
</tr>
<tr>
<td>Nosocomial Pneumonia</td>
<td>Gram – rods (Klebsiella, Serratia, E coli, pseudomonas), Staph aureus</td>
</tr>
<tr>
<td>Aspiration Pneumonia</td>
<td>Anaerobes (Bacteroides, peptostrepto), Strept pneumo, S aureus, H infl, Pseudomonas</td>
</tr>
<tr>
<td>Chronic Pneumonia</td>
<td>Nocardia, actinomyces, M TB, atypical mycobacterium, histoplasma, Blastomyces</td>
</tr>
<tr>
<td>Necrotizing Pneumonia and Lung Abscess</td>
<td>Anaerobic, S aureus, Klebsiella, Strep pyogenes</td>
</tr>
<tr>
<td>Immunocompromised Host</td>
<td>CMV, PCP, MAI, aspergillosis, candidiasis, ‘usual’ bacterial, viral and fungal</td>
</tr>
</tbody>
</table>

**Community Acquired Pneumonia**
- bacterial or viral (bacterial often after viral)
- bacterial invasion parenchyma causes alveoli filled with inflam exudate - consolidation
- predisposing conditions: extremes of age, chronic diseases (congestive heart failure, COPD, diabetes), congenital or acquired immune deficiencies, and decreased or absent splenic function (sickle cell disease or post splenectomy - encapsulated bacteria pneumococcus)

**Streptococcus Pneumoniae**
- most common cause community-acquired acute pneumonia
- numerous neutrophils containing Gram-positive diplococci
- penicillin treatment, but increasing penicillin-resistant strains; vaccines available

**Haemophilus Influenzae**
- pleomorphic, Gram-negative organism - LRTIs and meningitis in young children
- adults - common cause community-acquired acute pneumonia
- encapsulated (5%) and unencapsulated (95%)
- six serotypes encapsulated form (a to f), type b most frequent cause severe invasive disease
- pili on surface of H. influenzae mediate adherence to respiratory epithelium and also secretes a factor that disorganizes ciliary beating and a protease that degrades IgA
- can cause suppurative meningitis <5 yrs if not immunised, acute purulent conjunctivitis (pinkeye) in children and, in older patients, may cause septicemia, endocarditis, pyelonephritis, cholecystitis, suppurative arthritis
- most common bacterial cause of acute exacerbation of COPD

**Moraxella Catarrhalis**
- cause of bacterial pneumonia especially in elderly
- second most common bacterial cause of acute exacerbation of COPD
- with S. pneumoniae and H. influenzae is one of three most common causes of otitis media
**Staphylococcus Aureus**
- secondary bacterial pneumonia in children and healthy adults following viral respiratory illnesses (e.g., measles in children and influenza in both children and adults)
- high incidence of complications - lung abscess and empyema
- IVDU at high risk of developing staphyloccocal pneumonia in association with endocarditis
- important cause of nosocomial pneumonia

**Klebsiella Pneumoniae**
- most frequent Gram-negative bacterial pneumonia
- afflicts debilitated and malnourished people, particularly chronic alcoholics
- thick and gelatinous sputum - organism produces abundant viscid capsular polysaccharide

**Pseudomonas Aeruginosa**
- most commonly causes nosocomial infections
- CF patients, neutropenic and can invade blood vessels with extrapulmonary spread

**Legionella Pneumophila**
- artificial aquatic environments - water-cooling towers, tubing system domestic water supply
- inhalation of aerosolized organisms or aspiration of contaminated drinking water
- common with predisposing condition such as cardiac, renal, or haematologic disease
- transplant recipients, immunosuppressed susceptible – severe
- Legionella antigens in urine or positive fluorescent antibody test on sputum or culture

**Morphology**
- bacterial pneumonia has two gross patterns: bronchopneumonia and lobar pneumonia
- patchy consolidation = bronchopneumonia
- lobar pneumonia = fibrinosuppurative consolidation of large portion of lobe or entire lobe

- lobar pneumonia - four stages of inflammatory response:
  - congestion
    - lung heavy, boggy, red; vascular engorgement, intra-alveolar fluid with few neutrophils, numerous bacteria
  - red hepatisation
    - red, firm, airless, with liver-like consistency; massive confluent exudation with red cells), neutrophils, and fibrin filling alveolar spaces; pleural fibrinous reaction
  - gray hepatisation
    - grayish brown, dry surface; progressive disintegration of red cells and persistence of fibrinosuppurative exudate
  - resolution
    - consolidated exudate in alveolar spaces undergoes progressive enzymatic digestion to produce granular, semifluid, debris that is resorbed, ingested by macrophages, coughed up, or organized by fibroblasts; pleural reaction undergoes organization, leaving fibrous thickening or permanent adhesions

- bronchopneumonia: consolidated areas of acute suppurative inflammation
  - patchy through one lobe but more often multilobar and frequently bilateral and basal
  - histo: suppurative, neutrophil-rich exudate fills bronchi, bronchioles, alveolar spaces

- complications of pneumonia:
  1. tissue destruction and necrosis - abscess formation (esp pneumococci or Klebsiella)
  2. spread of infection to pleural cavity - intrapleural fibrinosuppurative reaction: empyema
  3. organization of exudate, may convert portion of lung into solid tissue
  4. bacteremic dissemination to heart valves, pericardium, brain, kidneys, spleen, or joints
    - metastatic abscesses, endocarditis, meningitis, or suppurative arthritis

**Clinical Course**
- abrupt onset high fever, shaking chills, cough productive of mucopurulent sputum
- when fibrinosuppurative pleuritis - pleuritic pain and pleural friction rub
- rapidly modified by Abs – need to determine organism and sensitivities

**Community-Acquired Atypical (Viral and Mycoplasmal) Infections**
- acute febrile respiratory disease characterized by patchy inflammatory changes in lungs, largely confined to alveolar septa and pulmonary interstitium
- "atypical" = no findings consolidation, only mod elevation WCC, and lack alveolar exudate
most common - Mycoplasma pneumoniae, esp children and young
also viruses, incl influenza A and B, RSV, adenovirus, rhinoviruses, rubeola, and varicella;
also Chlamydia pneumoniae; and Coxiella burnetti (Q fever)
common pathogenetic mechanism is attachment of organisms to upper respiratory tract epithelium followed by necrosis of cells and inflammatory response; then extends to alveoli, with interstitial inflammation, +/- outpouring of fluid into alveolar spaces; damage to resp epithelium inhibit mucociliary clearance, predispose to secondary bacterial infections

Morphology
- histologically interstitial nature of inflammatory reaction, localized within walls of alveoli
- mononuclear inflam infiltrate of lymphocytes, histiocytes, and occasionally plasma cells
- changes reflect alveolar damage similar to that seen diffusely in ARDS
- superimposed bacterial infection modifies the histologic picture
- some viruses - HSV, varicella, and adenovirus, may have necrosis of bronchial and alveolar epithelium and acute inflammation

Clinical Course
- extremely varied, cough may be absent, fever, headache, muscle aches, pains legs
- secondary bacterial infection by staph or strep

Influenza Infections
- two mechanisms for clearance of influenza virus
  o cytotoxic T cells kill virus-infected cells
  o intracellular anti-influenza protein (called Mx1) induced in macrophages by cytokines interferon-α and interferon-β
- epidemics occur through mutations of hemagglutinin and neuraminidase that allow the virus to escape most host antibodies (antigenic drift)
- rarely may cause interstitial myocarditis or after aspirin therapy Reye syndrome

Morphology
- UTRIs with mucosal hyperemia and swelling with predominantly lymphomonocytic and plasmacytic infiltration of submucosa accompanied by overproduction of mucus secretions
- swollen mucosa and viscid exudate may plug nasal channels, sinuses, or Eustachian tubes and lead to suppurative secondary bacterial infection
- tonsillitis frequent in children
- laryngotracheobronchitis and bronchiolitis - vocal cord swells, abundant mucous exudation
- impairment of bronchociliary function - bacterial superinfection

Severe Acute Respiratory Syndrome (SARS)
- dry cough, malaise, myalgias, fever and chills
- less commonly related to upper respiratory tract such as sore throat
- 2/3 progress to severe disease with shortness of breath, tachypnoea, and pleurisy, 10% die
- cause: coronavirus

Nosocomial/Hospital-Acquired Pneumonia
- common in underlying disease, immunosuppression, prolonged Abs, invasive access devices
- mechanical ventilation high risk
- gram-negative rods (Enterobact, Pseudomonas) and Staph aureus most common

Aspiration Pneumonia
- debilitated patients or those who aspirate gastric contents while unconscious
- abnormal gag and swallowing reflexes
- partly chemical, due to extremely irritating effects of gastric acid, and partly from oral flora
- often necrotizing, fulminant clinical course, frequent cause of death
- lung abscess formation a common complication

Lung Abscess
- local suppurative process, with necrosis of lung tissue
- oropharyngeal surgical procedures, sinobronchial infections, dental sepsis, and bronchiectasis

Aetiology and Pathogenesis
- commonly aerobic and anaerobic streptococci, Staph aureus, and Gram-negative organisms
- causes include:
o aspiration infective material: in acute alcoholism, coma, anaesthesia, sinusitis, gingivodental sepsis, and debilitation - cough reflexes depressed
o antecedent primary bacterial infection: post-pneumonic abscess formations
o septic embolism from thrombophlebitis or from vegetations of bacterial endocarditis
o neoplasia: secondary infection in segment obstructed by malignancy
o direct penetrations lungs; spread from neighbouring organ, haematogenous seeding
o primary cryptogenic lung abscesses (no cause found)

Morphology
- mm to 5-6cm; single or multiple
- due to aspiration are more common on the right (more vertical right main bronchus), single
- due to pneumonia or bronchiectasis usually multiple, basal, and diffusely scattered
- septic emboli – multiple, may affect any region of lungs
- suppurative destruction of lung parenchyma within central area of cavitation

Clinical Course
- like bronchiectasis: cough, fever, copious amounts of foul-smelling purulent sputum
- fever, chest pain, and weight loss common; clubbing
- rule out an underlying carcinoma (present in 10% to 15%)
- complications: extension into pleural cavity, haemorrhage, development of brain abscesses or meningitis from septic emboli, and (rarely) secondary amyloidosis

Chronic Pneumonia
- localized lesion in immunocompetent patient, with or without lymph node involvement
- granulomatous inflammation, which may be due to bacteria (Tb) or fungi (Histoplasma, blastomycosis, coccidioidomycosis)

Histoplasmosis
- inhalation of dust particles from soil contaminated with bird or bat droppings
- intracellular fungal parasite of macrophages
- similar presentation and morphology to Tb

Blastomycosis
- soil-inhabiting fungus

Coccidioidomycosis
- inhaled spores
- delayed type hypersensitivity to the fungus

Pneumonia in the Immunocompromised Host
- wide variety of opportunistic infectious agents, many rarely cause infection in normal hosts
- AIDS - often P. carinii
- local or diffuse pulmonary infiltrates
- bacteria (Pseudomonas aeruginosa, Mycobacterium, Legionella pneumophilia, and Listeria monocytogenes), viruses (CMV and herpesvirus), and fungi (Pneumocystis carinii, Candida species, Aspergillus species, the Phycomycetes, and Cryptococcus neoformans)

Pneumonia in HIV
- pulmonary disease leading cause of morbidity and mortality in HIV
- LRTI caused by "usual" pathogens one of most serious pulmonary disorders in HIV
- not all pulmonary infiltrates in HIV infectious - including Kaposi sarcoma, pulmonary non-Hodgkin lymphoma, and primary lung cancer
- CD4+ T cell count can define risk of infection with specific organisms
  o Bacterial/tubercular infections more likely at higher CD4+ counts (>200 cells/mm3)
  o Pneumocystis pneumonia at CD4+ counts below 200 cells/mm3
  o CMV and MAC infections are uncommon until CD4+ counts <50 cells/mm3

Lung Transplantation
- end-stage emphysema, idiopathic pulm fibrosis, CF, and primary pulmonary hypertension
- usually unilateral but if bilateral chronic infection is present (cystic fibrosis, bronchiectasis), both lungs replaced to remove reservoir of infection
- two major complications: infection and rejection

Tumors
- 90% carcinomas, 5% bronchial carcinoids, 2-5% mesenchymal and other neoplasms
Carcinomas
- largely due to carcinogenic effects of cigarette smoke
- age 40-70 yrs, M>F

Aetiology and Pathogenesis
- arise by stepwise accumulation of genetic abnormalities transforming benign bronchial epithelium
- association between frequency and amount of daily smoking, tendency to inhale, duration of smoking
- epithelial changes begin with squamous metaplasia and progress to squamous dysplasia, carcinoma in situ, and invasive carcinoma
- asbestos workers who do not smoke have a five times greater risk of lung cancer
- certain alleles CYP1A1 increased capacity to metabolize procarcinogens from cigarette
- three types of precursor epithelial lesions are recognized
  - (1) squamous dysplasia and carcinoma in situ
  - (2) atypical adenomatous hyperplasia
  - (3) diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
- classification: squamous cell > adenocarcinoma > small cell > large cell > carcinoid
- small cell (most often metastatic, high initial response to chemotherapy) versus non-small cell carcinomas (less often metastatic, less responsive)
- strongest relationship to smoking is with squamous cell and small cell carcinoma

Morphology
- distant spread through lymphatic and haematogenous pathways
- spreading widely at an early stage
- adrenals involved in more than half cases; also liver, brain, bone
- Small Cell Carcinoma – all are high grade; contain neurosecretory granules - can secrete ectopic hormones; strong relationship to cigarette smoking
- can cause partial obstruction with focal emphysema; total obstruction may lead to atelectasis; bronchiectasis; pulmonary abscesses; compression or invasion of SVC; pericarditis or pleuritis with effusions
- TNM system of staging
- insidious and aggressive neoplasms: cough, weight loss, chest pain, and dyspnoea
- CXR, sputum cytology, bronchial washings +/- biopsy

Local Effects of Lung Tumour Spread

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Pathologic Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia, abscess, lobar collapse</td>
<td>Tumour obstruction of airway</td>
</tr>
<tr>
<td>Lipid pneumonia</td>
<td>Tumour obstruction; accumulation of cellular lipid in foamy macrophages</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Tumour spread into pleura</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>Recurrent laryngeal nerve invasion</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Esophageal invasion</td>
</tr>
<tr>
<td>Diaphragm paralysis</td>
<td>Phrenic nerve invasion</td>
</tr>
<tr>
<td>Rib destruction</td>
<td>Chest wall invasion</td>
</tr>
<tr>
<td>SVC syndrome</td>
<td>SVC compression by tumour</td>
</tr>
<tr>
<td>Horner syndrome</td>
<td>Sympathetic ganglia invasion (Pancoast tumour)</td>
</tr>
<tr>
<td>Pericarditis, tamponade</td>
<td>Pericardial involvement</td>
</tr>
</tbody>
</table>

Paraneoplastic Syndromes
- SIADH, ACTH – cushings: PTHrP, prostaglandin E – hypercalcemia; calcitonin – hypocalcemia;
  Gonadotropins – gynecomasia; serotonin and bradykinin - carcinoid syndrome
- other systemic manifestations: Lambert-Eaton myasthenic syndrome (muscle weakness is caused by auto-antibodies directed to neuronal calcium channel), peripheral neuropathy; dermatologic abnormalities - acanthosis nigricans; hematologic abnormalities - leukemoid reactions; and HPOA with clubbing

Carcinoid Tumors
- 1-5% lung tumours; < 40 years
- neuroendocrine tumour - produce vasoactive amines
- intermittent attacks of diarrhoea, flushing, and cyanosis
Mediastinal masses
- lymphoma, thymoma, thyroid lesions, parathyroid tumours, metastatic ca etc

Metastatic neoplasms
- lung most common site of metastatic neoplasms; via blood or lymphatics or direct continuity
- multiple discrete nodules (cannonball lesions) or solitary nodule, endobronchial, pleural, pneumonic consolidation

Pleural Effusion
- common manifestation of both primary and secondary pleural diseases
  o increased hydrostatic pressure – CHF
  o increased vascular permeability – pneumonia
  o decreased osmotic pressure - nephrotic syndrome
  o increased intrapleural negative pressure – atelectasis
  o decreased lymphatic drainage - mediastinal carcinomatosis
- inflammatory or noninflammatory

<table>
<thead>
<tr>
<th>Condition</th>
<th>Type of Fluid</th>
<th>Common Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammatory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serofibrinous pleuritis</td>
<td>Serofibrinous exudate</td>
<td>Inflammation in adjacent lung Collagen vascular disease</td>
</tr>
<tr>
<td>Suppurative pleuritis (empyema)</td>
<td>Pus</td>
<td>Suppurative infection in adjacent lung</td>
</tr>
<tr>
<td>Hemorrhagic pleuritis</td>
<td>Bloody exudate</td>
<td>Tumour</td>
</tr>
<tr>
<td><strong>Noninflammatory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrothorax</td>
<td>Transudate</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Hemothorax</td>
<td>Blood</td>
<td>Ruptured aortic aneurysm, trauma</td>
</tr>
<tr>
<td>Chylothorax</td>
<td>Chyle (lymph)</td>
<td>Tumour obstruction of normal lymphatics</td>
</tr>
</tbody>
</table>

Inflammatory Pleural Effusions
- serous, serofibrinous, and fibrinous pleuritis
- common causes - inflammatory diseases within lungs: tuberculosis, pneumonia, lung infarcts, lung abscess, and bronchiectasis. RA, SLE, uraemia, metastatic, radiation therapy
- purulent pleural exudate (empyema) from bacterial or mycotic seeding
- hemorrhagic pleuritis in haemorrhagic diatheses, rickettsial diseases, and neoplastic

Noninflammatory Pleural Effusions
- clear and straw coloured, most common cause is cardiac failure, also renal failure and cirrhosis

Pneumothorax
- air or gas in the pleural cavities - spontaneous, traumatic, or therapeutic
- may complicate any form of pulmonary disease
- commonly associated with emphysema, asthma, and tuberculosis
- spontaneous idiopathic pneumothorax - young people - rupture apical subpleural blebs
- may cause compression, collapse, and atelectasis of lung
- tension pneumothorax may compress mediastinal structures and contralateral lung

Pleural tumours
- primary or secondary (metastatic involvement more common than primary tumours)
- solitary (localized) fibrous tumours: prev called "benign mesothelioma" - soft tissue tumours, rarely malignant

Malignant Mesothelioma
- arise from either visceral or parietal pleura
- heavy exposure to asbestos increases risk – poor prognosis
- chest pain, dyspnoea, and recurrent pleural effusions
- lung invaded directly and often metastatic spread to hilar lymph nodes, liver, other organs