Respiratory system

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The Lung

- **Function**: exchange of gases between the inspired air and blood.
- **Development**: an outgrowth from the ventral wall of the foregut
- **Blood supply**: pulmonary and bronchial arteries.
- **Pulmonary lobule:** a cluster of 3-5 terminal bronchiole each with its acinus

Lining:

Peudostratified tall columnar ciliated epithelial cells heavily admixed in the cartilagenous airways with mucous secreting goblet cells.

The bronchial mucosa also contain neuroendocrine cells

Mucus secreting goblet cells are also found in the submucosa of trachea and bronchi but not bronchioles.

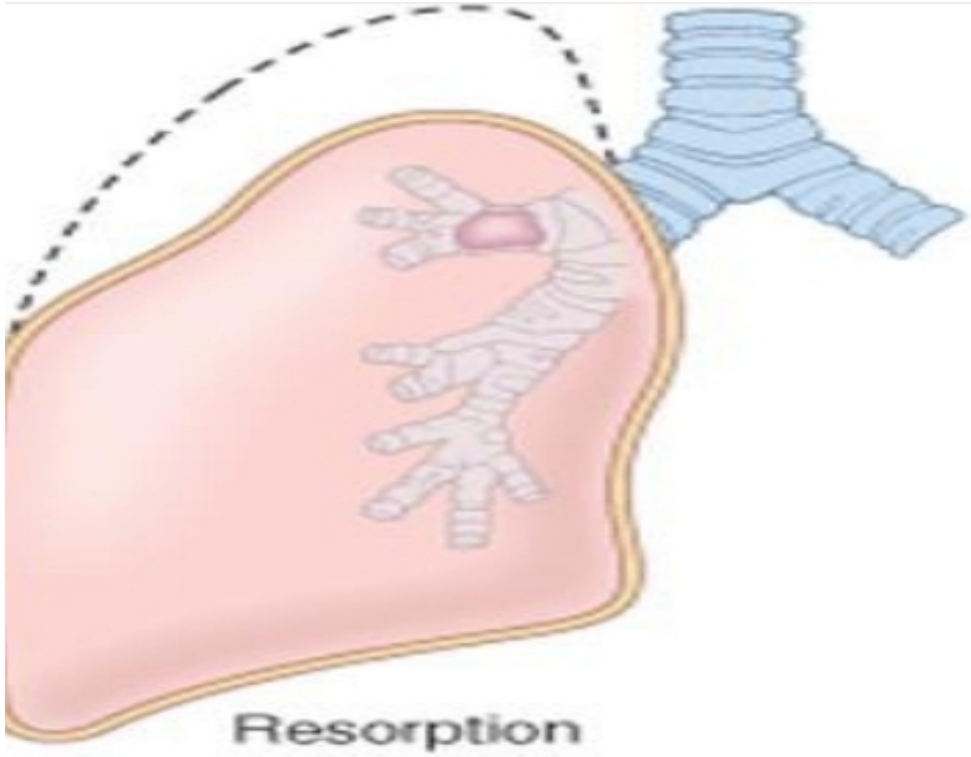
Atelectasis (lung collapse)

Neonatal atelectasis: incomplete expansion of the neonatal lung.

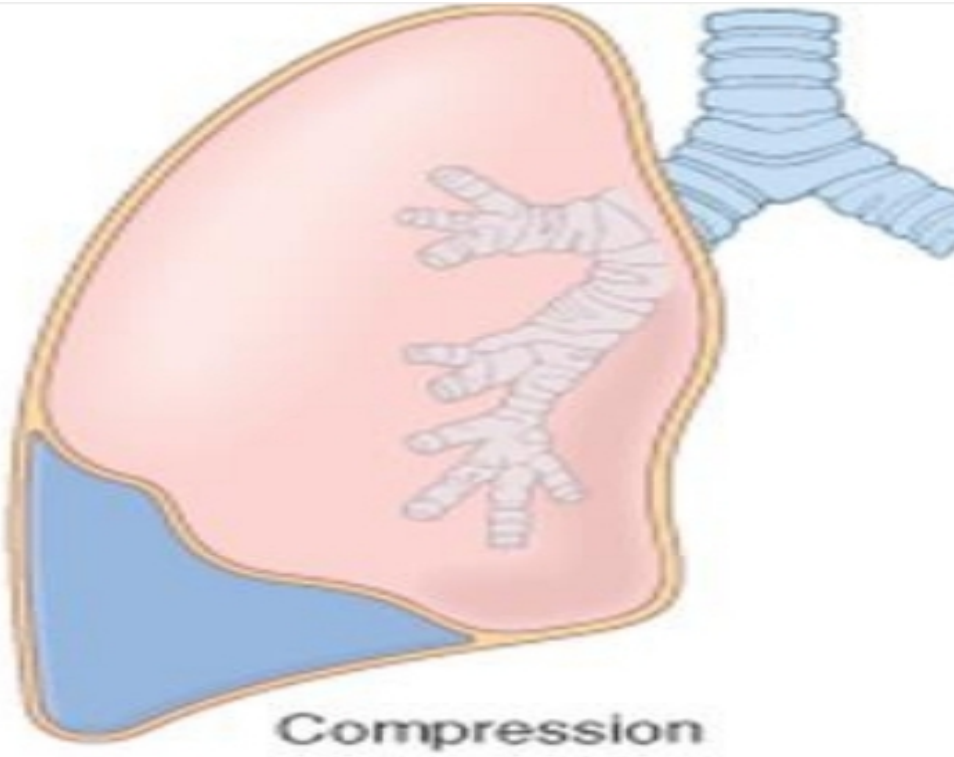
Acquired: collapse of a previously inflated lung.
Resorption atelectasis: a consequence of incomplete obstruction of an airway (reversible).

compression atelectasis: occurs when pleural cavity is partially or completely filled (fluid, air, blood, tumor). (reversible).

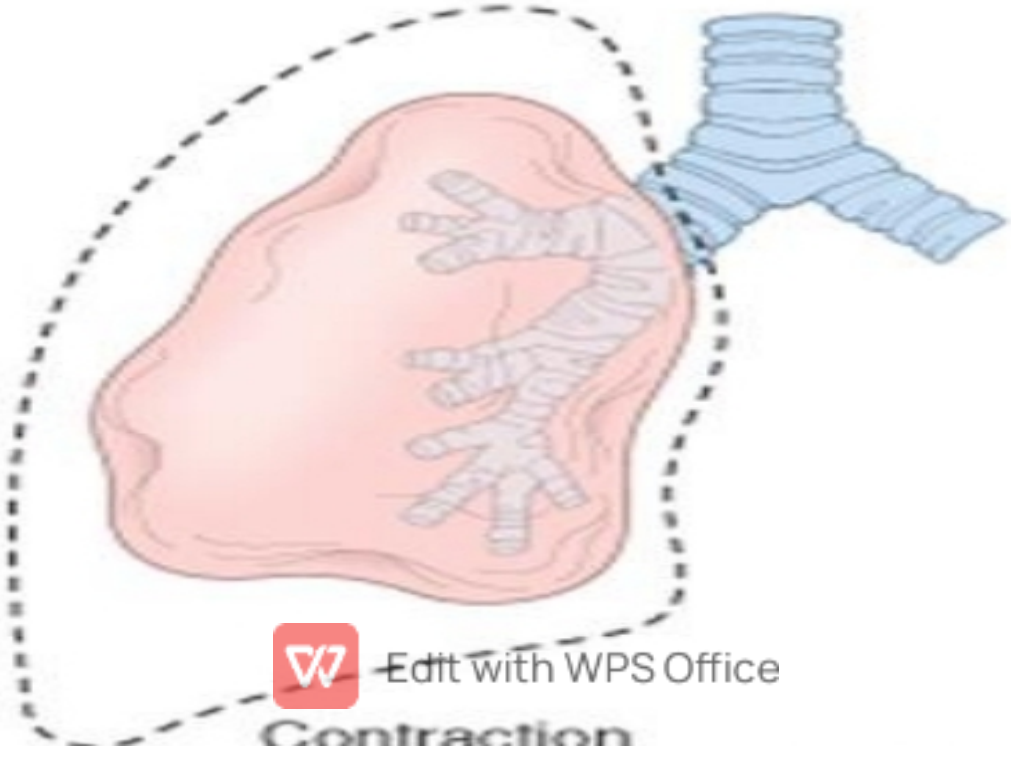
Contraction atelectasis: There is local or generalized fibrotic changes in the lung or pleura. (irreversible).



Resorption



Compression



Contraction

ADULT RESPIRATORY DISTRESS SYNDROME(ARDS)

 (previously “Shock lung”) is “progressive respiratory insufficiency caused by diffuse alveolar damage”

 The clinical setting associated with ARDS include:

A. Respiratory

1. Diffuse infections (viral, bacterial)
2. Aspiration
3. Inhalation (toxic gases, near drowning)
4. O2 therapy

B. Non-respiratory

1. Sepsis (septic shock) 2. Trauma (with hypotension)
3. Burns
4. Pancreatitis
5. Ingested toxins

Pathogenesis

In ARDS there is damage to alveolar capillary membrane by endothelial &/or epithelial injury.
This leads to three consequences

1. Increased vascular permeability (endothelial damage)
2. Loss of diffusion capacity of the gases.
3. Widespread surfactant deficiency (damage to type II pneumocytes).

 Gross features: in the **acute phase** thelungs are dark re airless, and heavy.

 Microscopic features:

 The histologic reflection of ARDS in the lungs is known as diffuse alveolar damage.

 Early stage is chcharacterized by

 Capillary **congestion** and stuffing by **neutrophils**
 Necrosis of alveolar epithelial cells
 Interstitial and intra-alveolar **edema** and **hemorrhage**
 The presence of **hyaline membranes** is characteristic.

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

prognosis

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

Restrictive airway disease:

reduced expansion of lung parenchyma with decrease in total lung capacity; normal FEV1; due to:

chest wall disorders (polio, obesity, pleural disease, kyphoscoliosis)

and **interstitial / infiltrative diseases** (ARDS, dust diseases, interstitial fibrosis)

Obstructive pulmonary disease

- Increased resistance to airflow due to obstruction. is usually measured by forced expiratory flow in 1 second (FEV1).

- Chronic obstructive pulmonary disease (COPD) includes **emphysema** and **chronic bronchitis and asthma**

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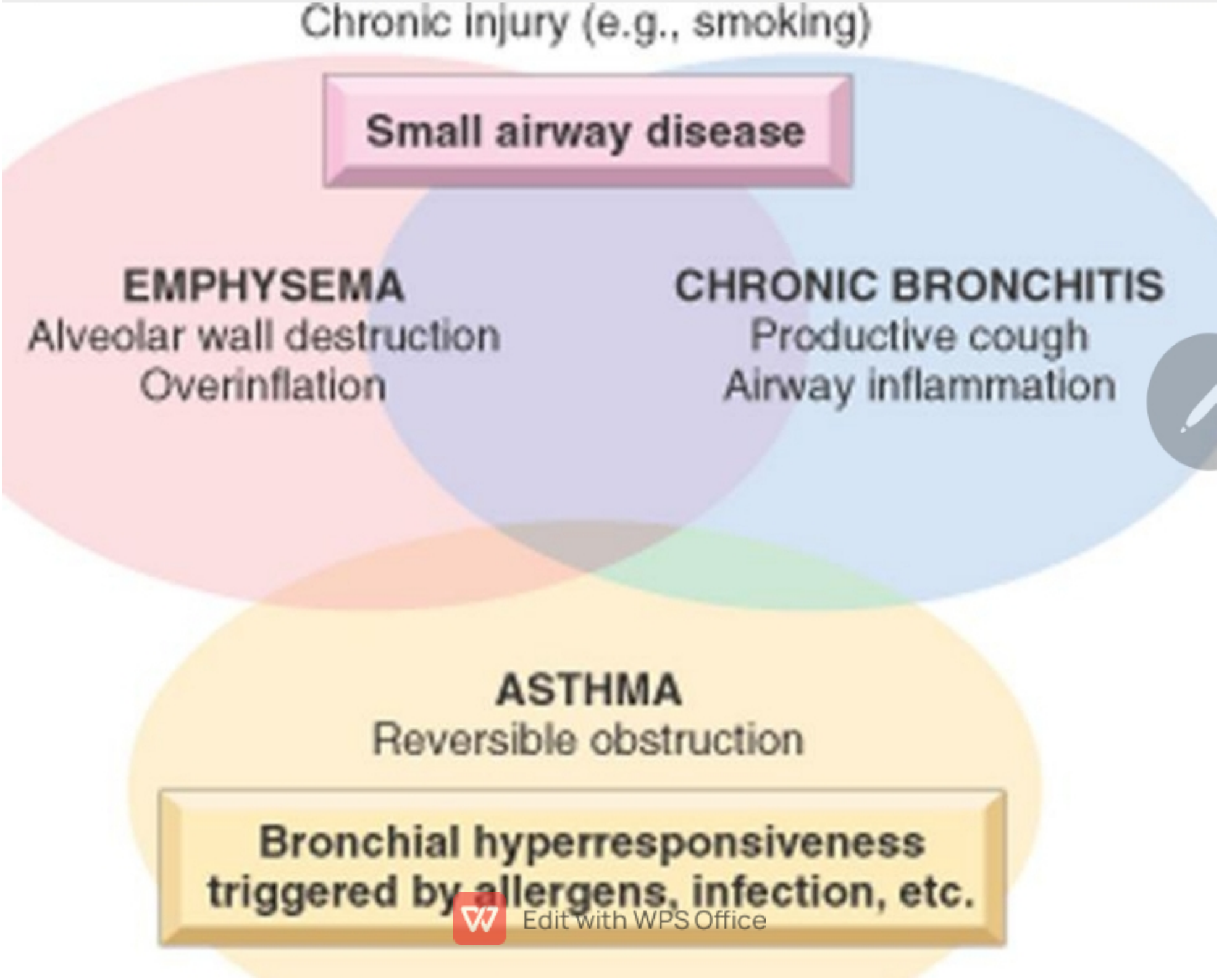
- A common extrinsic etiologic factor to both is smoking

- Bronchial asthma is another example of obstructive airway disease



Emphysema

 It is an abnormal permanent enlargement of airspaces distal to terminal bronchioles ؛accompanied by destruction of their walls without fibrosis.

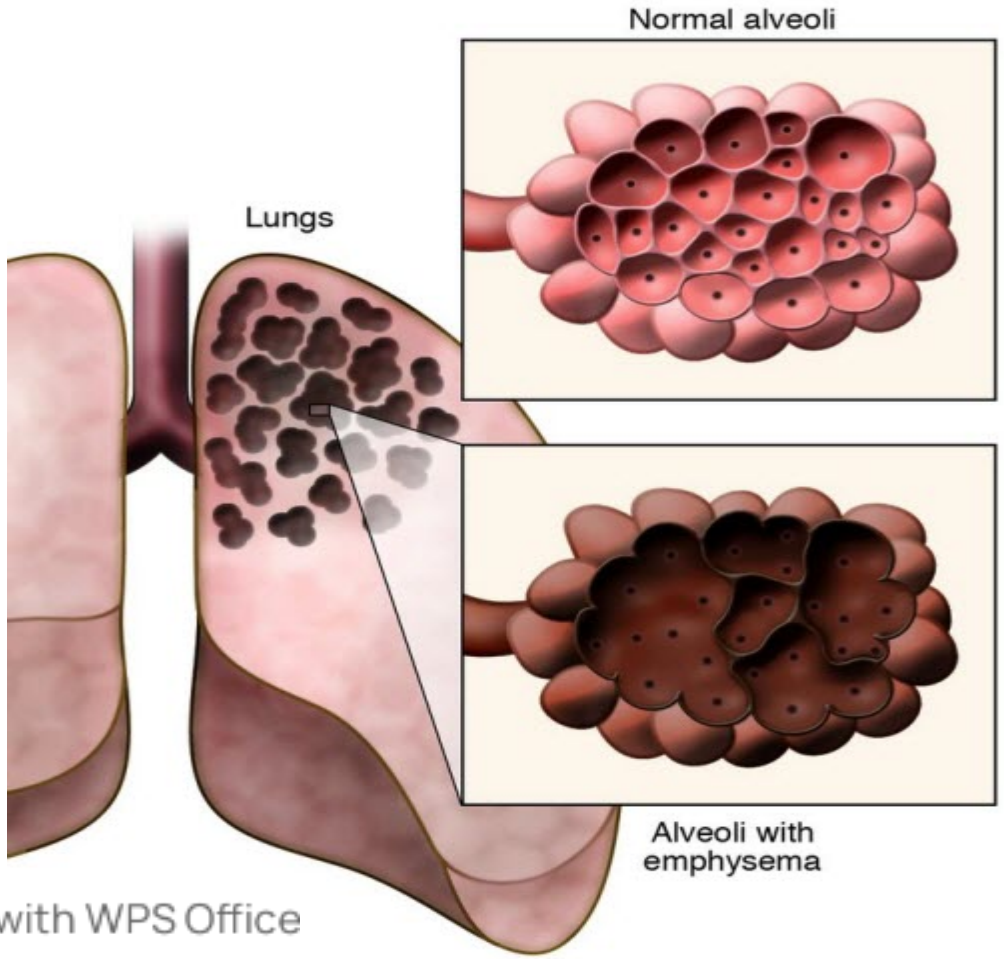
Types of Emphysema according to anatomicdistribution

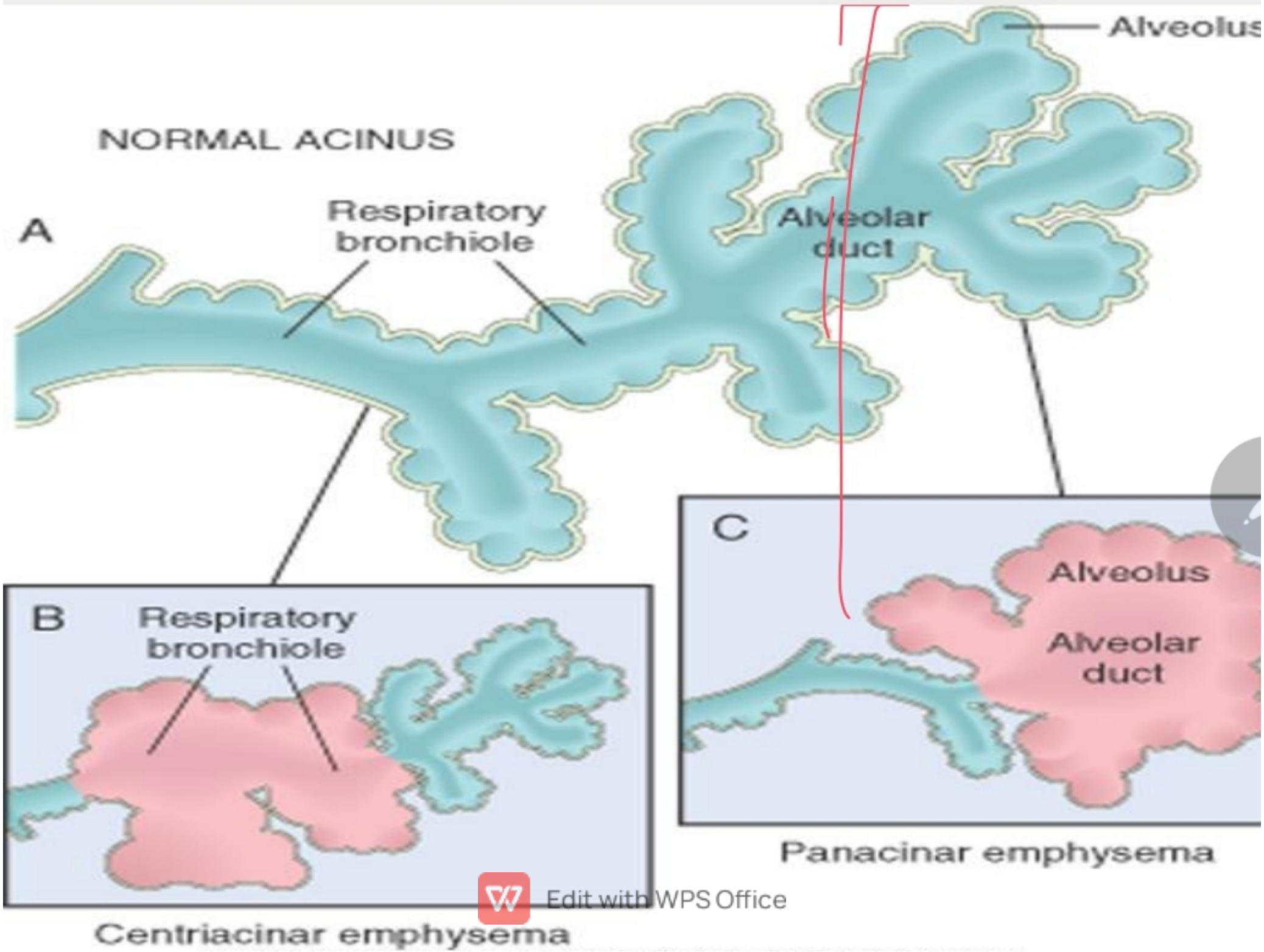
Centriacinar (Centrilobular)

Panacinar (Panlobular)

Distal acinar (Paraseptal)

Irregular





Pathogenesis of Emphesema

Destruction of lung parenchymal tissue due to chronic inflammation

Protease mediated destruction of elastin is an important feature.

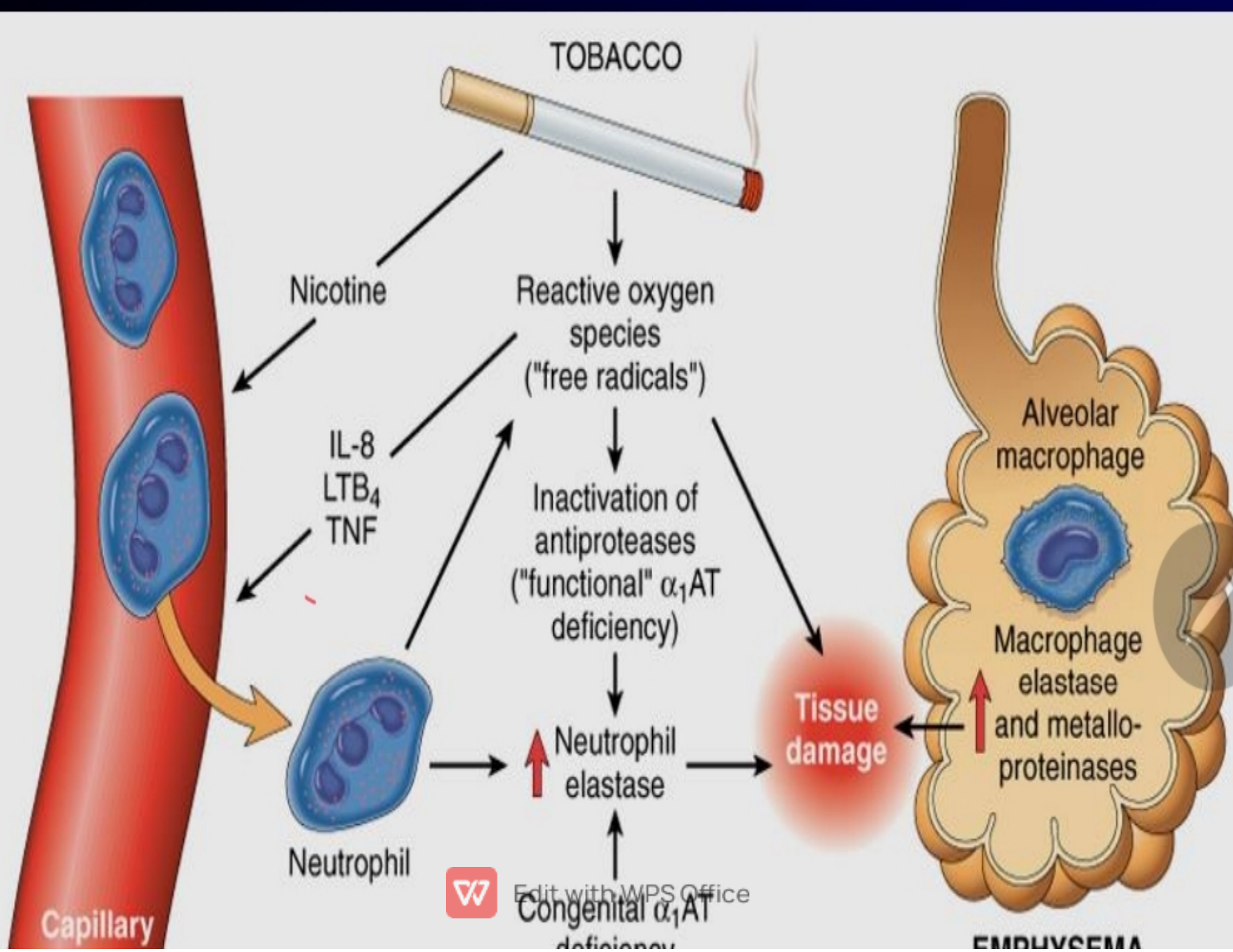
Increase in size and number of small fenestrae in alveolar walls which leads to loss of elastic recoil.

Breakdown and merging of fibrovascular trabeculae

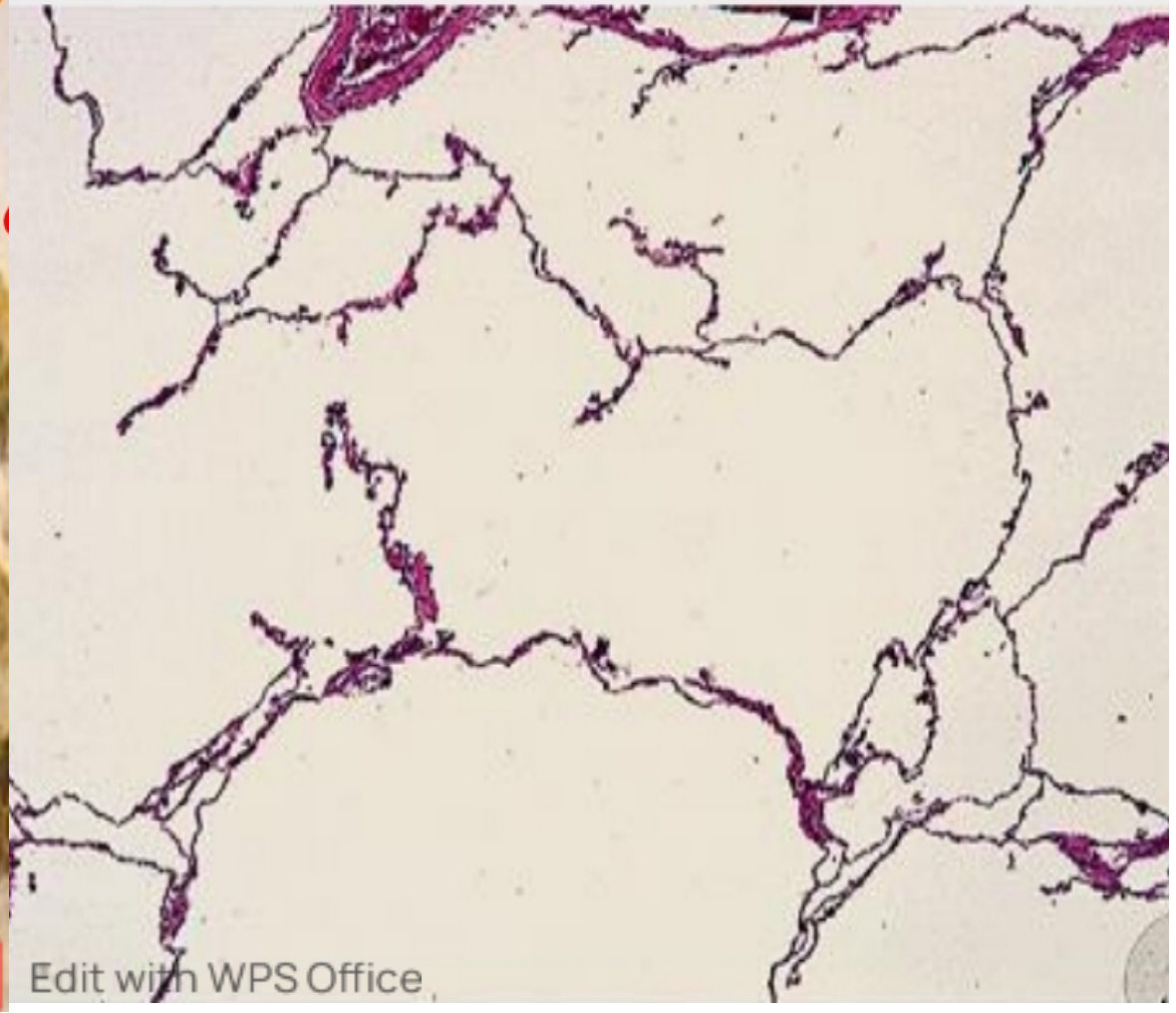
Remodeling of acini results in airspace enlargement

The **protease-antiprotease imbalance** and **oxidant-antioxidant imbalance** are additive in their effects and contribute to tissue damage.

α1-Antitrypsin (α1AT) deficiency can be either congenital or "functional" as a result of oxidative inactivation.



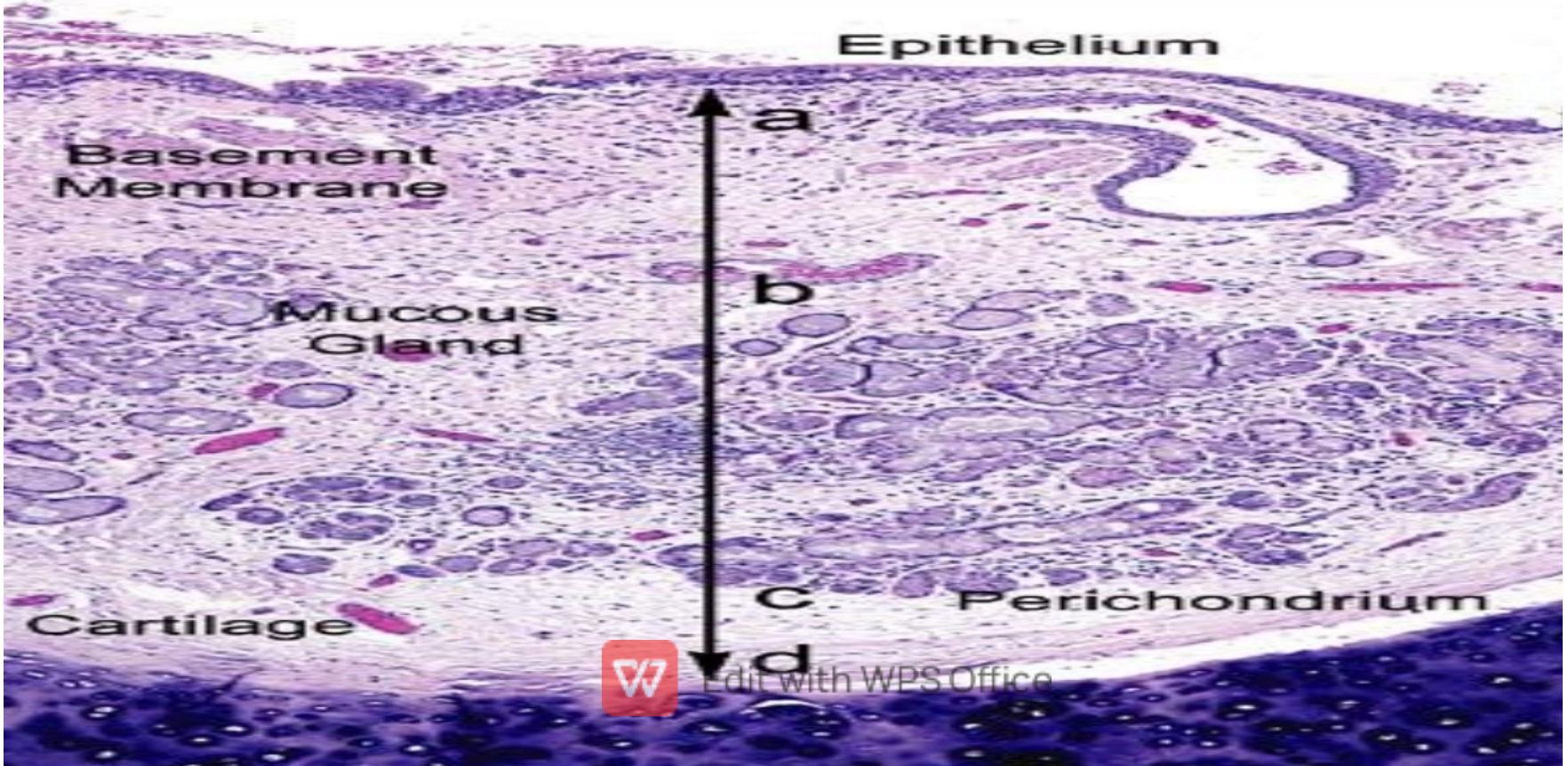
Microscopically: Large alveoli separated by thin septa with minimal focal centriacinar fibrosis. Pores of Kohn are large and septa appear to protrude blindly into alveolar spaces in a club shaped end.
There is an associated chronic bronchitis or bronchiolitis



Chronic Bronchitis

present in any patient who has persistent cough with sputum production for at least 3 months per year for at least 2 consecutive years.

 Prolonged disease leads to hypoxemia and cyanosis (Blue bloaters).



Pathogenesis

- **Chronic irritation** (tobacco smoke), grain, cotton, silica, bacterial and viral infection triggers acute exacerbation.
- **Hypersecretion of mucous** is associated with hypertroph of submucous glands.
- Mucus hypersecretion is stimulated by **proteases** released from neutrophils.
- Marked increase in **goblet cell** numbers in the lining of small airways (protective metaplastic reaction).
- These epithelial effects are mediated through Mepiderm growth factor (**EGF**) receptors

Bronchiectasis

A disease characterized by permanent dilatation of bronchi and bronchioles caused by destruction of the muscle and elastic tissue resulting from or associated with necrotizing infections

It could be seen in association with

congenital or hereditary conditions: primary ciliary dyskinesia, cystic fibrosis,

Post infection: TB, Staph. aureus, H. influenzae,adenovirus influenza virus, HIV and aspergillus.

Bronchial obstruction: Tumor, foreign bodies, mucous impaction.

Others: Rheumatoid arthritis, SLE, inflammatory bowel

Bronchial Asthma

It is a chronic inflammatory disorder of the airway that causes recurrent episodes of wheezes, breathlessness, chest tightness and cough particularly at night and/or earl morning.
There is widespread bronchoconstriction and airflow limitation that is at least partially reversible.

Status asthmaticus: an unremitting asthmatic attack in patient with long history of asthma and is usually fatal.

Extrinsic asthma: initiated by Type I hypersensitivity reaction induced by exposure to extrinsic antigen.

Intrinsic asthma: initiated by diverse non immune mechanisms (aspirin ingestion, pulmonary infections "viral", cold, stress, inhaled irritants, exercise).

Pathophysiology

Atopic or Extrinsic: initial sensitization affects T helper 2 cells, which release IL4 / 5, which promote IgE release by B cells, mast cells, and eosinophils

Re-exposure to allergen leads to mediator release from mucosal mast cells

Acute / intermediate response is bronchoconstriction, edema, mucus secretion and vasodilation with increased vascular permeability

Late phase reaction is due to influx of other inflammatory cells stimulated by chemokines released by mast cells, epithelial cells, T lymphocytes and other cytokines; includes release of major basic protein from eosinophils, which causes epithelial damage and airway constriction

Putative mediators are leukotrienes C4, D4, E4 and acetylcholine; minor mediators are histamine, prostaglandin D2; associated with serum eosinophilia, sputum eosinophils

Diffuse Interstitial (Infiltrative, Restrictive) Lung Diseases:

- Diffuse chronic involvement of pulmonary connective tissue (mainly the delicate interstitium) between the alveoli.
- Identified by reduced total lung vital capacity.
- Result in scarring and destruction of the lung
- End stage or honeycomb lung

Pathogenesis:

- accumulation of inflammatory and immune effector cells within the alveolar wall and spaces (alveolitis) early in the disease which leads to distorted alveolar structure and mediator release.
- mediators injure parenchyma and initiate fibrosis.

They include:

- Idiopathic Pulmonary fibrosis
- Collagen disorders
- Pneumoconiosis.
- Sarcoidosis

Idiopathic Pulmonary Fibrosis

- unknown etiology.
- repeated cycles of acute lung injury (alveolitis)
- healing at these sites leads to fibrosis.
- dypnea on exertion and dry cough

Pneumoconiosis:Coal workers' pneumoconiosis

- Non-neoplastic lung reaction to inhalation of mineral dust as well as inorganic particles and chemical fumes and vapors.

Pathogenesis depends on:

- the amount of dust retained in the lung and airways.
- the size, shape of particles. (1-5 micrometer)
- particle solubility and physiochemical reactivity.
- additional effect of other irritants (tobacco).
- Small particles cause acute lung injury.
- Large particles evoke fibrosis.

Sarcoidosis:

 It is a systemic disease of unknown cause in which there are non-caseating granulomas in many tissues and organs.

There is bilateral hilar lymphadenopathy and lung involvement in 90% of cases.

Pathogenesis:

immunological factors: accumulation of CD4 T cells, increased T- cell derived (TH1) cytokines resulting in T-macrophage activation and granuloma formation.

Genetic

familial and racial clustering

HLA (A1 and B8)

Environment (mycobacterium)

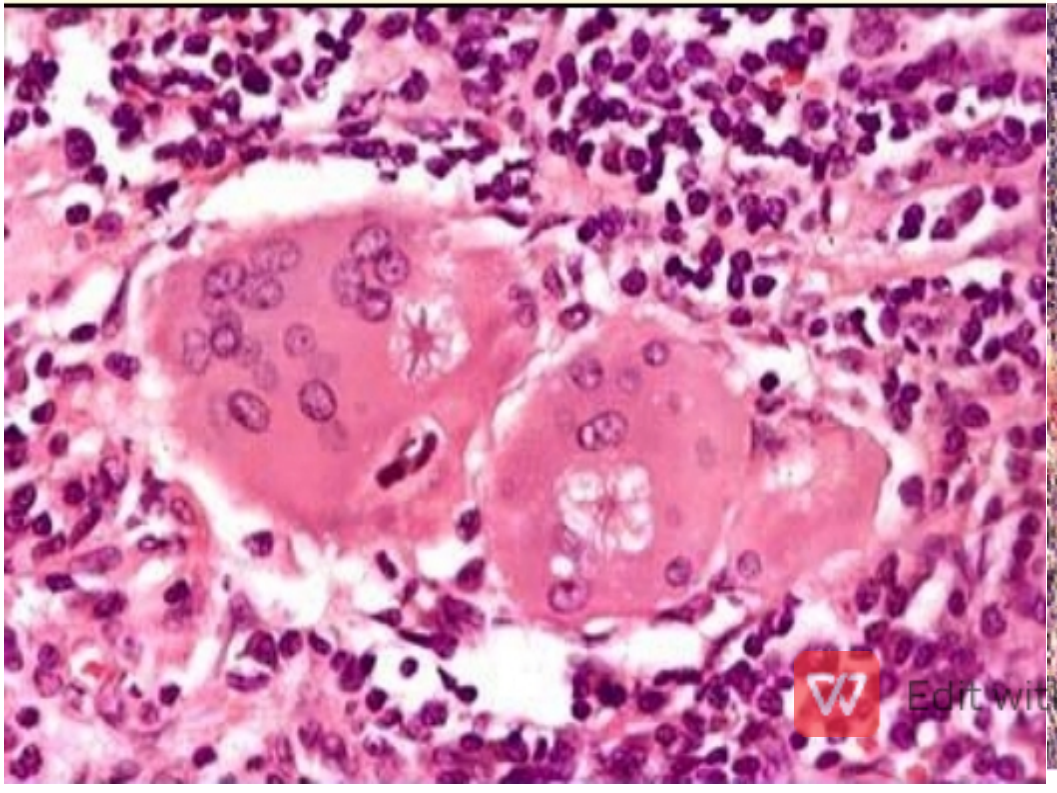
Morphology:

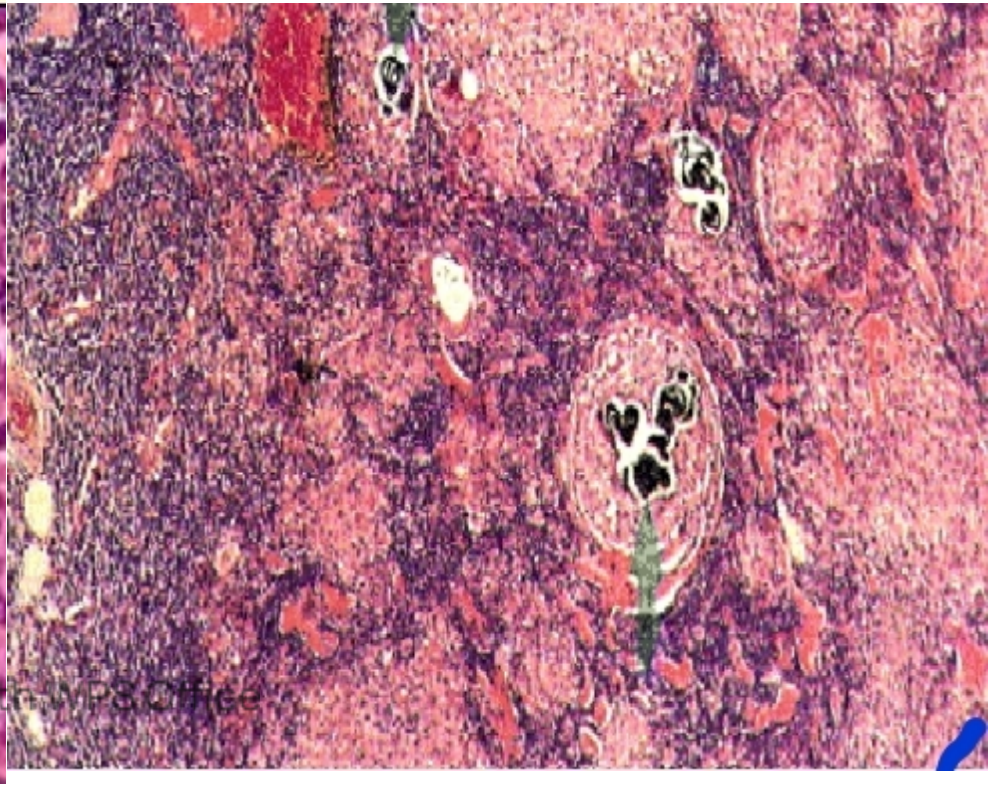
Non-caseating granuloma, Langhan's and foreign body giant cells.

Chronicity leads to formation of fibrous rim around granuloma or replacement by hyaline scar.

Schaumann bodies: laminated concretions (calcium and proteins).

Stellate inclusion asteroid bodies inside macrophage.





Hypersensitivity Pneumonitis:(Allergic alveolitis)

 It is a spectrum of immunologically mediated interstitial lung disorders caused by **intense and prolonged exposure to inhaled organic dusts** and related occupational antigens

.

 The organic dusts contain antigens made up of spores o thrombophilic bacteria, fungi, animal proteins or bacterial products.

 Progression to chronic fibrotic lung disease can be prevented by removal of the environmental agent.

 Examples are: **Farmer's lung, Pigeon' breeder, humidifier (air conditioner) lung**

pnemonia

Pneumonia is defined as any infection of lung parenchyma
Generally microorganisms are inhaled, but pneumonia ma
also occur through hematogenous spread or direct inocula

Pathophysiology

Pneumonia is due to impairment of normal defense mechanisms or lowered host resistance

Normal defense mechanisms are nasal clearance (sneezi
blowing, swallowing), tracheobronchial clearance (mucoc
action) and alveolar clearance (alveolar macrophages)

Impairment is due to primary or acquired immunosuppres
suppression of cough reflex (drugs, virus, coma, anesthes

injury to mucociliary apparatus (smoking, virus, Kartegeners syndrome),
injury to macrophages (tobacco, alcohol, anoxia),
pulmonary congestion / edema or accumulation of secretions (cystic fibrosis)

Note: viral pneumonia predisposes to bacterial pneumonia

Pneumonia can arise in seven distinct clinical settings

1. **Community-Acquired Acute Pneumonias**
2. **Community-Acquired Atypical Pneumonias**
3. **Nosocomial Pneumonia (hospital-acquired)**
4. **Aspiration Pneumonia**
5. **Necrotizing pneumonia & Lung Abscess**
6. **Chronic Pneumonia including tuberculous and fungal**
7. **Pneumonia in the Immunocompromised Host**

Community-Acquired Acute Pneumonias

- mostly bacterial in origin
- **S. pneumoniae** (pneumococcus) is the most common cause occur with increased frequency in those with underlying chronic diseases

- Can be lobar or bronchopnemonia

- complications :

Abscess, Empyema, Solid areas of fibrosis, Bacteremic

dissemination may lead to **meningitis, arthritis, or infective endocarditis.**

Community-Acquired Atypical Pneumonias

- denotes absence of physical findings of consolidation (due to lack of alveolar exudates)
- only moderate elevation of WBC count.
- **Mycoplasma pneumoniae** is the most common cause.

Lung Abscess

- **Predisposing factors:**
- a. Aspiration of infective material or gastric contents
- c. complication of necrotizing bacterial pneumonias
- d. Mycotic infections and bronchiectasis
- e. Bronchial obstruction, with bronchogenic carcinoma.
- f. within a necrotic portion of a tumor
- g. Septic embolism, from septic thrombophlebitis or from infective endocarditis
- h. hematogenous spread of bacteria

Primary Tuberculosis

• "a communicable chronic granulomatous disease caused by Mycobacterium tuberculosis".

• Characterized by Ghon's focus when combined with nodal involvement is referred to as the Ghon complex.

Secondary Tuberculosis (Postprimary) (Reactivation Tuberculosis)

• Reactivation or re-exposure

• only less than 5% with primary disease subsequently develop secondary tuberculosis

• localized to the apex

- **Progression of secondary TB:**

- Progressive pulmonary tuberculosis

- Miliary pulmonary disease

- Endobronchial, endotracheal, and laryngeal tuberculosis

- Systemic miliary tuberculosis

- Isolated-organ tuberculosis

- Tuberculous Lymphadenitis

- Intestinal tuberculosis

Lung tumors

Material for diagnosis

- Cytology Materials:
- o sputum smears
- o bronchial washing, scraping, or brushing
- o fine needle aspiration
- o pleural effusion
- o pleural washing after surgical resection

- **Biopsy Materials**

- 1. fiberoptic bronchoscopic guidance :
- • extremely small
- • sometimes crushed
- • Features of differentiation may not be present.

- 2. Tru-cut needle biopsy

- 3. transbronchial lung biopsy

• Surgical Material:

lobectomy or pneumonectomy: examine the following:

- • Margins (bronchial)
- • Surface (pleura)
- • Lymph nodes
- • Tumor staging

Malignant Epithelial Tumors

- Squamous Cell Carcinoma
- Small Cell Carcinoma
- Adenocarcinoma
- Large Cell Carcinoma
- Adenosquamous Carcinoma
- Neuroendocrine tumors.

Squamous Cell C arcinoma

- most strongly related to **cigarette** smoking
- • marked **male** predominance
- • At least 50% of all squamous cell carcinomas arise in a major bronchus (central)
- Most are moderately to poorly differentiated
- • Hypercalcemia is important PNS in SCC.

Small Cell Carcinoma

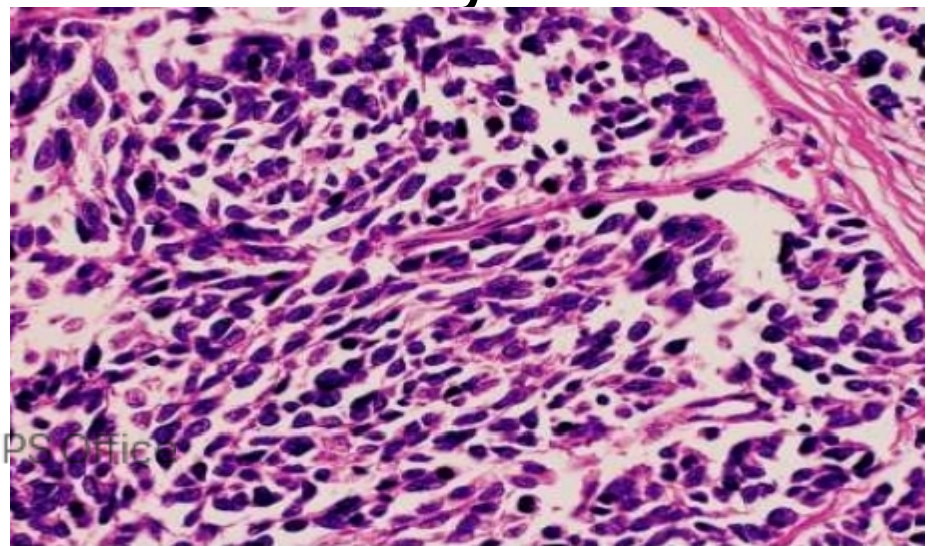
- a bronchial epithelial neoplasm with some neuroendocrine characteristics

- high degree of malignancy in spite of its high sensitivity to antitumor agents and radiation.

- male-to-female ratio is 4 to 1

- 5-year survival rate used to be extremely low

- may be associated with Cushing syndrome



Adenocarcinoma

• most frequent lung cancer occurring in Japan and some Asian countries

• • most arise in the **periphery** of bronchial trees, frequently producing pleural effusion

• • intrapulmonary metastasis is highest

• Adenocarcinomas should be classified by the predominant pattern of growth:

– **Lepidic pattern** (bronchioloalveolar carcinoma)
– • **Acinar pattern**
– • **Papillary pattern**
– • **Micropapillary pattern**
– • **Solid pattern**

Important molecular changes:

- **EGFR mutation** is seen in 10-15% of adenocarcinomas These tumors are responsive to treatment with tyrosine kinase inhibitors.

- **Fusion between (EML4) and ALK** present in 2-7% of adenocarcinomas may benefit from treatment with ALK inhibitors.

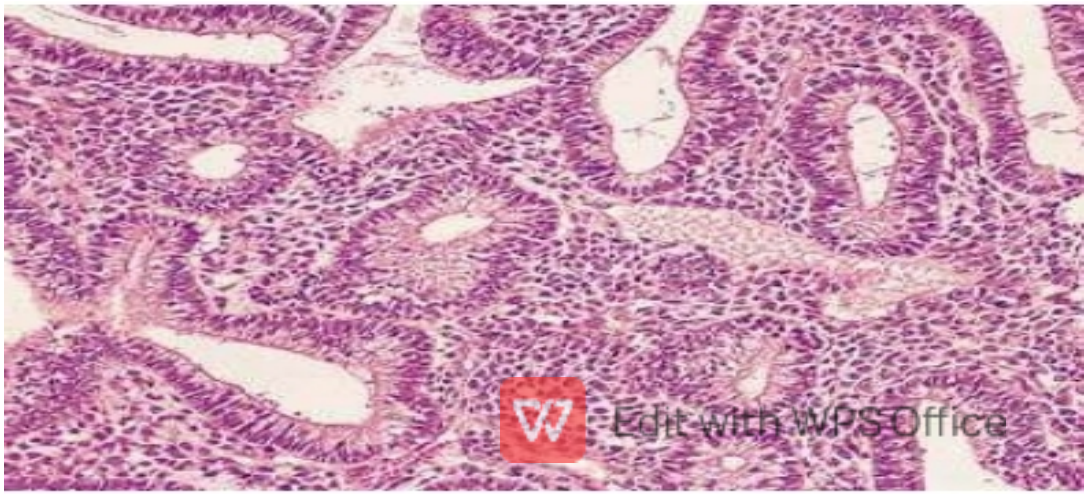
- **KRAS mutation** are associated with poor prognosis and EGFR acquired resistance

Pulmonary blastoma

• typically presents in adults, peripherally located, solitary, well circumscribed, and large

• **Microscopically**, it is characterized by the presence of well-differentiated tubular glands
in a cellular stroma

• Metastases supervene in close to half of the cases



Neuroendocrine tumors and proliferations

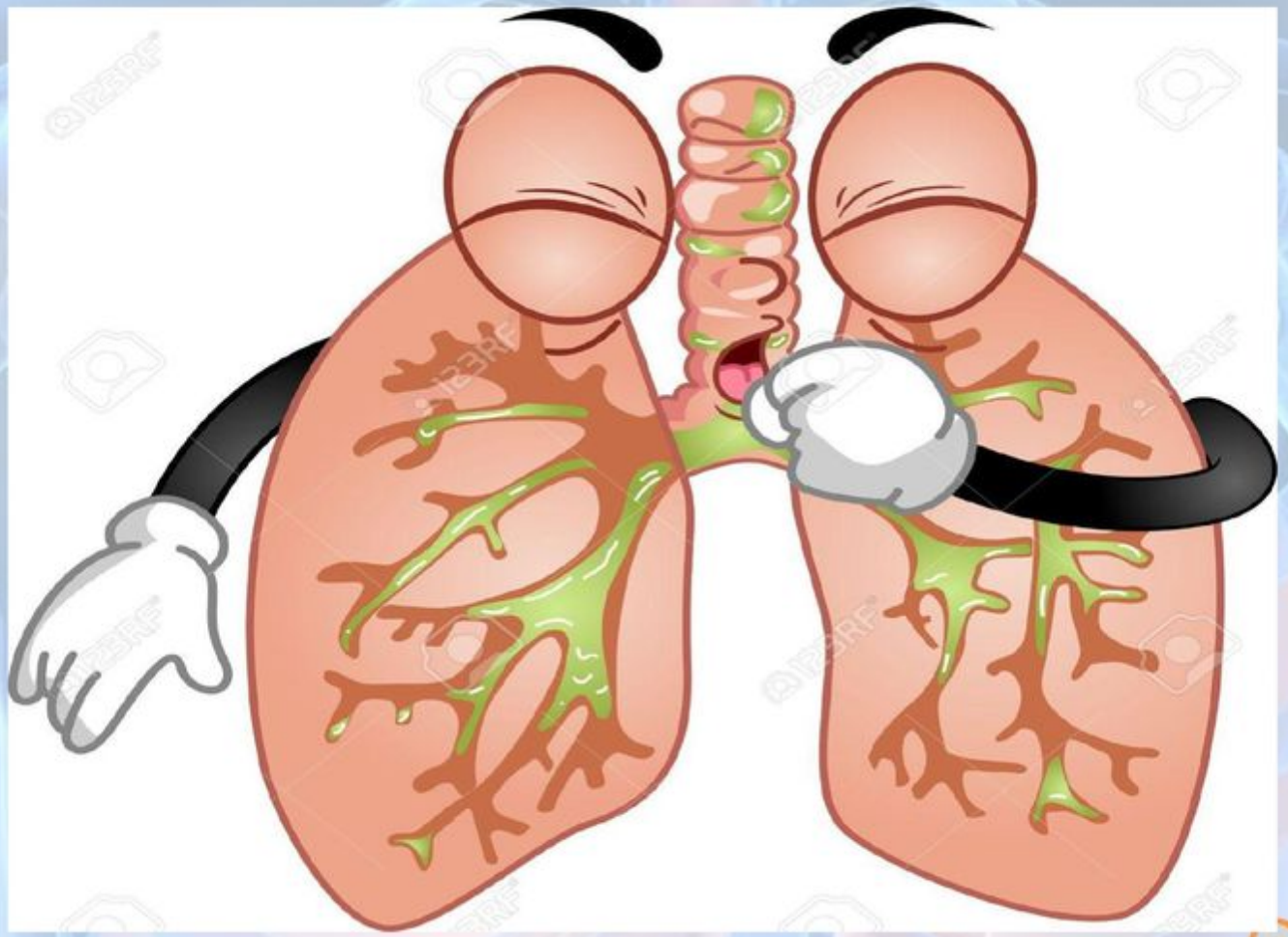
- **tumorlets**, small, inconsequential, hyperplastic nests of neuroendocrine cells
- **Carcinoid Tumors**
- **small cell carcinoma** and
  large cell neuroendocrine carcinoma of the lung.

- neuroendocrine differentiation can be demonstrated by immunohistochemistry in 10% to 20% of lung carcinomas that do not show neuroendocrine morphology by light microscopy

Carcinoid Tumors.(LOW GRADE NET)

• 1% to 5% of all lung tumors, younger than 40 years of age,
incidence is equal for both sexes
• are low-grade malignant epithelial neoplasms that are subclassified into typical and atypical

•> 2 mitoses/10HPF = Carcinoid
• 2-10 mitoses /10 HPF = Atypical carcinoid
• > 10 mitoses / 10 HPF = Neuroendocrine carcinoma.



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