CHRONIC OBSTRUCTIVE PULMONARY DISEASES

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Pulmonary function testing

- **Pulmonary function testing** (**PFT**) is a complete evaluation of the respiratory system including patient history, physical examinations, chest x-ray examinations, arterial blood gas analysis, and tests of pulmonary function.
- The primary purpose of pulmonary function testing is to identify the severity of pulmonary impairment.

- **Indications:**
- Pulmonary function testing is a diagnostic and management tool used for a variety of reasons, such as:

1. Chronic shortness of breath; dyspnea
2. Asthma
3. Chronic obstructive pulmonary disease
4. Restrictive lung disease
5. Preoperative testing
6. Impairment or disability

- **Lung volumes**
- There are four lung volumes and four lung capacities.
- A lung's capacity consists of two or more lung volumes.
- The lung volumes are tidal volume (V_T), inspiratory reserve volume (IRV), expiratory reserve volume (ERV), and residual volume (RV).
- The four lung capacities are total lung capacity (TLC), inspiratory capacity (IC), functional residual capacity (FRC) and vital capacity (VC).

- **Tidal volume (TV or V_T):** That volume of air moved into or out of the lungs during quiet breathing.
- **Total lung capacity (TLC):** The volume of air in the lungs at maximal inflation, the sum of VC and RV.
- **Vital capacity (VC):** The volume of air breathed out after the deepest inhalation.
- **Residual volume (RV):** The volume of air remaining in the lungs after maximal exhalation.

- **Expiratory reserve volume (ERV):** The maximal volume of air that can be exhaled from the end-expiratory position.
- **Inspiratory reserve volume (IRV):** The maximal volume that can be inhaled from the end-inspiratory level.
- **Inspiratory capacity (IC):** The sum of IRV and TV.
- **Inspiratory vital capacity (IVC):** The maximum volume of air inhaled from the point of maximum expiration.

- **Functional residual capacity (FRC):** The volume of air in the lungs at the end-expiratory position.
- **Residual volume (RV/TLC%):** Expressed as percent of TLC.
- **Alveolar gas volume (V_A).**
- **Actual volume of the lung (V_L)** including the volume of the conducting airway.
- **Forced vital capacity (FVC):** The determination of the vital capacity from a maximally forced expiratory effort.
- **Forced expiratory volume (time) (FEV_t):** A generic term indicating the volume of air exhaled under forced conditions in the first seconds.

DISEASES OF THE LUNG

OBSTRUCTIVE VERSUS RESTRICTIVE PULMONARY DISEASES

- **Diffuse pulmonary diseases can be classified into two categories:**

1. **Obstructive (airway) disease**: characterized by limitation of airflow, usually resulting from an increase in the resistance caused by partial or complete obstruction at any level, and
2. **Restrictive disease**: characterized by reduced expansion of lung parenchyma accompanied by decreased total lung capacity.

- ***The major diffuse obstructive disorders are emphysema, chronic bronchitis, bronchiectasis, and asthma.***
- *In patients with* these diseases, **FVC** is either *normal or slightly decreased*, while the **FEV1** is *significantly decreased*.
- **Thus, *the ratio of FEV to FVC is characteristically decreased.***
- ***Expiratory obstruction*** may result either from anatomic airway narrowing, classically observed in **asthma**, or from **loss of elastic recoil**, characteristic of **emphysema**.

- By contrast, **in *diffuse restrictive diseases*, *FVC* *is* *reduced*** and the **expiratory flow rate** is ***normal*** or ***reduced*** proportionately.
- Hence, ***the ratio of FEV to FVC is near normal***.

- ***The* restrictive defect occurs in two conditions:**

A. ***Chest wall disorders in the presence of normal lungs*** *(e.g., with severe* obesity, diseases of the pleura, and neuromuscular disorders, such as the Guillain-Barré syndrome, that affect the respiratory muscles) and

B. Acute or chronic interstitial lung diseases.

I. ***The classic acute restrictive disease* is *ARDS***.

II. ***Chronic restrictive diseases* include:**
Pneumoconioses, interstitial fibrosis of unknown etiology, and most of the infiltrative conditions (e.g., sarcoidosis).

OBSTRUCTIVE LUNG (AIRWAY) DISEASES

- **Definition:**
- **Chronic obstructive pulmonary diseases** (**COPD**) is a commonly used clinical terms for a group of pathological conditions in which there is ***chronic, partial or complete, obstruction to the airflow at any level from trachea to the smallest airways resulting in functional disability of the lungs.***
- They are ***diffuse*** preventable and treatable lung diseases characterized by long-term breathing problems and limitation of airflow that is usually ***progressive*** and ***not fully reversible***.

- They are associated with *abnormal inflammatory response* of the lungs to *noxious particles or gases*, primarily caused by cigarette smoking.
- The four disorders in this group; emphysema, chronic bronchitis, asthma, and bronchiectasis have distinct clinical and anatomic characteristics.
- Overlaps between emphysema, bronchitis, and asthma are common.
- In view of their propensity to coexist, emphysema and chronic bronchitis often are clinically grouped together under the rubric of ***chronic obstructive pulmonary disease (COPD)***.

- **It should be recognized that:**

1. ***The definition of emphysema is morphological, whereas chronic bronchitis is defined on the basis of clinical features*** *such as the presence of* chronic and recurrent cough with excessive mucus secretion.
2. ***Second,*** the ***anatomic distribution is partially different***; ***chronic bronchitis*** initially involves the ***large airways***, whereas ***emphysema*** affects the ***acinus***.
3. ***In severe or advanced*** *cases of both*, small airway disease ***(chronic bronchiolitis)*** is characteristic.

- The primarily ***irreversible airflow obstruction of COPD*** distinguishes it from asthma, which is characterized largely by ***reversible airflow obstruction***; however, patients with COPD commonly have some degree of reversible obstruction as well.
- Now, small airways disease involving inflammation of *small bronchi* and *bronchioles* ***(bronchiolitis)*** has also been added to the group of COPD.

- **Etiology:**

1. Tobacco smoking is the most common primary cause of COPD.
2. Air pollution and occupational exposure from indoor fires are significant causes in some developing countries.

- One of the common sources of air pollution is poorly vented heating and cooking fires.
- Typically, these exposures must occur over several decades before symptoms develop.

3. A person's genetic makeup play a smaller role.

- Long-term exposure to these irritants causes an inflammatory response, resulting in narrowing of the small airways and breakdown of lung tissue.
- Most cases of COPD can be prevented by reducing exposure to risk factors.
- This includes decreasing rates of smoking and improving indoor and outdoor air quality.
- In contrast to asthma, the airflow reduction does not improve much with the use of a bronchodilator.

- **Smoking**
- The primary risk factor for COPD globally is tobacco smoking.
- Of those who smoke, about 20% will get COPD, and of those who are lifelong smokers, about half will get COPD.
- The likelihood of developing COPD increases with the total smoke exposure.
- Women are more susceptible to the harmful effects of smoke than men.
- Women who smoke during pregnancy may increase the risk of COPD in their children.

- In non-smokers, second-hand smoke is the cause of about 20% of cases of COPD.
- Other types of smoke, such as, marijuana, cigar, and water-pipe smoke, also confer a risk of COPD.
- Water-pipe smoke appears to be as harmful as smoking cigarettes.

- **Air pollution**
- Poorly ventilated cooking fires, often fueled by coal or biomass fuels such as wood and dung, lead to indoor air pollution and are one of the most common causes of COPD in developing countries.
- These fires are a method of cooking and heating for nearly 3 billion people, with their health effects being greater among women due to more exposure.
- They are used as the main source of energy in 80% of homes in India, China and sub-Saharan Africa.

- People who live in large cities have a higher rate of COPD compared to people who live in rural areas.
- While urban air pollution is a contributing factor in exacerbations, its overall role as a cause of COPD is unclear.
- Areas with poor outdoor air quality, including that from exhaust gas, generally have higher rates of COPD.
- The overall effect in relation to smoking, however, is believed to be small.

- **Occupational exposures**
- Intense and prolonged exposure to workplace dusts, chemicals, and fumes increases the risk of COPD in both smokers and non-smokers.
- Workplace exposures are believed to be the cause in 10–20% of cases of COPD.
- In the United States, they are believed to be related to more than 30% of cases among those who have never smoked and probably represent a greater risk in countries without sufficient regulations.

- High levels of dust in coal mining, gold mining, and cotton textile industry, occupations involving cadmium and iso-cyanates, and fumes from welding lead to COPD.
- Working in agriculture is also a risk of COPD.
- Silica dust and fiberglass dust exposure can also lead to COPD, with the risk unrelated to that for silicosis.
- The negative effects of dust exposure and cigarette smoke exposure appear to be additive or possibly more than additive.

- **Genetics**
- Genetics play a role in the development of COPD.
- It is more common among relatives of those with COPD who smoke than unrelated smokers.
- Currently, the only clearly inherited risk factor is alpha 1-antitrypsin deficiency (AAT).
- This risk is particularly high if someone deficient in alpha 1-antitrypsin also smokes.
- It is responsible for about 1–5% of cases and the condition is present in about three to four in 10,000 people.

- **Others:**
- The risk of COPD is greater in poor people, may be due to associated air pollution and/or malnutrition.
- People with asthma and airway hyper-reactivity are at increased risk of COPD.
- Low birth weight may also play a role, as do a number of infectious diseases, including HIV/AIDS and tuberculosis.

- **Protease-antiprotease hypothesis:**
- ***Alpha-1-antitrypsin (α-1-AT)***, also called ***α1-protease inhibitor (α-1-Pi)***, is a glycoprotein that forms the normal constituent of α1-globulin fraction of plasma proteins on serum.
- The single gene locus that codes for α-1-AT is located on the ***long arm of chromosome 15***.
- It is normally *synthesized in the liver* and is distributed in the circulating blood, tissue fluids and macrophages.

- Normal **function** of α1-AT is to *inhibit proteases* and hence its name α1-protease inhibitor.
- *Proteases*; mainly ***elastases*** are ***derived from neutrophils***.
- Neutrophil elastase has the capability of *digesting lung parenchyma* but is *inhibited from doing so by anti-elastase effect of α1-AT*.
- There are several known alleles of α1-AT which have *autosomal co-dominant inheritance pattern* and are classified as normal (PiMM), deficient (PiZZ), null type (Pi null null) having no detectable level, and dysfunctional (PiSS) type having about half the normal level.

- The most common abnormal phenotype in ***classic α1-AT deficiency*** is *homozygous state PiZZ* resulting from *single amino acid substitution Glu→Lys* which causes spontaneous polymerization of α1-AT and *inhibits its release from the liver*.
- The remaining material of α1-AT in the liver *causes hepatic cirrhosis*.
- Clinically significant deficiency is also associated with *homozygous Pi null null* and *heterozygous Pi nullZ*.

- The *heterozygote pattern of PiMZ* has intermediate levels which is not sufficient to produce clinical deficiency, but heterozygote individuals *who smoke heavily have higher risk of developing emphysema*.
- The α1-AT deficiency develops in adults and causes pulmonary emphysema in smokers as well as in non-smokers, though *the smokers become symptomatic about 15 years earlier than non-smokers*.
- The other organ showing effects of α1-AT deficiency is the liver which may *develop obstructive jaundice early in infancy*, and *cirrhosis and hepatoma late in adulthood*.

Patho-Physiology of COPD

- *COPD is chronic incompletely reversible poor airflow and inability to breathe out fully due to air trapping.*
- *Poor airflow result from breakdown of lung tissue* ***(emphysema)*** *and* ***small airways disease (obstructive bronchiolitis)***.
- COPD develops as ***chronic inflammatory response*** to ***inhaled irritants***, and/or ***chronic bacterial infections*** *which aggravates inflammation*.

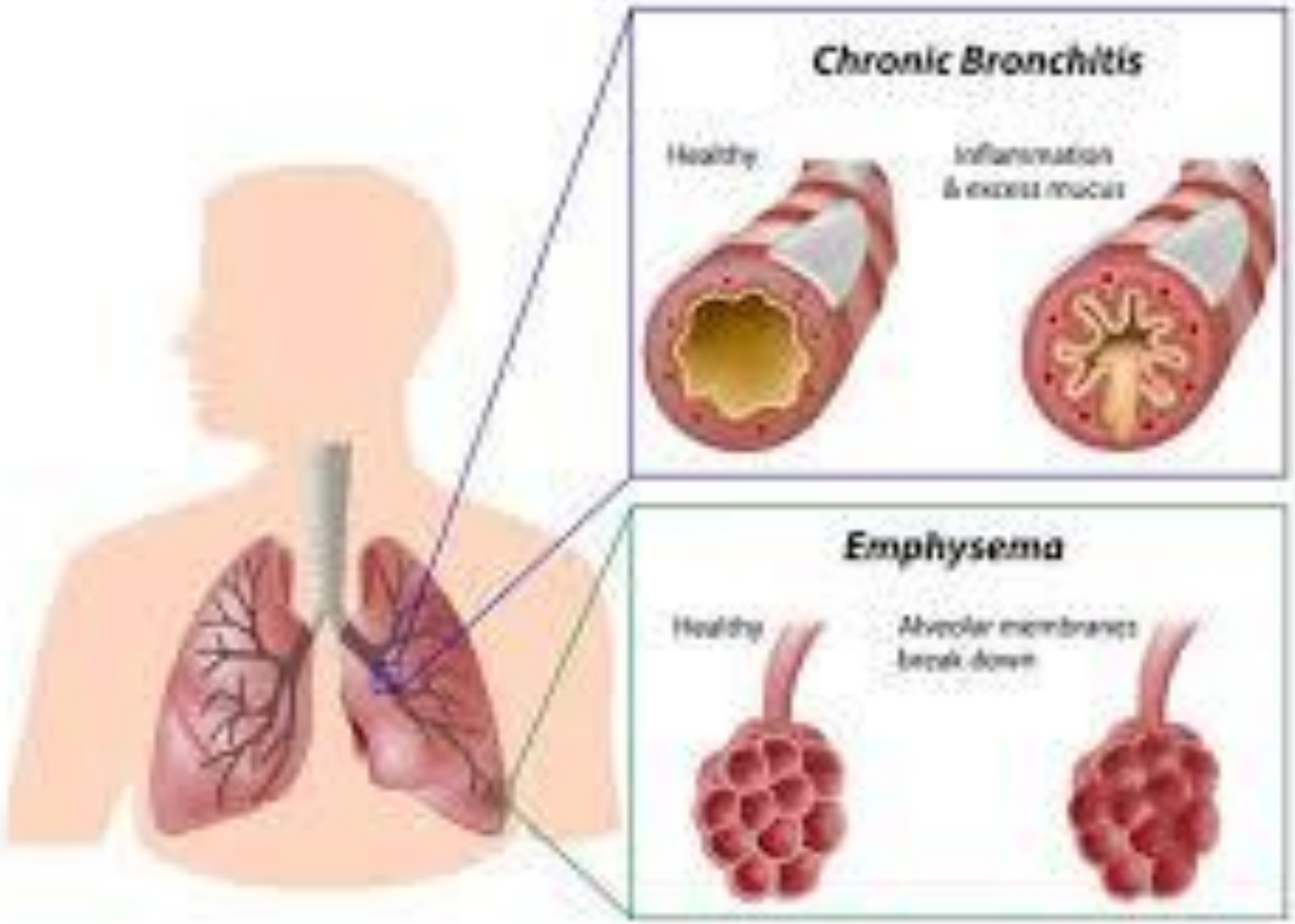
- Inflammatory cells involved include neutrophil granulocytes and macrophages.
- Part of the cell response is due to ***inflammatory mediators*** e.g., chemotactic factors.
- Those who smoke have *Tc1 lymphocyte* and some people with COPD have *eosinophil involvement* similar to that in asthma.
- **Oxidative stress** due to high levels of *free radicals* in tobacco smoke and released by inflammatory cells, and breakdown of extracellular matrix (ECM) of the lungs by proteases that are *insufficiently inhibited by protease inhibitors* result in ***emphysema***.

- Narrowing of airways due to inflammation and scarring within them contributes to the *inability to breathe out fully* as the pressure in the chest is compressing the airways at this time.
- This result in more air from the previous breath remaining within the lungs when the next breath is started, resulting in an *increase in the total volume of air in the lungs at any given time*, a process called *hyperinflation* or *air trapping*.
- Hyperinflation from exercise is due to shortness of breath in COPD, as *breathing in is less comfortable when the lungs are partly filled*.

- Hyperinflation worsen during exacerbation of COPD due to increased airway inflammation.
- Some patients have airway *hyper-responsiveness to irritants* similar to those found in asthma.
- *Low oxygen, and high carbon dioxide levels in the blood*, can occur from poor gas exchange due to decreased ventilation from airway obstruction, hyperinflation, and a reduced desire to breathe.
- Insufficient ventilation, and *low blood oxygen levels*, if continues for long period, results in ***narrowing of the arteries in the lungs***.

- Emphysema leads to breakdown of capillaries in the lungs as well.
- Both of these changes result in increased blood pressure in the pulmonary arteries; ***pulmonary hypertension*** which may cause ***cor-pulmonale***.
- Severe destruction of small airways lead to formation of large air pockets; known as ***bullae*** that replace the lung tissue, this form of disease is called ***bullous emphysema***.

Chronic Obstructive Pulmonary Disease (COPD)



CHRONIC BRONCHITIS

- **Chronic bronchitis is defined by:** ***the presence of persistent productive cough for at least 3 consecutive months in at least 2 consecutive years.***
- The condition is more common in middle-aged males than females.
- Approximately 20% of adult men and 5% of adult women have chronic bronchitis, but only a minority of them develop serious disabling COPD or cor-pulmonale.

- Some studies indicate that 20% to 25% of men in the 40- to 65-year-old age group have the disease.
- In spite of its name; chronic inflammation of the bronchi is not a prominent feature.
- *In early stages of chronic bronchitis*, productive cough is caused by over-secretion of mucus, but airflow is not obstructed.
- Some patients may have hyper-responsive airways with intermittent broncho-spasm and wheezing.
- Some bronchitic patients, especially heavy smokers, develop chronic outflow obstruction, usually with associated emphysema.

ETIOLOGY OF CHRONIC BRONCHITIS

- The two most important etiological factors responsible for the majority of cases of chronic bronchitis are: the cigarette smoking and the atmospheric pollution.
- Chronic bronchitis is common among cigarette smokers and urban dwellers in smog-ridden cities.
- Other contributory factors are occupation, infection, familial and genetic factors.

1. Smoking:

- The most commonly identified factor implicated in causation of chronic bronchitis and in emphysema is heavy smoking.
- Heavy cigarette smokers have 4 to 10 times higher chance to develop chronic bronchitis.
- Prolonged cigarette smoking appears to act on the lungs in a number of ways:

a) It impairs ciliary movement.

b) It inhibits the function of alveolar macrophages.

c) It leads to hypertrophy and hyperplasia of mucus-secreting glands.

d) It causes considerable obstruction of small airways.

e) It stimulates the vagus and causes broncho-constriction.

2. Atmospheric pollution:

- The incidence of chronic bronchitis is higher in industrialized urban areas where air is polluted.
- Some of the atmospheric pollutants which increase the risk of developing chronic bronchitis are sulfur dioxide, nitrogen dioxide, particulate dust and toxic fumes.

3. Occupation.

- Workers engaged in certain occupations such as in cotton mills (byssinosis), plastic factories etc. are exposed to various organic or inorganic dusts which contribute to disabling chronic bronchitis in such individuals.

4. Infection:

- Bacterial, viral and mycoplasmal infections *do not initiate* chronic bronchitis but usually occur secondary to bronchitis.
- Cigarette smoke, however, predisposes to infection responsible for acute exacerbation in chronic bronchitis.

5. Familial and genetic factors:

- There is poorly-defined familial tendency and genetic predisposition to develop chronic bronchitis.
- Nonsmoker family members who remain in air-pollution of the home are significantly exposed to smoke (passive smoking) and hence have increased blood levels of carbon monoxide.

PATHOGENESIS OF CHRONIC BRONCHITIS

- The distinctive feature of chronic bronchitis is **hyper-secretion of mucus, beginning in the large airways.**
- Cigarette smoking, other air pollutants, such as sulfur dioxide and nitrogen dioxide and other environmental irritants induce hypertrophy of mucous glands in the trachea and main bronchi, leading to a marked increase in mucin-secreting goblet cells in the surface epithelium of smaller bronchi and bronchioles.

- These irritants cause inflammation with CD8+ lymphocytes, macrophages, and neutrophils infiltration, but in contrast with asthma, there are no eosinophils in chronic bronchitis.
- It is postulated that many of the respiratory epithelial effects of environmental irritants e.g., mucus hyper-secretion are mediated by local release of T cell cytokines such as IL-13.
- **Microbial infection often is present but has a secondary role**, chiefly by maintaining the inflammation and exacerbating symptoms.

- The transcription of the mucin gene *MUC5AC in* bronchial epithelium and the production of neutrophil elastase are increased as a consequence of exposure to tobacco smoke.
- Whereas the defining feature of chronic bronchitis (mucus hypersecretion) is primarily a reflection of *large bronchial involvement*, **the morphologic basis of airflow obstruction in chronic bronchitis is more peripheral and results from:**

1. **Small airway disease,** induced by goblet cell metaplasia, mucous plugging of the bronchiolar lumen, inflammation, and bronchiolar wall fibrosis, and
2. **Coexistent emphysema.**

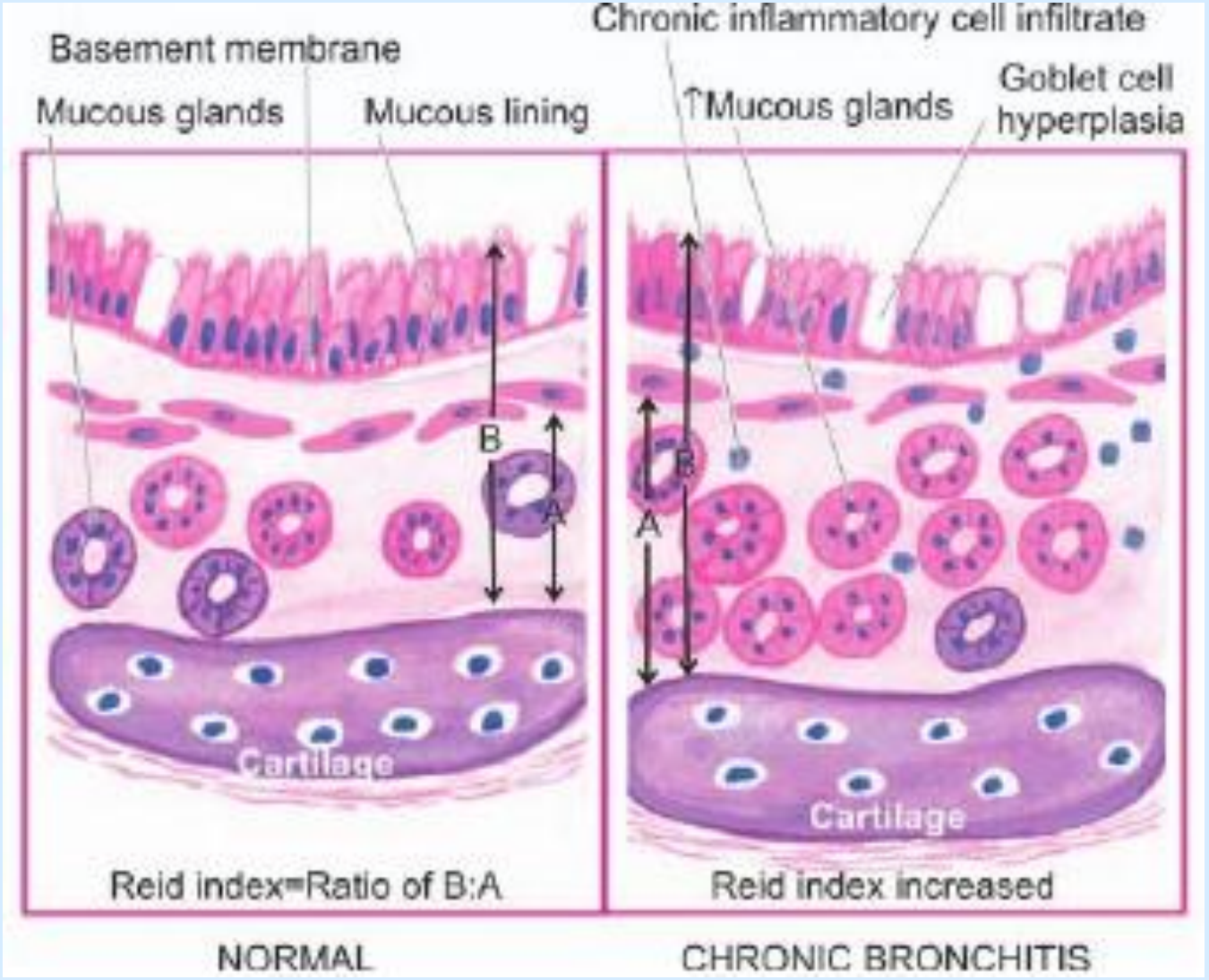
- **In general, while small airway disease**; **chronic bronchiolitis** is an important component of *early and relatively mild airflow obstruction*, *chronic bronchitis with significant airflow obstruction is almost always complicated by emphysema.*

MORPHOLOGY OF CHRONIC BRONCHITIS

- **Grossly:**
- The mucosal lining of the larger airways usually is thickened, hyperemic and edematous.
- It often is covered by a layer of mucinous or muco-purulent secretions.
- Lumina of the bronchi and bronchioles may contain mucus plugs and purulent exudate.
- The smaller bronchi and bronchioles also may be filled with similar secretions.

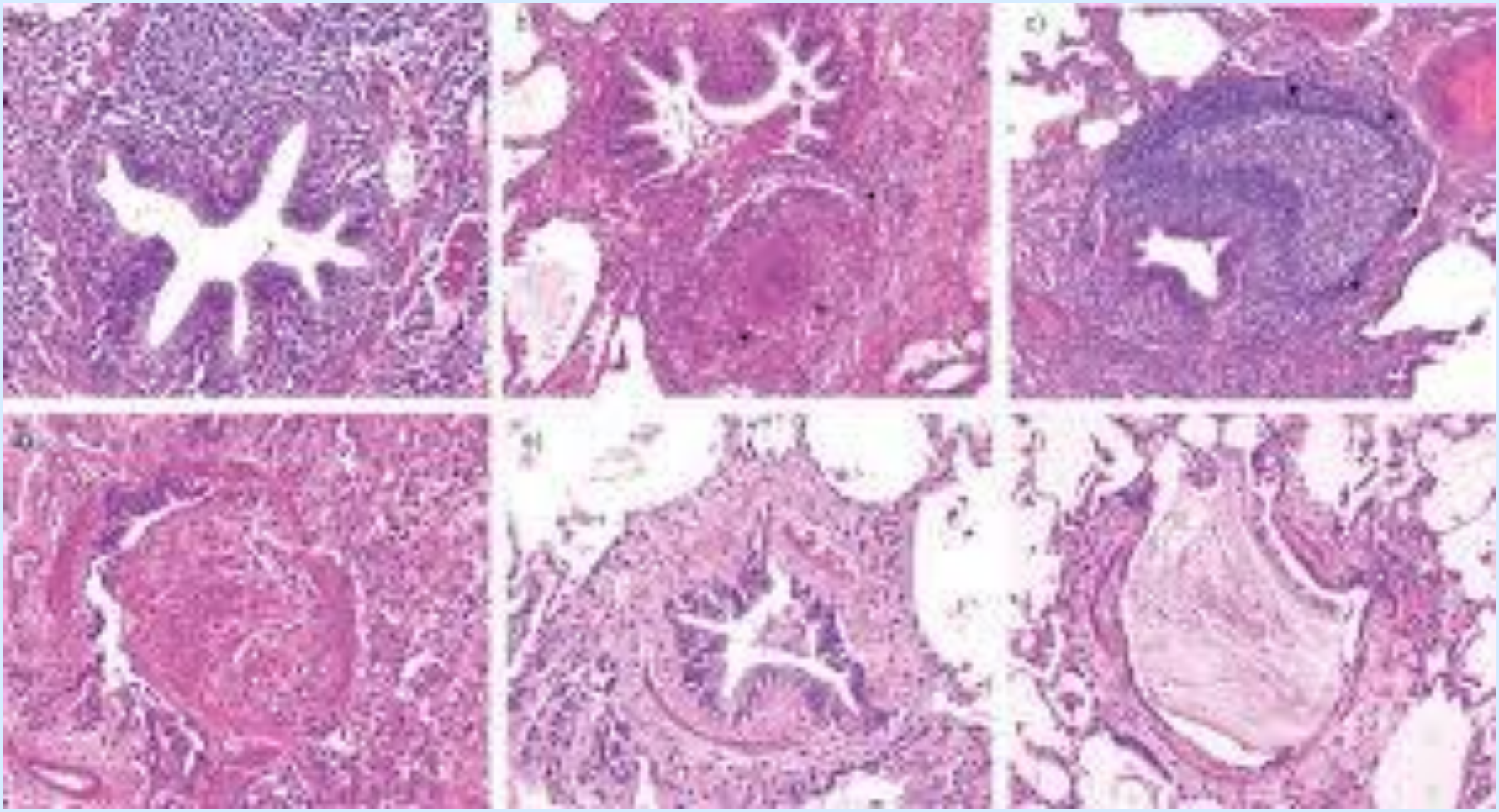
- **On histological examination:**
- The diagnostic feature of chronic bronchitis in the trachea and larger bronchi is enlargement of the mucus-secreting glands.
- The magnitude of increase in size is assessed by the ratio of the thickness of submucosal gland layer to that of the bronchial wall (the Reid index, normally 0.4).
- Little chronic inflammatory cell infiltrate, largely mononuclear cellsadmixed with neutrophils, are present in variable density in the bronchial mucosa.

- The bronchial epithelium may show squamous metaplasia and dysplasia.
- The non-cartilage containing small airways show goblet cell hyperplasia and intra-luminal and peri-bronchial fibrosis.



Diagrammatic representation of increased Reid's index in chronic bronchitis

- **Chronic bronchiolitis (small airway disease)**, characterized by goblet cell metaplasia, mucous plugging, inflammation, and fibrosis, is also present.
- In the most severe cases, there is complete obliteration of the lumen as a consequence of fibrosis (bronchiolitis obliterans).
- Submucosal fibrosis leads to luminal narrowing and airway obstruction.
- Changes of emphysema often coexist.



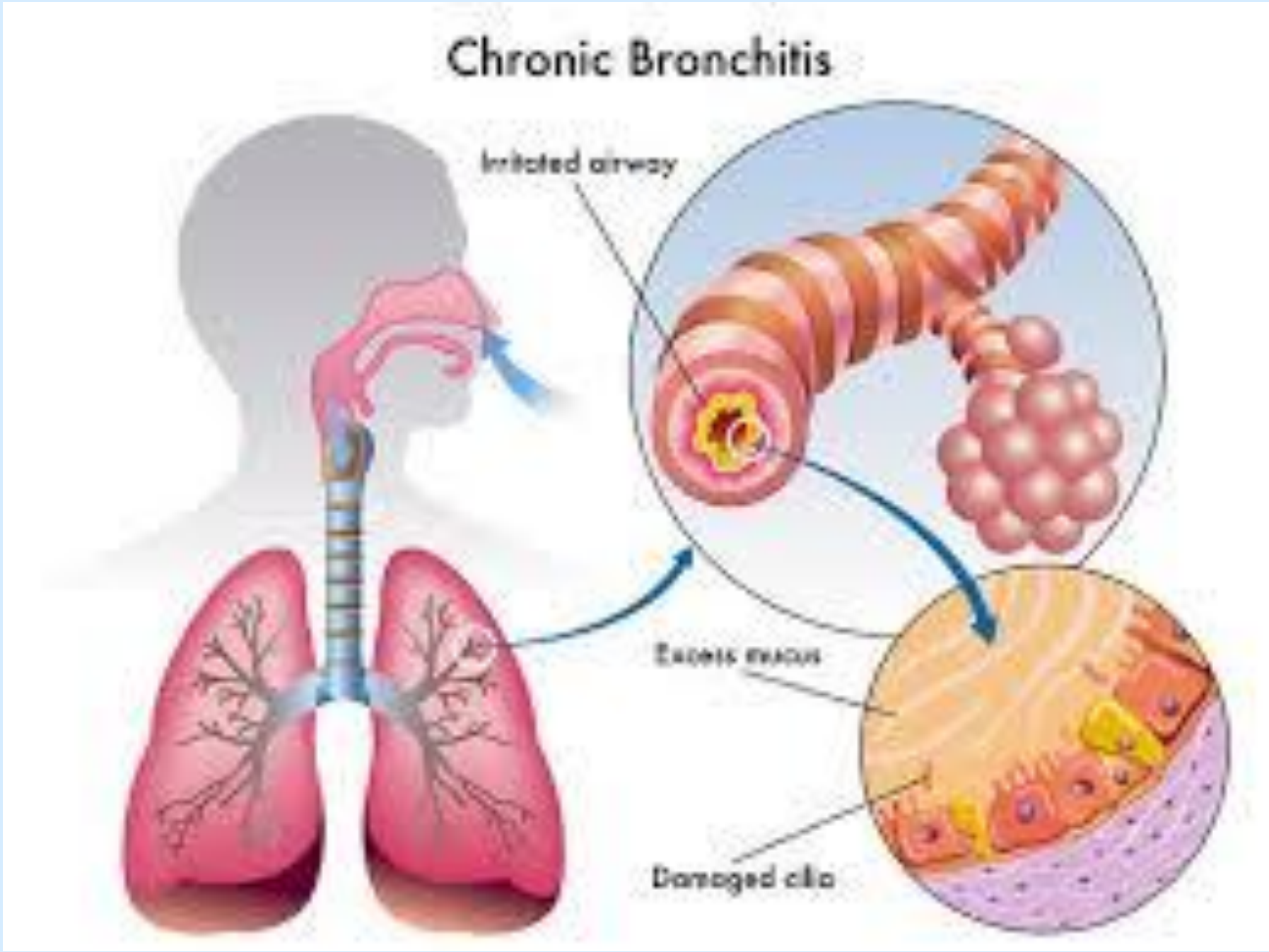
Small airways diseases, excluding asthma

Clinical Features of Chronic Bronchitis

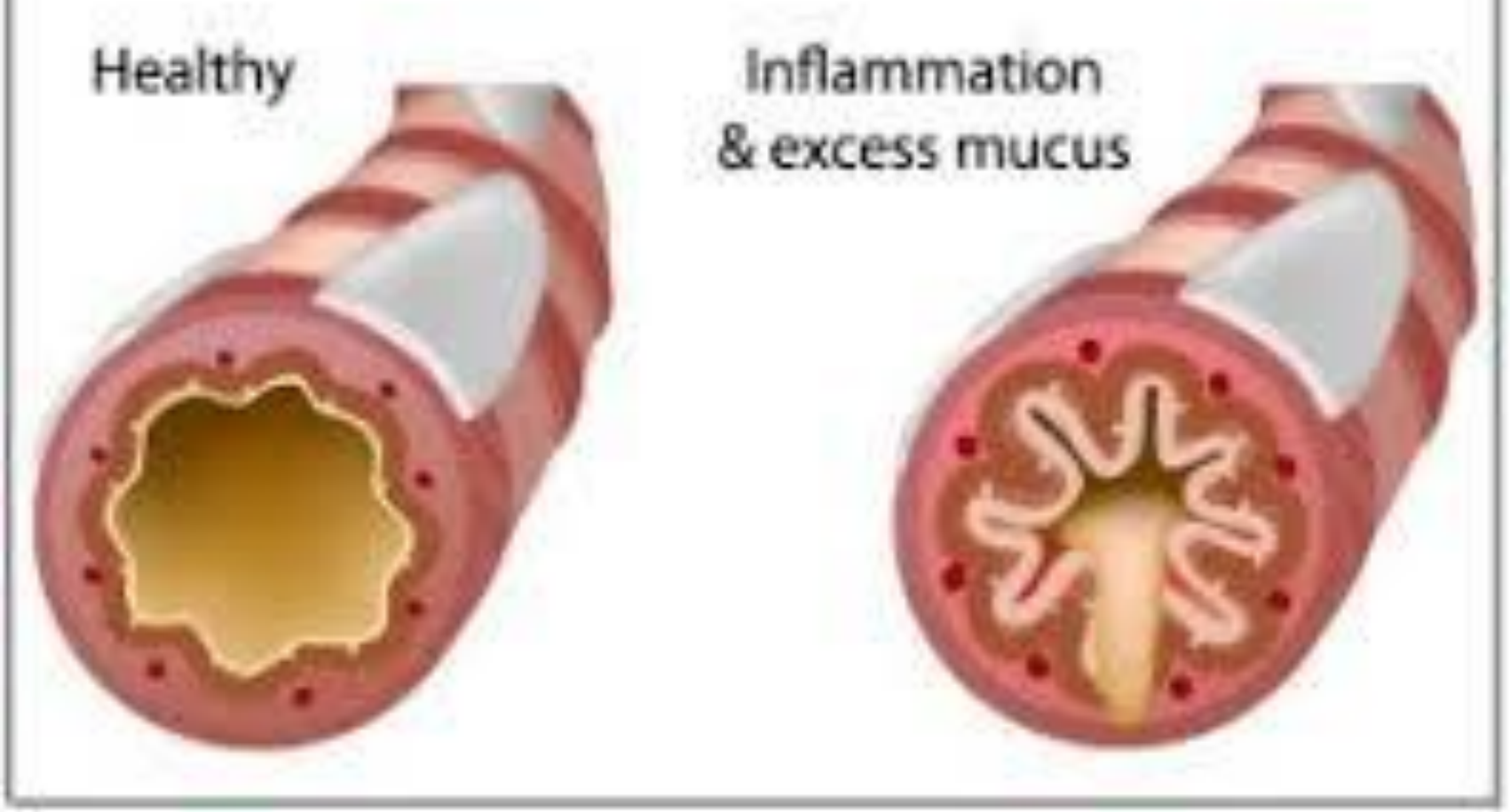
- There is considerable overlap of clinical features of chronic bronchitis and pulmonary emphysema as quite often the two coexist.
- Differentiation of this form of COPD from that caused by emphysema can be made in the classic case, but many such patients have both conditions.
- Some important features of ***'predominant bronchitis'*** are :

1. Persistent cough with copious expectoration of long duration; initially beginning in a heavy smoker with ***'morning catarrh'*** or ***'throat clearing'*** which worsens in winter.
2. Recurrent respiratory infections are common.
3. Dyspnea is generally not prominent at rest but is more on exertion.
4. Patients are called ***'blue bloaters'*** due to cyanosis and edema.
5. Features of right heart failure (cor-pulmonale) are common.
6. Chest X-ray shows enlarged heart with prominent vessels.

- This clinical syndrome is accompanied by hypercapnia, hypoxemia.
- With progression, chronic bronchitis is complicated by pulmonary hypertension and cardiac failure.
- Recurrent infections and respiratory failure are constant threats.


Chronic Bronchitis
Irritated airway
Excess mucus
Damaged cilia

Chronic Bronchitis



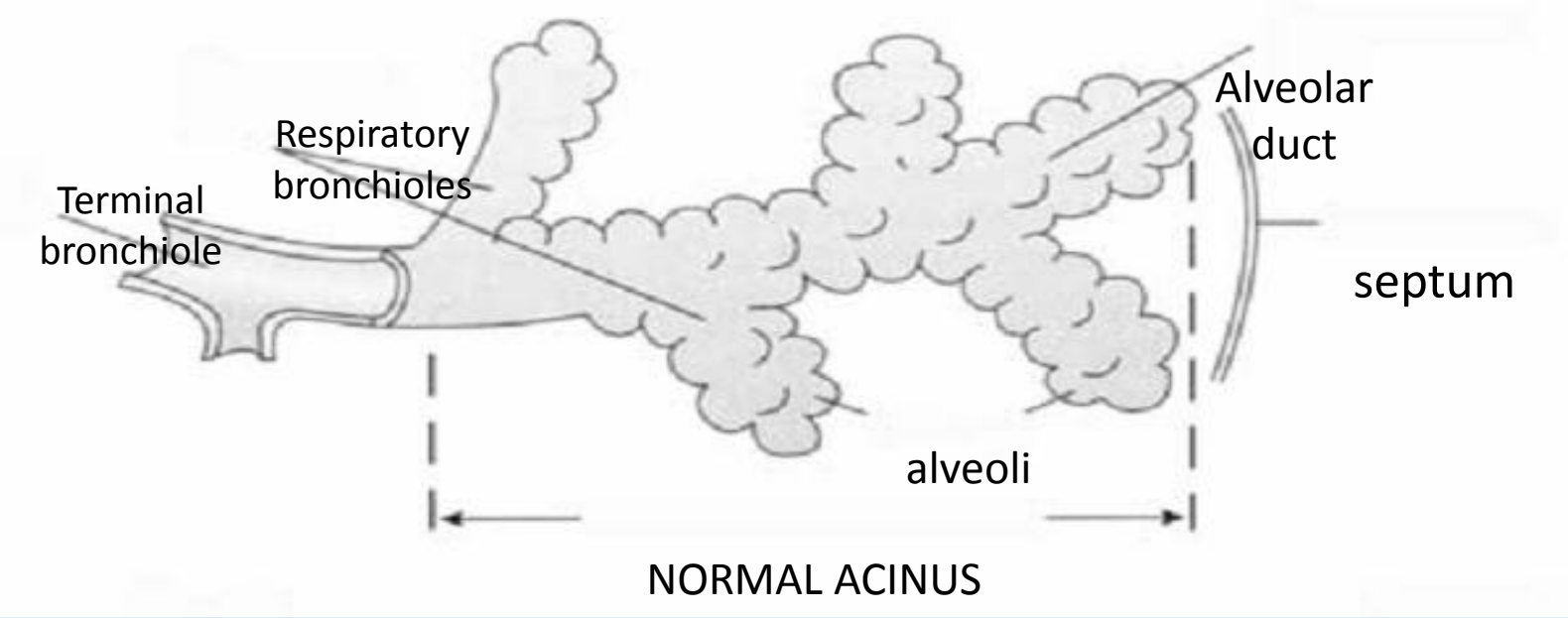
Emphysema

- **Definition:**
- *An abnormal permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls and of the alveolar septa (containing alveolar capillaries) without significant fibrosis.*

Obstructive Respiratory Disorders

Emphysema

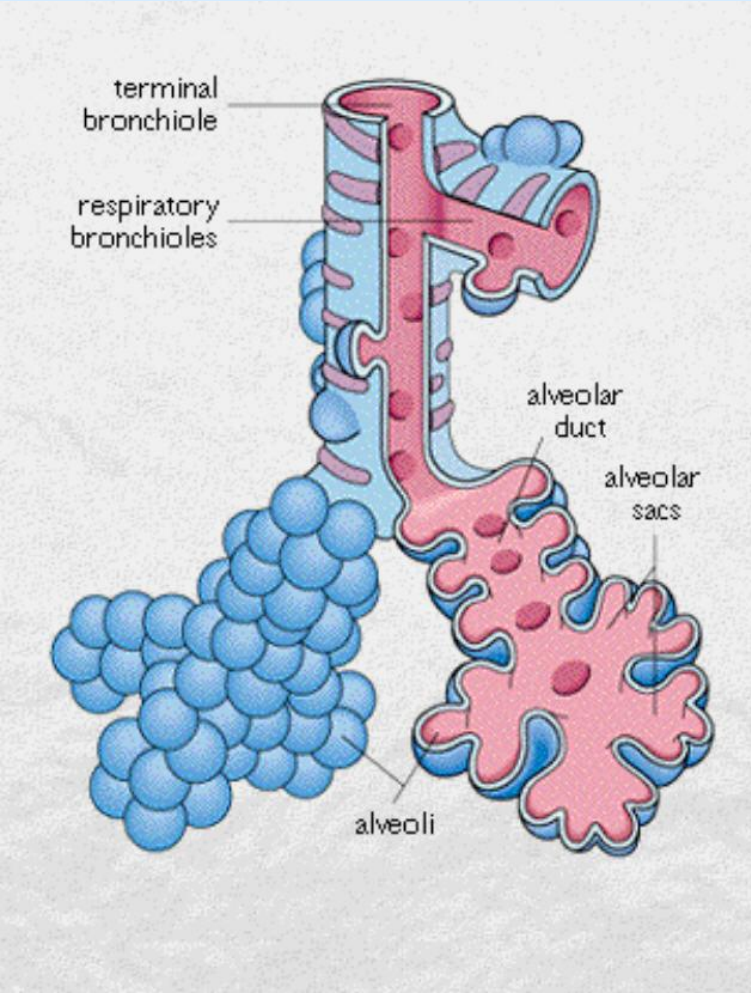
Normal acinus



Obstructive Respiratory Disorders

Emphysema

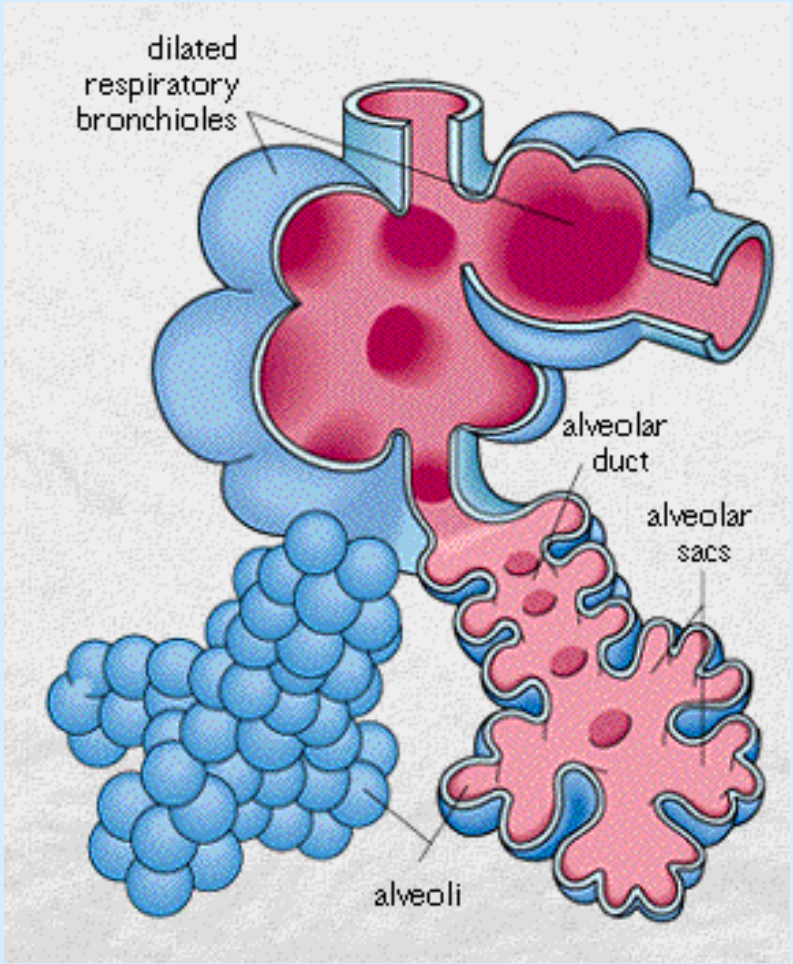
Normal lung



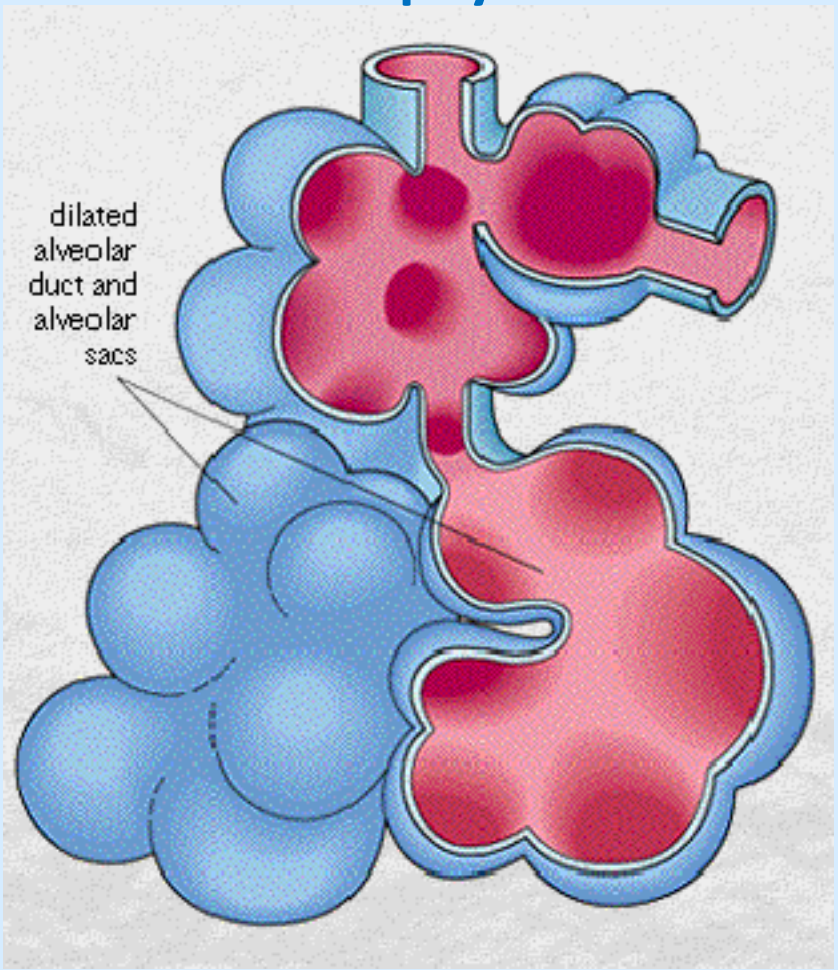
Obstructive Respiratory Disorders

Emphysema

Centrilobular emphysema



Panacinar emphysema



PATHOGENESIS OF EMPHYSEMA

- Exposure to toxic substances such as tobacco smoke and inhaled pollutants induces ongoing inflammation with accumulation of neutrophils, macrophages and lymphocytes in the lung.
- Elastases, cytokines (including IL-8) and oxidants are released causing epithelial injury and proteolysis of the extracellular matrix (ECM).
- Elastin degradation products further increase the inflammation.

- Unless checked by anti-elastases (e.g., α1-antitrypsin) and antioxidants, the cycle of inflammation and ECM proteolysis continues.
- More than 80% of patients with congenital α1-antitrypsin deficiency develop symptomatic panacinar emphysema, which occurs at an earlier age and with greater severity if the affected person smokes.
- The mechanism of alveolar wall destruction in emphysema by elastolytic action is based on the imbalance between proteases; chiefly elastase and anti-proteases; chiefly anti-elastase by:

- ❑ Decreased anti-elastase activity i.e. deficiency of α-1 antitrypsin.
- ❑ Increased activity of elastase i.e. increased neutrophilic infiltration in the lungs causing excessive elaboration of neutrophil elastase.
- Smoking promotes emphysema by both decreasing the amount of anti-elastase as well as by increasing the elastolytic protease in the lungs.

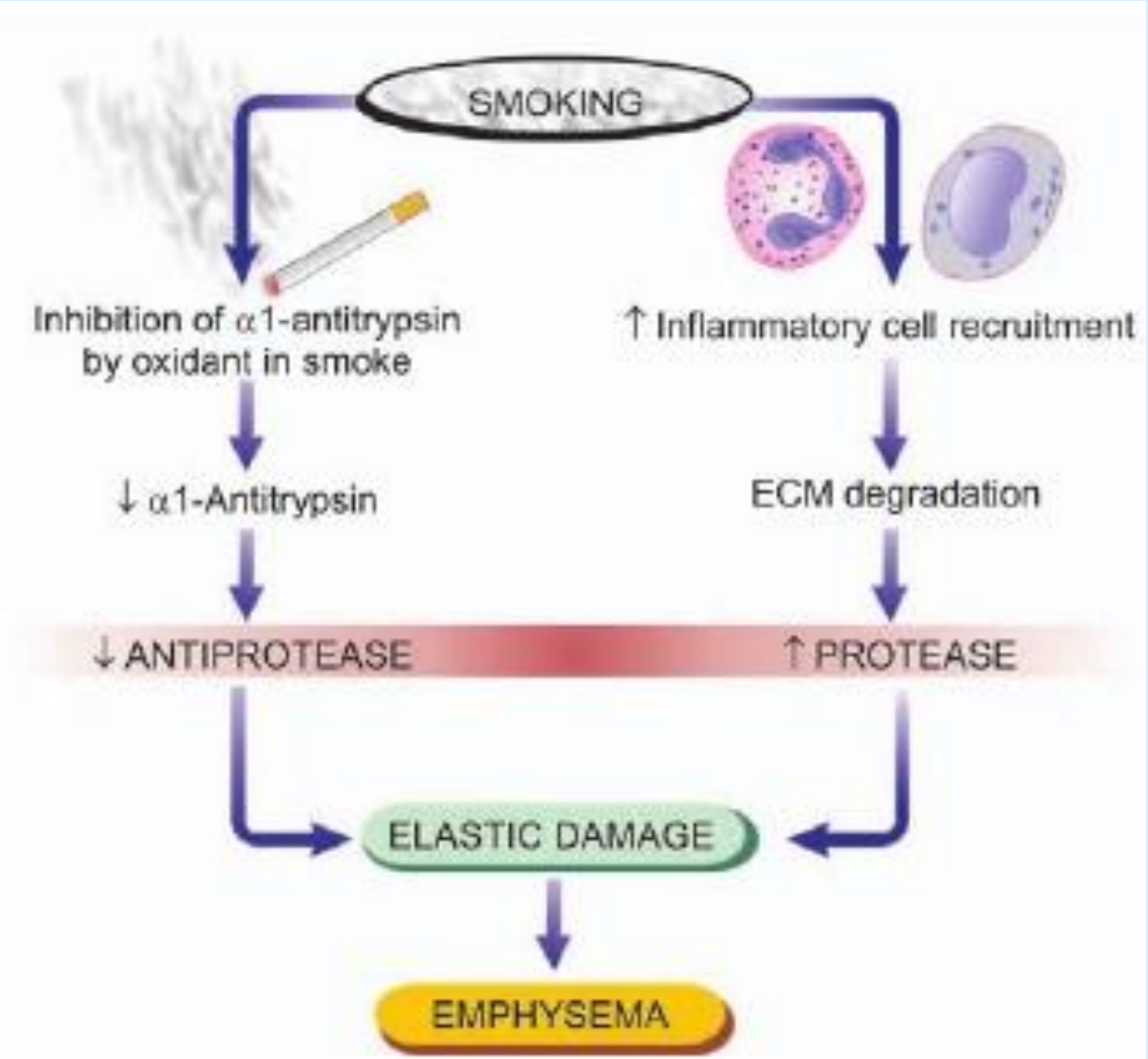
- **These are due to:**

1. Oxidant in cigarette smoke has inhibitory influence on α-1-antitrypsin, thus lowering the level of anti-elastase activity.
2. Smokers have up to ten times more phagocytes and neutrophils in their lungs than nonsmokers; thus they have very high elastase activity.

- There is marked individual variation in the susceptibility to the development of emphysema/COPD.
- Multiple genetic factors control the response to injury after smoking.
- *TGF-B gene exhibits polymorphisms that influence susceptibility* to the development of COPD by regulating the response of mesenchymal cells to injury.
- With certain polymorphisms, mesenchymal cell response to TGF-β signaling is reduced, which results in inadequate repair of elastin injury caused by inhaled toxins.

- Matrix metalloproteinases (MMPs), especially MMP-9 and MMP-12, have pathogenic role in emphysema.
- MMP-9 gene polymorphisms and higher levels of both MMP-9 and MMP-12 have been found in some emphysema patients.
- Moreover, MMP-12–deficient mice are protected from cigarette smoke-induced emphysema.
- Interactions between inflammatory mediators, cell signaling and inappropriate activation of repair mechanisms result in tissue destruction without fibrosis (emphysema), or interstitial fibrosis.

- Recent data indicate that ***mesenchymal cell response*** may be a key factor in determining which of these two processes ensues.
- In emphysema there is *loss of not only epithelial and endothelial cells but also mesenchymal cells*, leading to ***lack of ECM***, the scaffolding upon which epithelial cells are grown.
- Thus, ***emphysema can be thought of as resulting from insufficient wound repair.***
- By contrast, *patients with fibrosing lung diseases* have ***excessive myofibroblastic or fibroblastic response to injury***, leading to unchecked ***scarring***.



Pathogenesis of alveolar wall destruction in emphysema by protease-antiprotease mechanism.

Types of Emphysema

- Pulmonary emphysema, is classified according to the portion of the acinus involved (its *anatomic distribution* within the *lobule*).
- *The **acinus** is the* structure distal to terminal bronchioles (consists of 3 to 5 generations of respiratory bronchioles and a variable number of alveolar ducts and alveolar sacs).
- A cluster of three to five acini is called a *lobule*.
- A lobule is composed of about 5 acini distal to a terminal bronchiole.

- ***There are* four major types of emphysema:**

1. Centriacinar (centrilobular) emphysema,
2. Panacinar (panlobular) emphysema,
3. Distal acinar emphysema (paraseptal), and
4. Irregular emphysema (para-cicatricial).

- Some added one more type which is:
- **Mixed (unclassified) emphysema**
- Only the first two types cause clinically significant airway obstruction.
- Centriacinar emphysema is about 20 times more common than panacinar disease.

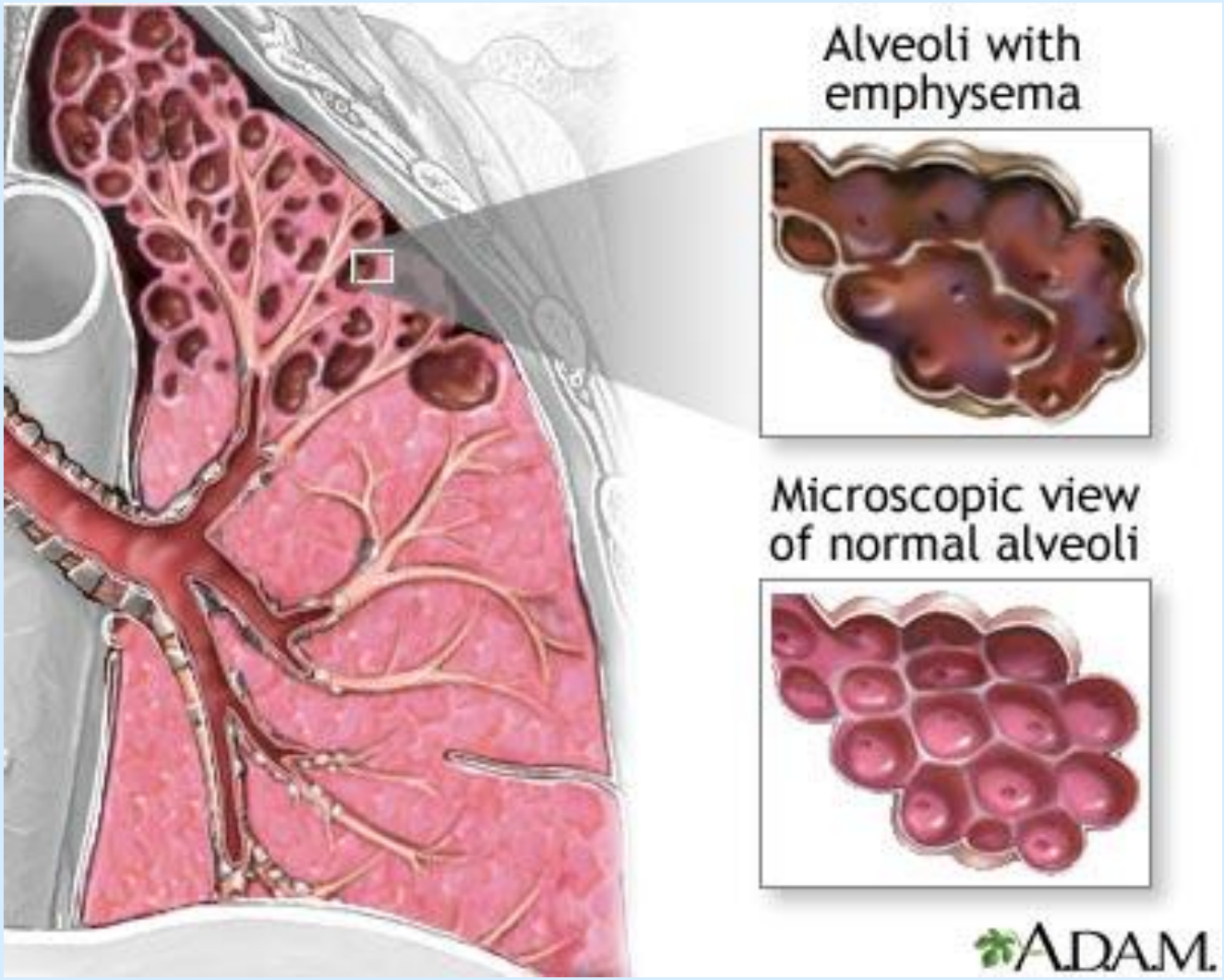
- A number of other conditions to which the term ***'emphysema'*** is loosely applied are, in fact, examples of ***'over-inflation'***. **These are:**

1. Compensatory overinflation (compensatory emphysema)
2. Senile hyperinflation (aging lung, senile emphysema)
3. Obstructive overinflation (e.g., infantile lobar emphysema)
4. Unilateral translucent lung (unilateral emphysema)
5. Interstitial emphysema (surgical emphysema)

Emphysema


Normal alveoli
Alveoli with emphysema
Alveoli
Damaged alveoli

Emphysema


Alveoli with emphysema
Microscopic view of normal alveoli
A.D.A.M.

MORPHOLOGY OF EMPHYSEMA

- Emphysema can be diagnosed with certainty only by ***macroscopic appearance; gross picture*** but *histological examination* of sections of the whole lung added more features.

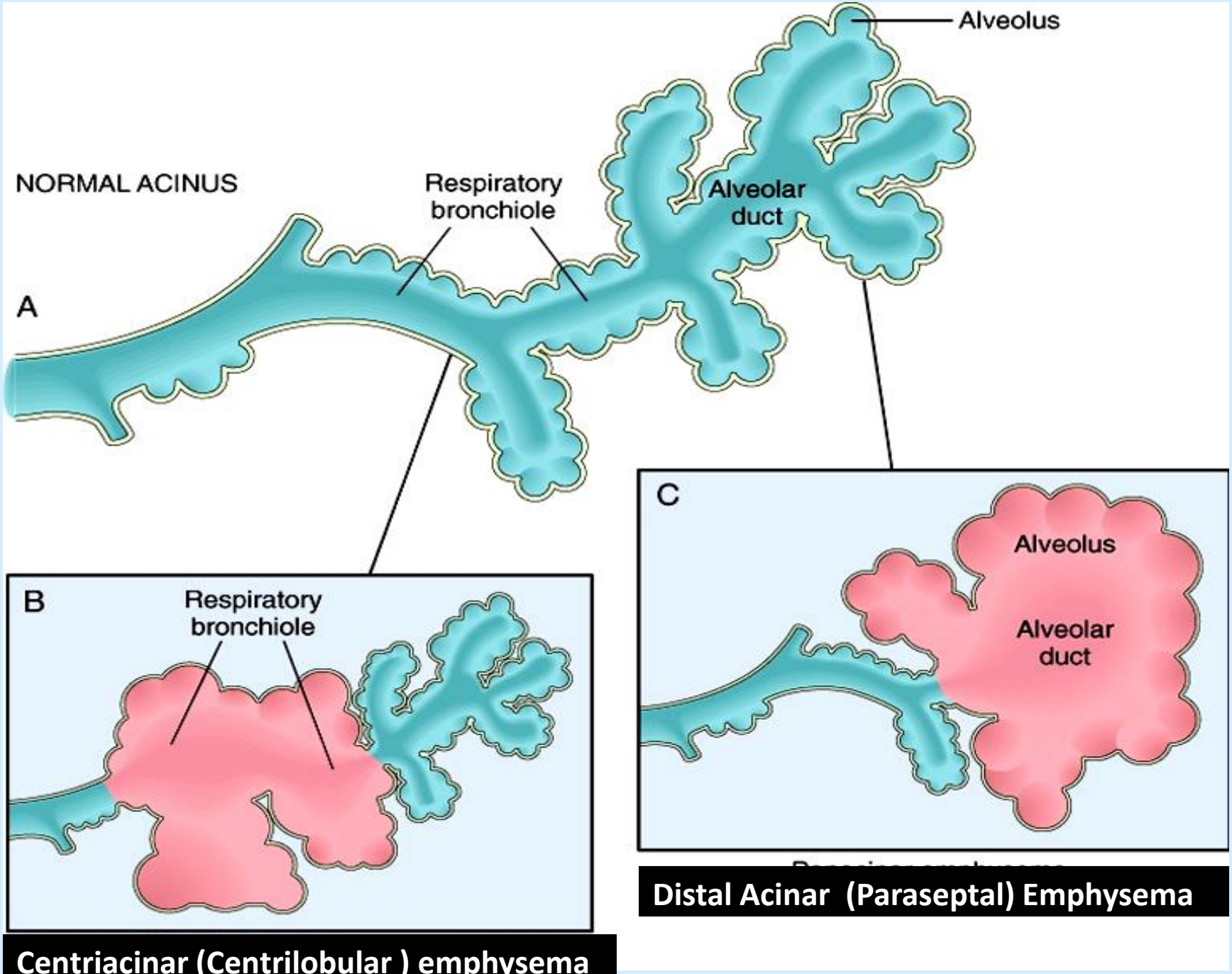
- ***Grossly:***
- The lungs are voluminous, pale with little blood.
- The edges of the lungs are rounded.
- Mild cases show dilatation of air spaces visible with hand lens.
- Advanced cases show subpleural bullae and blebs bulging outwards from the surface of the lungs with rib markings between them.
- The ***bullae*** are air-filled cyst-like or bubble-like structures, larger than 1 cm in diameter formed by rupture of adjacent air spaces.

- ***Blebs*** are the result of rupture of alveoli directly into the subpleural interstitial tissue and are the common cause of spontaneous pneumothorax.
- ***In panacinar emphysema*****,** when the pathological process is well developed, it produces pale, voluminous lungs that obscure the heart when the anterior chest wall is removed at autopsy.
- The macroscopic features of ***centriacinar emphysema*** are less impressive.
- The lungs are a deeper pink than in panacinar emphysema and less voluminous, unless the disease is well advanced.

- Generally, *in centriacinar emphysema the upper two thirds of the lungs are more severely affected than the lower lungs*.

- ***Microscopically:***
- Depending upon the type of emphysema, there is dilatation of air spaces and destruction of septal walls of part of the acinus involved i.e. respiratory bronchioles, alveolar ducts and alveolar sacs.
- **Destruction of alveolar walls without fibrosis, leads to enlarged air spaces.**
- Bullae and blebs when present show chronic inflammation but little fibrosis of their walls.
- In addition to alveolar loss, ***the number of alveolar capillaries is diminished***.

- Terminal and respiratory bronchioles may be deformed because of the loss of septa that help tether these structures in the parenchyma.
- With the ***loss of elastic tissue in the surrounding alveolar septa***, radial traction on the small airways is reduced.
- As a result, they tend to ***collapse during expiration***, an important cause of ***chronic airflow obstruction in severe emphysema***.
- Changes of bronchitis may be present.
- *Bronchiolar inflammation and submucosal fibrosis* are consistently present in ***advanced disease***.



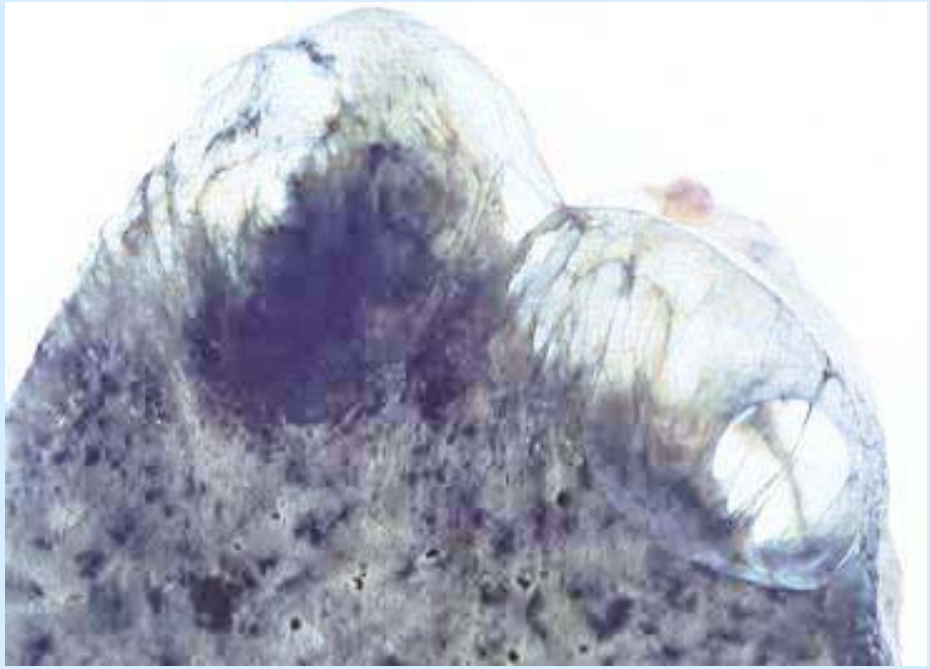
Distal Acinar (Paraseptal) Emphysema

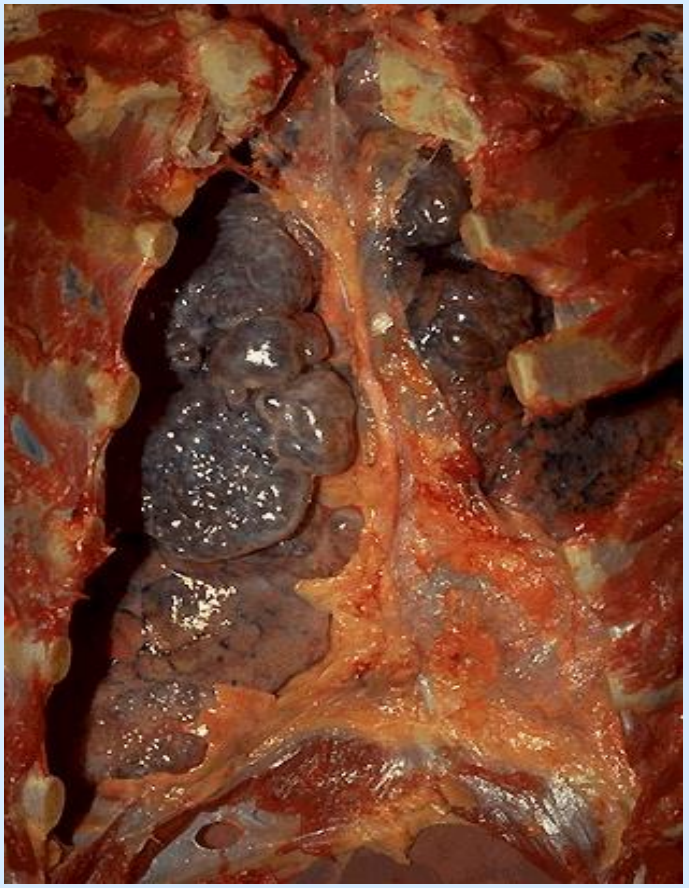
Centriacinar (Centrilobular) emphysema

Obstructive Respiratory Disorders

Emphysema

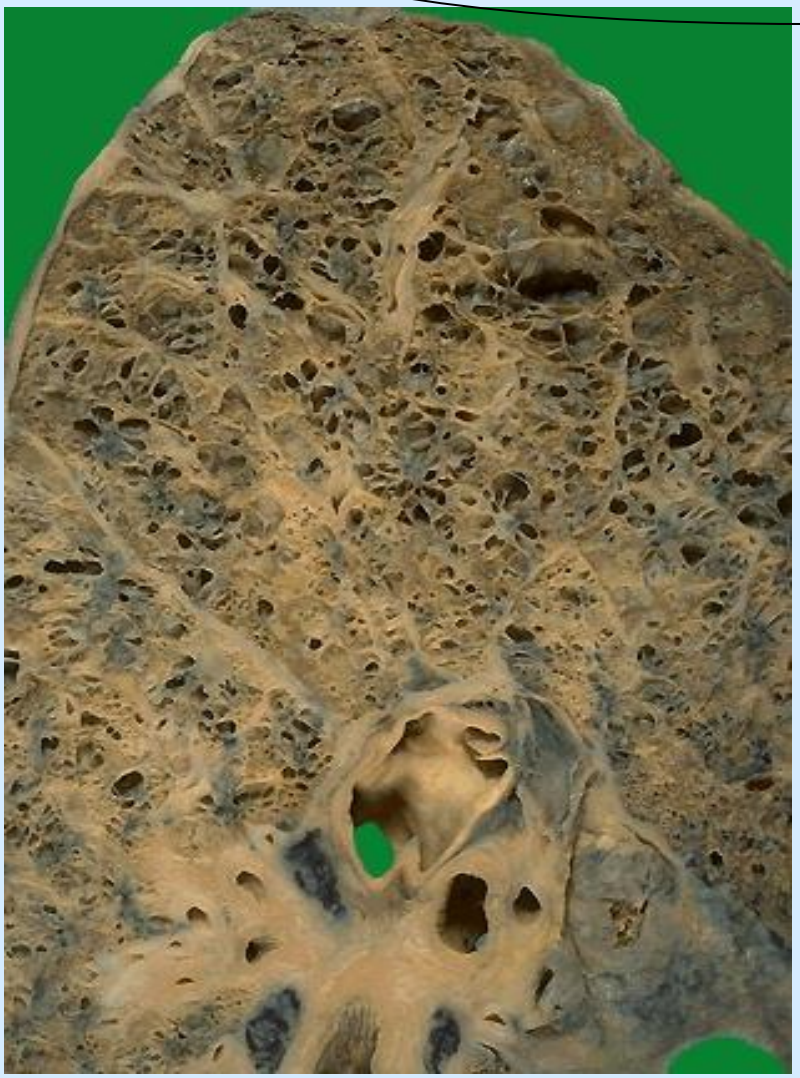
Gross Picture:

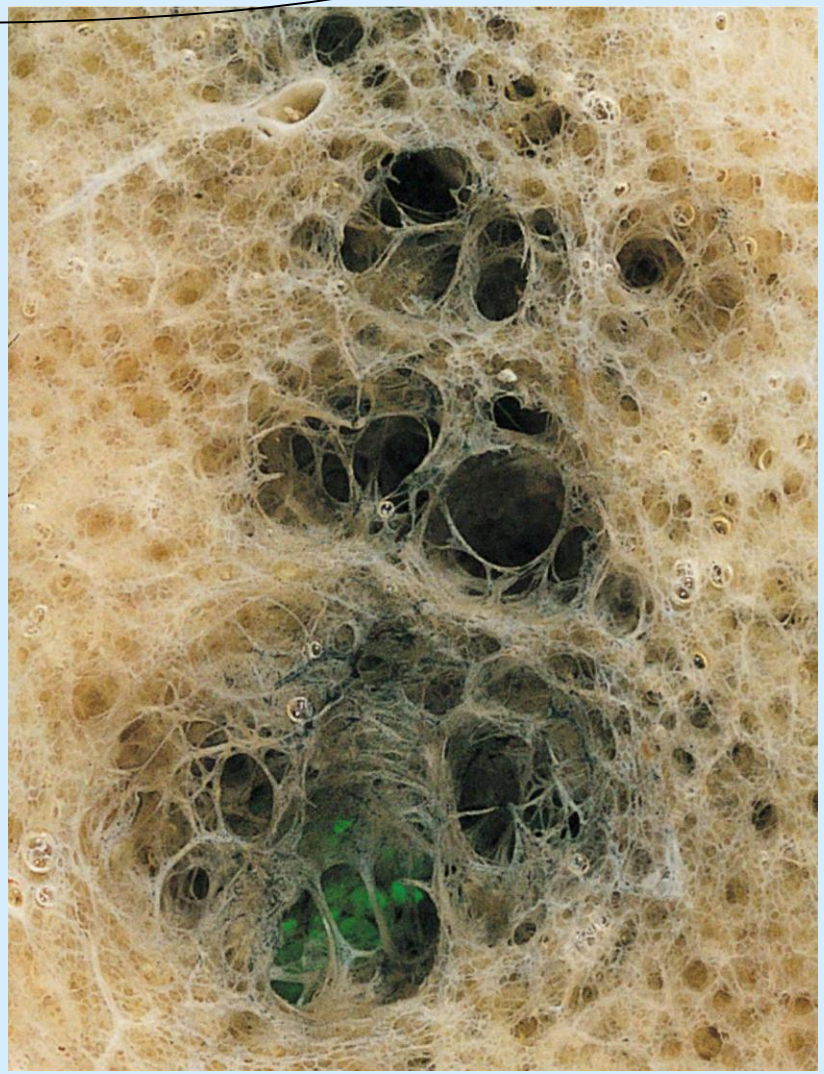




Obstructive Respiratory Disorders

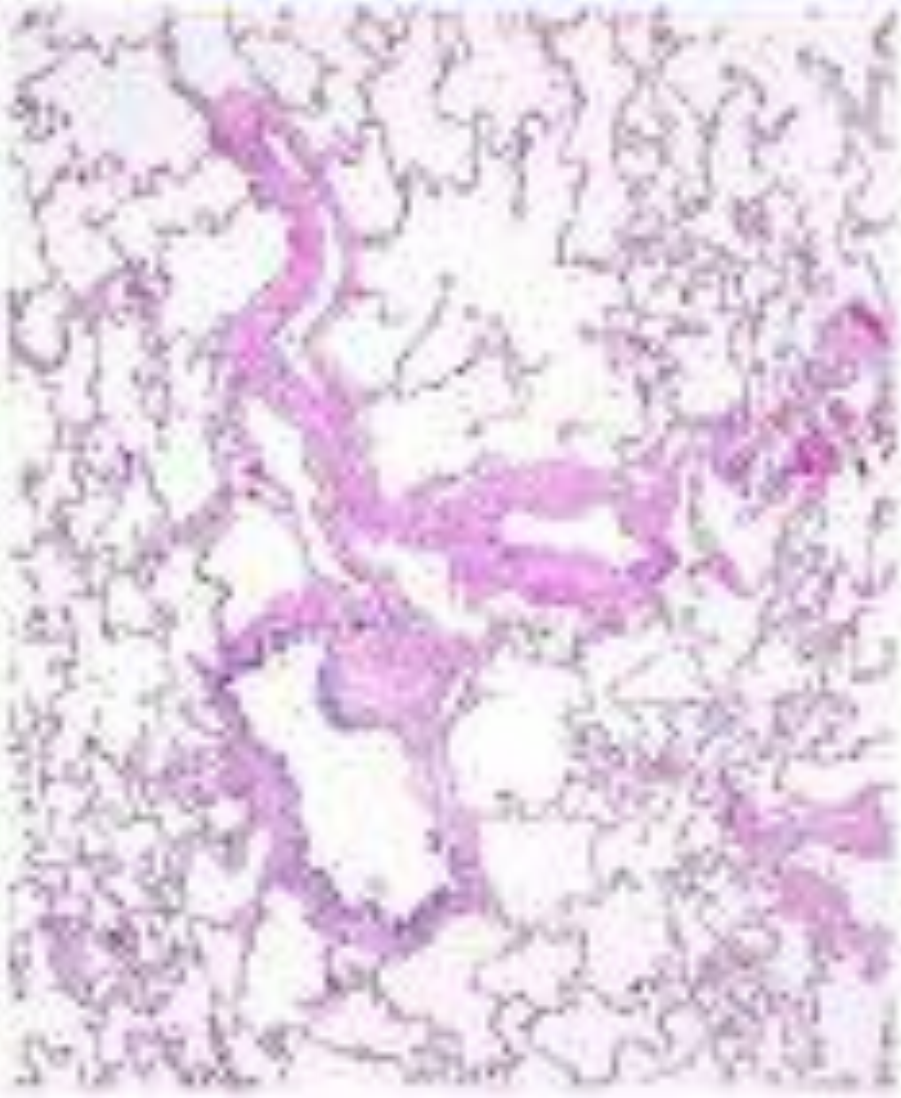
Emphysema





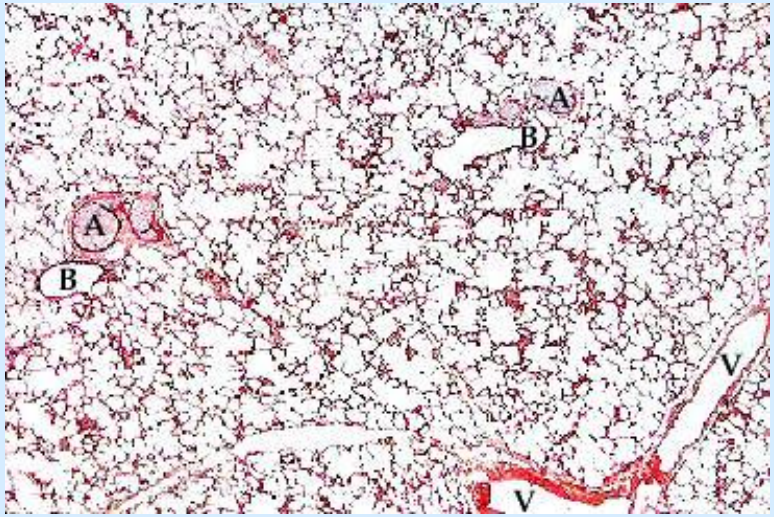
Normal

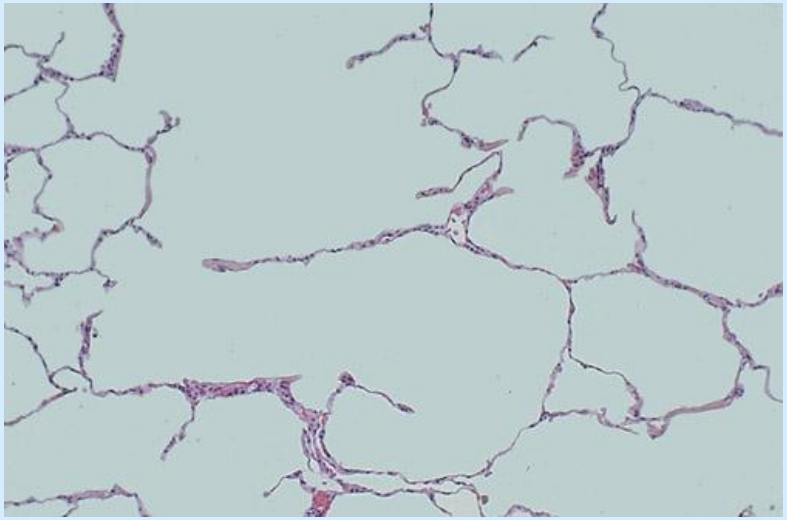
Emphysema



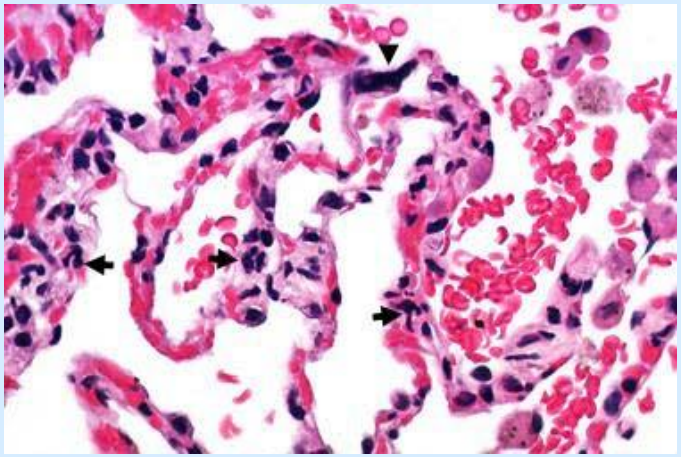
Obstructive Respiratory Disorders

Emphysema

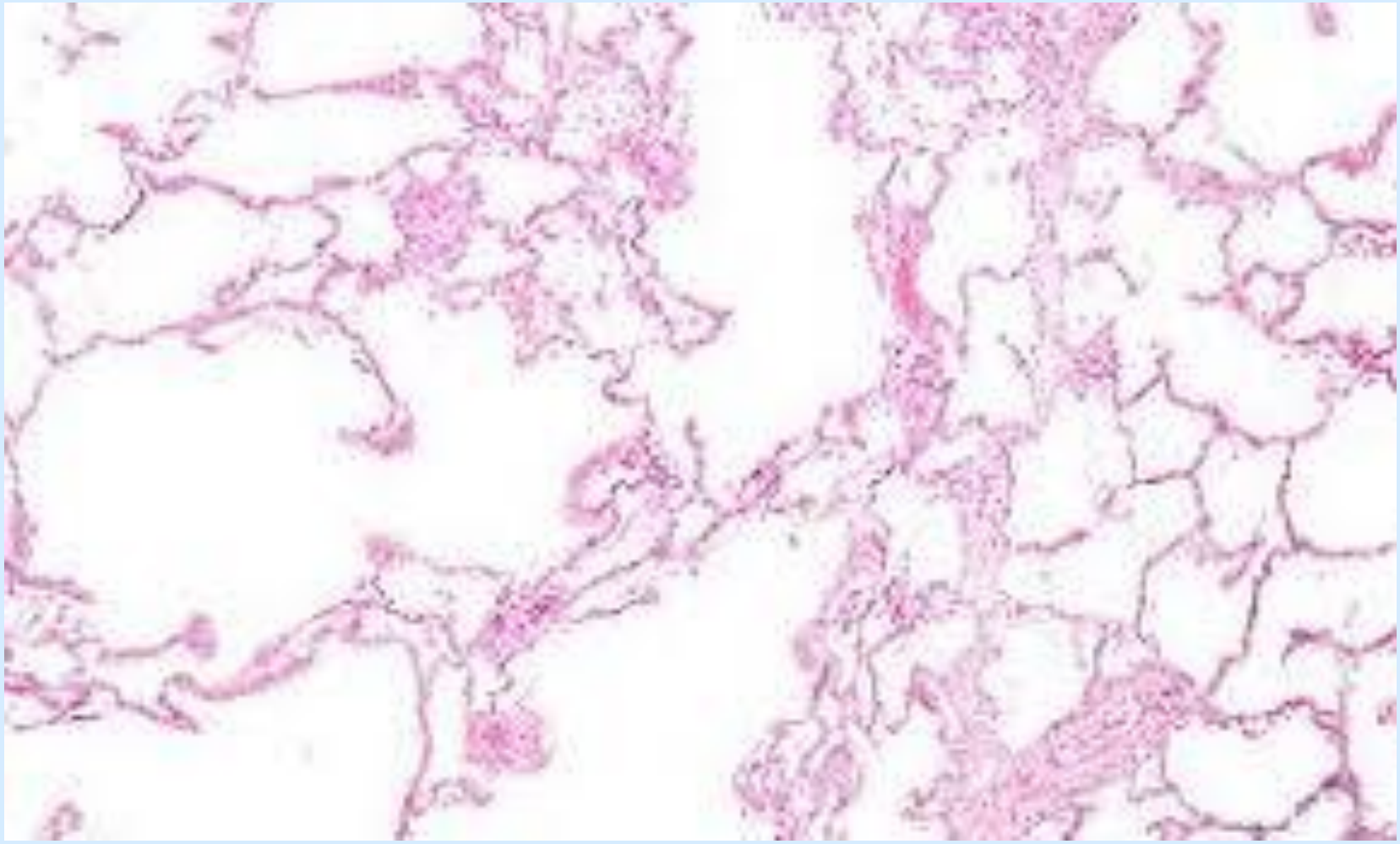




Microscopic Picture:



Emphysema



Morphology of Individual Types of Emphysema

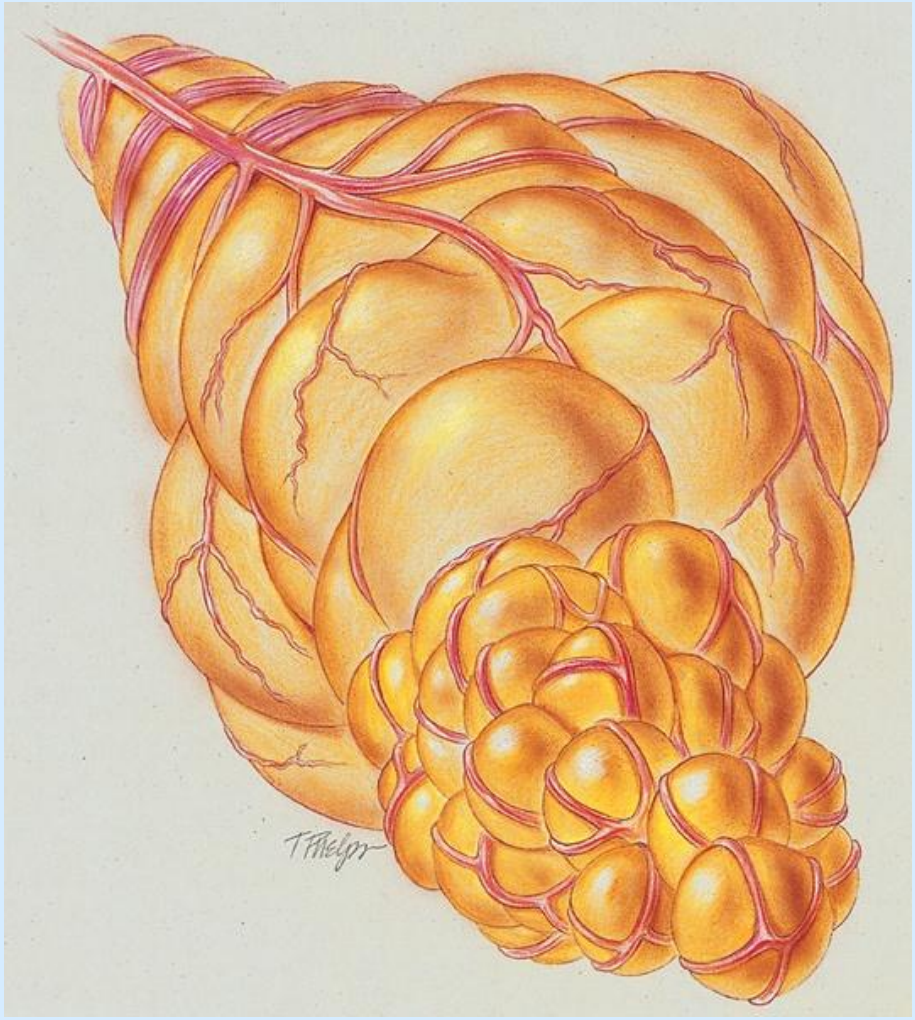
1. ***Centriacinar (Centrilobular) Emphysema*** is one of the common types of emphysema.

- The distinctive feature of centriacinar (centrilobular) emphysema is the pattern of involvement of the lobules.
- *The central or proximal parts of the acini, formed by respiratory bronchioles, are affected, while distal alveoli are spared.*

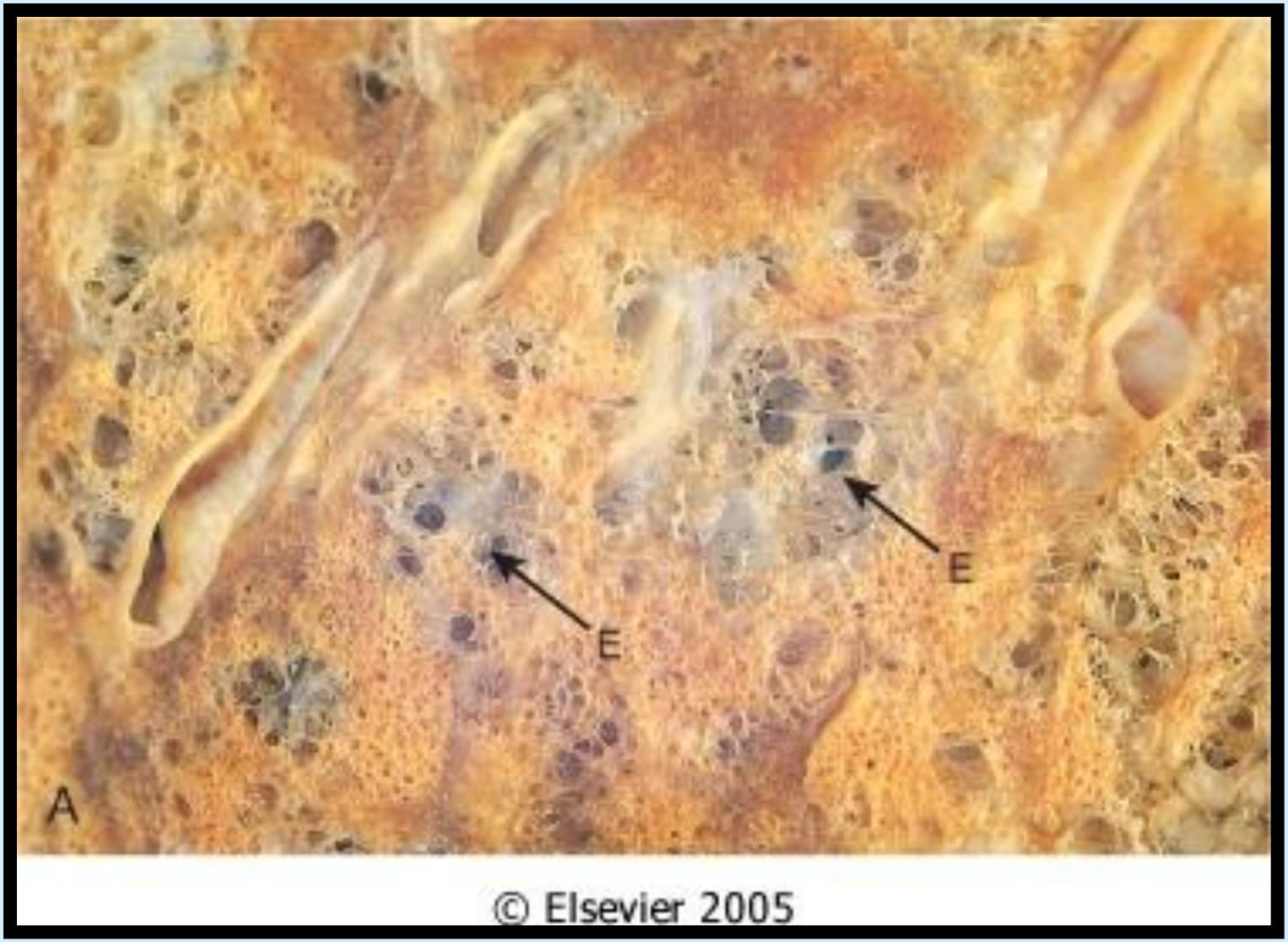
- Thus, both emphysematous and normal air spaces exist within the same acinus and lobule.
- In *severe* centriacinar emphysema the *distal acinus* also becomes involved, and thus, the *differentiation* from panacinar emphysema becomes difficult.
- *This type of emphysema is most commonly seen as a consequence of* ***cigarette smoking*** *in people who do not have congenital deficiency of α1-antitrypsin.*
- It usually coexists with chronic bronchitis and in coal miners' pneumoconiosis.

- **Grossly:**
- The lesions are more common and *severe* in the *upper lobes*, particularly in the *apical segments*.
- The characteristic appearance is obvious in cut surface of the lung.
- It shows distended air spaces in the center of the lobules surrounded by a rim of normal lung parenchyma in the same lobule.
- The lobules are separated from each other by fine fibrous tissue septa.
- Large amount of black pigment is often present in the walls of the emphysematous spaces.

- **Microscopically:**
- There is distension and destruction of the respiratory bronchiole in the center of lobules, surrounded peripherally by normal uninvolved alveoli.
- The terminal bronchioles supplying the acini show chronic inflammation and are narrowed.



Centrilobular emphysema: Abnormal weakening and enlargement of the respiratory bronchioles in the proximal portion of the acinus.



Centriacinar emphysema. Central areas show marked emphysematous damage (E), surrounded by relatively spared alveolar spaces

2. ***Panacinar (Panlobular) Emphysema*** is the other common type of emphysema.

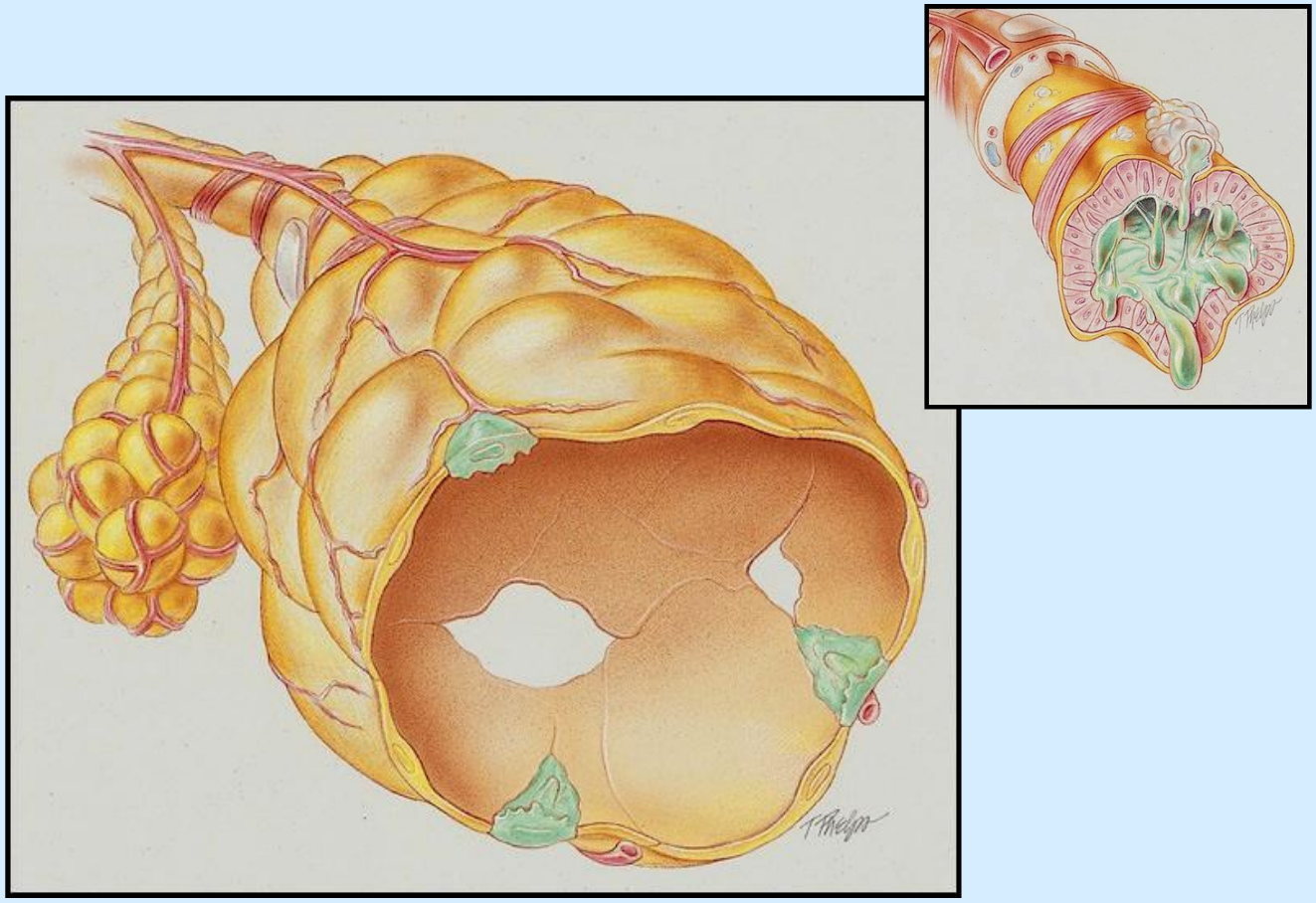
- *In panacinar (panlobular) emphysema, all portions of the acinus are uniformly enlarged, from the level of the respiratory bronchiole to the terminal blind alveoli, but not of the entire lung.*
- In contrast with centriacinar emphysema, panacinar emphysema tends to occur more commonly in the *lower lung zones* and is the type of emphysema that occurs in ***α1-antitrypsin deficiency***.

- Panacinar emphysema is found in middle-aged smokers and is the one that produces the most characteristic anatomical changes in the lung in emphysema.

- **Grossly**:
- In contrast to centriacinar emphysema, panacinar emphysema involves the ***lower zone*** of the lungs more frequently and more severely than the upper zone.
- The involvement may be confined to few lobules, or may be more widespread affecting a lobe or part of a lobe of the lung.
- The lungs are *enlarged* and *overinflated*.

- **Microscopically:**
- *Usually all the alveoli within a lobule are affected* to the same degree.
- *All portions of the acini are distended*; respiratory bronchioles, alveolar ducts and alveoli, and their walls stretched and thin.
- *Ruptured alveolar walls and spurs of broken septa* are seen between the adjacent alveoli.
- *The capillaries are stretched and thinned*.
- Special stains show *loss of elastic tissue*.
- *Inflammatory changes are usually absent*.

Emphysema



Panlobular emphysema: Excessive bronchial secretions, a common secondary anatomic alteration of the lungs.

Panacinar emphysema involving the entire pulmonary architecture.

3. Distal Acinar (Paraseptal) Emphysema

- This type of emphysema ***involves the distal part of the acinus while the proximal part is normal***.
- *The cause of this type* of emphysema *is unknown,* and it is seldom associated with COPD but is a common cause of *spontaneous pneumothorax in young adults*.
- Paraseptal or distal acinar emphysema is *localized along the pleura* and *along the lobular connective tissue septa*, and *at the margins of the lobules*.
- It occurs *adjacent to areas of fibrosis*, *scarring*, or *atelectasis* and is usually *more severe* in the ***upper half of the lungs*** more severely than the lower.

- The characteristic finding is the presence of *multiple*, *contiguous*, *enlarged air spaces* ranging in diameter from less than 0.5 mm to more than 2.0 cm, sometimes forming *cystic structures* that, with progressive enlargement, are referred to as ***bullae*** in the subpleural portion of the lung.

4. *Irregular Emphysema (Para-cicatricial Emphysema)*

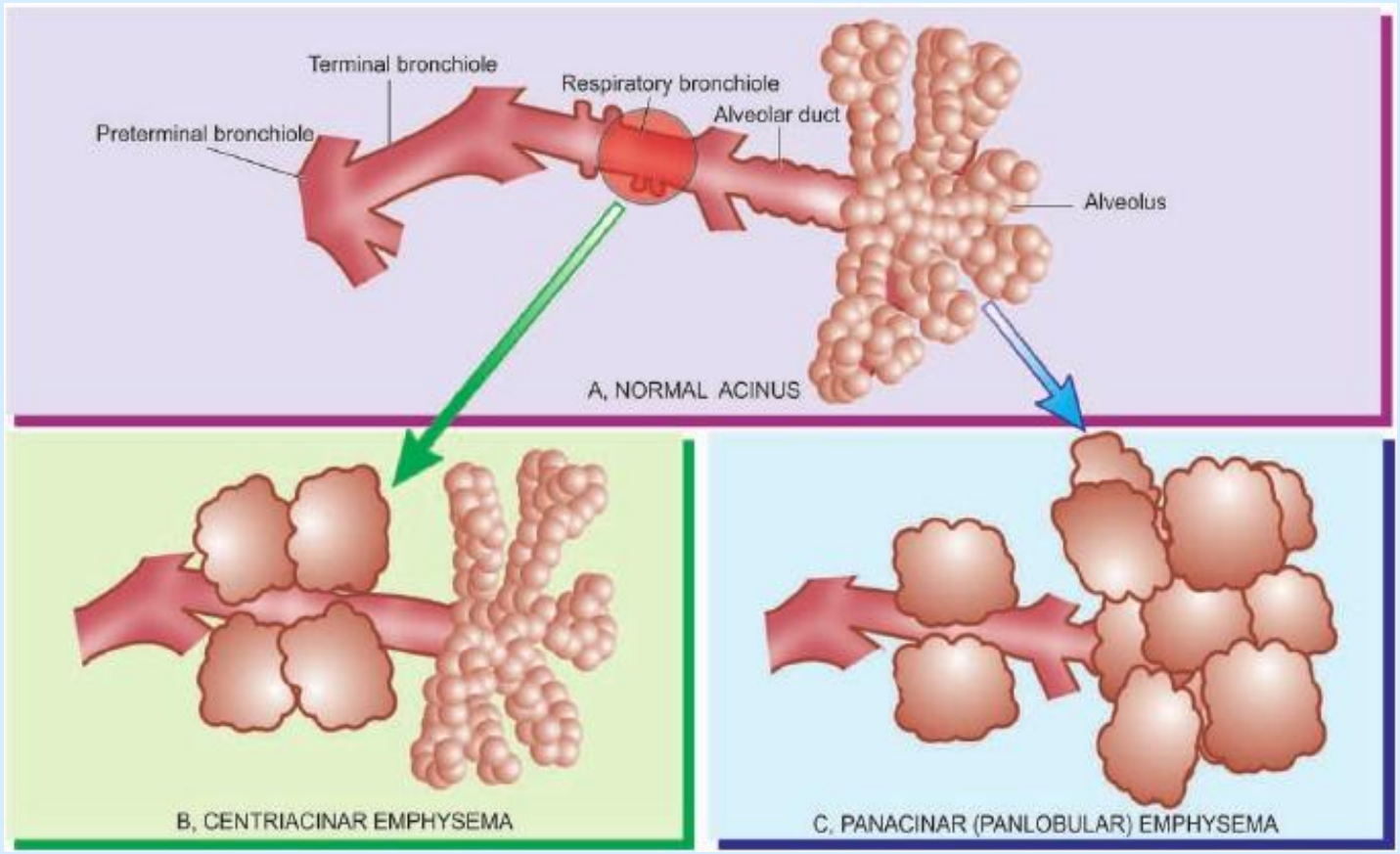
- The involvement is *irregular as regards the portion of the acinus involved as well as within the lung as a whole*.
- *It is almost invariably associated with scarring*, such as that resulting from *healed inflammatory diseases*.
- Although *clinically asymptomatic*, this may be ***the most common form of emphysema*** and may be only an incidental autopsy finding.

❖ Mixed (Unclassified) Emphysema:

- Quite often, *the same lung may show more than one type of emphysema*.
- It is usually due to *more severe involvement resulting in loss of clear-cut distinction between one type of emphysema and the other*.
- Thus, the lungs of an elderly smoker at autopsy may show *continuation of centriacinar emphysema in the upper lobes, panacinar in the lower lobes, and paraseptal emphysema in the subpleural region.*

Obstructive Respiratory Disorders

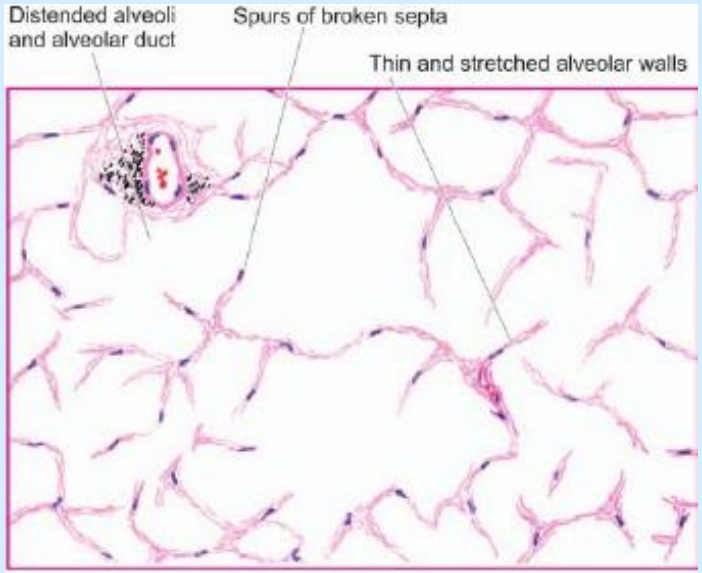
Emphysema

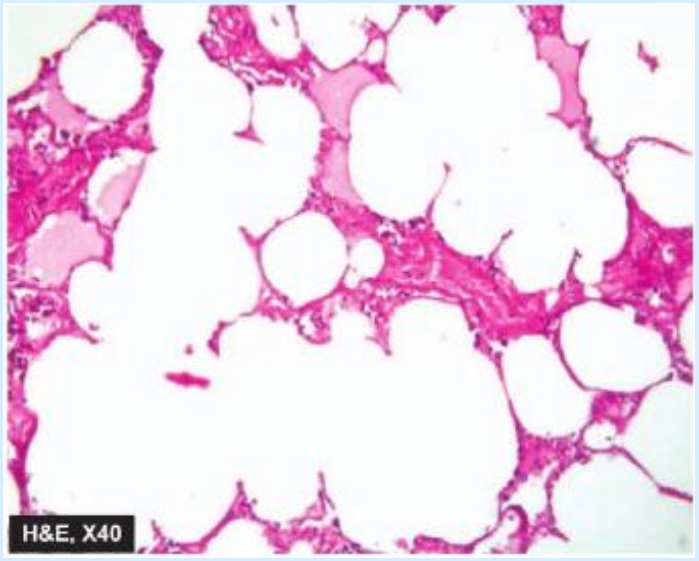


The anatomic regions of involvement in an acinus in major forms of emphysema.

Obstructive Respiratory Disorders

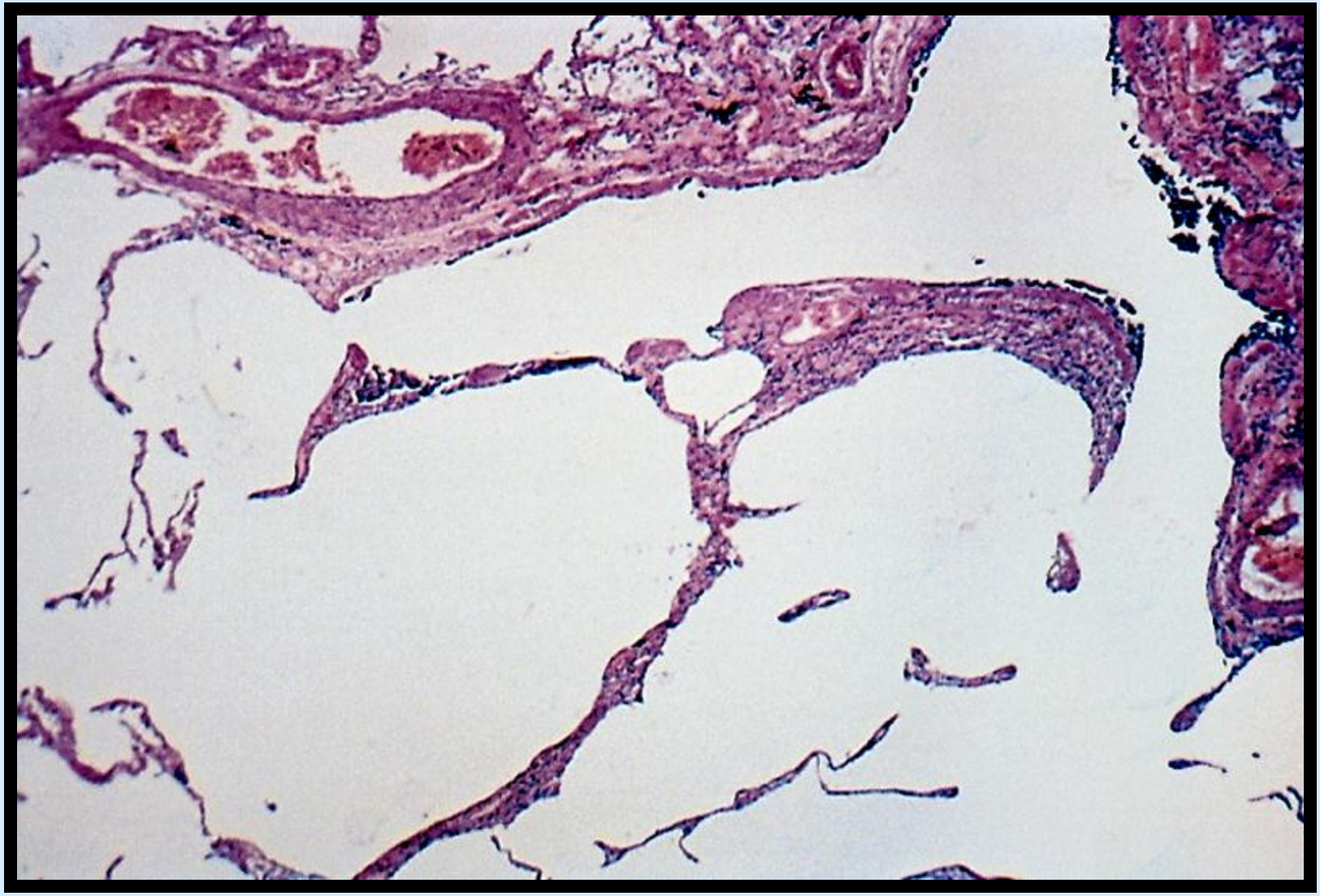
Emphysema





Panacinar (Panlobular) emphysema showing involvement of the entire lobules and whole of acinus.

Emphysema



Clinical Features of Emphysema

- Cases of ***'predominant emphysema'*** *develop clinical features after about one-third of the pulmonary parenchyma is damaged* which occurs most severely in panacinar emphysema.
- The age at the time of diagnosis is often a decade later (about 60 years) than the age for predominant bronchitis (about 50 years).
- Though there is considerable overlap between the clinical features of chronic bronchitis and emphysema, the following features generally characterize ***'predominant emphysema'***:

1. There is long history of slowly increasing severe exertional dyspnea.
2. Patient is quite distressed with obvious use of accessory muscles of respiration.
3. Chest is barrel-shaped and hyperresonant.
4. Cough occurs late after dyspnea starts and is associated with scanty mucoid sputum.
5. Recurrent respiratory infections are not frequent.
6. Patients are called ***'pink puffers'*** as they remain well oxygenated and have tachypnea.

7. Weight loss is common.
8. Features of right heart failure (cor-pulmonale) and hypercapneic respiratory failure are the usual terminal events.
9. Chest X-ray shows small heart with hyper-inflated lungs.

- ***Dyspnea*** *usually is the first symptom; it begins insidiously* but is steadily progressive.
- In patients with underlying chronic bronchitis or chronic asthmatic bronchitis, ***cough and wheezing*** may be the initial complaints.

- Pulmonary function tests reveal ***reduced FEV1*** with ***normal or near-normal FVC***.
- ***Hence, the ratio of FEV1 to FVC is reduced***.
- The classic presentation in emphysema with ***no "bronchitic"*** component is one in which the patient is ***barrel chested*** and ***dyspneic***, with obviously *prolonged expiration, sitting forward in a hunched-over position*, attempting to squeeze air out of the lungs with each expiratory effort.
- In those patients, *air space enlargement is severe and diffusing capacity is low*.

- ***Dyspnea and hyperventilation are prominent***, so that until very late in the disease, ***gas exchange is adequate and blood gas values are relatively normal***.
- Because of *prominent dyspnea and adequate oxygenation of hemoglobin*, those patients are called ***"pink puffers".***
- ***Weight loss*** is common and may be so severe as to suggest a hidden malignant tumor.

- At the other extreme of the clinical presentation in emphysema is a patient who also has ***pronounced chronic bronchitis*** and a history of *recurrent infections with purulent sputum*.
- ***Dyspnea usually is less prominent***, with *diminished respiratory drive*, so the patient ***retains carbon dioxide***, becomes ***hypoxic***, and often is ***cyanotic***.
- For reasons not entirely clear, such patients tend to be ***obese***, hence the designation ***"blue bloaters".***

- Most patients with emphysema and COPD, however, fall somewhere ***between these two classic extremes***.
- In all cases, ***secondary pulmonary hypertension*** develops gradually, *arising from both hypoxia-induced pulmonary vascular spasm and loss of pulmonary capillary surface area from alveolar destruction.*
- ***Death from emphysema*** is related to either ***pulmonary failure***, with respiratory acidosis, hypoxia, and coma, or right-sided heart failure ***(cor pulmonale).***

Contrasting Salient Features of 'Predominant Bronchitis' and 'Predominant Emphysema

- The commonest form of COPD is the combination of chronic bronchitis and pulmonary emphysema.
- *Chronic bronchitis, however, does not always lead to emphysema nor all cases of emphysema have changes of chronic bronchitis.*
- The association of the two conditions is principally linked to the *common etiologic factors* most importantly tobacco smoke and air pollutants.
- Other less significant contributory factors are occupational exposure, infection and somewhat poorly-understood familial and genetic influences.

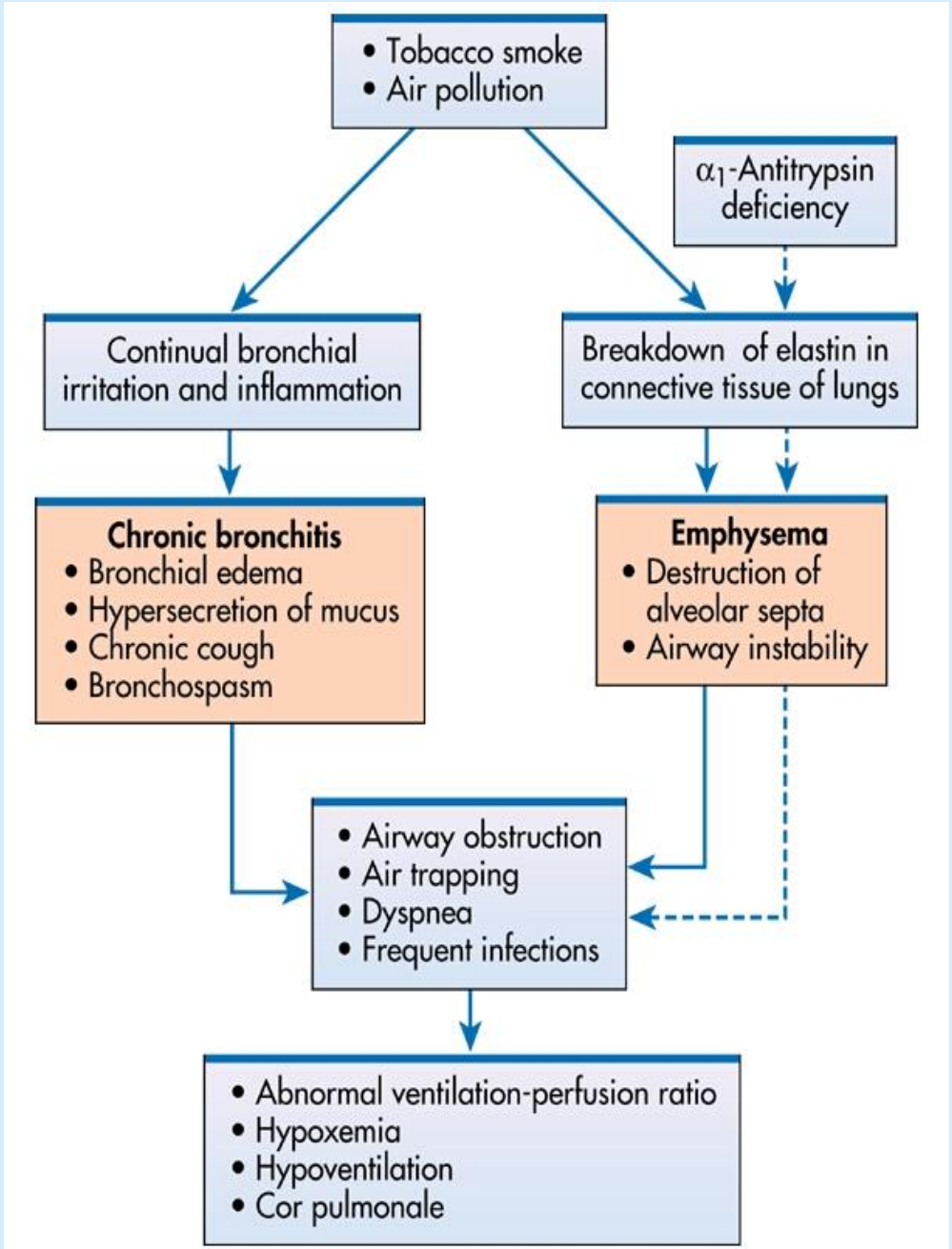
Obstructive Respiratory Disorders
Emphysema

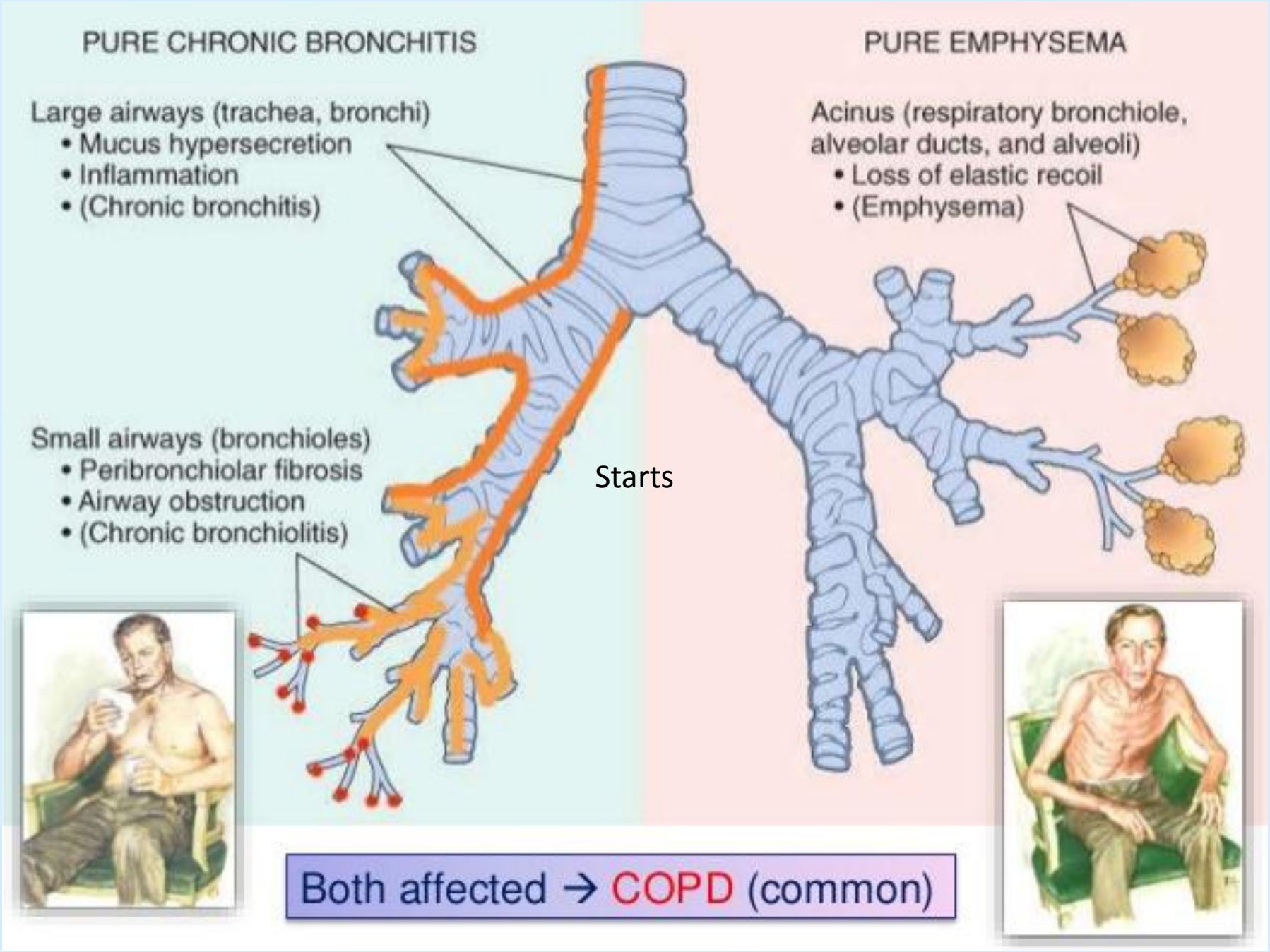
Comparison of Symptoms for
Chronic Bronchitis and Emphysema

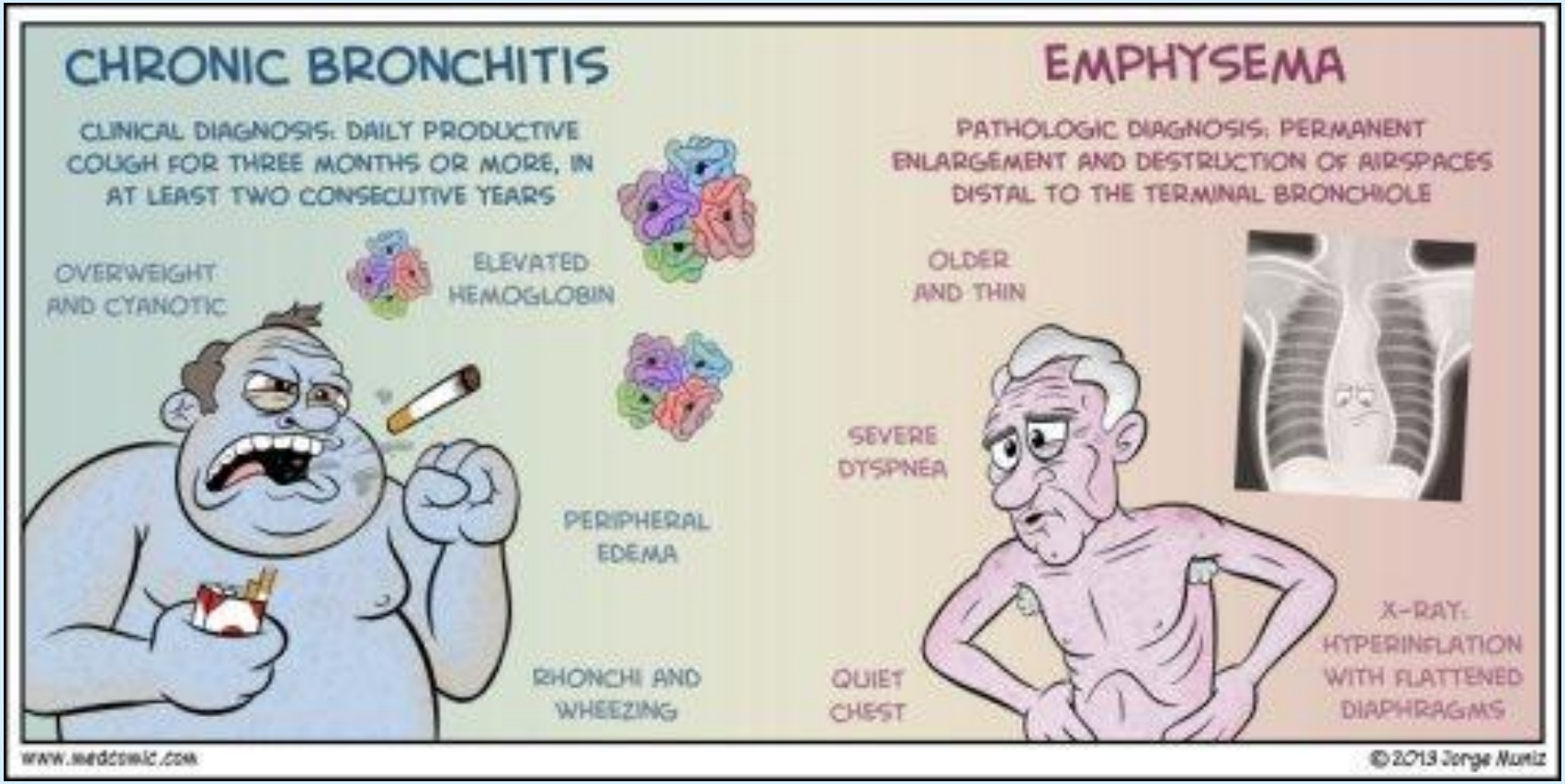
Chronic bronchitis	**Emphysema**
Mild dyspnea	Dyspnea is severe
Productive cough	Dry or no cough
Cyanosis is common	Cyanosis is rare
Respiratory infection is common	Infrequent infections
Onset usually after 40 years of age	Onset usually after 50 years of age
History of cigarette smoking	History of cigarette smoking
Cor-pulmonale is common	Cor-pulmonale in terminal stages

Feature	Predominant Bronchitis	Predominant Emphysema
Age at diagnosis	About 50 years	About 60 years
Underlying pathology	Hypertrophy of mucus-producing cells	Inflammatory narrowing of bronchioles and destruction of septal walls
Dyspnea	Late, mild	Early, severe
Cough	Starts before dyspnea	Starts after dyspnea
Sputum	Copious, purulent	Scanty, mucoid, less frequent
Bronchial infections	More frequent	Less frequent
Respiratory insufficiency	Repeated	Terminal

Feature	Predominant Bronchitis	Predominant Emphysema
Cyanosis	Common (‘blue-bloaters’)	Rare (‘pink-puffers’)
Lung capacity	Normal	Increased (barrel-chest)
Blood gas values	↓pO2 , ↓pCO2, no compensatory Hyperventilation	pO2 and pCO2 usually within normal limits due to compensatory hyperventilation
Cor-pulmonale	Frequent	Rare and terminal
Chest X-ray	Large heart, prominent vessels	Small heart, hyper-inflated lungs




PURE CHRONIC BRONCHITIS
PURE EMPHYSEMA
Large airways (trachea, bronchi)
• Mucus hypersecretion
• Inflammation
• (Chronic bronchitis)
Acinus (respiratory bronchiole, alveolar ducts, and alveoli)
• Loss of elastic recoil
• (Emphysema)
Small airways (bronchioles)
• Peribronchiolar fibrosis
• Airway obstruction
• (Chronic bronchiolitis)
Starts
Both affected → COPD (common)


CHRONIC BRONCHITIS
CLINICAL DIAGNOSIS: DAILY PRODUCTIVE COUGH FOR THREE MONTHS OR MORE, IN AT LEAST TWO CONSECUTIVE YEARS
OVERWEIGHT AND CYANOTIC
ELEVATED HEMOGLOBIN
PERIPHERAL EDEMA
RHONCHI AND WHEEZING
EMPHYSEMA
PATHOLOGIC DIAGNOSIS: PERMANENT ENLARGEMENT AND DESTRUCTION OF AIRSPACES DISTAL TO THE TERMINAL BRONCHIOLE
OLDER AND THIN
SEVERE DYSPNEA
QUIET CHEST
X-RAY: HYPERINFLATION WITH FLATTENED DIAPHRAGMS
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Conditions Related to Emphysema

- Under this heading are covered a group of lung conditions of heterogeneous etiology characterized by overinflation of the parts of acini but without significant destruction of the walls and are sometimes loosely termed emphysema.

1. ***Compensatory emphysema (Compensatory Overinflation)*** is a term used to designate the *compensatory dilation of alveoli in response to loss of lung substance*, such as occurs in residual lung parenchyma after surgical removal of a diseased lung or lobe so as to fill the pleural cavity.

- Histological examination shows dilatation of alveoli but no destruction of septal walls and hence the term "***compensatory overinflation"*** is preferable over 'compensatory emphysema'.

2. *Senile Hyperinflation (Aging Lung, Senile Emphysema)*

- In old people, the lungs become voluminous due to loss of elastic tissue, thinning and atrophy of the alveolar ducts and alveoli.
- The alveoli are thin-walled and distended throughout the lungs but there is no significant destruction of the septal walls and, therefore, the preferable designation is ***'senile hyperinflation'*** over 'senile emphysema.'

2. ***Obstructive Overinflation*** refers to a condition in which *the lung expands because air is trapped within it*.

- A common cause is *subtotal obstruction* by a tumor or foreign object.
- Partial obstruction to the bronchi causes over-inflation of the region supplied by obstructed bronchus.
- Obstructive overinflation is a life-threatening emergency if the affected portion extends sufficiently to compress the remaining normal lung.

- ***Infantile lobar emphysema*** is a variant of obstructive overinflation occurring in infants in the *first few days of life who develop respiratory distress* or who have *congenital hypoplasia of bronchial cartilage*.
- In all such cases, air enters the lungs during inspiration but cannot leave on expiration resulting in ballooning up of the affected part of the lung.

3. *Unilateral Translucent Lung (Unilateral Emphysema):*

- This is a form of overinflation in which one lung or one of its lobes or segments of a lobe are radiolucent.
- The condition occurs in adults and there is generally a history of serious pulmonary infection in childhood, probably bronchiolitis obliterans.
- The affected lung is grossly overinflated.
- Microscopy shows overinflated alveoli and there is histological evidence of preceding widespread bronchiolitis obliterans.

4. ***Mediastinal (Interstitial) Emphysema*** is the condition resulting when *air enters the connective tissue stroma of the lung*, *mediastinum*, and *subcutaneous tissue*.

- This may occur spontaneously with a sudden *increase in intraalveolar pressure* (as with vomiting or violent coughing) resulting in ***a tear, with dissection of air into the interstitium***.
- It may also occur in cases of rupture esophagus, trauma to the lung, or major bronchus and trachea, fractured rib puncturing the lung parenchyma, and in decompression sickness.

- Sometimes it develops in children with whooping cough.
- It is particularly likely to occur ***in patients on respirators*** who have ***partial bronchiolar obstruction***.
- When the interstitial air enters the subcutaneous tissue, *the patient may literally blow up like a balloon*, with marked *swelling of the head and neck and crackling crepitation all over the chest*.
- In most cases, *the air is resorbed spontaneously* after the *site of entry is sealed*.

- ***Bullous emphysema*** refers merely to any form of *emphysema that produces large subpleural blebs or bullae;* spaces greater than 1 cm in diameter in the distended state.
- Such ***blebs*** represent localized accentuations of one of the four forms of emphysema.
- Most often the blebs are ***subpleural***, and on occasion they ***may rupture***, leading to ***pneumothorax***.

Bullous emphysema & Large subpleural bullae

BRONCHIAL ASTHMA

- **Definition:**
- Asthma is a chronic inflammatory airways disease that manifested clinically by paroxysms and recurrent episodes of ***wheezing***, breathlessness, chest tightness, and cough, particularly at night and/or early in the morning.
- However, severe and unremitting form termed ***status asthmaticus*** may prove fatal.

- Asthma is characterized by increased responsiveness of the tracheobronchial tree to a variety of stimuli resulting in widespread spasmodic narrowing of the air passages which may be relieved spontaneously or by therapy.
- Some of the stimuli that trigger attacks in patients have little or no effect in persons with normal airways.
- Asthma occurs at all ages but nearly 50% of cases develop it before the age of 10 years.
- In adults, both sexes are affected equally but in children there is 2:1 male-female ratio.

- The hallmarks of the disease are *intermittent and reversible airway obstruction, chronic bronchial inflammation with eosinophils, bronchial smooth muscle cell hypertrophy and hyperreactivity, and increased mucus secretion.*
- Many cells play a role in the inflammatory response, in particular eosinophils, mast cells, macrophages, lymphocytes, neutrophils, and epithelial cells.

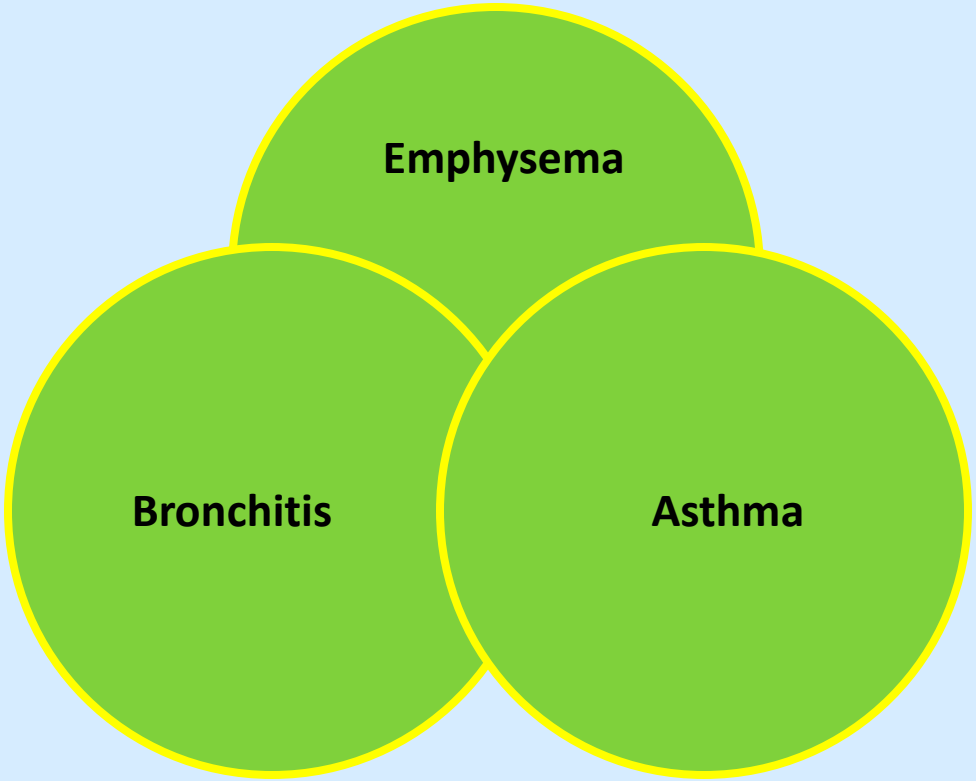
- Based on the stimuli initiating bronchial asthma, two broad etiologic types are traditionally described

1. ***Atopic, extrinsic, or allergic*** *as there is evidence of* allergen sensitization.
- It often occurs in patient with history of allergic rhinitis, eczema, and

2. ***Non-atopic, or intrinsic.***

- *In either type, episodes* of bronchospasm can be triggered by diverse mechanisms, such as respiratory infections especially viral, environmental exposure to irritants e.g., smoke, fumes, cold air, stress, and exercise.

- **A third type is a mixed pattern** in which the features do not fit clearly into either of the two main types.
- There is emerging evidence for differing patterns of inflammation: eosinophilic, neutrophilic, mixed inflammatory, and pauci-granulocytic.
- These subgroups may differ in etiology, immunopathology, and response to treatment.
- Asthma may be classified according to the agents or events that trigger bronchoconstriction.



Chronic obstructive pulmonary diseases

Bronchitis, emphysema, and asthma may present alone or in combination

ETIO-PATHOGENESIS OF BRONCHIAL ASTHMA

- **The major etiologic factors of asthma are:**

A. Genetic predisposition to type I hypersensitivity (atopy),
B. Acute and chronic airway inflammation, and
C. Bronchial hyper-responsiveness to a variety of stimuli.

- The inflammation involves many cell types and numerous inflammatory mediators, but ***the role of type 2 helper T (TH2) cells may be critical to the pathogenesis of asthma.***
- The classic atopic form of asthma is associated with an excessive TH2 reaction against environmental antigens.
- Cytokines produced by TH2 cells account for most of the features of asthma.
- IL-4 stimulates IgE production, IL-5 activates eosinophils, and IL-13 stimulates mucus production and also promotes IgE production by B cells.

- IgE coats submucosal mast cells, which, on exposure to allergen, release granule contents.
- This induces two waves of reaction: ***an early (immediate) phase*** and ***a late phase***.
- ***The early reaction*** is dominated by broncho-constriction, increased mucus production and variable vasodilatation.
- Bronchoconstriction is triggered by direct stimulation of subepithelial vagal receptors.
- ***The late-phase reaction*** consists of inflammation, with activation of eosinophils, neutrophils, and T cells.

- In addition, epithelial cells are activated to produce chemokines that promote recruitment of more TH2 cells and eosinophils (including eotaxin, a potent chemoattractant and activator of eosinophils), as well as other leukocytes, thus amplifying the inflammatory reaction.
- Repeated bouts of inflammation lead to structural changes in the bronchial wall, collectively referred to as ***airway remodeling*****.**

- These changes include *hypertrophy of bronchial smooth muscle and mucus glands, and increased vascularity and deposition of subepithelial collagen,* which may occur as early as several years before initiation of symptoms.
- Asthma is a ***complex genetic disorder*** in which multiple susceptibility genes interact with environmental factors to initiate the pathological reaction.
- There is significant variation in the expression of these genes and in the ***combinations of polymorphisms*** that ***affect the immune response or tissue remodeling***.

- One of the susceptibility loci is on t***he long arm of chromosome 5 (5q),*** where several genes involved in *regulation of IgE synthesis* and *mast cell and eosinophil growth and differentiation map.*
- The genes at this locus *include: IL13 (genetic polymorphisms linked with susceptibility to the development of atopic asthma), CD14 (single-nucleotide polymorphisms associated with occupational asthma), class II HLA alleles (tendency to produce IgE antibodies),* β2-adrenergic receptor gene, and IL-4 receptor gene (atopy, total serum IgE level, and asthma).

- Another important locus is on ***20q where ADAM-33*** that *regulates proliferation of bronchial smooth muscle and fibroblasts* is located; this *controls airway remodeling*.
- *Up-regulation of various chitinase enzymes* is important in TH2 inflammation and severity of asthma; *high serum YKL-40 levels (a chitinase family member with no enzymatic activity)* correlate with *the severity of asthma*.

Types of Asthma

1. Atopic, extrinsic, or allergic

- This is ***the most common*** type of asthma.
- It usually begins in *childhood or in early adult life*.
- Most patients have *personal and/or family history* of preceding *allergic diseases* such as rhinitis, urticaria or infantile eczema.
- Hypersensitivity to various extrinsic antigenic substances or ***'allergens'*** is usually present in these cases.

- Most allergens cause ill-effects by ***inhalation*** e.g. house dust, pollens, animal danders, moulds etc.
- The disease may be triggered by eating some foods e.g., milk, eggs, bananas etc.,.
- Infections can also trigger atopic asthma.
- There are ***increased levels of IgE in the serum*** with the specific offending inhaled antigen representing an *IgE-mediated type I hypersensitivity reaction* which includes an *'acute immediate response'* and a *'late phase reaction'.*
- ***A positive skin test*** with the offending antigen results in an *immediate wheal-and flare reaction*.

- Atopic asthma also can be diagnosed based on serum ***radio-allergo-sorbent tests (RASTs)*** that identify the presence of IgE specific for a panel of allergens.
- ***Occupational asthma*** stimulated by fumes, gases and organic and chemical dusts is a variant of extrinsic asthma.

- **Occupational Asthma**
- This form of asthma is stimulated by fumes (epoxy resins, plastics), organic and chemical dusts (wood, cotton, platinum), gases (toluene), and other chemicals.
- Asthmatic attacks usually develop after repeated exposure to the inciting antigen(s).

2. *Non-atopic, intrinsic or idiosyncratic asthma*

- This type of asthma develops ***later in adult life*** with negative personal or family history of allergy, negative skin test and normal serum levels of IgE.
- Most of these patients develop typical symptoms after URT infection by viruses e.g., rhinovirus, para-influenza virus) and inhaled air pollutants e.g., sulfur dioxide, ozone, nitrogen dioxide.
- *It is thought that virus-induced inflammation of the respiratory mucosa lowers the threshold of the subepithelial vagal receptors to irritants.*

- Associated nasal polypi and chronic bronchitis are commonly present.
- Sometimes there are no recognizable allergens but about 10% of patients become hypersensitive to drugs, most notably to small doses of aspirin (aspirin-sensitive asthma).

- **Drug-Induced Asthma**
- Several pharmacologic agents provoke asthma, *aspirin* being the most striking example.
- Patients with aspirin sensitivity present with recurrent rhinitis and nasal polyps, urticaria, and bronchospasm.
- The precise mechanism remains unknown, but it is presumed that aspirin inhibits the cyclooxygenase pathway of arachidonic acid metabolism without affecting the lipoxygenase route, thereby shifting the balance of production toward leukotrienes that cause bronchial spasm.

Contrasting Features of the Two Major Types of Asthma

Feature	Extrinsic Asthma	Intrinsic Asthma
Age at onset	In childhood	In adult
Personal/family history	Commonly present	Absent
Preceding allergic illness (atopy)	Present (e.g. rhinitis, urticaria, eczema)	Absent
Allergens	Present (dust, pollens, danders etc)	None
Drug hypersensitivity	None	Present (usually to aspirin)
Serum IgE levels	Elevated	Normal
Associated chronic bronchitis, nasal polyps	Absent	Present
Emphysema	Unusual	Common

3. Mixed type of asthma

- Many patients do not clearly fit into either of the above two categories and have mixed features of both.
- Either type of asthma can be precipitated by cold, exercise and emotional stress.

MORPHOLOGY OF BRONCHIAL ASTHMA

- The pathologic changes are similar in both major types of asthma.
- The morphological changes in asthma are described in persons who die of prolonged severe attacks (status asthmaticus) and in mucosal biopsy specimens of persons challenged with allergens, and changes are expected to be similar in non-fatal cases.

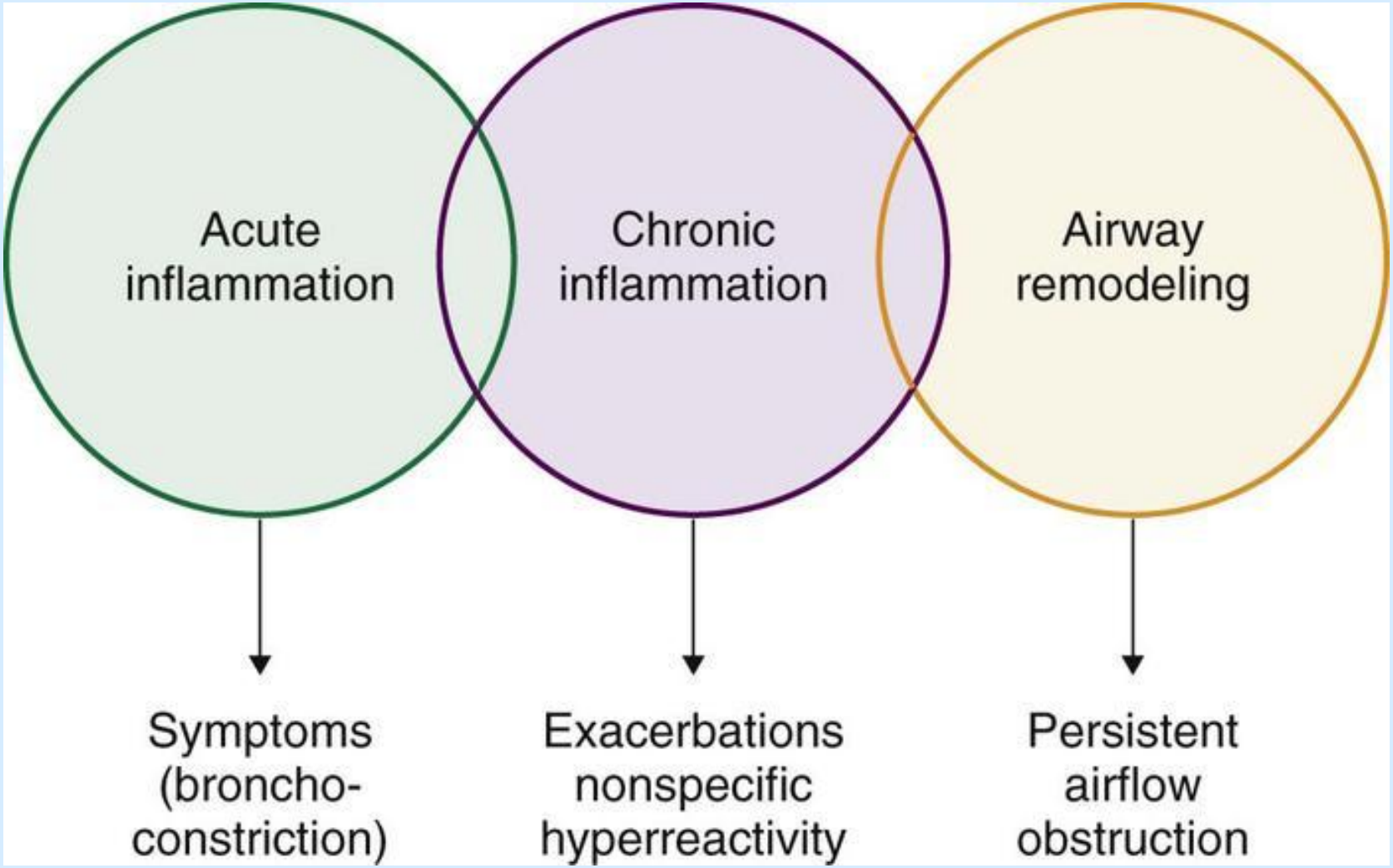
- **Grossly:**
- The lungs are overdistended due to overinflation.
- The most striking macroscopic finding is occlusion of bronchi and bronchioles by ***thick, viscid and tenacious mucous plugs seen in the cut surface.***
- There may be small areas of atelectasis.

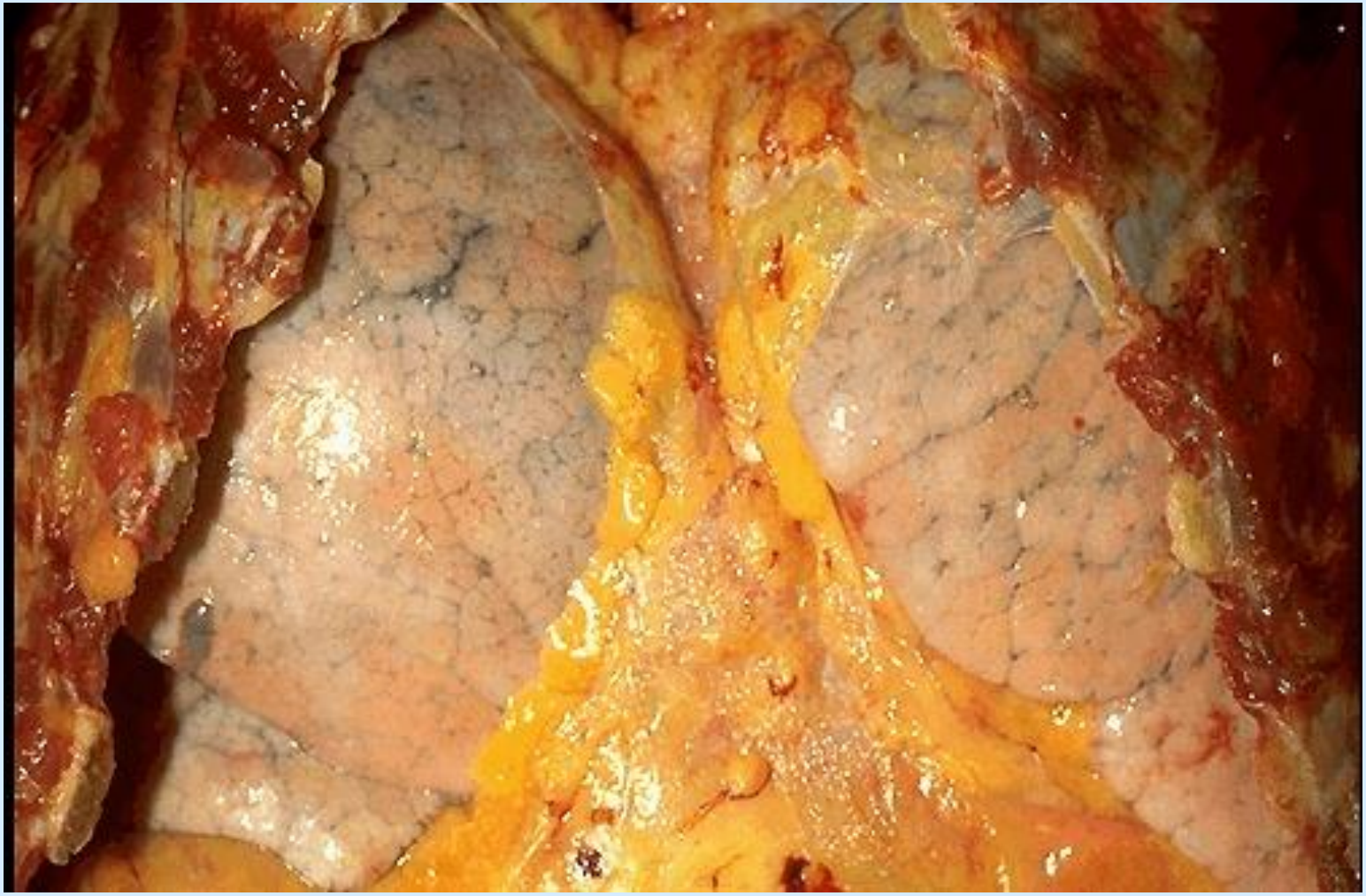
- **Microscopically:**
- The sputum contains numerous eosinophils and diamond-shaped crystals derived from eosinophils called **Charcot- Leyden crystals.**
- The mucus plugs contain normal or degenerated respiratory epithelium forming twisted strips called **(Curschmann spirals).**
- The bronchial wall shows thickened basement membrane of the bronchial epithelium, submucosal edema and inflammatory infiltrate consisting of lymphocytes and plasma cells with prominence of eosinophils.

- There is hypertrophy of submucosal glands as well as of the bronchial smooth muscle.
- Changes of bronchitis and emphysema may supervene, especially in intrinsic asthma.

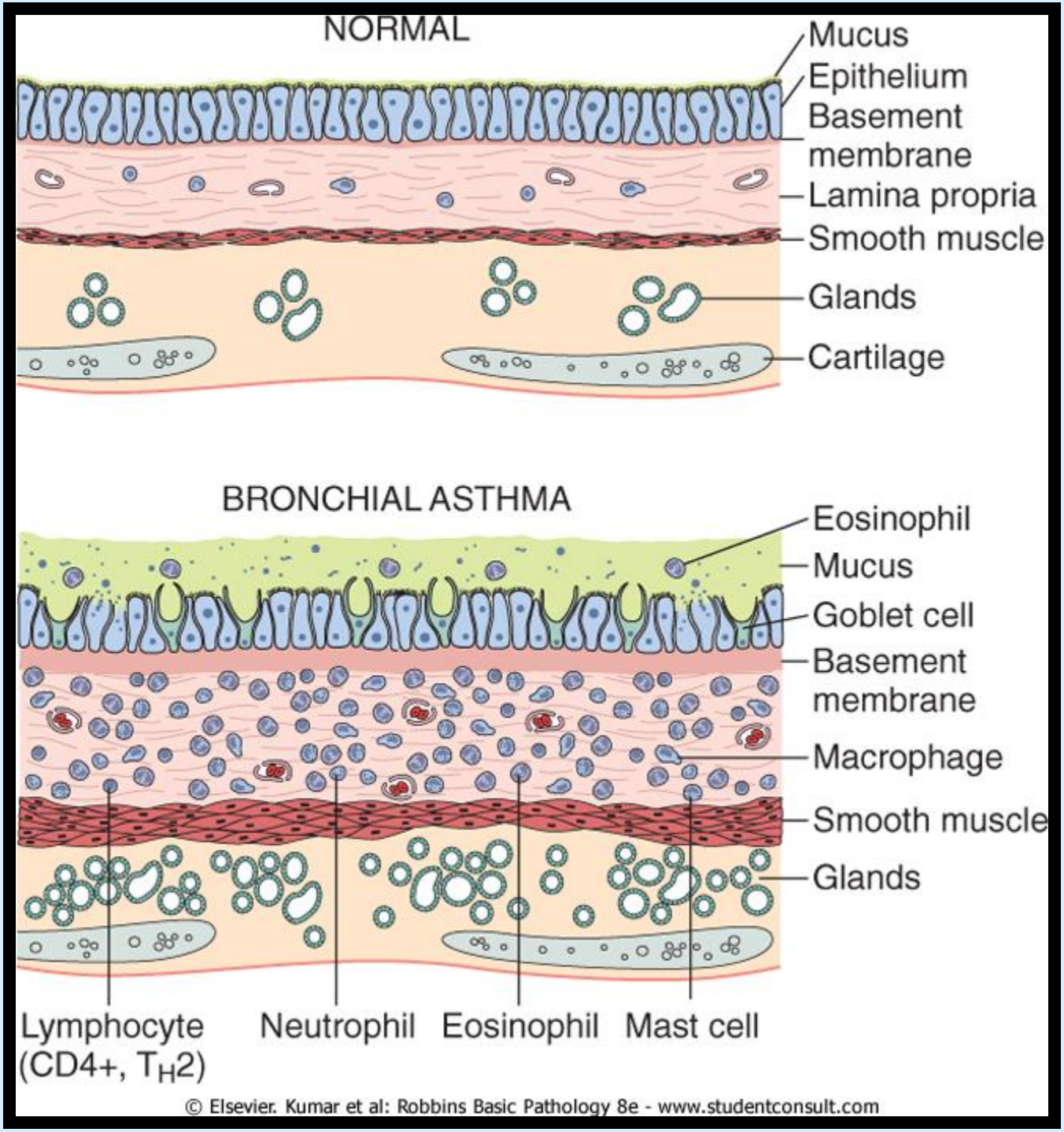
- ***The following are characteristic morphologic changes occurring in asthma, and collectively called "airway remodeling":***

1. Thickening of airway wall
2. Sub-basement membrane fibrosis
3. Increased vascularity in submucosa
4. An increase in size of the submucosal glands and goblet cell metaplasia of the airway epithelium
5. Hypertrophy and/or hyperplasia of the bronchial muscle.

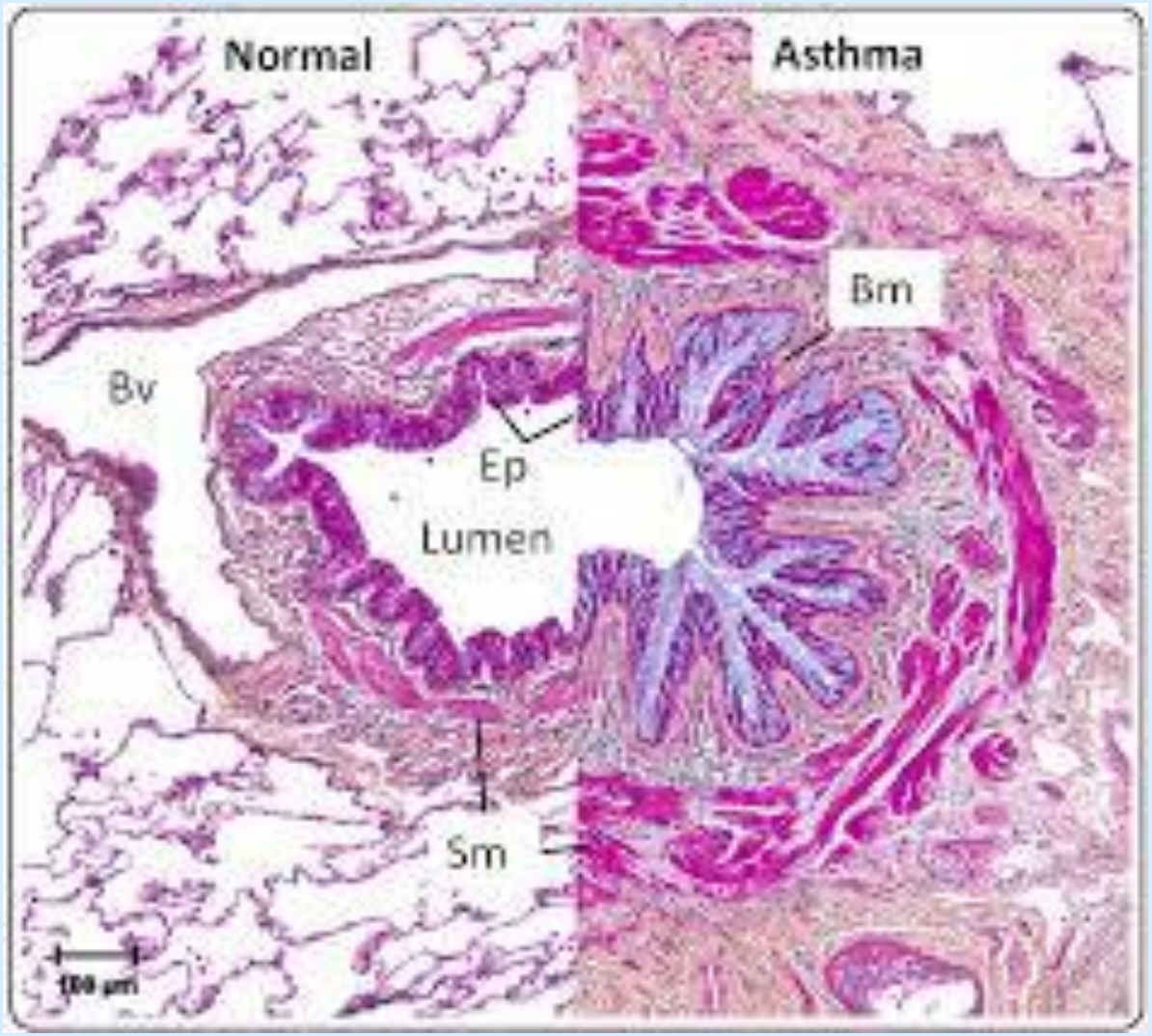

Acute inflammation
Chronic inflammation
Airway remodeling
Symptoms (broncho-constriction)
Exacerbations nonspecific hyperreactivity
Persistent airflow obstruction



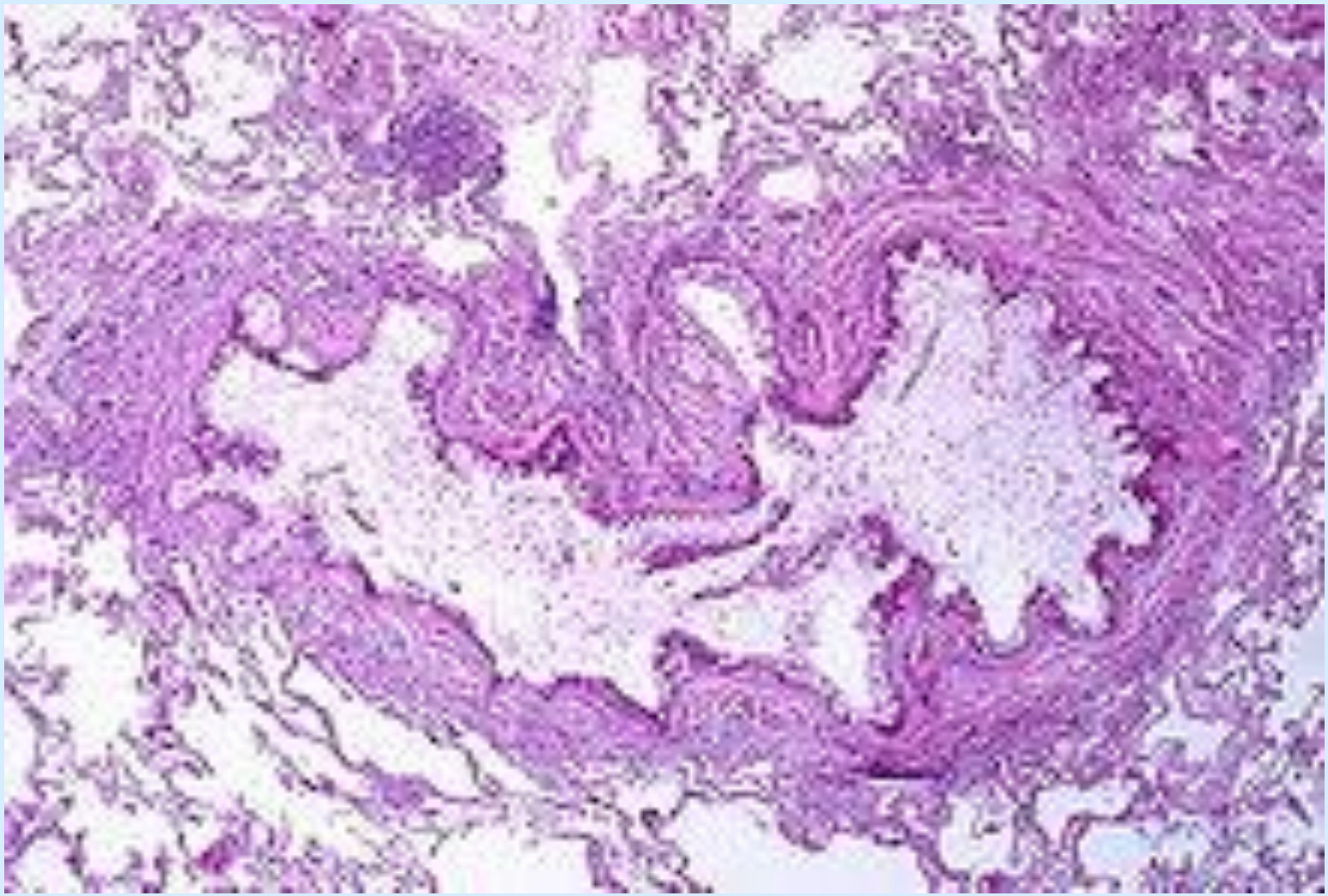
Hyperinflated lungs of a patient who died with status asthmaticus.



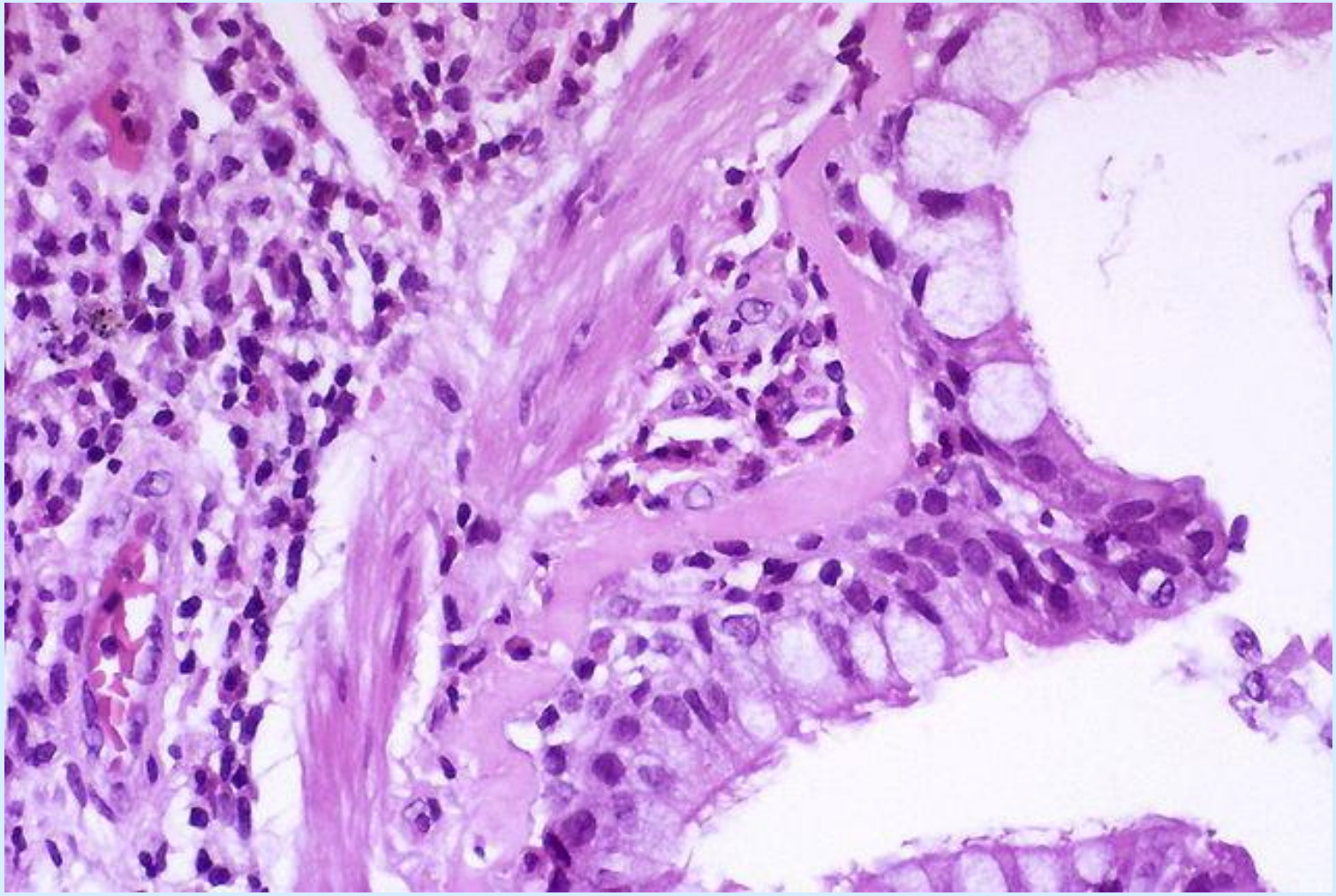
BRONCHIAL ASTHMA



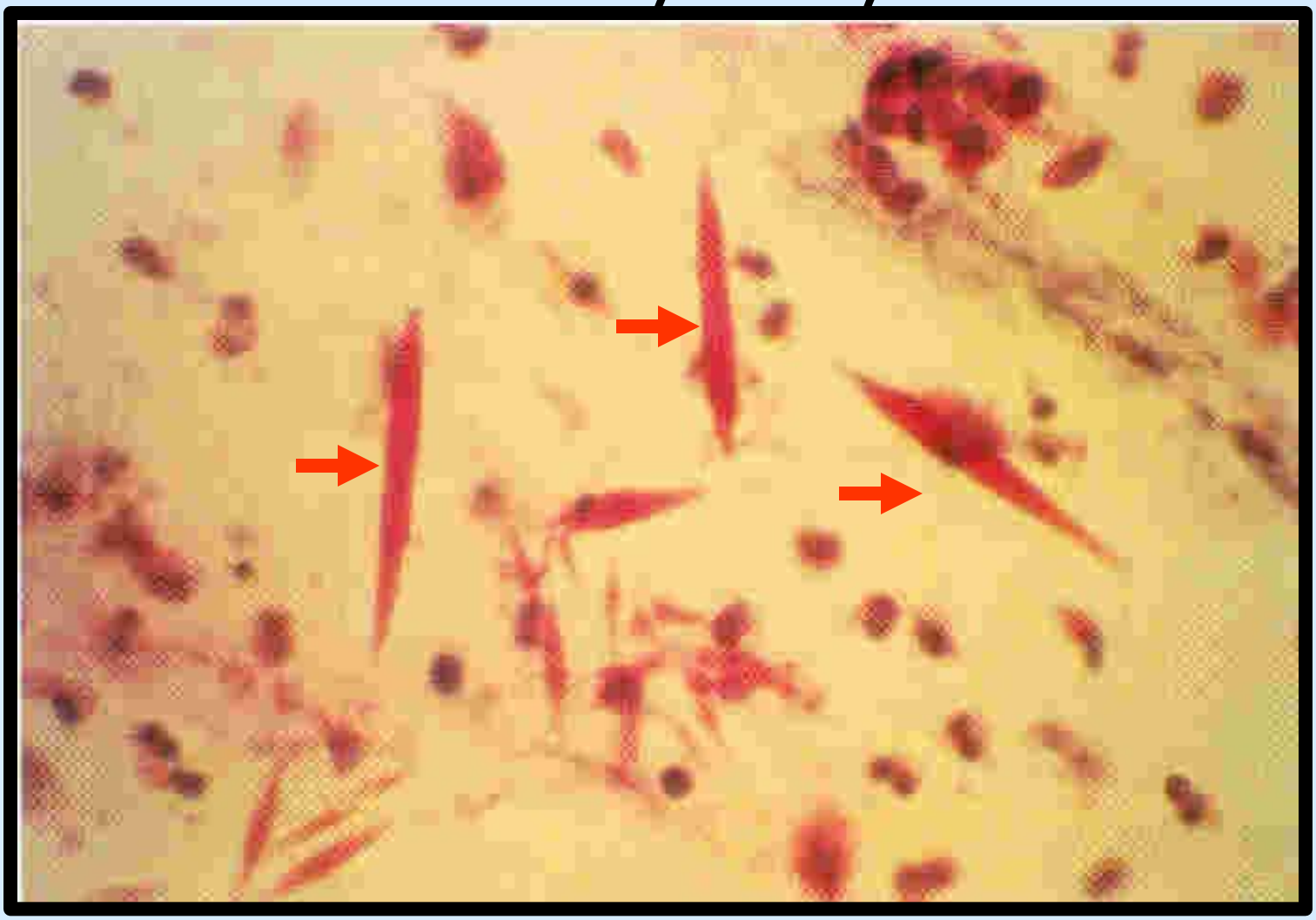
BRONCHIAL ASTHMA



BRONCHIAL ASTHMA



Charcot-Leyden Crystals



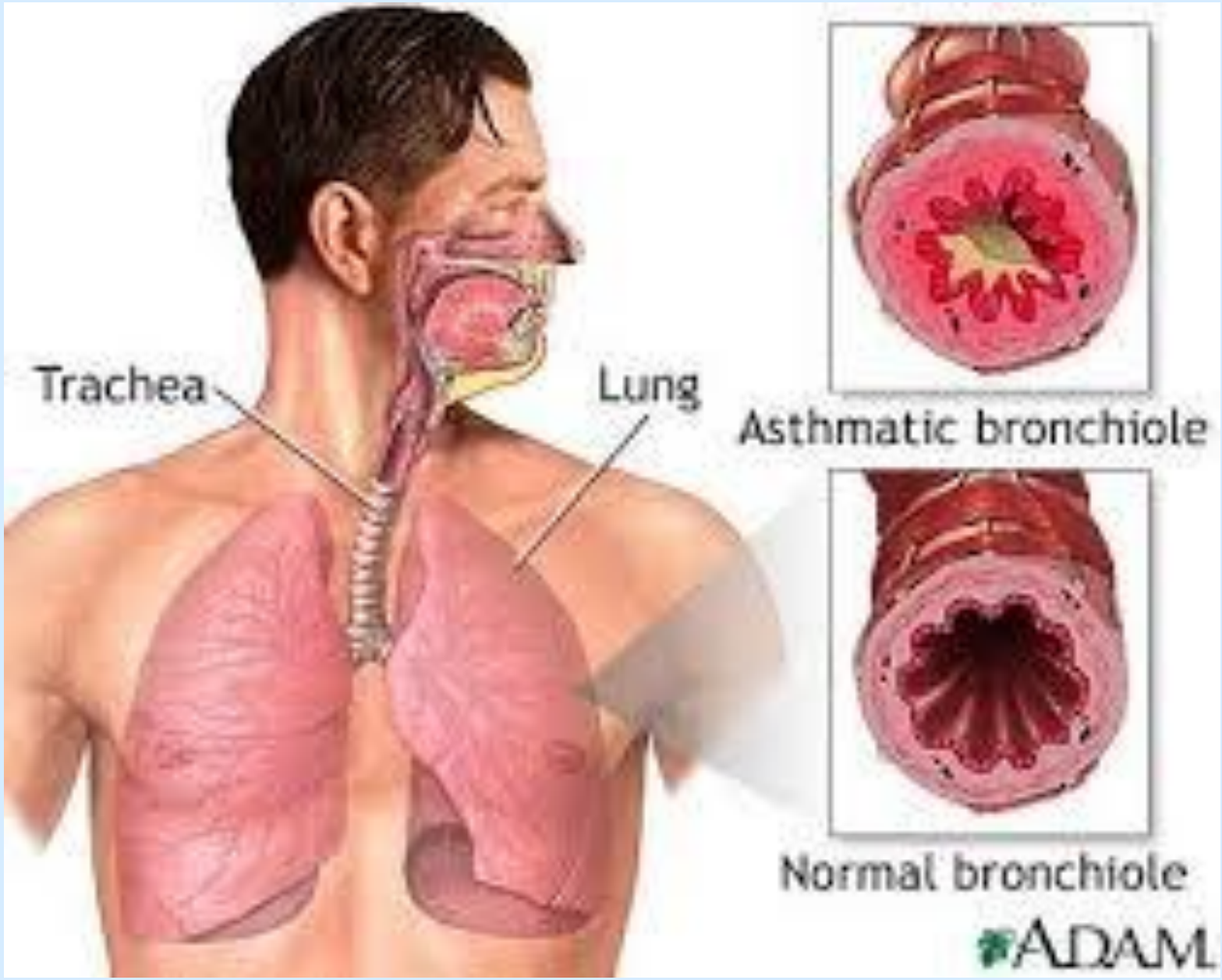
The sputum usually contains numerous eosinophils and diamond-shaped crystals (it formed by the fusion of the eosinophilic particles derived from eosinophils).

CLINICAL FEATURES OF ASTHMA

- An attack of asthma is characterized clinically by ***severe dyspnea cough and wheezing;*** the chief difficulty lies in expiration.
- Patients suffer from episodes of acute exacerbations interspersed with symptom-free periods.
- Most attacks typically last for few minutes to hours, and subside either spontaneously or with therapy, usually bronchodilators and corticosteroids.

- The victim labors to get air into the lungs and then cannot get it out, so that there is progressive hyperinflation of the lungs with air trapped distal to the bronchi, which are constricted and filled with mucus and debris.
- Occasionally severe paroxysm occurs that does not respond to therapy and persists for days and even weeks results in more serious condition called ***status asthmaticus***.
- Intervals between attacks are characteristically free from overt respiratory difficulties, but persistent, subtle deficits can be detected by spirometry.

- The clinical diagnosis is supported by demonstration of circulation eosinophilia and sputum demonstration of Curschmann's spirals and Charcot-Leyden crystals.
- More chronic cases may develop cor-pulmonale.
- *The associated hypercapnia, acidosis,* and severe hypoxia may be fatal, although in most cases the condition is more disabling than lethal.


Trachea
Lung
Asthmatic bronchiole
Normal bronchiole
ADAM

BRONCHIECTASIS

- **Bronchiectasis is defined as** irreversible permanent dilatation of the bronchi and bronchioles developing secondary to inflammatory weakening of the bronchial walls caused by destruction of the muscle and the supporting elastic tissue, resulting chronic necrotizing infections.

- The most characteristic clinical manifestation of bronchiectasis is ***persistent cough*** with ***expectoration of copious amounts of foul-smelling, purulent sputum.***
- Post-infectious cases commonly develop in *childhood and in early adult life.*
- It is not a primary disease but rather secondary to persisting infection or obstruction caused by a variety of conditions.
- Diagnosis depends on an appropriate history along with radiographic demonstration of bronchial dilation.

ETIO-PATHOGENESIS OF BRONCHIECTASIS

- ***The origin of inflammatory destructive process of bronchial walls is nearly always a result of two basic mechanisms, endobronchial obstruction and infection.***
- Endobronchial obstruction by foreign body, neoplastic growth or enlarged lymph nodes causes resorption of air distal to the obstruction with consequent atelectasis and retention of secretions.

- ***Infection*** may be ***secondary*** to local obstruction and impaired systemic defense mechanism promoting bacterial growth, or may be a ***primary*** event i.e. bronchiectasis developing in suppurative necrotising pneumonia.
- **The conditions that most commonly predispose to bronchiectasis include:**

A. Bronchial obstruction.

- *Common causes are tumors, foreign* bodies, and occasionally impaction of mucus.
- Other causes of bronchial obstruction include compression by enlarged hilar lymph nodes and post-inflammatory scarring (e.g., healed tuberculosis).
- Bronchiectasis can also complicate atopic asthma and chronic bronchitis.

- Obstructive bronchiectasis, unlike the congenital-hereditary forms, is usually confined to one part of the bronchial system (localized to the obstructed lung segment).

B. Congenital or hereditary conditions: e.g.,:

1. ***Congenital bronchiectasis*** caused by developmental defect of the bronchial system.
2. ***In cystic fibrosis,*** *widespread severe bronchiectasis* results from obstruction caused by the secretion of abnormally viscid mucus thus predisposing to infections of the bronchial tree. This is an important and serious complication.
3. ***In primary or hereditary immunodeficiency states, particularly immunoglobulin deficiencies,*** localized or diffuse bronchiectasis develop due to increased susceptibility to repeated bacterial infections.

4. ***Immotile cilia syndrome*** including Kartagener's syndrome (bronchiectasis, situs inversus and sinusitis) is characterized by ultrastructural changes in the microtubules causing immotility of cilia, sperms and other cells.
5. ***Kartagener syndrome is a rare autosomal recessive disorder*** that is frequently associated with bronchiectasis and with infertility in males. In this condition, structural abnormalities of the cilia impair mucociliary clearance in the airways, leading to persistent infections, and reduce the mobility of spermatozoa.

C. ***As secondary complication.***

i. ***Atopic bronchial asthma patients*** have often positive family history of allergic diseases and may rarely develop diffuse bronchiectasis.

ii. ***Necrotizing, or suppurative, pneumonia,*** *with* virulent organisms such as *Staphylococcus aureus or Klebsiella spp., may predispose affected patients to the* development of bronchiectasis.

iii. ***Post-tuberculosis bronchiectasis*** is a significant cause of morbidity in endemic areas.

MORPHOLOGY OF BRONCHIECTASIS

- ***The disease characteristically affects distal bronchi and bronchioles,*** *particularly those air passages that are most* ***vertical.***
- The airways may be **dilated to as much as four times their usual diameter.**
- Usually, the most severe involvement is found in the *more distal bronchi and bronchioles.*

- ***Grossly:***
- The lungs may be involved diffusely or segmentally.
- Bilateral involvement of lower lobes occurs most frequently.
- More vertical air passages of left lower lobe are more often involved than the right.
- The pleura is usually fibrotic and thickened with adhesions to the chest wall.
- When caused by tumors or aspiration of foreign bodies the involvement may be ***sharply localized to a single segment of the lungs.***

- On ***gross examination*** of the lung the airways can be followed almost to the pleural surfaces.
- By contrast, in ***normal lungs,*** the bronchioles cannot be followed by ordinary gross examination beyond a point 2 to 3 cm from the pleural surfaces.

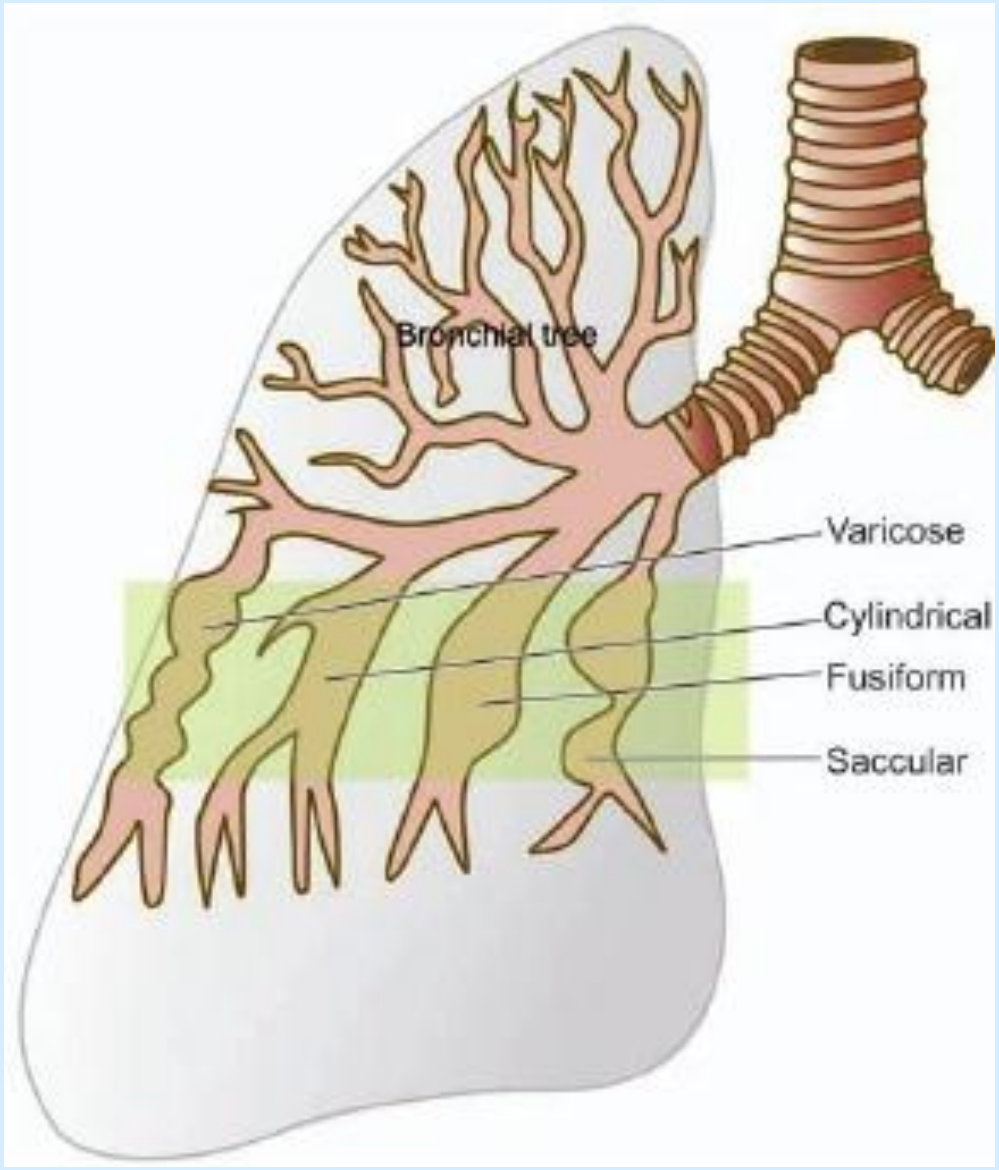
- The dilated airways, depending upon their gross or bronchographic appearance, have been **sub-classified into the following different types:**

A. **Cylindrical**: They are the most common type. It is characterized by tube-like bronchial dilatation.

B. **Fusiform:** They have spindle-shaped bronchial dilatation.

C. **Saccular:** They have rounded sac-like bronchial distension.

D. **Varicose:** They have irregular bronchial enlargements.



Types of bronchial dilatations in bronchiectasis

- ***Cut surface of the affected lobes,*** generally the lower zones, shows characteristic honey-combed appearance.
- The bronchi are extensively dilated nearly to the pleura.
- Their walls are thickened and the lumina are filled with mucus or muco-pus.
- The intervening lung parenchyma is reduced and
- fibrotic.

- **Microscopically:**
- The ***histological findings*** vary with the activity and chronicity of the disease.

1. The bronchial epithelium may be normal, ulcerated or may show squamous metaplasia.
2. The bronchial wall shows infiltration by acute and chronic inflammatory cells and destruction of normal muscle and elastic tissue with replacement by fibrosis.
3. The intervening lung parenchyma shows fibrosis, while the surrounding lung tissue shows changes of interstitial pneumonia.

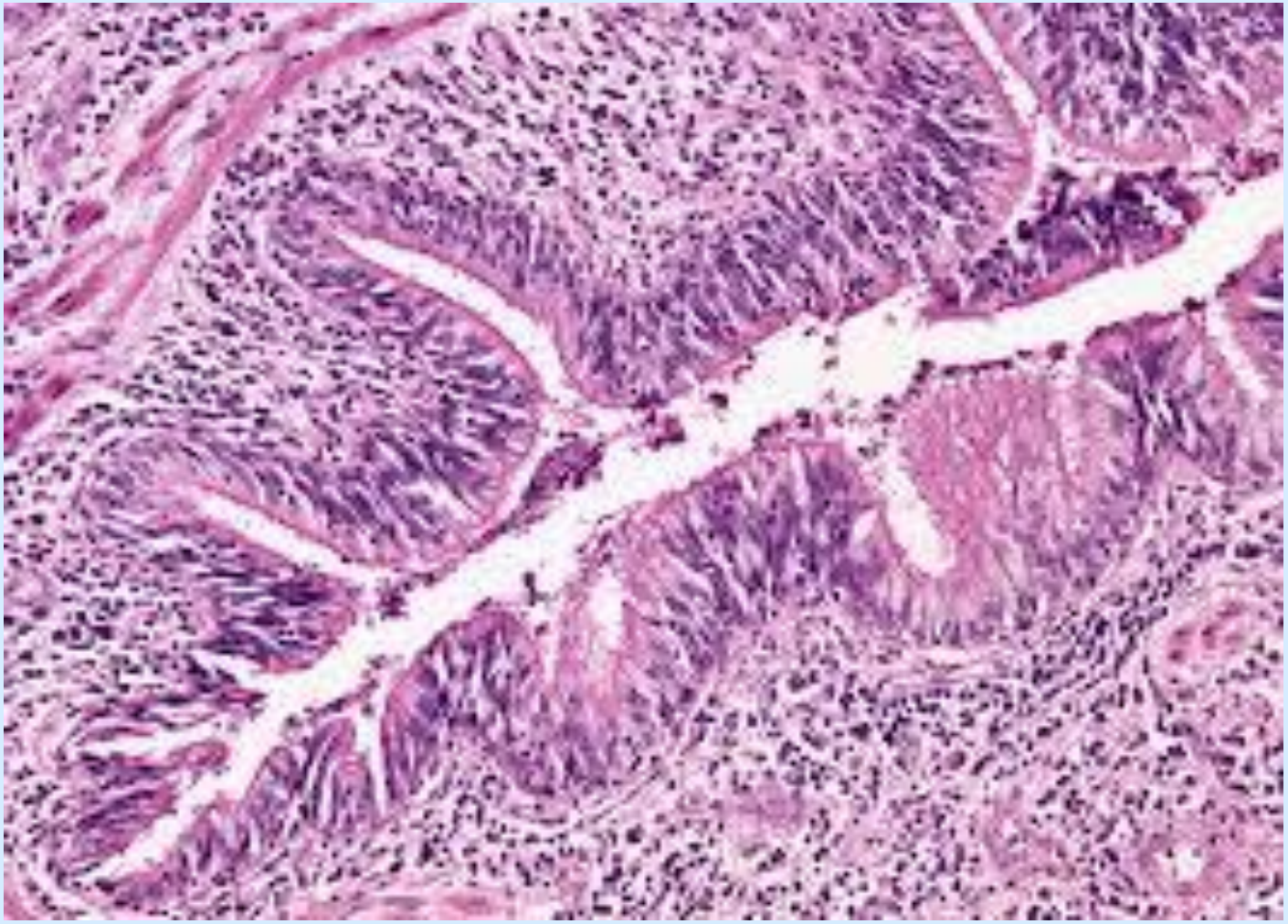
4. The pleura in the affected area is adherent and shows bands of fibrous tissue between the bronchus and the pleura.

- In the full-blown active case, an **intense acute and chronic inflammatory exudate within the walls of the bronchi and bronchioles and the desquamation** of lining epithelium cause extensive areas of ulceration.

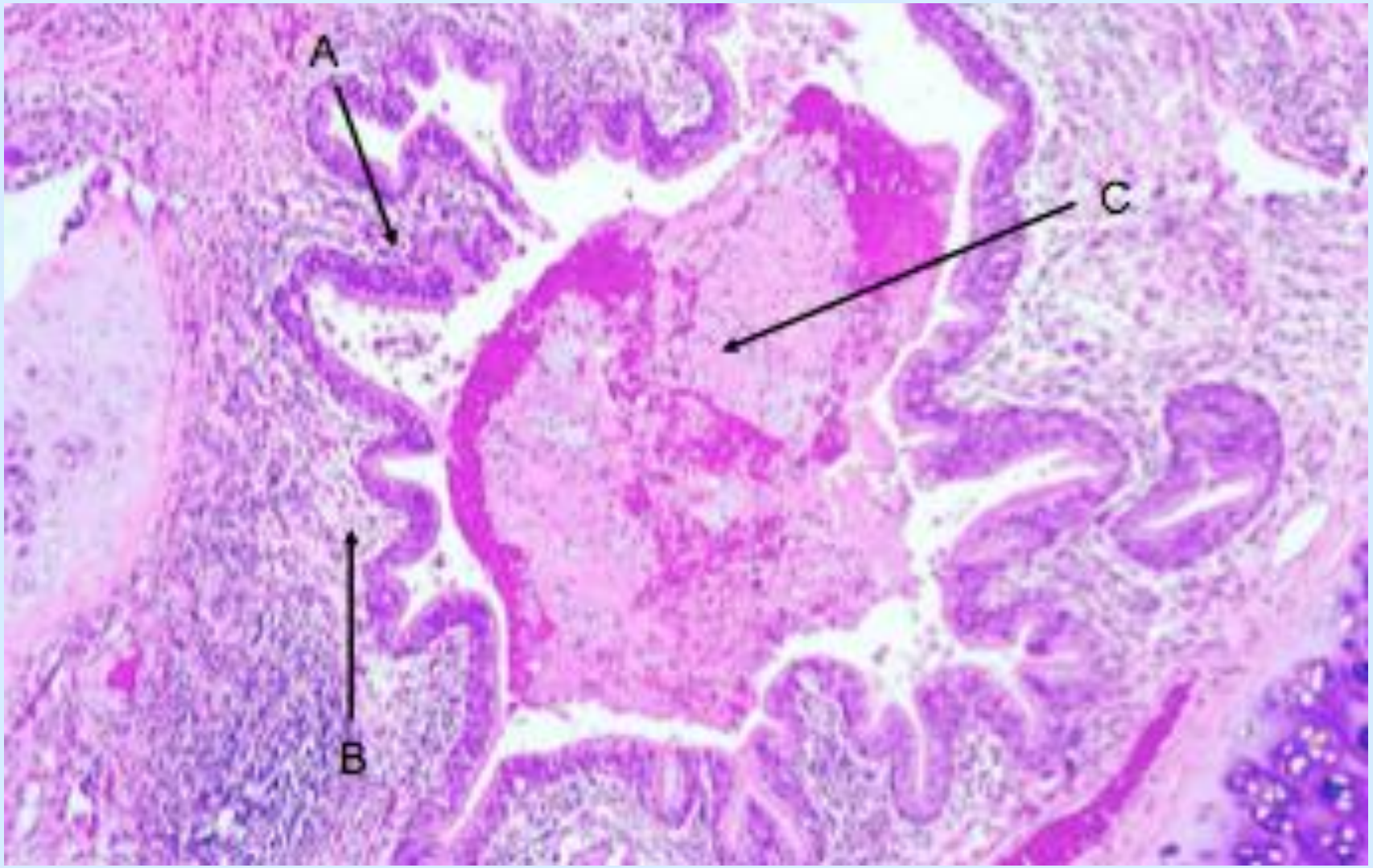
- In the usual case, a **mixed flora can be cultured from the involved** bronchi, including staphylococci, streptococci, pneumococci, enteric organisms, anaerobic and micro-aerophilic bacteria, and (particularly in children) *Hemophilus influenzae and Pseudomonas aeruginosa.*
- *When healing occurs, the lining epithelium* may regenerate completely; however, usually abnormal dilation and scarring persist.

- Fibrosis of the bronchial and bronchiolar walls and **peribronchiolar fibrosis develop in more chronic cases.**
- In some instances, the necrosis destroys the bronchial or bronchiolar walls resulting in the formation of an abscess cavity within which a fungus ball may develop.

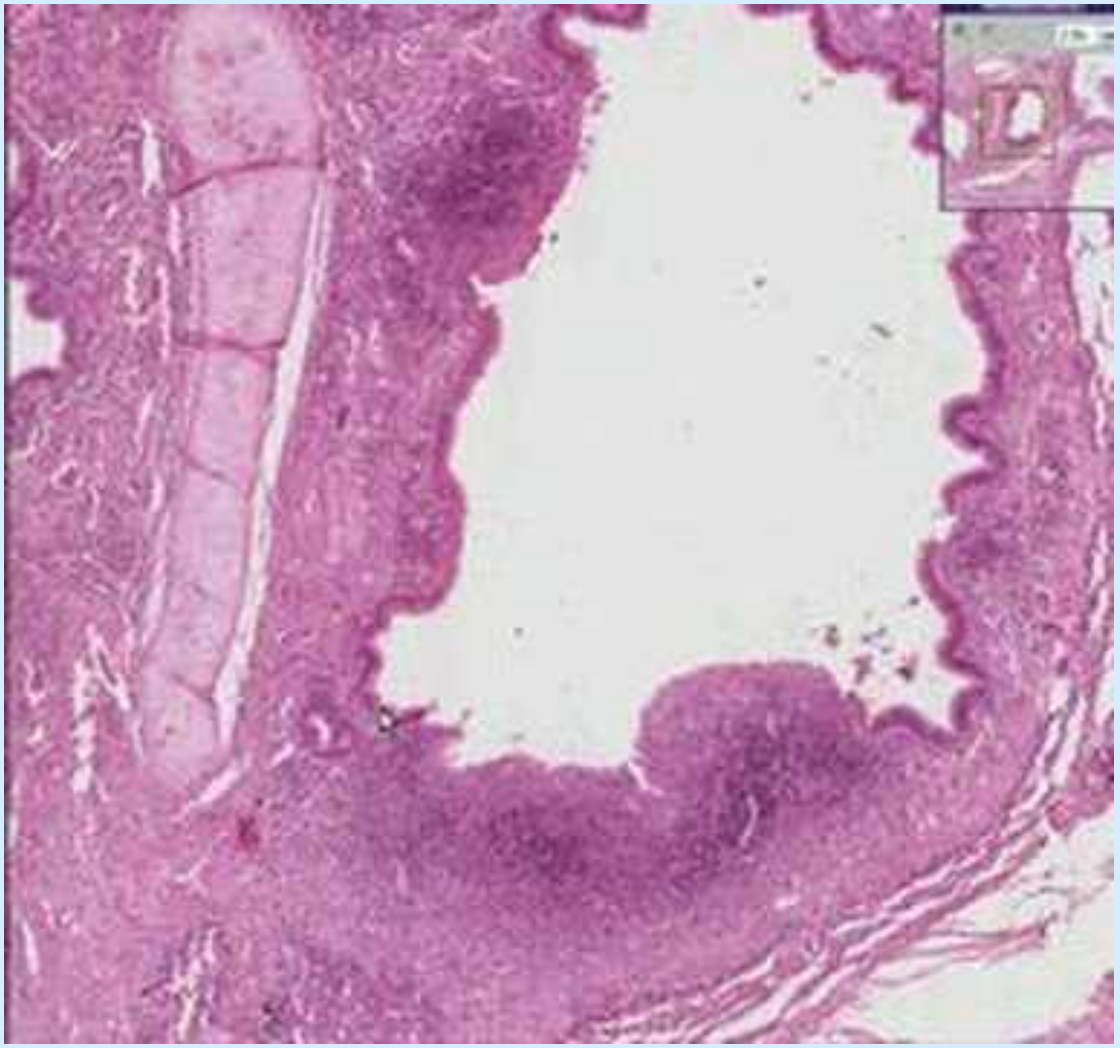
BRONCHIECTASIS



BRONCHIECTASIS



BRONCHIECTASIS



CLINICAL FEATURES OF BRONCHIECTASIS

- The clinical manifestations of bronchiectasis typically consist of ***chronic cough with foul-smelling sputum production, hemoptysis and recurrent pneumonia.***
- Symptoms are episodic and are precipitated by URT infections or introduction of new pathogenic agents.
- Clubbing of the fingers may develop.
- **Sinusitis** is commonly accompanying diffuse bronchiectasis.

- **Late complications** occurring in cases uncontrolled for years include development of amyloidosis, metastatic abscesses to the brain.
- In cases of severe, widespread bronchiectasis, significant obstructive ventilatory defects are usual, with hypoxemia, hypercapnia, pulmonary hypertension, and rarely cor-pulmonale.


THANK YOU