Obstructive lung diseases (↓elastic recoil)

-COPD → 4th leading cause of death / heavily associated with smoking

1) Emphysema :-

Permanent enlargment of the airspaces distal to the terminal bronchioles (in the acini) with destruction of their walls → irreversible

-small airway fibrosis

A) Centriacinar (centrilobular) :

The most common clinically significant type, in the central or proximal parts of the acini (respiratory bronchioles), more pronounced in the upper lobes (apex)

B) Panacinar (panlobular) :

-α_1-antitrypsin deficiency, all the acinus are involved (uniformly enlarged), in the lower zones (most severe at the bases) & in the anterior margins of the lung

C) Distal acinar (paraseptal) :

-associated with spontaneous pnemothorax in young adults, adjacent to the pleura, lobular connective tissue septa & to fibrosis, scaring or atelectasis

-on X-ray : it's darker, there's loss of lung markings (the white lines that represent vessels), mediastinum is shifted to the left, form cyst like structures.

D) Irregular emphysema :

-airspace enlargment with fibrosis, in any part of the acini (not uniform), asymptomatic & insignificant

* Pathogenesis :

1- Toxic injury (smoking) → inflammation → ↑LTB4, IL-8 & TNF

2. Protease - antiprotease imbalance (α_1-antitrypsin deficiency)

3. Oxidative stress 4. infection : it's Not an initiating factor

* Morphology :

Voluminous lungs

Abnormally large alveoli are separated by thin septa with only focal centriacinar fibrosis

* Symptoms dont appear until at least 1/3 of the parenchyma is damaged :-

- Dyspnea, weight loss, barrel-chested, prolonged expiration, hunched over position, breathes through pursed lips, hyperventilation, adequate oxygenation of hemoglobin → no cyanosis pink puffers.

* Conditions related to emphysema :-

1. Compensatory hyperinflation : compensatory dilation of alveoli in response to loss of lung substance elsewhere (surgical removal).
2. Obstructive overinflation : lung expands because air is trapped within it due to obstruction by a tumor or foreign object (act as ball valve) or collaterals bring in air behind the obstruction.
3. Bullous emphysema : any form of emphysema that cause cystically dilated structures (large subpleural blebs or bullae) / pneumothorax if rupture
4. interstitial emphysema : entrance of air into the connective tissue or subcutaneous tissue.

* Outcome :

- ↓capillary bed area due to destruction of alveolar walls / compression of the respiratory bronchioles & lung vasculature by the enlarged airspaces / inflammatory changes in small airways
- Hypoxia → hypoxia induced pulmonary vascular spasm → pulmonary hypertension → right-sided heart failure (cor pulmonale). → poor prognosis

2) Chronic bronchitis :-

- Persistent productive cough for at least 3 consecutive months in at least 2 consecutive years in the absence of any other identifiable cause.
- ↓ lung function → cor pulmonale
- Atypical squamous metaplasia & dysplasia of the respiratory epithelium → rich soil for cancerous transformation
- In early stages airflow is not obstructed.

*Pathogenesis:-

1. Hypersecretion of mucus → increase in goblet cells in the epithelial surfaces of smaller brancl & bronchioles → hypertrophy of submucosal glands in the trachea & bronchi → assessed by Reid index (the ratio of the thickness of the mucous gland layer to the thickness of the wall between epithelium & cartilage / normal reid index : 0.4 & is increased in chronic bronchitis)
2. Acquired cystic fibrosis transmembrane conductane regulator (CFTR) dysfunction → abnormal dehydrated mucus
3. inflammation : without eosinophils / fibrosis involving small airways
4. infection : isn't an initiating factor

- Airway obstruction due to coexistent emphysema or small airway disease : chronic bronchiolitis → goblet cell metaplasia mucous pulgging, inflammation & submucosal fibrosis (bronchiolar wall fibrosis)
- In severe cases → Bronchiolitis obliterans : complete obliteration of the lumen due to fibrosis.
- For many years no respiratory functional impairmant is present, but eventually dyspnea on exertion develops.
- Chronic bronchitis & COPD patients show rapid disease progression & poorer outcomes than emphysema alone

*Symptoms :

less dyspnea, absence of increased respiratory drive → hypoxia & cyanosis, patients tend to be obese, blue bloaters carbon dioxide retention

2 صفحات آخر (15-4) دول

3) Asthma :-

- Chronic inflammatory disorder (with eosinophils) causes recurrent episoides of ① wheezing, ② dyspnea, ③ chest tightness & ④ cough

* Major factors :-

1. Type 1 hypersensitivity (atopy) 2. Acute & chronic airway inflammation
3. Hyper responsiveness to certain antigens/allergens that cause asthmatic attack

* Triggers :-

1. respiratory infections (especially viral) 2. airborne irritants (smoke, fumes)
3. cold air 4. stress 5. exercise

* Pathogenesis :-

1. Sensitization : first exposure to allergen → recognized by antigen presenting cells (dendritic cells) → activating type 2 helper T-lymphocytes to produce → IL-4 & IL-13 → activate B-cells to produce IgE (attach to Fc receptors on the mast cells "no degranulation of mast cells → so no symptoms in patient")
   - IL-13 → ↑ mucous production
   - IL-5 → activate eosinophils → degranulation of eosinophils

2. Re-exposure : cross linking between IgE associated on Fc receptor & antigen → degranulation of mast cells
   - early phase reaction (immediate reaction) : bronchoconstriction (bronchospasm ; intermittent & reversible airway obstruction) / vasodilation / ↑ mucus production / ↑ vascular permeability / recruitment of leukocytes .
   - late phase reaction : epithelial cells → eotaxin → recruit TH_2 , eosinophils ..... → amplifying the inflammatory reaction .

* Airway remodeling :-

1. hypertrophy & hyperplasia of bronchial smooth muscle
2. // of mucus glands 3. goblet cells metaplasia 4. ↑ vascularity
5. thickening of submucosal basement membrane
6. deposition of subepithelial collagen (type 1 & 3 → fibrosis)

*Morphology:
1- occlusion of bronchi & bronchioles by thick mucous pulgs (conbain whorls of shed epithelium "Curschmann spiralis: in sputum, not specific").
2- Charcot-Leyden crystals: eosinophil protein galectin-10

*Managment:
1-Anti-inflammatory drugs glucocorticoids 2. bronchodilators (β-agonists)
3. LT inhibitors

*Atopic asthma: type 1 IgE-mediated hypersensitivity reaction, beginning in childhood, +ve family history of atopy / asthma, attacks are preceded by allergic rhinitis, urticaria or eczema, exposure to antigen → type 2 helper cells
-Diagnosis: skin prick test, serum radioallergosorbent tests (RASTs).

*Non-atopic asthma: no evidene of allergen sensitization, -ve skin test, +ve family history is less common, triggered by viral respiratory infections & inhaled air pollutants (sulfur dioxide, ozone, nitrogen dioxide)

*Drug induced asthma: Aspirin induced asthma:
inhibits cyclooxygenase → abnormality in prostaglandin metabolism
-recurrent rhinitis, nasal polyps, urticaria & bronchospasm

*Occupational asthma: repeated exposure to the antigen at the workplace, triggered by fumes (plastics), dusts (wood, cotton, platinum), gases (toluene).

*Status asthmaticus: severe paroxysm that does not responed to therapy & persist for days to weeks.
-hypercapnea, acidosis & severe hypoxia.

4) Bronchiectasis :-

- Permanent dilation of branchi & branchioles caused by destruction of smooth muscle & supporting elastic tissue
- It's not a primary disease

* Pathogenesis :-

1. Obstruction → impairs clearance of secretions → superimposed infection

"chronic"

2. Persistant necrotizing infection → poor clearance of secretions → obstruction

→ inflammatory damage to the bronchial wall & fibrosis + accumulating exudate → airway distention → irreversible dilation

* The conditions that predispose to bronchiectasis :-

1. Bronchial obstruction : localized bronchiectasis by tumors, foreign bodies & mucus or as a complication of atopic asthma & chronic bronchitis
2. Cystic fibrosis : widespread severe bronchiectasis - obstruction by abnormally viscus mucos & secondary infections.
3. Immunodeficiency states : localized/diffuse, due to recurrent bacterial infections
4. Necrotizing or suppurative pneumonia : Staph. aureus or Klebsiella spp.
5. Primary ciliary dyskinesia (immotile cilia syndrome) : persistant infections, bronchiectasis + sterility in males.

* Morphology : lower lobes bilaterally (location), in distal branchi & branchioles, the airway may be dilated as much as 4 times as their usual diameter

- In active cases : exudate within the walls of the branchi & branchioles → desquamation of lining epithelium & extensive ulceration mixed flora are cultured from sputum
- When healing occurs : lining epithelium regenerate completely/abnormal dilation & scaring/peribronchial fibrosis/fibrosis of bronchil & bronchiolar wall/abscess formation

* Symptoms : Sever persistant cough with mucopurulent sputum
- Severe widspread bronchiectasis : obstructive ventilatory defects, hypoxia, hypercapnia, pulmonary hypertension & cor pulmonale.

Chronic interstitial (restrictive, infiltrative) lung diseases

- Inflammation & fibrosis of the lung interstitium (+/- intra-alveolar) → ↓ (lung compliance, capacity & volume)
* Clinically: dyspnea, tachypnea, end-inspiratory crackles & cyanosis
- abnormal ventilation-perfusion ratio → hypoxia
- on X-ray: bilateral lesions (in both lungs) → multiple nodules, irregular line, ground gloss appearance, patchy process (not diffuse)
- Distinguishing between these restrictive diseases is easier at the early stage but advanced forms are hard to differentiate

hypoxia → secondary pulmonary hypertension → cor pulmonale

End stage or honeycomb lung: diffuse scaring & gross destruction of the lung, restrictedly dilated spaces "have a thick wall, lined by metaplastic bronchioles epithelium", expansion of the alveolar septa & fibrosis.

1) Granulomatous diseases:-

- Granuloma: epithelioid histiocytes (activated macrophages) surrended by lymphocytes.

A) Sarcoidosis:-

- Systemic disease of unknown etiology, diagnosis of exclusion (there's no definitive test), progressive chronicity, periods of activity interspersed with remissions (spontaneosly or by steroid therapy)
- on X-ray: bilateral hilum lymphadenopathy
- Cell mediated response to an unidentified antigen driven by CD4+ helper T cells.
- Morphology: Non-caseating (no central necrosis) epithelioid granuloma → discrete, compact collection of epithelioid cells rimed by an outer zone of CD4+ T cells with intermixed multinucleated giant cells / pale cells "light cytoplasm" with prominent nuclei.
- In granuloma → Asteroid bodies: satellate inclusions within giant cells
Schaumann bodies: laminated concretions (like onion skin) composed of calcium & proteins

- Mostly asymptomatic.
* In lungs: granulomas in interstitium, high frequency in bronchial submucosa, lesions along the lymphatics around branchi & blood vessels.
- BAL fluid → CD4+ T cells - gradual respiratory symptoms.
- Strong tendency for lesions to heal
- In 5-15% of cases → honeycomb lung
- No lesions inside the alveolar spaces but the walls are expanded by nodular proliferation composed of cells.
* In lymph nodes: any node can be affected particularly the hilar & mediastinal nodes (enlarged painless, discrete "nonmatted", nonadherent & do not ulcerate "unlike TB").
* In skin: - Septal panniculitis (fat inflammation),
- Erythema nodosum: hallmark of acute sarcoidosis, painful, raised, red, tender nodules, granulomas are uncommon.
- Subcutaneous nodules: discrete painless, abundant granulomas
* In eye & lacrimal glands → uveitis, iritis, iridocyclitis, posterior uveal tract disease (choroiditis), corneal opacities
- Sicca syndrome: inflammation in lacrimal glands
- Parotitis with painful enlargment of the parotid glands
- Xerostomia: dry mouth.
- Mikulicz syndrome: uveoparotid involvement.
* Spleen: contains granuloma, splenomegaly
* Liver: granulomas in portal triads, hepatomegaly
* BM: hypercalcemia & hypercalciuria "not related to bone destruction"
- Granulomas → macraphages → 1-α-hydroxylase → ↑active vitamin D → ↑calcium absorption.

B) Hypersensitivity pneumonitis :- "allergic alveolitis" :-
- Immunologically mediated, caused by intense, prolonged exposure to inhaled organic antigens. Primarily affects the alveoli.
- ↑ CD4+ & CD8+ lymphocytes (CD8+ > CD4+)
* Histologic changes are centered on bronchioles :-
- interstitial pneumonitis: eosinophils are rare.
- loose, poorly formed granulomas, without necrosis : in a peribronchiolar location, not discrete.
- interstitial fibrosis, honeycombing & obliterative bronchiolitis.
- bilateral, upper lobe dominant interstetial fibrosis.
- UIP.
- Acute reaction : fever cough dyspnea arising 4 to 8 hrs after exposure, if antigenic exposure is terminated after acute attack → complete resolution, diagnosis is obvious → lung biopsy is not required for diagnosis.
- Chronic phase: insidious onset of progressive cough, dyspnea, malaise, fatigue & weight loss → irreversible chronic interstitial pulmonary disease.
- on X-ray : ground glass opacity.
* Hot tub lung → nontuberculous mycobacterium.
* Pigeon breeder's lung → proteins from serum or feathers.
* Humidifier or air conditioner lung → thermophilic bacteria in heated water reservoirs.
* Farmer's lung : exposure to dusts generated from humid, warm, newly harvested hay that permits the rapid proliferation of the spores & mold.

2) Fibrosing diseases :-

A) Idiopathic pulmonary fibrosis :- Cryptogenic fibrosing alveolitis :-

- unknown etiology, characterized by patchy, progressive bilateral interstitial fibrosis, affects males > 50, diagnosis of exclusion
- Usual interstitial pneumonia (UIP) : temporal heterogeneity is typical (early lesions "fibroblastic foci" & late lesions "honeycomb fibrosis, more collagenous & less cellular" coexist)

* Pathogenesis :

1. Genetic predisposition (surfactant or telomerase mutations)
2. Defective repair
3. Repeated cycles of epithelial activation/injury

* Morphology : Cobblestone appearance of the pleural surface due to retraction of scars along the interlobular septa

- Lower lobe, subpleural regions & along the interlobular septa are mostly affected
- Mild to moderate inflammation ± foci of squamous metaplasia & smooth muscle hyperplasia
- pulmonary arterial hypertensive changes (intimal fibrosis & medial thickening).
- Gradual onset of nonproductive cough.
- Dry or velcro-like crackles during inspiration.
- Cyanosis, cor pulmonale & peripheral edema
- Prognosis is poor, median survival after diagnosis 3 years.
- lung transplantation is the only definitive treatment.

* Management : anti-inflammatory therapies
anti-fibrotic // (more important)

B) Nonspecific interstitial pneumonia (NSIP):-

- Chronic interstitial lung disease of unknown etiology, has distinct features
- Better prognosis than IPF/- female nonsmokers with dyspnea & cough of several months
- Idiopathic or associated with collagen vascular disorders (rheumatoid arthritis).
- on X-ray: bilateral, symmetric, predominantly lower lobe reticular opacities.

*Cellular pattern: patchy but uniform mild to moderate interstitial chronic inflammation & fibrosis.

*Fibrosing pattern: fibrotic lesions of the same stage of development.

C) Cryptogenic organizing pneumonia:-

- Unknown etiology but seen as a response to infections or inflammatory injury of the lungs
- on X-ray: subpleural or peribronchial patchy airspace consolidation (radiopaque or white areas).
- Masson bodies: intraalveolar plugs of loose organizing connective tissue (of the same age) in the air spaces inside the lungs not in the interstitium → no interstitial fibrosis or honeycomb lung
- The underlying lung architecture is normal
- Some patients recover spontaneously while most require oral steroids.

D) Pneumoconioses:-

- Workplace exposure to dusts

*The development of a pneumoconioses depends on:

1. The amount of dust retained in the lung (depends on: concentration of dust/ duration of exposure / effectiveness of clearance mechanisms).
2. The size & shape of the particles (the most dangerous: 1-5 μm in diameter).
3. Solubility & reactivity:-

- Asbestosis, silica, beryllium: smaller size → more solubility → acute lung injury.
- Coal dust (inert): larger // → less // → gradual fibrosis.

1 Coal worker's pneumoconiosis (CWP) :-

- Coal is mainly carbon ± trace metals, inorganic minerals & crystalline silica.
- Contaminating silica in the coal dust → progressive disease.
- Coal workers develop emphysema & chronic bronchitis independent of smoking

* Asymptomatic Anthracosis : inhaled carbon pigment is engulfed by alveolar or interstitial macrophages → accumulation without a cellular reaction
* Simple CWP : benign disease with little to no pulmonary dysfunction
  - Coal macules & nodules → (< 1 cm)
    ↳ 1-2 mm : dust laden macrophages & small amounts of collagen
  - Adjacent to respiratory bronchioles → centrilobular emphysema
  - Upper lobes & upper zones of lower lobes are involved.
* Complicated CWP → mild forms : don't affect lung function significantly
  ↳ Progressive masive fibrosis (PMF) : extensive fibrosis & compromised lung function / coalescence of coal nodules / multiple, dark black scars (> 2 cm & up to 10 cm) consist of dense collagen & pigment
  ↑ pulmonary dysfunction → pulmonary hypertension → cor pulmonale
  - PMF is generic : can be a complication of any one of the pneumoconiosis
  - Once established PMF tends to progress (continue to worsen) even in the absence of further exposure.
* No increased risk of lung carcinoma in coal miners.

II Silicosis :-

- The most prevalent chronic occupational disease in the world.
- Amorphus silica is less pathogenic
- Crystalline silica (toxic) → Quartz is most implicated in silicosis
  - is rarely pure in the workplace
  - when mixed with other minerals, the fibrogenic effect is reduced
- After inhalation, macrophages activate the inflammasome → IL-1, TNF...
- Affects upper zones of the lungs (retracted & scared).
- Thickening of the pleural lining of the lung.
- Early stages: nodules (tiny, barely palpable, discrete, pale to black)

* Silicotic nodules: concentrically arranged hyalinized collagen fibers surrounding amorphous center (due to the fact that the inorganic matrix of silica cannot be digested by macrophages)

- Nodules may be coalesce into hard, collagenous scars → PMF
- Fibrotic lesions in hilar lymph nodes & pleura
- Polarized microscopy reveals weakly birefringent silica.
- Most patients do not develop shortness of breath until late in course
- Silicoses in slow to kill

* ↑ susceptibility to tuberculosis (inhibits the ability of pulmonary macrophages to kill phagocytosed mycobacteria).
* Double risk for developing lung cancer.

III Asbestosis :-

Asbestos

- Family of crystalline hydrated silicates with a fibrous geometry.

* Pathogenesis : once phagocytosed by macrophages → activate inflammasome & damage phagolaysosomal membranes → proinflammatory factors & fibrogenic mediators → cellular & fibrotic lung reactions

tumor initiator & a promoter "mediated by the oncogenic effects of free radicals.

* Morphology : diffuse pulmonary interstitial fibrosis "indistinguishable from UIP"

- Asbestos bodies : golden brown, fusiform or beaded rods with a translucent center / formed of asbestos fibers coated with an iron-containing proteinaceous material.
- Begins in the lower lobes & subpleurally
- Pleural plaques : dense collagen, asymptomatic, in anterior & posterior lateral aspects of parietal pleura & over the domes of diaphragm
- Static or progress to honeycomb lung, congestive heart faliure, cor pulmonale & death

* Fivefold increase of lung carcinoma
* Asbestos + smoking → 55-fold increase in the risk
- The relative risk for mesothelioma is 1000 times > risk for lung cancer.
- Smoking → ↑ risk for lung carcinoma but not for mesothelioma

* Asbestos is associated with :

1. Parenchymal interstitial fibroses (asbesbosis)
2. Fibrous plaques 3. pleural effusions 4. lung carcinomas
5. Laryngeal carcinoma 6. Mesotheliomas.

* The risk of cancer is increased in → family members of asbestos workers
individual exposed outside of the workplace

3) Pulmonary eosinophilia:-
- Immunologic origin.

4) Smoking-related interstitial diseases:
A) Desquamative interstitial pneumonia (DIP):
- Accumulation of large numbers of macrophages containing dust-brown pigment (smoker's macrophages) in the alveolar air spaces
- Sparse inflammation in alveolar septa.
- Male=Female, 4th-5th decade
- Insidious onset of dyspnea & dry cough over weeks or months.
- Mild restrictive abnormality → good prognosis.
- Excellent response to steroids & smoking cessation.

B) Respiratory bronchiolitis-associated interstitial lung disease:
- Pigmented intraluminal macrophages akin to those in DIP but in a bronchiolocentric distribution (1st & 2nd order respiratory bronchioles).
- Aggregates of smoker's macrophages within: respiratory bronchioles, alveolar ducts & peribronchiolar spaces → mild peribronchiolar fibrosis.
- Central emphysema (not severe)
- Desquamative interstitial pneumonia is different parts of the same lung.
- Symptoms are usually mild → gradual onset of dyspnea & cough (average exposures of over 30 pack-years of cigarette smoking)
- Cessation of smoking → improvment
→ this term is used for patients who develop significant pulmonary symptoms, abnormal pulmonary function & imaging abnormalities.

Lung tumors

- 90-95% of primary lung tumors (originated in the lungs) are carcinomas.

1) Carcinoma of the lung:-

- Squamous cell & Small cell carcinomas have the strongest association with smoking

Small cell lung cancer (SCLC)	Non small cell lung cancer (NSCLC: adenocarcinoma, squamous & large cell carcinoma & large cell neuroendocrine carcinomas)
* Metastatic * Not curable by surgery * best treated by chemotherapy ± radiation therapy	* Resectable * Respond poorly to chemotherapy

* **Pathogenesis:-**
Carcinogens → genetic abnormalities → mutations → transformation of benign progenitor cells into neoplastic cells.

* **Genetic abnormalities:-**
1. Early event: inactivation of tumor suppressor genes (on chromosome-3 "3p")
2. Late event: mutations in TP53 & KRAS
3. Mutations that activate the epidermal growth factor receptor (EGFR) → adenocarcinoma in nonsmoking women.

- Habitual heavy smokers (two packs a day for 20 years) have 60X more risk than nonsmokers.
- Women are more susceptible to carcinogens in tobacco smoking than men.
- Although smoking cessation decreases the risk over time, it never returns to baseline levels
- Not all smokers suffer from lung cancer (it depends on genetic variants)

A) Adenocarcinoma :-

- The most common primary tumors, peripherally located, grow slowly, form smaller masses, metastasize widely at an early stage, misdiagnosed with pneumonia.
- Variety of growth patterns (acinar "gland-forming", papillary, mucinous & solid types).

I Atypical adenomatous hyperplasia (AAH):

- ≤5mm lesion, dysplastic pneumocytes lining alveolar wall that are mildly fibrotic, no invasion, nuclear hyperchromasia, prominent nucleoli & pleomorphism.

II Adenocarcinoma in situ (AIS):

- ≤3cm, dysplastic cells growing along pre-existing structures, preservation of alveolar architecture (no destruction), no stromal invasion, nodesmoplasia.

III Microinvasive adenocarcinoma: tumors (≤3cm), invasion (≤5mm)

IV Invasive adenocarcinoma: tumor of any size, invasion (>5mm)

- glandular differentiation or mucin production by the tumor cells.

B) Squamous cell carcinomas :-

- More common in men, arise centrally in major bronchi → spread to local hilar nodes & outside the thorax.
- Central necrosis & cavitation → misdiagnosed with TB.

*Preneoplastic lesions:

Squamous metaplasia/dysplasia → carcinoma in situ → Squamous cell carcinoma.

- When it begins to obstruct the lumen of a major bronchus → Symptomatic stage.
- Well differentiated squamous cell neoplasms synthesize keratin pearls.

C) Small cell lung carcinomas (SCLC) :-

- The most aggressive lung tumors, metastasize to hilar & mediastinal LN.
- Arise in a major bronchi or in the periphery of the lung.
- No known pre-invasive phase.
- Pale grey tumor, small tumor cells (round to fusiform, scant cytoplasm finely granular chromatin a salt & pepper appearance, cells are twice the size of resting lymphocytes).
- Mitotic figures, necrosis, crush artifact, neuroendocrine markers, nuclear molding "due to close apposition of tumor cells that have scant cytoplasm.
- Azzopardi effect: basophiling staining of vascular walls due to accumulation of the DNA of necrotic tumor cells.

D) Large cell carcinomas:

- Undifferentiated, lack cytologic features of small cell carcinoma, no glandular or squamous differentiation, moderate amount of cytoplasm.
- Mixed patterns: adenosquamous carcinoma, mixed adenocarcinoma, small cell carcinoma.

Spread & metastasis of tumors

- to LN: around the carnia, mediastinum, in neck & clavicular regions → Virchow node (left supraclavicular node, silent, has drainage from the lung & upper GI).
- to adj structures: → pleural/pericardial space → inflammation & effusion.
  - → compress/infiltrate SVC → venous congestion/vena cava syndrome.
  - → Pancoast tumors (syndrome): apical neoplasms, invade the brachial or cervical sympathetic plexus to cause:
    1. Severe pain "in the distribution of the ulner nerve".
    2. destruction of the 1st & 2nd ribs.
    3. Horner syndrome: ptosis, miosis, anhidrosis, ipsilateral enophthalmos.

* Tumer-Node-Metastasis (TNM): indicate the size & spread of primary neoplasm.
* Lung cancer: Silent, insidious & aggressive (late diagnosis).
- Is recognized through biopsy of tissues involved by metastatic disease.
- Poor prognosis, 5-year survival rate is only 18.7%
* Adenocarcinoma & squamous cell carcinoma have better prognosis than SCLC.
* SCLCs: spread by the time they are first detected even if the primary tumors appears to be small & localized.

Paraneoplastic syndrome

- SCC → secretion of PTH related hormone, parathormone, PE → Hypercalcemia
  - → hypertrophic pulmonary osteoarthropathy (associated with fingers clubbing)
- Adeno
- SCLC → ADH → syndrome of inapropriate secretion of ADH, hyponatremia
  - ACTH → cushing syndrome
  - GH, GHRH → acromegaly
- Carcinoid

* Neuromascular syndromes.
* Coagulation abnormalities.

2) Carcinoid tumors :-

- Malignant, low grade neuroendocrine carcinomas, well demarcated, originate in main bronchi, peripheral carcinoid are less common "asymptomatic" metastasize to the hilar nodes, distant metastases are rare, resectable & curable, part of MEN syndrome
- in cytoplasm: dense-core neurosecretory granules.

* Grow in one of two patterns → intraluminal polypoid obstruction
  ↳ collar-button lesion (mucosal plaque penetrating the bronchial wall)
* Carcinoid syndrome: intermittent attacks of diarrhea, flushing & cyanosis

Typical carcinoids	Atypical carcinoid
- Absent rare mitosis	- higher mitotic rate
- no necrosis/atypia	- necrosis
- nests of uniform cells (abundant cytoplasm, salt & pepper chromatin	- higher incidence of metastasis.
- Survival rate is higher	- TP53 mutations

3) Malignant mesothelioma :-

- Cancer of mesothelial cells lining parietal or visceral pleura.
- Highly related to asbestos → remain in the body for life → the risk does not diminish over time
- Extensive pleural fibrosis & plaque.
- begin in a localized area & spread widely but distant metastasis are rare.

① Epithelial: cuboidal cells with papillary buds line tubular & microcystic spaces, confused with pulmonary adenocarcinoma
② Sarcomatous: spindled cells grow in sheets.
③ biphasic: epithelial & sarcomatous.

- Lung is invaded directly

* Normal mesothelial cells: biphasic → pleural lining cells.
  → underling fibrous tissue.

Pulmonary diseases of vascular origin

1) Pulmonary embolism :-

A) Thromboembolism :-

-Arise from thrombi within the large deep veins of the legs (popliteal vein & large veins above it).

-In patients with thrombophilia (↑ tendency to clotting).

*Risk factors :-

1. Surgery, prolonged bed rest (immobalization of the legs)
2. CHF
3. Trauma (burns or multiple fractures)
4. Women parturition period or the use of OCPs (↑estrogen)
5. Disseminated cancer, factor V Leiden.

Stasis

hypercoagulability

*Consequences: ischemia, ↑ pulmonary artery pressure & vasospasm ("TxA2, serotonin")

↳ depend on: ① The size & number of emboli

- Small: clinically silent "mostly", removed by fibrinolytic activity, causes alveolar hemorrhage, dyspnea (obstruction of small to medium pulmonary branches → pulmonary infarction)
- Large: no morphologic alternations.
  - ↳ saddle embolus: at bifurcation of pulmonary trunk → sudden death
- Massive pulmonary embolism: >60% of the total pulmonary vasculature is obstructed by a large embolus or multiple small emboli
- Progressively worsening dyspnea: recurrent showers of emboli → pulmonary hypertension, chronic right-sided HF, pulmonary vascular sclerosis

② The cardiopulmonary status.

*Infarction: compromised cardiovascular status (CHF), wedge-shaped with their base at the pleural surface & the apex panting toward the hilus of the lung.

-The more peripheral the embolic occlusion, the higher the risk for infarction.

- Pulmonary infarcts: hemorrhagic with red-blue areas of coagulative necrosis, the adj pleura surface is covered by fibrinous exudate, the occluded vessel is located near the apex of the infarcted area.

*Managment:-
- Prophylactic therapy for bedridden patients
- Anti-coagulation // for pulmonary embolism
- Thrambolytic // for massive // //

B) Nonthrombotic pulmonary emboli:-
- Potentially lethal
- ex: air, fat, amniotic fluid embolism, foreign body embolism (in IV drug abusers) bone marrow embolism (hematopoietic & fat elements within a pulmonary artery, after massive trauma & in patients with bone infarction secondary to sickle cell anemia).

2) Pulmonary hypertension:-
- 25 mm Hg or more at rest (pressure)

*Morphology:
- In muscular & elastic arteries: medial hypertrophy.
- In small arteries & arterioles: // // & intimal fibrosis.
- Right ventricular hypertrophy.
- Plexiform lesion: capillary formations producing a network with the lumens of dilated thin-walled, small arteries & may extend outside the vessel. Are most prominent in group 1 & 2.

* Group 1 : Pulmonary arterial hypertension :-
- affects small pulmonary muscular arterioles :
I) heritable forms
II) autoimmune disease (systemic sclerosis)
III) CT diseases, HIV & congenital heart disease with left to right shunts
IV) Idiopathic : genetic basis
* Group 2 : hypertension due to left-sided heart disease :- congenital/acquired
- Mitral stenosis
* Group 3 : Pulmonary hypertension due to lung disease / hypoxia :-
- obliterate alveolar capillaries → ↑ resistance
- Obstructive sleep apnea, COPD & interstitial lung disease
  - ↳ associated with obesity & hypoxemia
  - ↳ leads to right-sided heart failure
* Group 4 : thromboembolic pulmonary hypertension :-
↓ functional cross-sectional area of the pulmonary vascular bed → ↑ resistance
* Pulmonary hypertension with unclear or multifactorial mechanisms.

3) Diffuse alveolar hemorrhage syndrome :-

A) Goodpasture syndrome (Anti-glomerular basement membrane antibody disease with pulmonary involvment) :- in active smokers

- Autoantibodes against type IV collagen → destruction & inflammation of the basement membranes
  - → in pulmonary alveoli → necrotizing hemorrhagic interstitial pneumonitis
  - → in renal glomeruli → glomerulonephritis → renal faliure

* Microscopically → early : focal necrosis, intraalveolar hemorrhage & hemosidren laden macrophages.
  - later : fibrous thickening of septa, hyperbrophic type II pneumocytes & organization of blood in alveolar spaces.

- DIF : deposition of IgG, sometimes IgA or IgM

* Managment : plasmapheresis immunosuppressive therapy, renal transplantation

B) Granulomatosis with polyangiitis "GPA" (Wegener granulomatosis) :-

- Triad → necrotizing angiitis (inflammation of the walls of blood vessels).
  - aseptic necrosis of URT & lungs.
  - focal glomerulonephritis (necrotizing & crescentic).
- Parenchymal necrotizing poorly formed granulomatous inflammation.

* In most of the cases : anti-neutrophil cytoplasmic antibodes "proteinase 3" (PR3-ANCAs) (C-ANCA)

Tuberculosis

- Chronic granulomatous disease caused by mycobacterium tuberculosis
- Risk factors: poor crowded communities, chronic illnesses & older adults
* Mycobacteria: acid fact bacilli "rods" (↑lipids → resist decolorization & appear pink-purple "red" on ziehl neelsen stain.
* M. tuberculosis hominis: most cases of tb, the reservoir of infection found in individuals with active pulmonary disease, airborne transmission or by contaminated secretions.
* M. bovis: contracted by drinking contaminated milk, causes oropharyngeal & intestinal tuberculosis
* M. avium complex: less virulent, affects immunocompromised
* Infection: presence of organisim, may or may not develop a disease.
* Disease: tissue damage
* Pathogenesis:-
- Primary tuberculosis: in previously unexposed immunocompetent individual:
  - ↳ before activation of cell mediated immunity:
    mycobacterium bind mannose or complement receptors to enter the macrophages → maturation arrest, prevent phagolysosome formation
    → patient has only infection (no lesion or tissue damage)
  - ↳ initiation & consequences of cell mediated immunity:
    antigen presenting cells → IL-12 → activates T_H1 → IFN-γ
    → macrophage activation (phagolysosome maturation, ↑NO, ROS & autophagy) → mycrobial killing
    ↑TNF → monocyte recruitment → epithelioid granuloma
- mostly self-limited, asymptomatic
- defects in T_H1 response, IL-12, IFN,γ, TNF, NO → poorly formed granulomas, absence of resistance, disease progression.

- Fibrocalcific nodule at the site of infection (close to pleura in the distal air spaces "in the lower part of the upper lobe & upper part of the lower lobe", infection, not active disease)
* Ghon focus: gray-white inflammatory consolidation (central caseous necrosis).
* Ghon complex: involvement of lymph nodes & prenchyma.
* Tuberculin (mantoux) test: intracutaneous injection of 0.1 ml. of sterile purified protein derivative (PPD)
- Positive test does not differentiate between infection & disease.
* TB → central caseation
→ without central caseation (rare)
- Secondary tuberculosis (reactivation TB):
- localized to the apex apical pleura
→ asymptomatic, heal with fibrosis (spontaneously or after therapy)
lymph nodes are less involved
→ may progress & extend along different pathways → systemic manifestations (due to the release of TNF & IL-1)
* Miliary pulmonary disease: organisms reach the bloodstream then recirculate to the lung.
* Systemic miliary tuberculosis: organisms disseminate hematogenously throught the body.
- Morphology: same as primary TB
- Culture is the standard diagnostic modality.