The respiratory system

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Congenital anomalies

- **Agenesis or hypoplasia** (both lungs, one lung, single lobes);
  - **hypoplasia** most often secondary: congenital diaphragmatic hernia, renal cystic disease, renal agenesis, anencephaly, prolonged rupture of fetal membranes

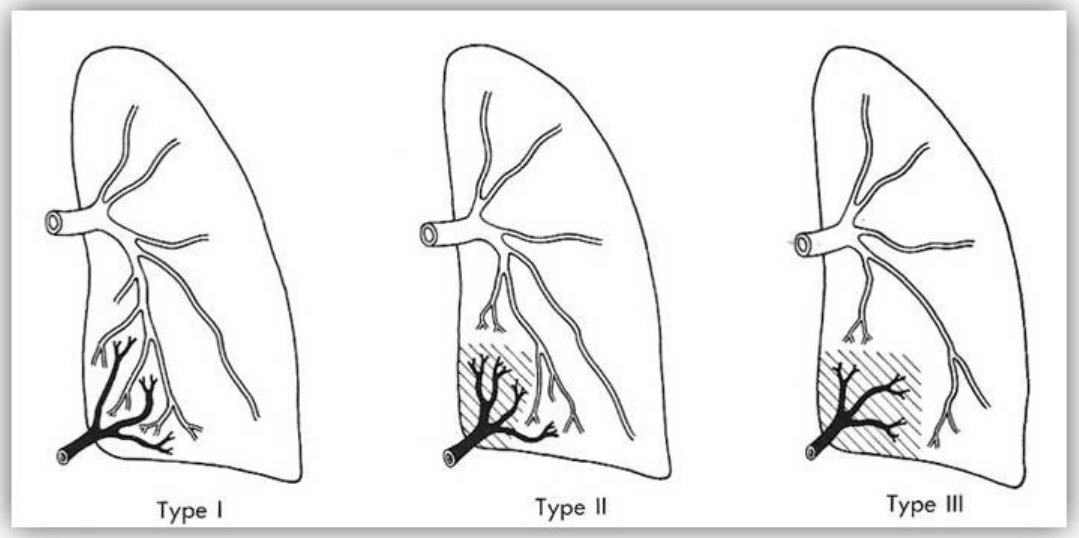
- **Tracheal or bronchial anomalies**
  - atresia
  - stenosis
  - tracheooesophageal fistula

- **Congenital lobar emphysema**

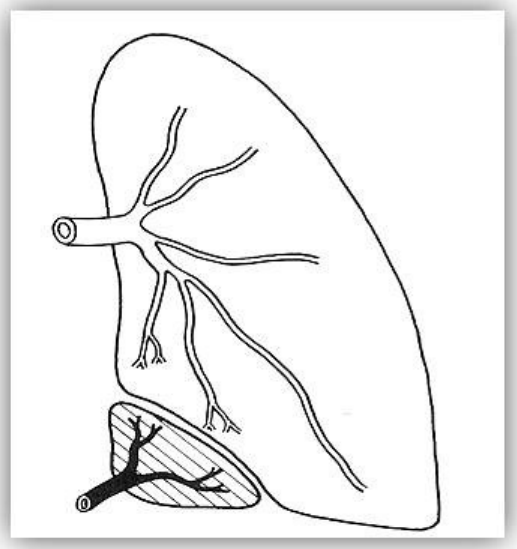
(overdistension of a lobe due to intermittent bronchial obstruction….related to abnormal bronchial cartilage, allowing inspiration, restricting expiration)

- **Bronchogenic/foregut cysts**
  - hilus or middle mediastinum
  - bronchogenic – most common
  - esophageal or enteric

Pulmonary sequestration



Intralobar



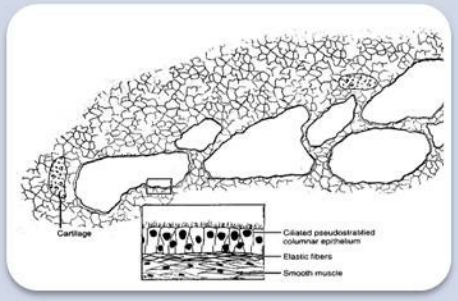
Extralobar

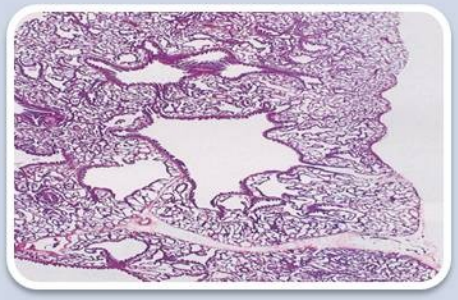
……no normal connection to the airway system

Congenital pulmonary airway malformation (CPAM)

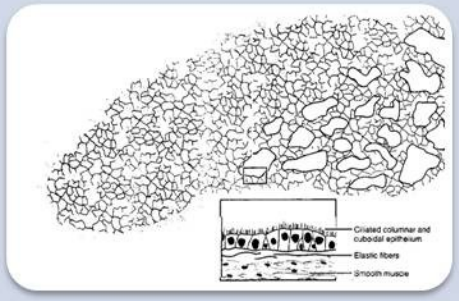
(congenital cystic adenomatoid malformation (CCAM)).

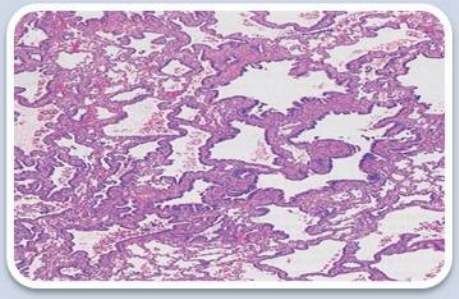
Type I



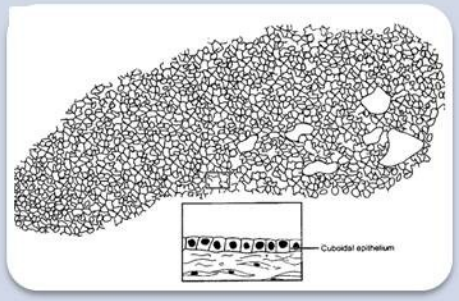


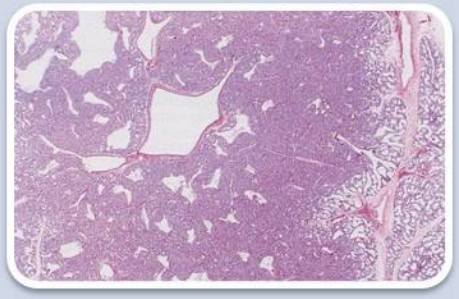
Type II





Type III





Good prognosis……poor prognosis.

Atelectasis; collapse

- **Atelectasis**

- primary; neonatal; immature neonates, lack of surfactant

- **Collapse** (secondary, previously inflated lungs) = acquired atelectasis

1. Obstruction (resorption of the air after the blockage)
2. Compression (hydrothorax, pneumothorax, pleural exsudate)
3. Contraction atelectasis (fibrotic changes prevent full expansion)

Immaturity:
- hyaline mebrane disease (HMD) or idiopathic distress syndrome
- bronchopulmonary dysplasia

- Complication of prematurity (less than 36 weeks gestation)
- Due to deficiency of pulmonary surfactant
- Tachypnoe, dyspnoe, expiratory grunting, cyanosis
- Diffuse alveolar damage with hyaline mebranes
- Bronchopulmonary dysplasia – lung organisation after HMD (+oxygen toxicity); interstitial and peribronchial fibrosis

Pulmonary edema (congestion)

- **Hemodynamic**

1. Increased pulmonary venous pressure – venostatic edema (left sided heart failure, volume overload, pulmonary vein obstruction)
2. Decreased oncotic pressure (hypoalbuminemia, nephrotic syndrome, liver disease, protein loosing enteropathies)
3. Lymphatic obstruction

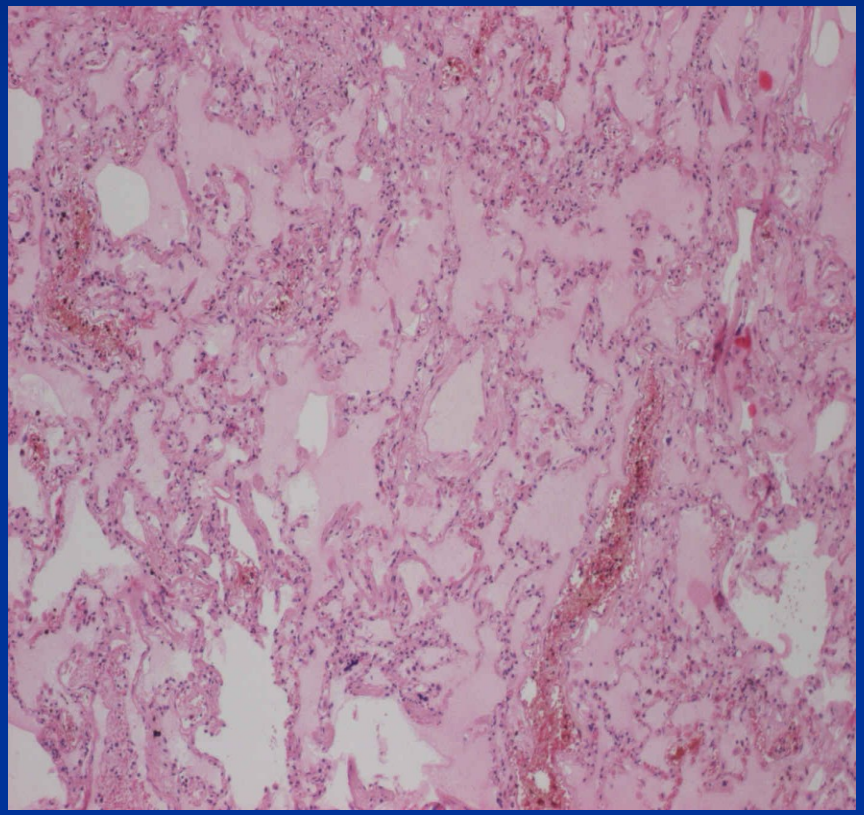
- **Due to microvascular injury (alveolar injury; leakage of fluids and proteins into interstitium and later into alveoli)**

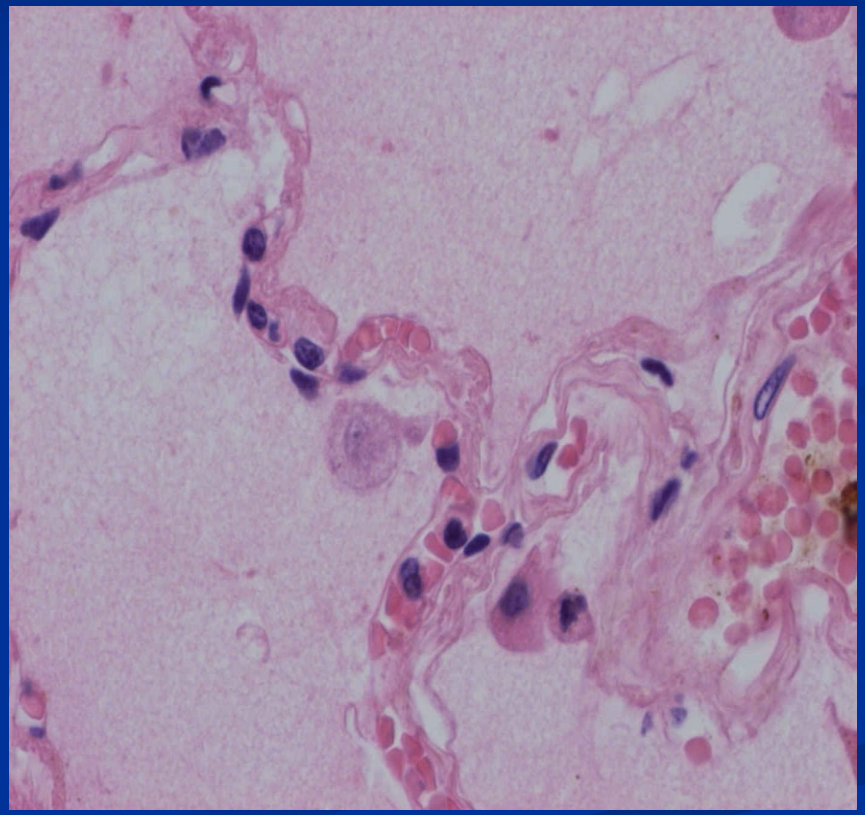
1. Infections (pneumonia, septicemia), shock, trauma
2. Inhalation of toxic gases
3. Liquid aspiration
4. Drugs, chemicals
5. Radiation

- **Undetermined origin**

1. High altitude
2. CNS trauma

Pulmonary edema





Adult respiratory distress syndrome (ARDS)/acute lung injury (ALI) – diffuse alveolar damage (DAD) – shock lung – acute alveolar injury.

Acute respiratory failure after a systemic or pulmonary insult (direct or indirect lung injury); short history of dyspnoe, tachypnoe and respiratory distress/failure.

- **Shock (haemorrhagic, cardiogenic, septic, anaphylactic, endotoxic,…)**
- **Diffuse pulmonary infections, sepsis**
- **Gastric aspiration**
- **Chemical injury** (heroin, methadon, barbiturate overdose, acetylsalicylic acid)
- **Trauma (direct pulmonary or multisystem trauma)**
- **Haematologic conditions** (DIK, multiple trasfusions)
- **Pancreatitis**
- **Uremia**
- **Inhaled irritants** (oxygen toxicity, smoke, toxic gases)
- **Hypersenzitivity reaction** (organic solvents, drugs – anticancer treatment)

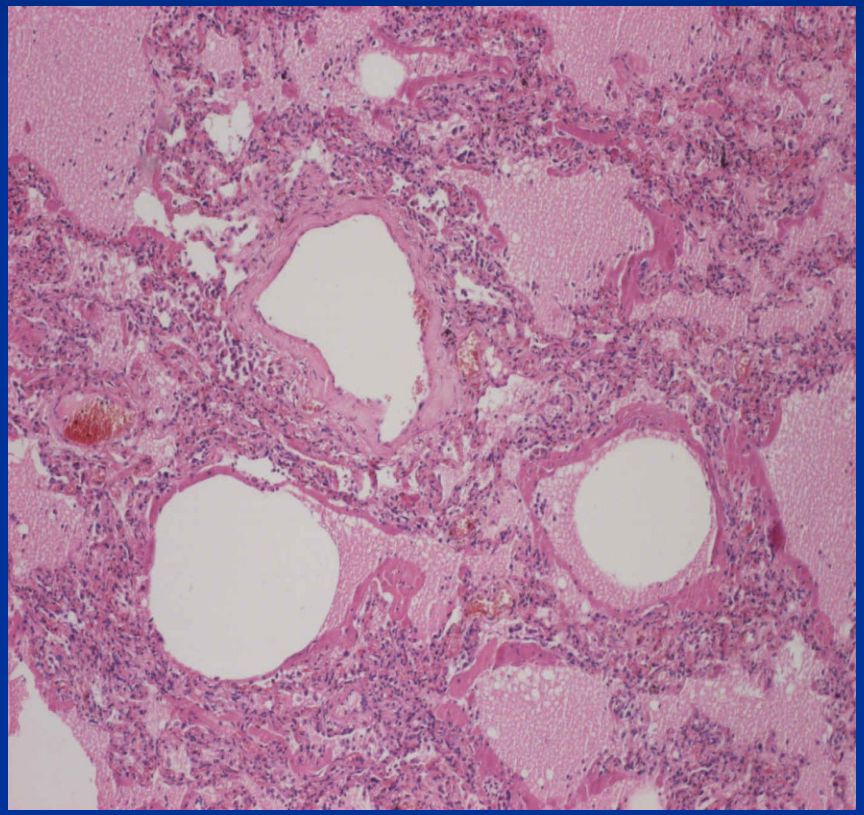
Morphology of ARDS (DAD)

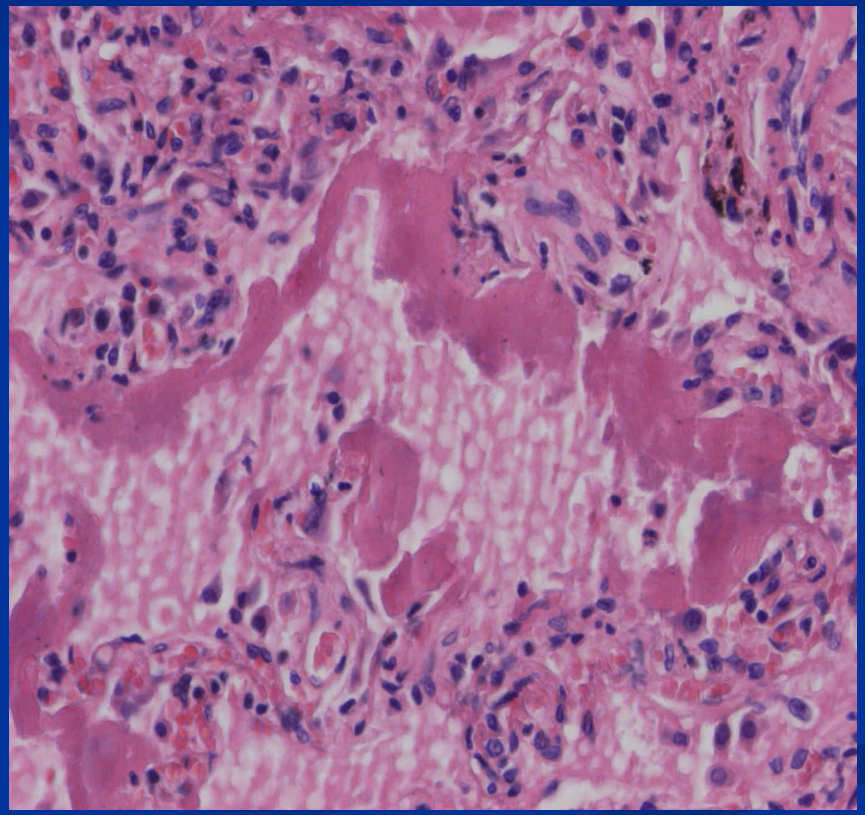
- **Macroscopy** (congestion, redness of the lungs, hypoinflation)

- **Microscopy**

1. **Exsudative stage: e**dema, interstitial and intraalveolar, inflammation, fibrin deposition, hyaline membranes
2. **Organizing stage:** proliferation of type II cells and regeneration of epithelial lining, organisation of fibrin exsudate resulting in intraalveolar fibrosis, interstitial fibrosis due to proliferation of interstitial cells and deposition of collagen

ARDS – hyaline membranes





- **Obstructive pulmonary diseases**

(increase in resistence to airflow due to partial or complete obstruction at any level)

- Chronic bronchitis
- Emphysema
- Asthma
- Bronchiectasia

Chronic bronchitis + emphysema = chronic obstructive pulmonary disease (COPD)

- **Restrictive pulmonary diseases**

(reduced expansion of lung parenchyma with decreased total lung capacity)

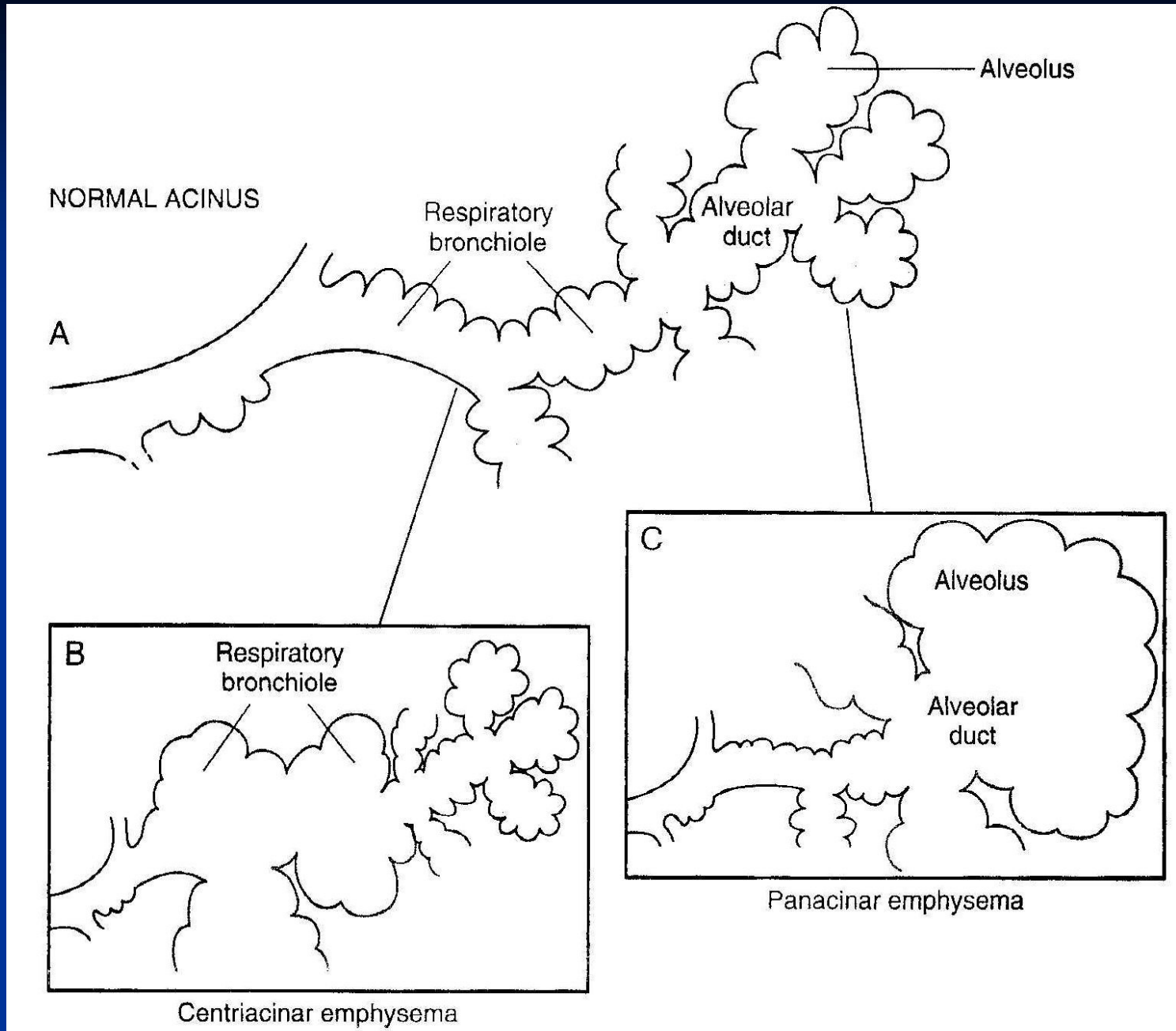
- Chest wall disorders in presence of normal lungs (kyphoscoliosis, pleural diseases, severe obesity, neuromuscular disorders such as poliomyelitis)
- Acute or chronic interstitial and infiltrative diseases

Emphysema

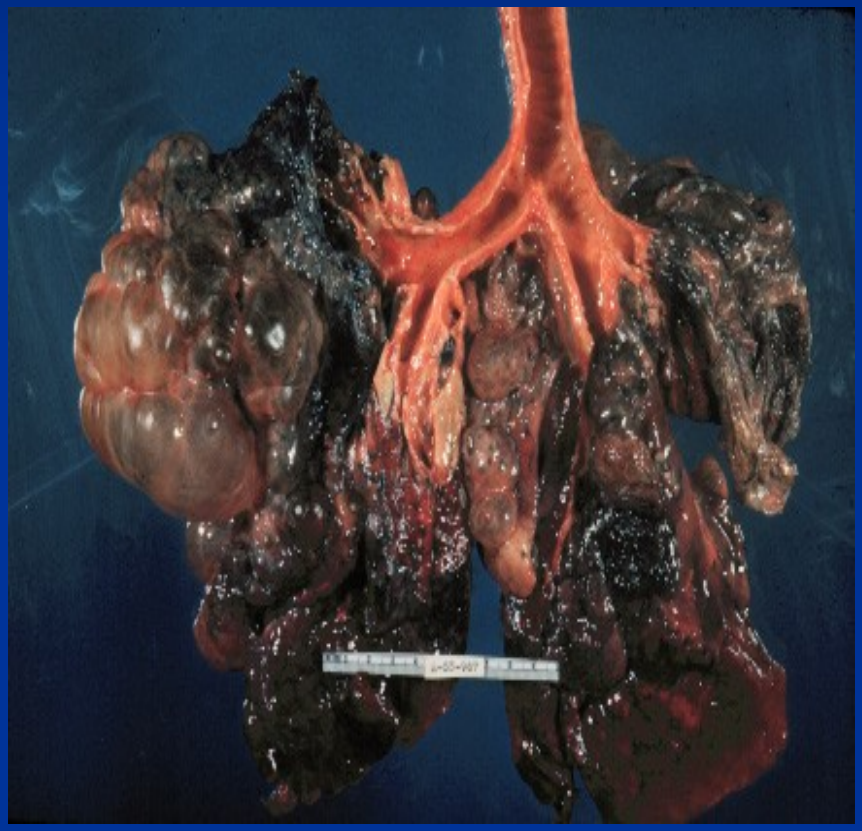
Abnormal permanent enlargement of the airspaces distal to terminal bronchiole, accompanied by the destruction of their wall and without obvious fibrosis; protease-antiprotease theory: inbalance between proteases and anti-proteases in the lung (genetics, smoking) + oxidant-antioxidant imbalance (reacitve oxygen species in tabacco smoke).

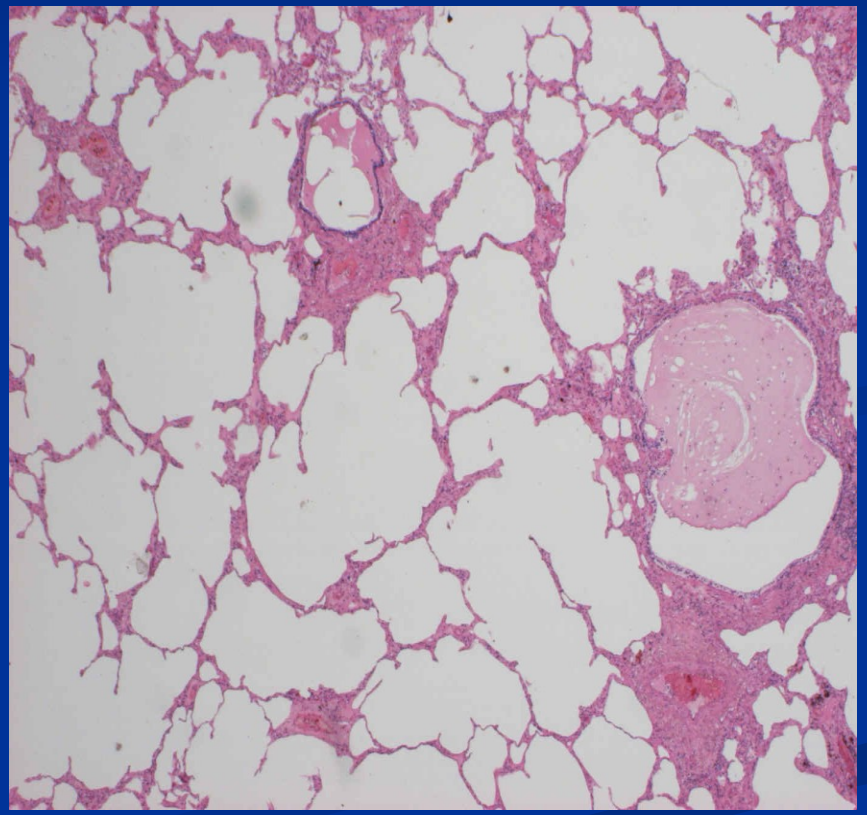
- **Centrilobular/centriacinar** (predominantly in **heavy smokers**, associated with chronic bronchitis)
- **Panlobular/panacinar** (alfa-1-antitrypsin deficiency)
- **Paraseptal, distal acinar** (adjacent to areas of fibrosis, scarring, atelectasis; spontaneous pneumothorax of young adults; upper half of the lungs)
- **Irregular** (associated with scarring)

- Others: compensatory (hyperinflation) emphysema, bullous emphysema, interstitial emphysema (arteficial ventilation, rupture of an emphysematous bulla)


NORMAL ACINUS
Alveolus
Respiratory bronchiole
Alveolar duct
A
B
Respiratory bronchiole
C
Alveolus
Alveolar duct
Centriacinar emphysema
Panacinar emphysema

Emphysema





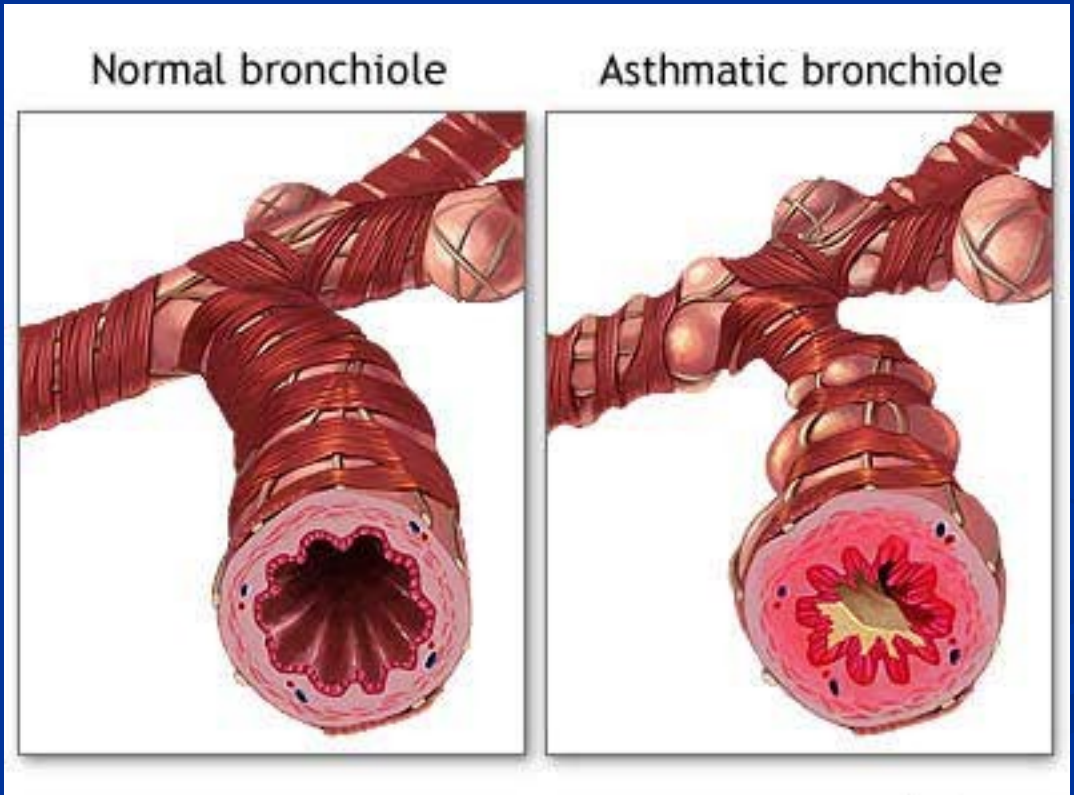
Chronic bronchitis

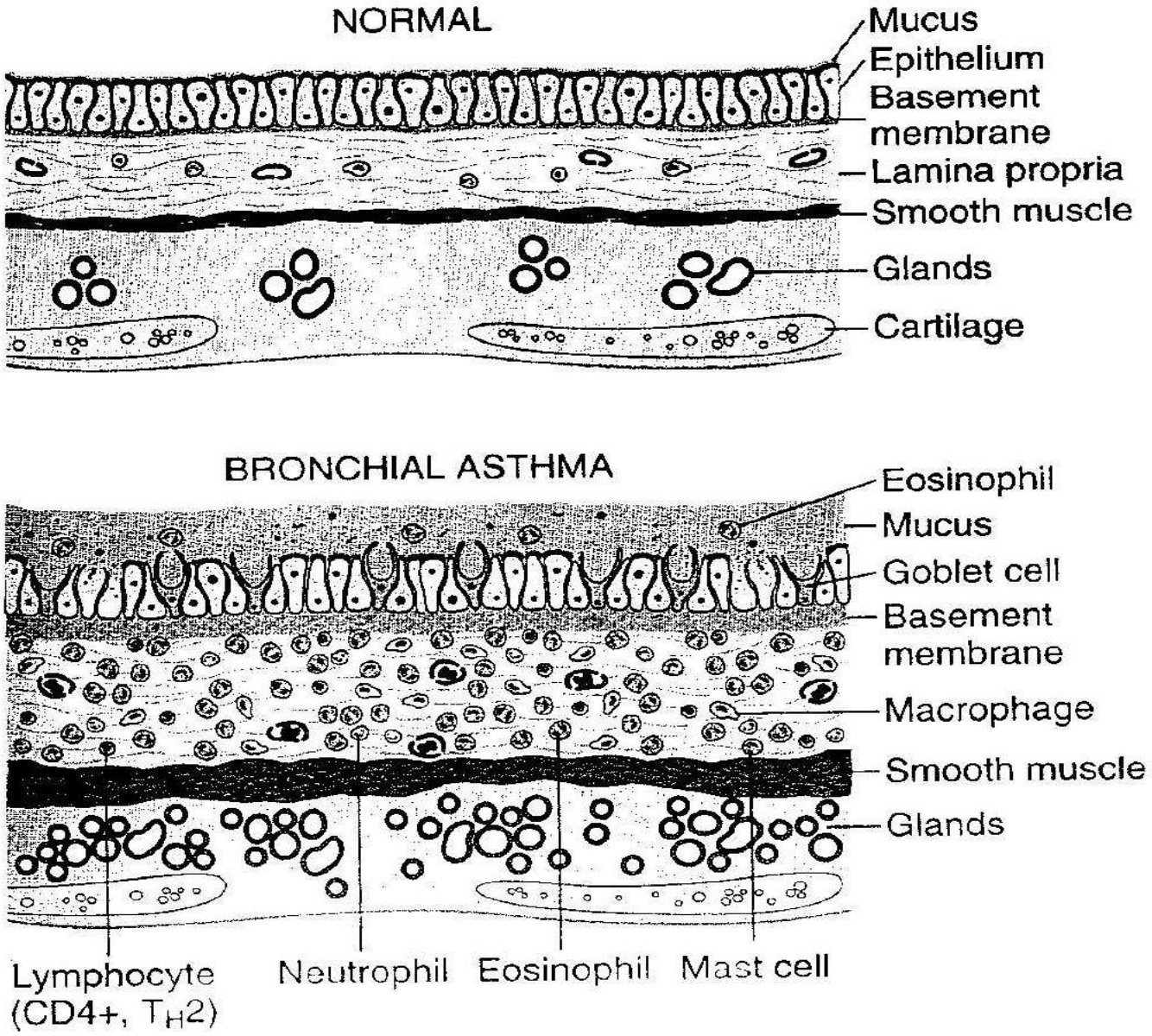
- Smoking!!!!
- Progression to chronic obstructive airway disease
- Incresing breathlessness, hypoxia, respiratory failure (type I hypocapnic, type II hypercapnic) → pulmonary hypertension, cor pulmonale and heart failure
- Atypical metaplasia and dysplasia of respiratory epithelium – cancerogenesis

- Clinical deffinition: cough with sputum production for at least 3 months in two consecutive years
- Chronic irritation, infection, congestion of the lungs – venostasis, allergy, mucoviscidosis,…

Asthma bronchiale

- Chronic inflammatory disorder of the airways; reversible small airways obstruction characterised by bronchospasm, inflammation and oedema. Paroxysmal episodes of wheezing, breathlessness, chest tightness, cough, at night/in the morning
- Overdistended lungs, mucous plugs in bronchi, mucous gland and smooth muscle hypertrophy




NORMAL
Mucus
Epithelium
Basement membrane
Lamina propria
Smooth muscle
Glands
Cartilage
BRONCHIAL ASTHMA
Eosinophil
Mucus
Goblet cell
Basement membrane
Macrophage
Smooth muscle
Glands
Lymphocyte (CD4+, T_H2)
Neutrophil
Eosinophil
Mast cell

Asthma bronchiale

- **Extrinsic, atopic**
  (IgE-mediated external allergens)
- **Intrinsic, non-atopic, idiopathic**
  (secondary to infection?)
- **Aspirin – induced**
  (decreased PGs or increased LT leading to airway hyperreactivity)
- **Allergic bronchopulmonary aspergillosis**
  (inhalation of spores, immediate type I and delayed type III hypersensitivity reaction)
- **Occupational**
  (thought to be a combination of type I and type III hypersensitivity)
- **(Exercise – induced)**

Bronchiectasis: permanent dilatation of bronchi and bronchioles

- Results from pulmonary inflammation and scarring due to infection, bronchial obstruction or lung fibrosis (e.g. after radiotherapy)
- Secondary inflammation lead to further destruction of airways
- Chronic cough with dyspnoe and production of copious amount of foul-smelling sputum
- Complications: pneumonia, abscess (also metastatic (e.g. in brain), amyloid, pulmonary fibrosis, cor pulmonale
- In congenital and hereditary conditions, in chronic infections, after radiotherapy in lung and breast cancer, distal to bronchial obstruction, immunodeficiency, post-transplantation, in SLE, RA

Bronchiectasis: permanent dilatation of bronchi and bronchioles

caused by destruction of the muscle and elastic tissue.

Etiopatogenesis, predisposing conditions:

- **Congenital and hereditary conditions**
  (mucoviscidosis, intralobar sequestration, immunodeficicency status, primary cilliary diskenesis,))
- **Postinfectious conditions**
  (necrotising infections bacterial (BK, SA, HI, PA), viral (HIV, influenza, adenovirus), fungal (Aspergillus))
- **Bronchial obstruction**
  (tumors, foreign bodies,…)
- **Others**
  (rheumatoid arthritis, lupus erythematodes, IBD, post-transplantation)

Chronic interstitial disease/chronic interstitial lung disease (ILD) (restrictive pulmonary diseases)

- **Fibrosing**
  - Idiopathic pulmonary fibrosis (usual interstitial pneumonia)
  - Cryptogenic organizing pneumonia
  - Connective tissue disorders related ILD
  - Pneumoconiosis
  - Drug reactions
  - Radiation pneumonitis
- **Granulomatous**
  - Sarcoidosis
  - Hypersenzitivity pneumonitis/extrinsic allergic alveolitis
- **Eosinophilic pnemonia**
- **Smoking-related**
  - Desquamative interstitial pneumonia
  - Respiratory bronchiolitis-associated interstitial lung disease
- **Other**
  - Pulmonary alveolar proteinosis

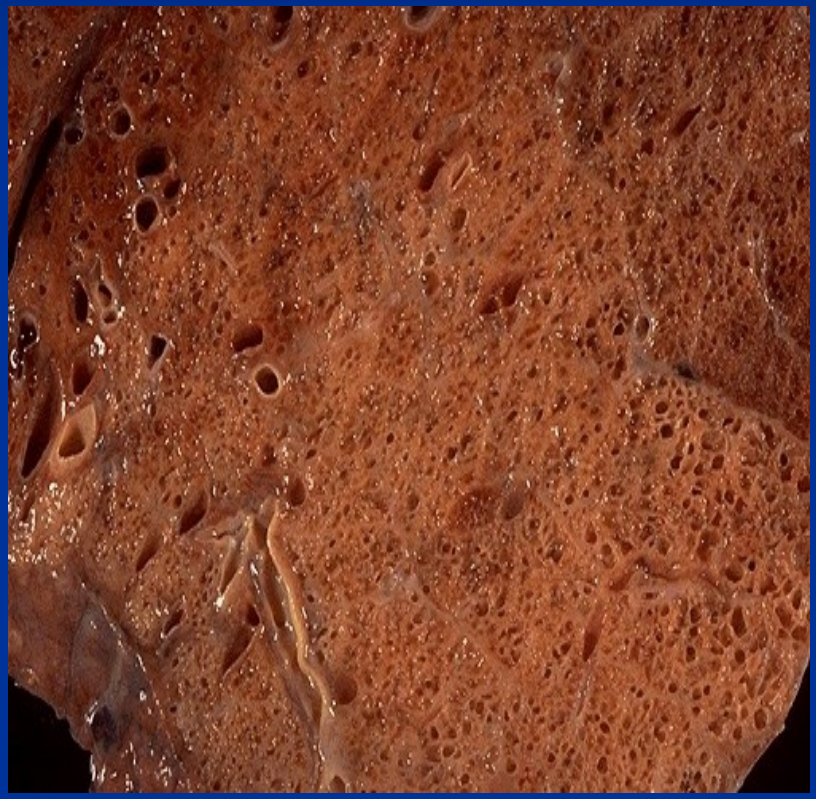
Idiopathic pulmonary fibrosis
(usual interstitial pneumonia; cryptogenic fibrosing alveolitis)

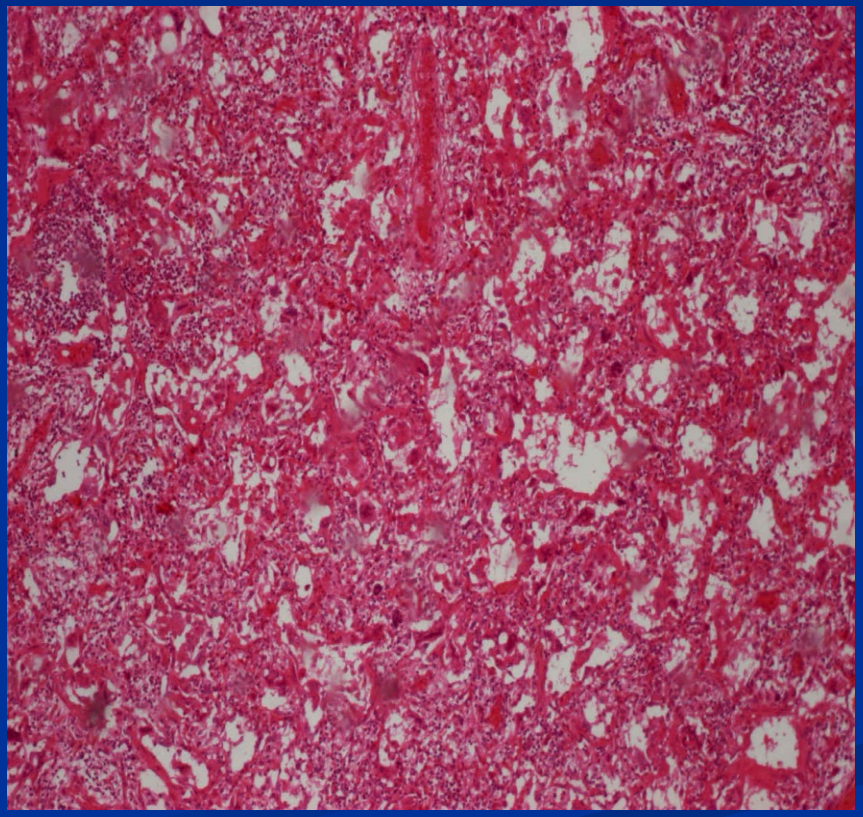
- Hamman-Rich syndrome: previously: rapidly progressive type of IPF; now: acute lung injury, acute interstitial pneumonia
- Pathogenesis: repeated cycles of acute lung injury (alveolitis) by some unidentified agent (inhaled agents, dusts, blood toxins, unknown Ag) followed by fibroblastic proliferation, widespread fibrosis and loss of lung function (end-stage lung, honeycomb lung)
- Modification of inflammatory response (T_H2 type) - genetic and enviromental factors
- Clinical course: gradually increasing dyspnoe, dry cough, hypoxemia, cyanosis, clubbing; progression unpredictable
- Treatment: steroids, cyclophosphamide, azathioprine; lung transplantation

Morphology of IPF

- Pleural surfaces cobblestoned due to the retraction of scars along interlobular septa
- Fibrosis predominantly in the subpleural regions and along interlobular septa
- Microscopically: patchy interstitial fibrosis
- Dense interstitial fibrosis, cystic spaces lined by hyperplastic type II pneumocytes or bronchiolar epithelium (honeycomb fibrosis)
- Mild to moderate inflammation (lymphocytes, plasma cells, eosinophils, neutrophils, mast cells) in fibrotis areas
- Squamous metaplasia, smooth muscle hyperplasia
- Secondary pulmonary hypertensive changes (intimal fibrosis, medial thickening of pulmonary arteries)

Idiopathic pulmonary fibrosis





Cryptogenic organizing pneumonia (COP) = bronchiolitis obliterans organizing pneumonia (etiology unknown)

- Cough, dyspnea, subpleural or peribronchial patchy ares of consolidation radiologically
- Polypoid plugs of loose organizing connective tissue within alveolar ducts, alveoli (intraalveolar fibrosis) and often bronchioles
- No interstitial fibrosis, no honeycomb lung
- Intraalveolar fibrosis also as a response to infections or inflammatory injury of the lungs

  (inhaled toxins, drugs, collagen vascular diseases, GVHD)

Pulmonary involvement in collagen vascular diseases

- Systemic lupus erythematodes, rheumatoid arthritis, progressive systemic sclerosis (scleroderma), dermatomyositis-polymyositis, mixed connective tissue disease

- Nonspecific interstitial pneumonia, UIP, vascular sclerosis, organising pneumonia and bronchiolitis;
  in RA: chronic pleuritis, pleural effusion, rheumatoid nodules, IP, pulmonary hypertension

Pneumoconioses

- Non-neoplastic lung reaction (usually occupational) to inhalation of organic (mineral dusts) as well as inorganic particulates and chemical fumes and vapors

- Amount of the dust; size and shape (1-5μm), solubility, additional irritants

- e.g. quartz (form of crystalline silica): direct injury to tissue and cell membranes, triggering of macrophages to release of proinflammatory and fibrosing mediators)

Coal workers´ pneumoconiosis (CWP)

Usually benign, minority cases develop pulmonary dysfunction, hypertension and cor pulmonale.

- **Asymptomatic antracosis** (no fibrosis, antracotic pigment in pulmonary lymphatics and lmyph nodes)
- **Simple CWP (coal macules and nodules);** carbon-laden macrophages + collagen fibers; primarily ar respiratory bronchies; centrilobular emphysema
- **Complicated CWP** or progressive massive fibrosis with pulmonary dysfunction (multiple scars, dense collagenand pigment)
- **Caplan´s syndrome**: CWP+rheumatoid arthritis

Coal dust inhalation; contamination by silica favor the progressive disease.

Silicosis

- **Inhalation of silica** (in both amorphous (less active) and crystalline forms (quartz, crystobalit, tridymite) followed by ingestion of silica particules by macrophages

- **Silicotic nodules** (concentric layers of hyalinized collagen with a dense capsule, polarization reveals silica particules)
- **Hard collageneous scars** (central softening and cavitation due to superimposed tbc or to ischemia; sheets of calcification in lymph nodes)

- Progressive clinical course, even if the patient is no longer exposed

- Crystalline silica from occupational sources was suggested to be carcinogenic in humans
- Increased susceptibility to tbc in silicosis (depression of cell mediated immunity) - silicotuberculosis

Asbestos – related diseases

- Localized fibrous plaques or diffuse pleural fibrosis
- Pleural effusions
- Parenchymal interstitial fibrosis (asbestosis)
- Lung carcinoma
- Mesothelioma
- Laryngeal and perhaps extrapulmonary neoplasms

- Both forms of asbestos (amphiboles (more pathogenic, 1x8 μm) and serpentines) are fibrogenic
- Asbestos bodies: fusiform rods coated with an iron containing proteinaceous material

- **Drug induced lung disease**
  (bleomycin, methotrexate, amiodarone (anti-arrhytmic,…)

- **Radiation induced lung diseases**
  (acute and chronic radiation pneumonitis)

- **Granulomatous diseases**

1. **Sarcoidosis** (noncaseating granulomas; 90 % lung and hilar lymph nodes involvement; **disordered immune regulation** (cell mediated response to an unidentified **agents) in genetically predisposed individuals** (HLA-A1, HLA-B8, familiar and racial clustering) **exposed to certain enviromental agents**(e.g. mycobacteria, *Rickettsia* species, *Propionibacterium acnes*))

   other organs affected: spleen, liver, bone marrow, skin, eye and associated glands, salivary glands, muscle

2. **Hypersenzitivity pneumonitis/extrinsic allergic alveolitis):** inhalation of organic dusts and related occupational antigens (spores of thermophilic bacteria, fungi, animal proteins, bacterial products); farmer´s lungs, Pigeon breeder´s lung (birds), air conditionar lung (thermophilic bacteria)

- Interstitial pneumonitis
- Noncaseating granulomas
- Interstitial fibrosis and obliterative bronchiolitis

Pulmonary eosinophilia

- Acute eosinophilic pneumonia with respiratory failure (unknown etiology, steroid therapy)
- Simple pulmonary eosinophilia (Loffler syndrome)
- Tropical eosinophilia (microfilariae)
- Secondary eosinophilia (in fungal, parasitic, bacterial infections, in hypersenzitivity pneumonitis)
- Chronic eosinophilic pneumonia

Smoking related interstitial disease

- **Desquamative interstitial pneumonia**

(usually minimally fibrosis and no progressive course)

- **Pulmonary Langerhans cell histiocytosis/histiocytosis X**

- **Respiratory bronchiolitis-associated interstitial lung disease**

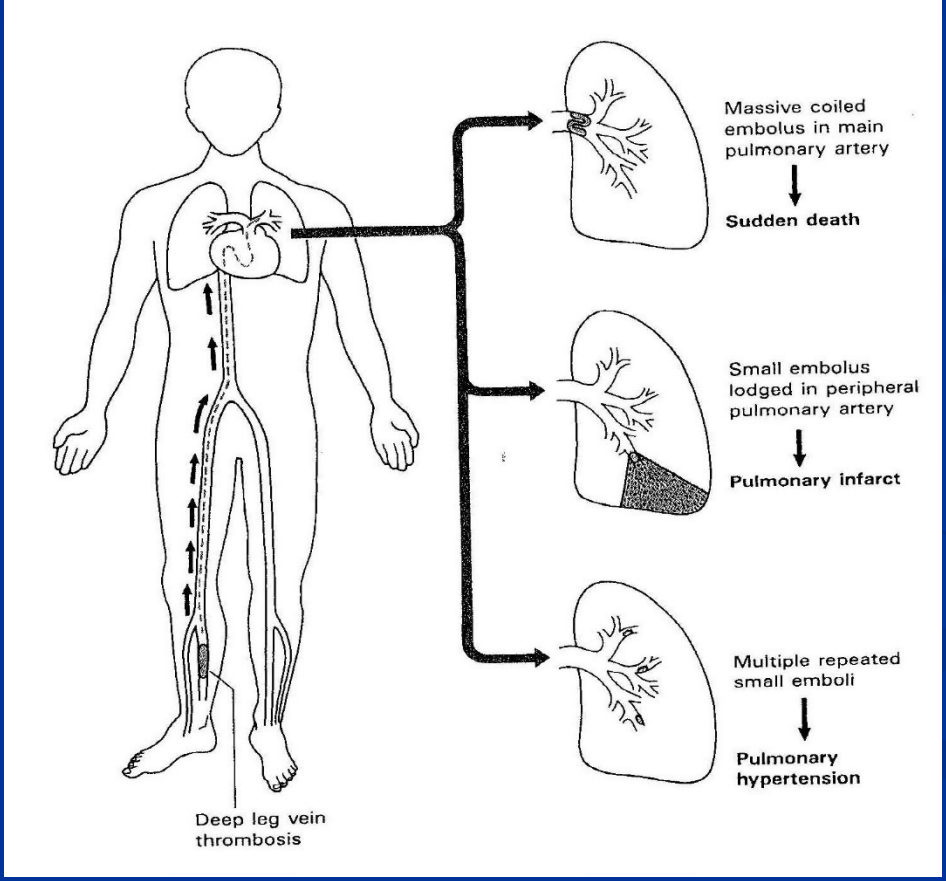
(usually mild symptoms, cessation of smoking=improvemement)

Pulmonary alveolar lipoproteinosis

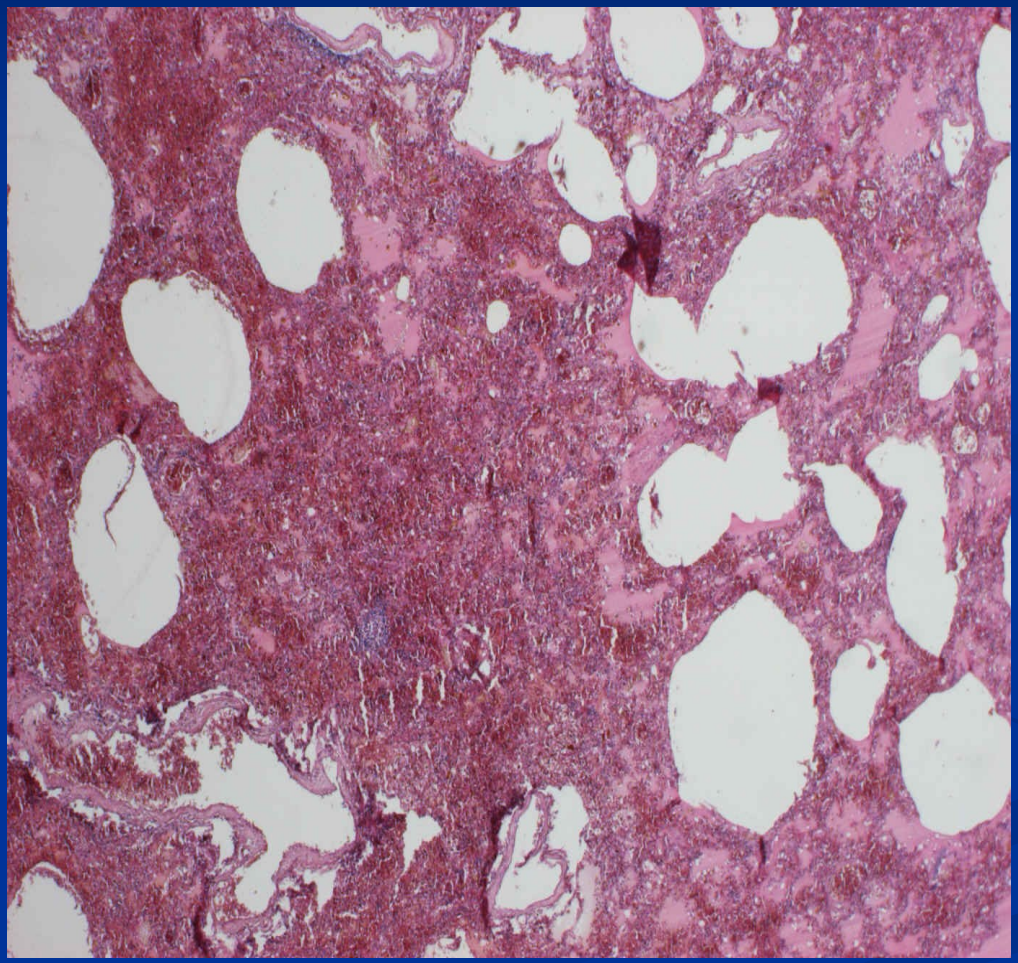
- **alveolar homogeneous granular precipitate within alveoli** (PAS+, surfactant +)
  - **Acquired** (unknown etiology, autoimmune?)
  - **Congenital** (mutation in genes encoding surfactant proteins)
  - **Secondary** (silicosis and other inhalation syndromes, malignancies, immunodeficiency syndromes,…)

Pulmonary embolism

- Hypercoagulable state
- Primary (factor V Leiden, antiphospholipid syndrome,…)
- Secondary (obesity, surgery, oral contraceptives, pregnancy,…)



Pulmonary infarction



Pulmonary hypertension

- Pulmonary blood pressure =1/8 of systemic blood pressure
- Pulmonary hypertension, cor pulmonale

- Chronic obstructive and restrictive lung diseases (hypoxy + destruction of parenchyma)
- Antecedent congenital or aquired heart disease (venostasis before left heart)
- Recurrent thrombemboli
- Autoimmune disorders involving pulmonary vasculature
- Venooclusive lung disease (musculoelastic thickening of subpleural and interlobular septal veins)
- Primary idiopathic pulmonary hypertension

- Morphology: circular medial hypertrophy (arterioles and small arteries), subintimal fibrosis, plexogenic pulmonary arteriopathies in left to righ shunts or in primary PH (a tuft of capillary formations, small aneurysms with thromboses, fibrinoid necroses of arterioles)

Diffuse pulmonary haemorrhage syndrome

- Goodpasture syndrome (autoimmune, antibodies against alpha-3 chain of collagen IV)
  - Proliferative, rapidly progressive glomerulonephritis
  - Necrotizing hemorrhagic interstitial pneumonitis

- Idiopathic pulmonary hemosiderosis

- Vasculitis-associated hemorrhage
  - Hypersenzitivity angiitis
  - Granulomatosis with polyangiitis/Wegener granulomatosis
  - Churg-Strauss syndrome (allergic angiitis and granulomatosis)
  - Lupus erythematodes

Pulmonary infections

- **Factors which favor the pneumonia**

- Chronic diseases
- Immunologic defficiency, immunosuppressive treatment
- Unusual virulent infections, nosocomial infections
- Loss or suppression of the cough reflex (neuromuscular disorders, chest pain, drugs; could cause aspiration of gastric content,…)
- Injury of mucociliary apparatus (smoking, viral disease, genetic disorders, inhallation of hot or corrosive gases,…)
- Pulmonary congestion and edema
- Accumulation of secretion (bronchial obstruction, mucoviscidosis,…)

Pneumonia syndromes

- Community-acquired acute pneumonia

(streptococcus pn., haemophilus inf., Moraxella cat., Staphylococcus a., Legionella pn., Klebsiella pn., Pseudomonas ae.,….)

- Community-acquired atypical pneumonia

(Mycoplasma pn., Chlamydia spp., Coxiella burnetti, viruses,…)

- Nosocomial pneumonia

(G- rods (Klebsiella spp., Serratia marcescens, E. coli, Pseudomonas spp.,…))

- Aspiration pneumonia

(mixture od anaerobic and aerobic flora)

- Chronic pneumonia

(Nocardia, Actinomyces, granulomatous (mycobacterium tbc, atypical mycobacteria, Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatidis)

- Necrotizing pneumonia and lung abscess

(mixture of aerobic and anaerobic flora, Staphylococcus a., Klebsiella pn., Streptococcus pyogenes and pneumoniae)

- Pneumonia in the immunocompromised host

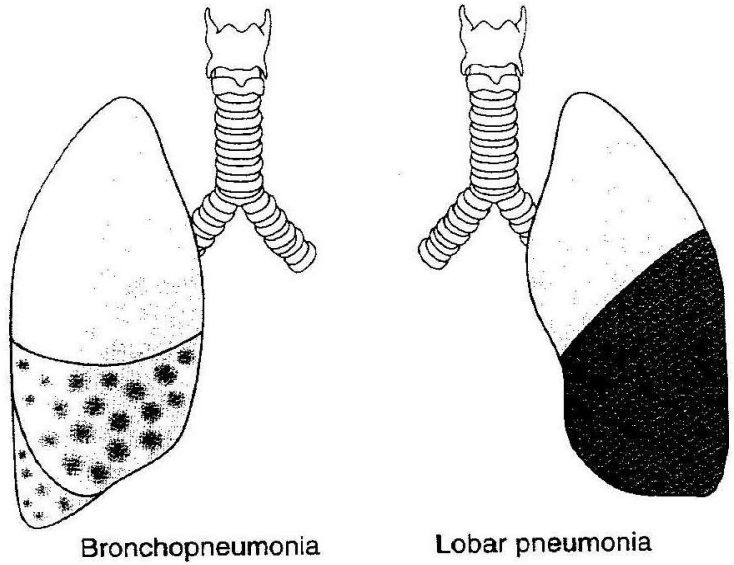
(CMV, Pneumocystis c., Mycobacterium avium intracellulare, aspergillus, Candida a. and others listed above,…),

Pneumonia

- **Alveolar inflammation**
- **Bronchopneumonia and lobar pneumonia**

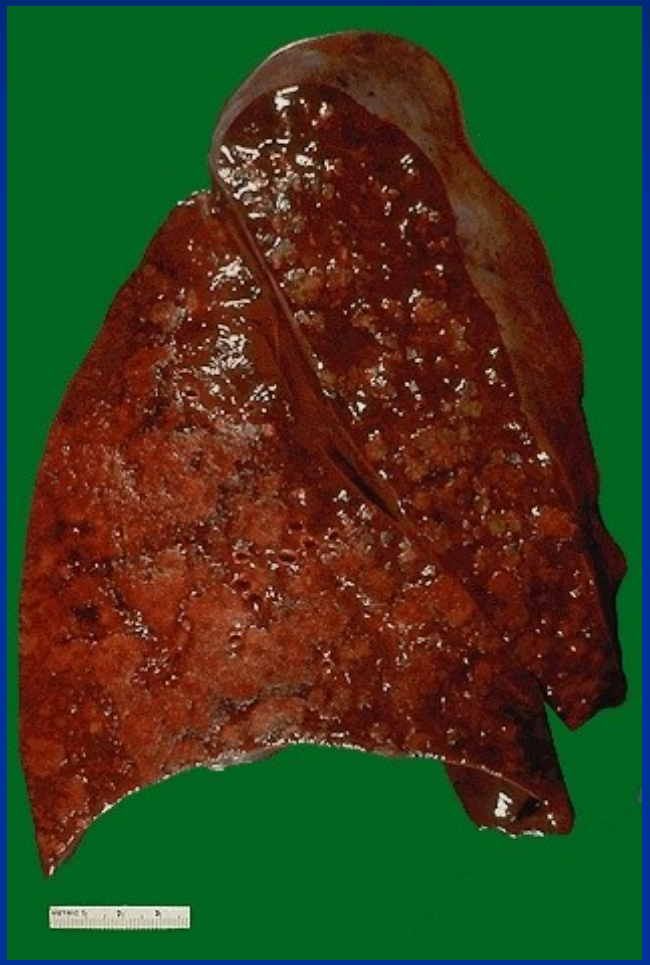
- Patchy consolidation
- Centred on bronchioles or bronchi
- Purulent inflammation
- Often in infancy or old age
- Often secondary

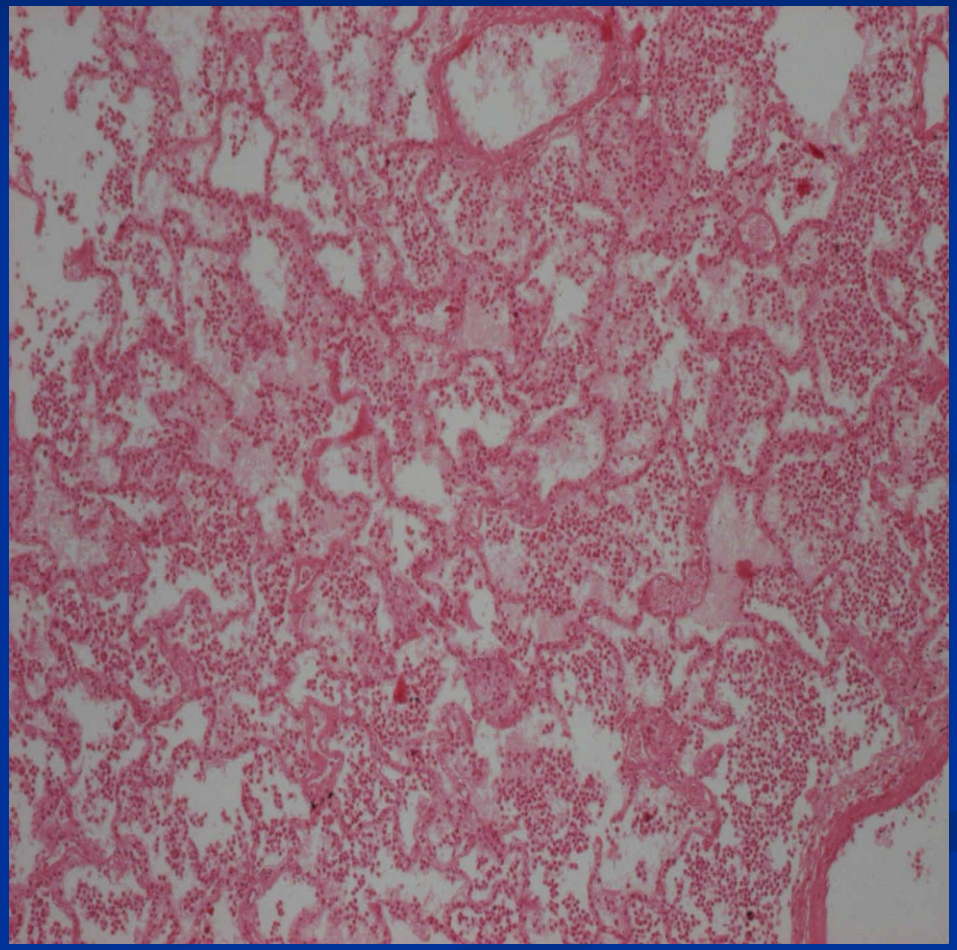
Complication:
abscess, empyema, bacteremic dissemination



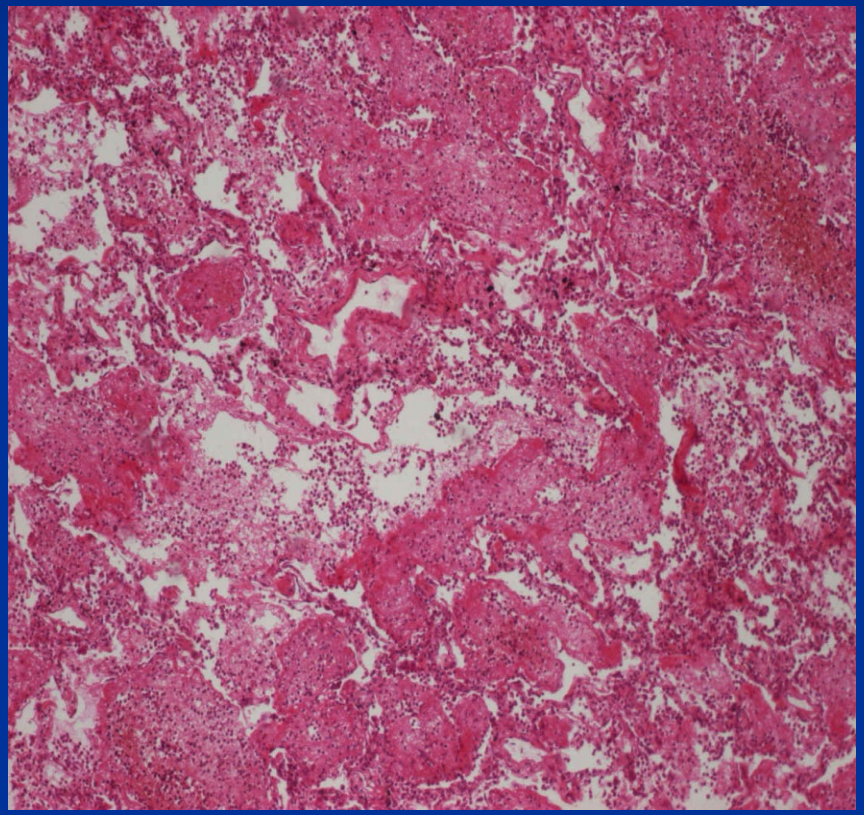
- Affects segments or whole lobe
- 4 stages (congestion, red hepatization, grey hepatization, resolution)
- Uncommon in infancy and old age
- Males more than females
- 90 % due to Streptococcus pneumoniae
- Cough and fever with sputum
- Fibrinous inflammation
- Healing complicated by fibrotisation/ carnification of the lungs

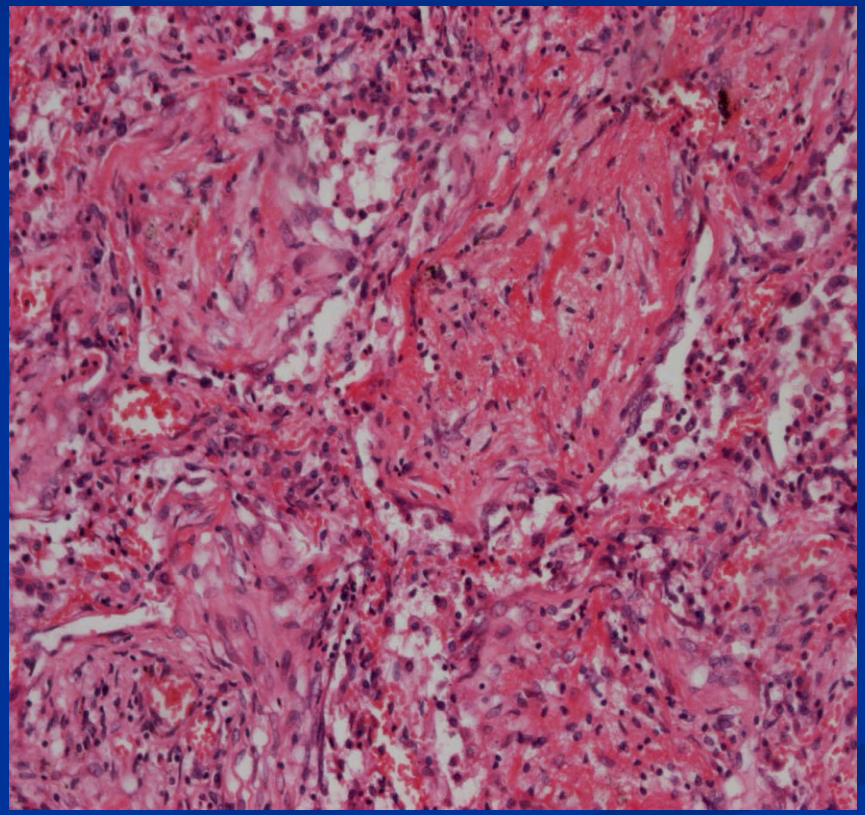
Bronchopneumonia



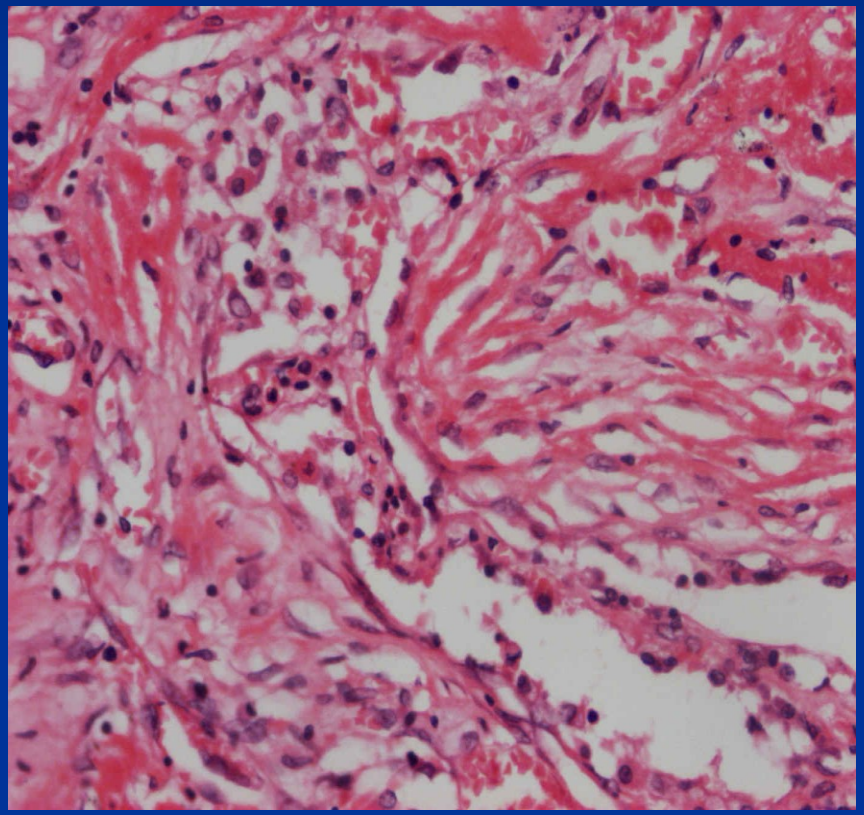


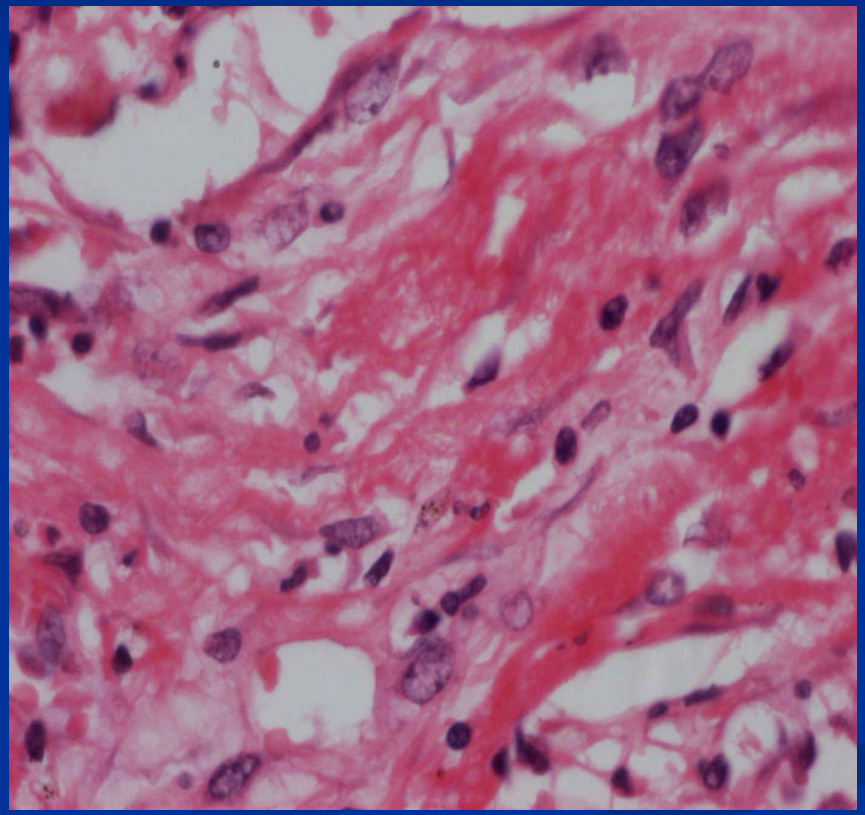
Lobar pneumonia – fibrinous – crupous pneumonia





Carnification of the lung





Atypical pneumonias

- Inflammatory changes predominantly interstitially – within alveolar walls

- Complication: ARDS

- Clinically:

- cough could be absent
- fever, headache, muscle pain
- poor finding at physical examination, severe X-ray finding (…atypical…)

Atypical pneumonias (usually interstitial)

Infective

In non-immunosuppressed hosts

- Viral and mycoplasma pneumonia
- Legionnaires´disease *(Legionella pneumoniae)*

In immunosuppressed hosts

-*Pneumocytis carinii*
-Fungi (e.g. *Candida albicans, Aspergillus*)
-Viruses (CMV, HSV, varicella zoster)

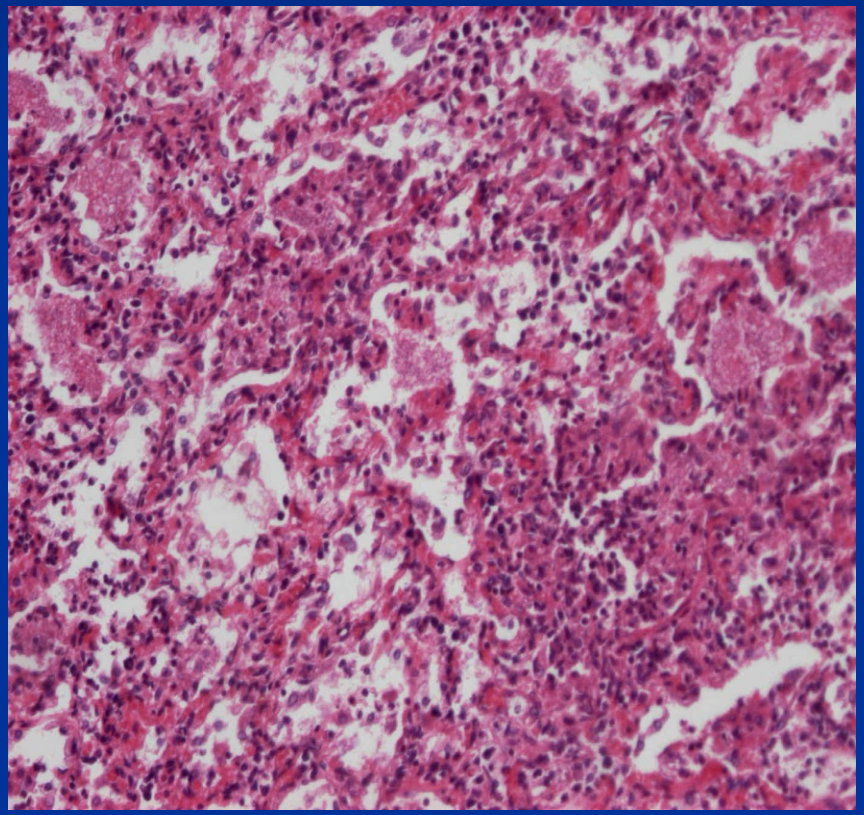
Non-infective

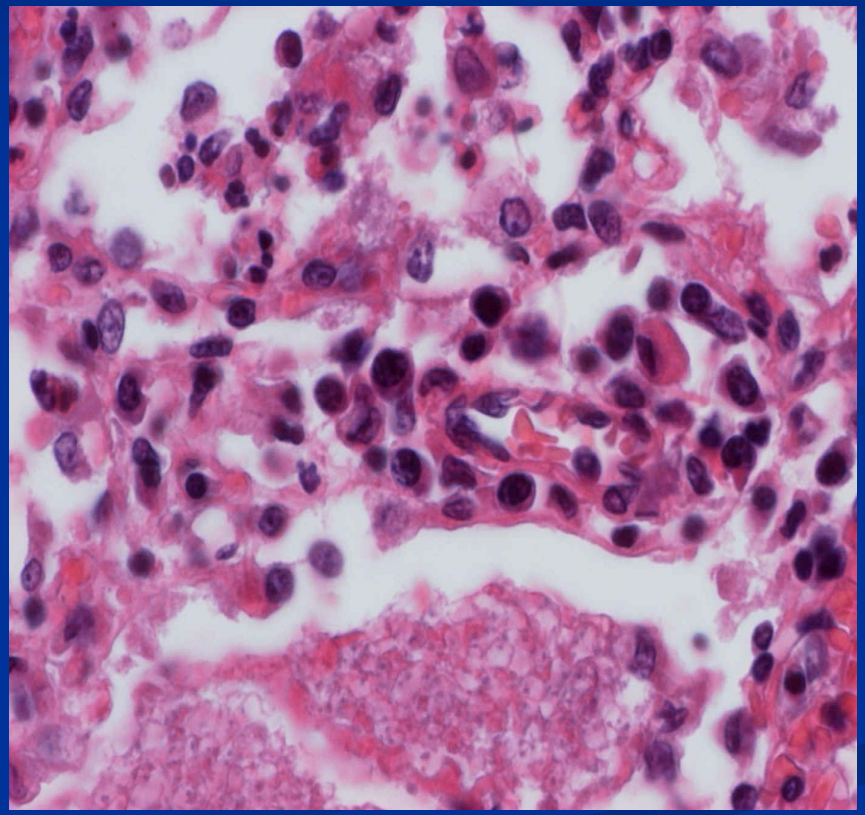
- Idiopatic interstitial pneumonitis and fibrosis (v.s. autoimmune)
- Cryptogenic organizing pneumonia = bronchiolitis obliterans
- Aspiration pneumonia (primarily non interstitial, often with lung abscess)
- Eosinophilic (v.s. allergic) and hypersensitivity pneumonitis
- Pulmonary involvement in collagen vascular diseases

(systemic lupus erythematodes, rheumatoid arthritis, progressive systemic sclerosis (scleroderma), dermatomyositis-polymyositis, mixed connective tissue disease)

Alveolar walls = interstitium in lungs…..in interstitial inflammation the inflammatory infiltrate withihn the alveolar walls…complication of alveolocapillary gas exchange

Interstitial pneumonia – Pneumocystis carinii

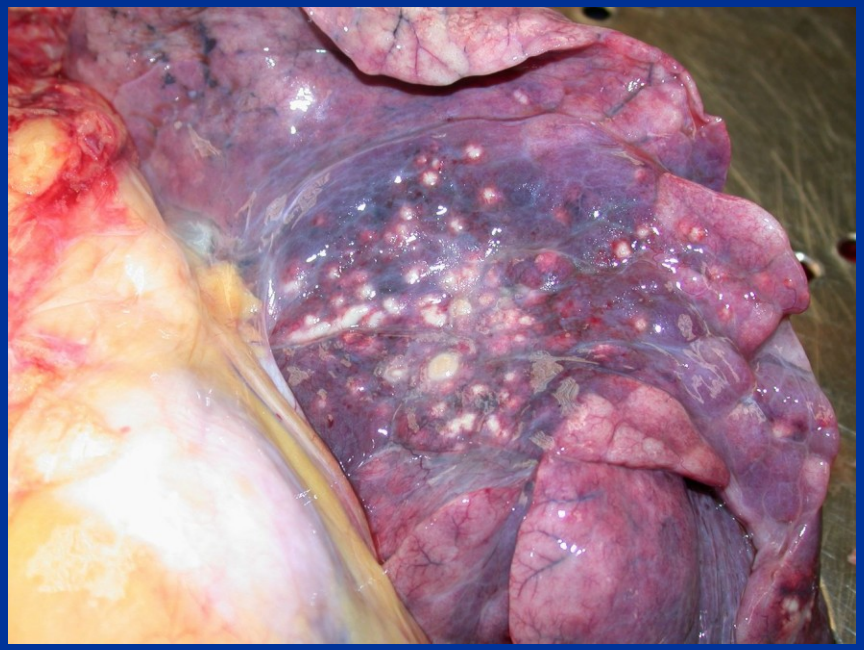


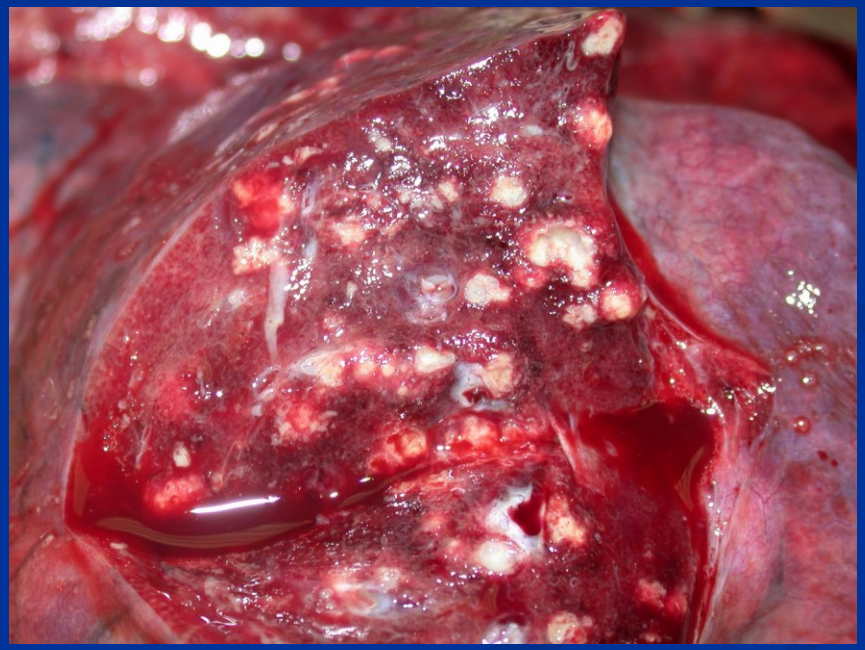


Abscess

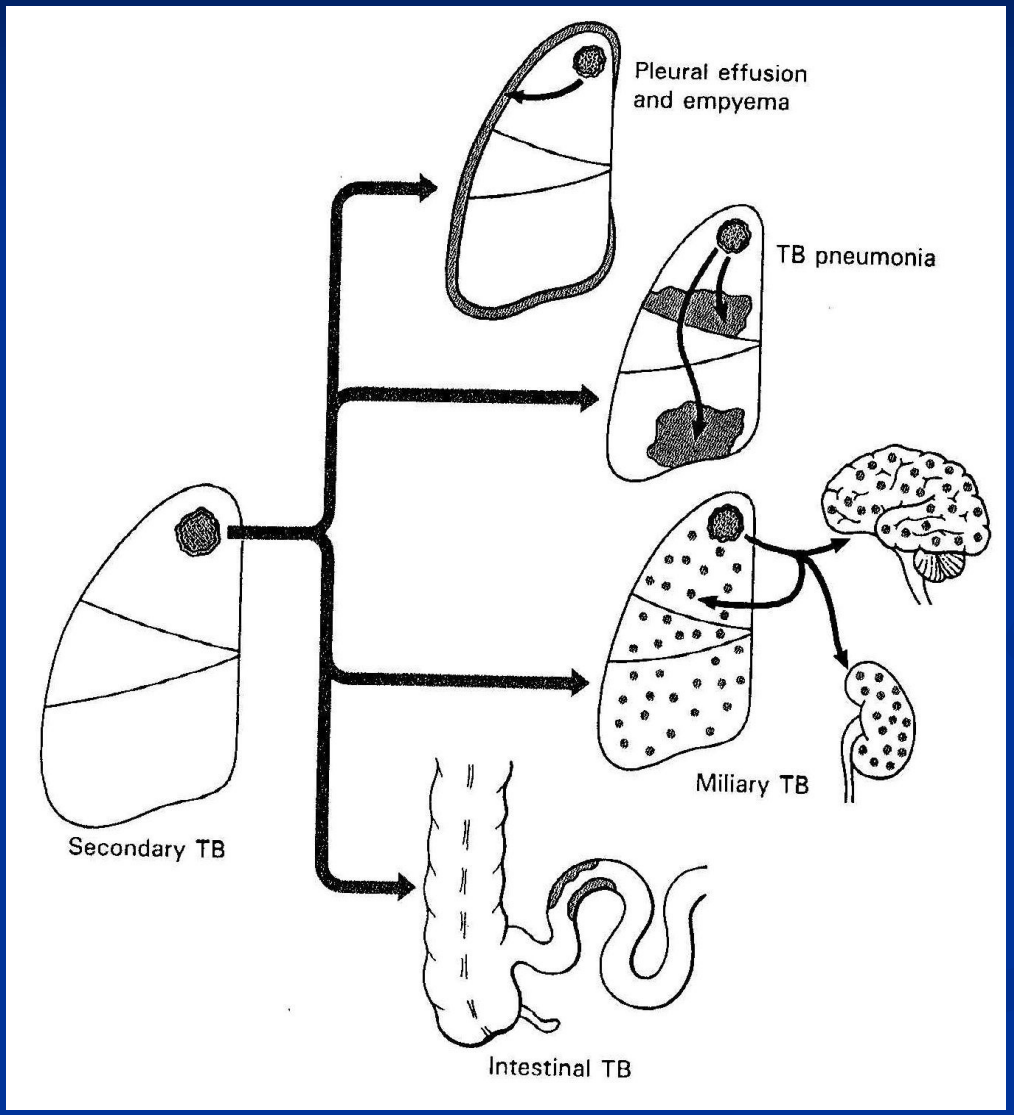
- Aspiration of infective material
- Antecedent primary bacterial infection
- Septic embolism
- Neoplasia
- Others and cryptogenic

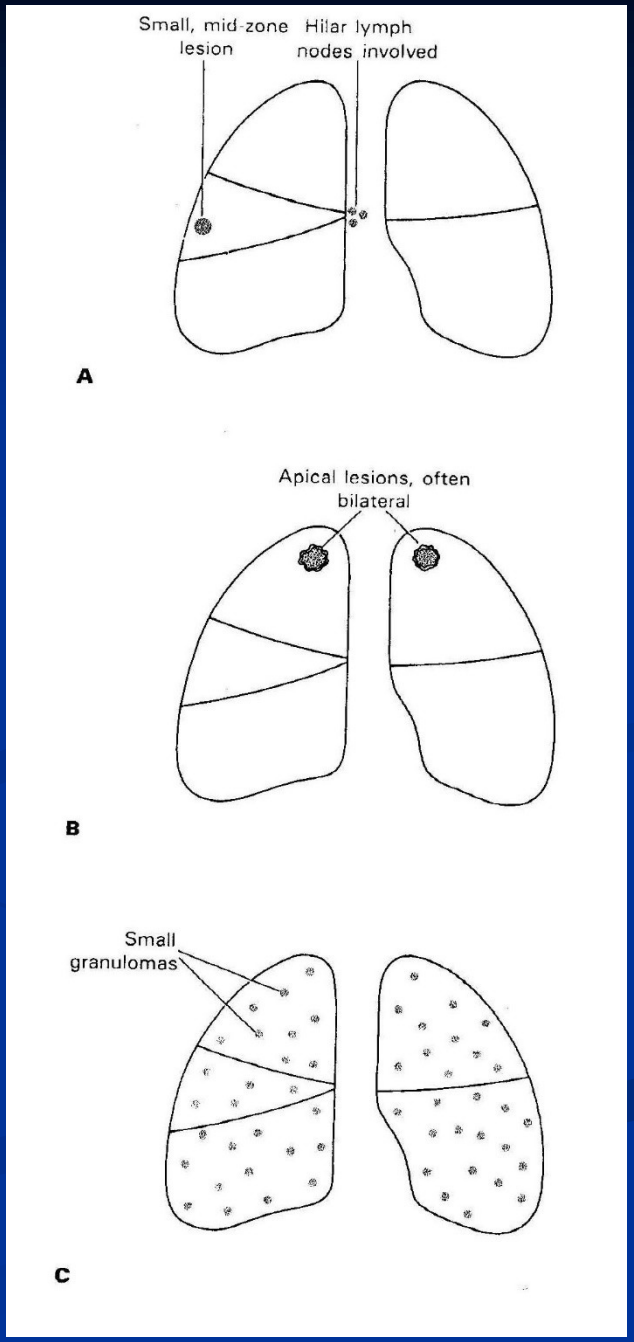
Absceding bronchopneumonia



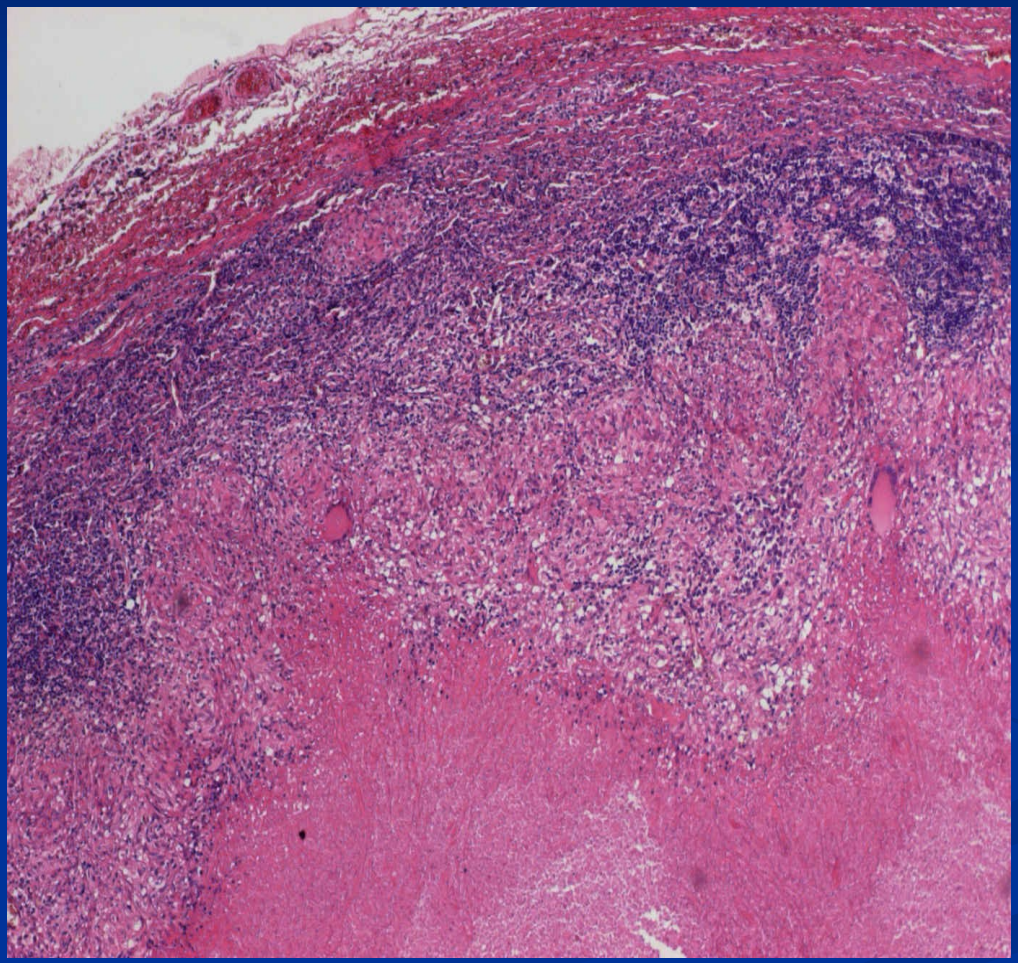


TBC of the lungs





Tbc lymphadenitis

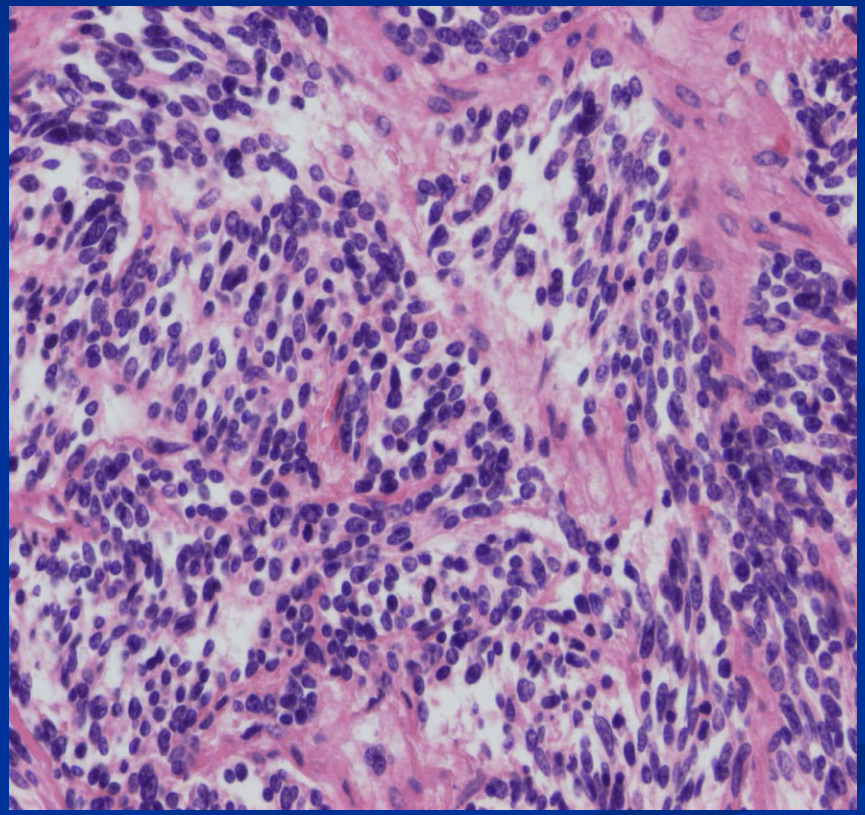


Tumors of the lung

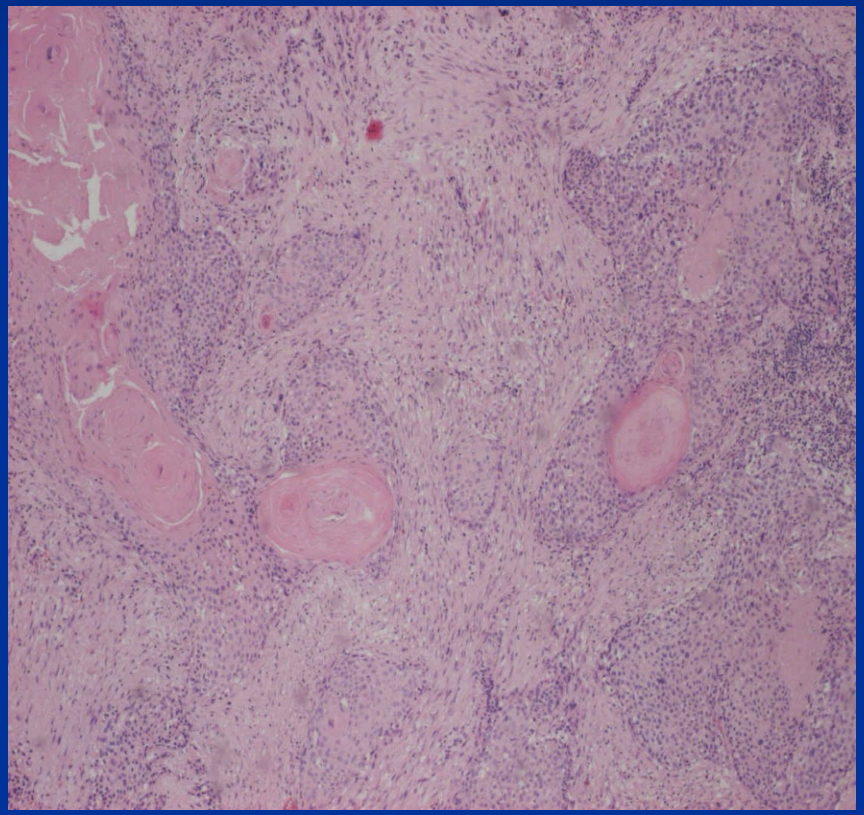
- **Epithelial**
  - Benign (adenomas)
  - Malignant (carcinomas)
    - squamous cell carcinoma
    - adenocarcinoma
    - small cell (neuroendocrine) carcinoma
    - large cell undifferentiared carcinomas
- **Mesenchymal**
- **Others**

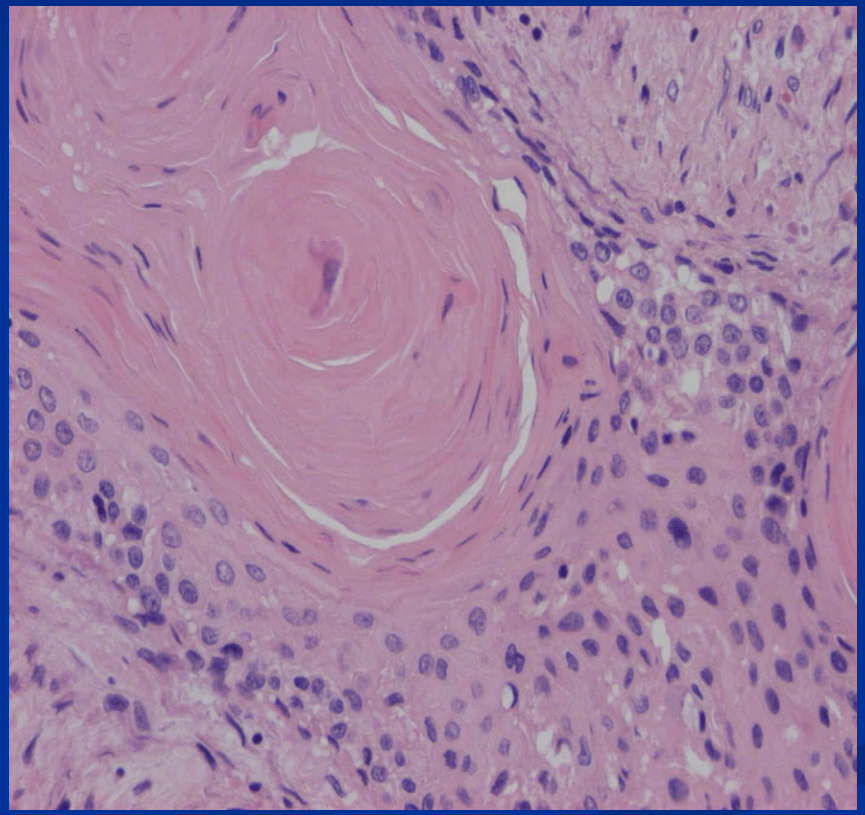
+ secondary/metastatic lung tumours

Neuroendocrine carcinoma (small cell carcinoma)

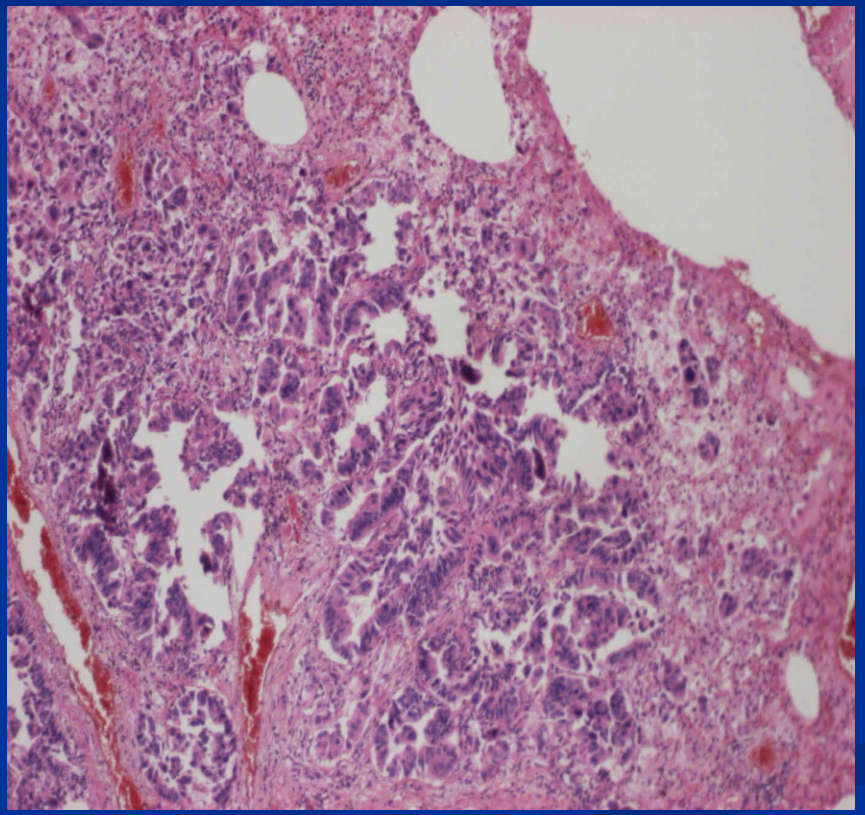


Squamous cell carcinoma





Adenocarcinoma of the lungs



Paraneoplastic syndrome

- Antidiuretic hormone
- Adrenocorticotropic hormone
- Parathormone
- Calcitonin
- Gonadotropins
- Serotonin and bradykinin

- Neuroendocrine neoplasias (carcinoids and small cell carcinomas)

Complications of lung cancer