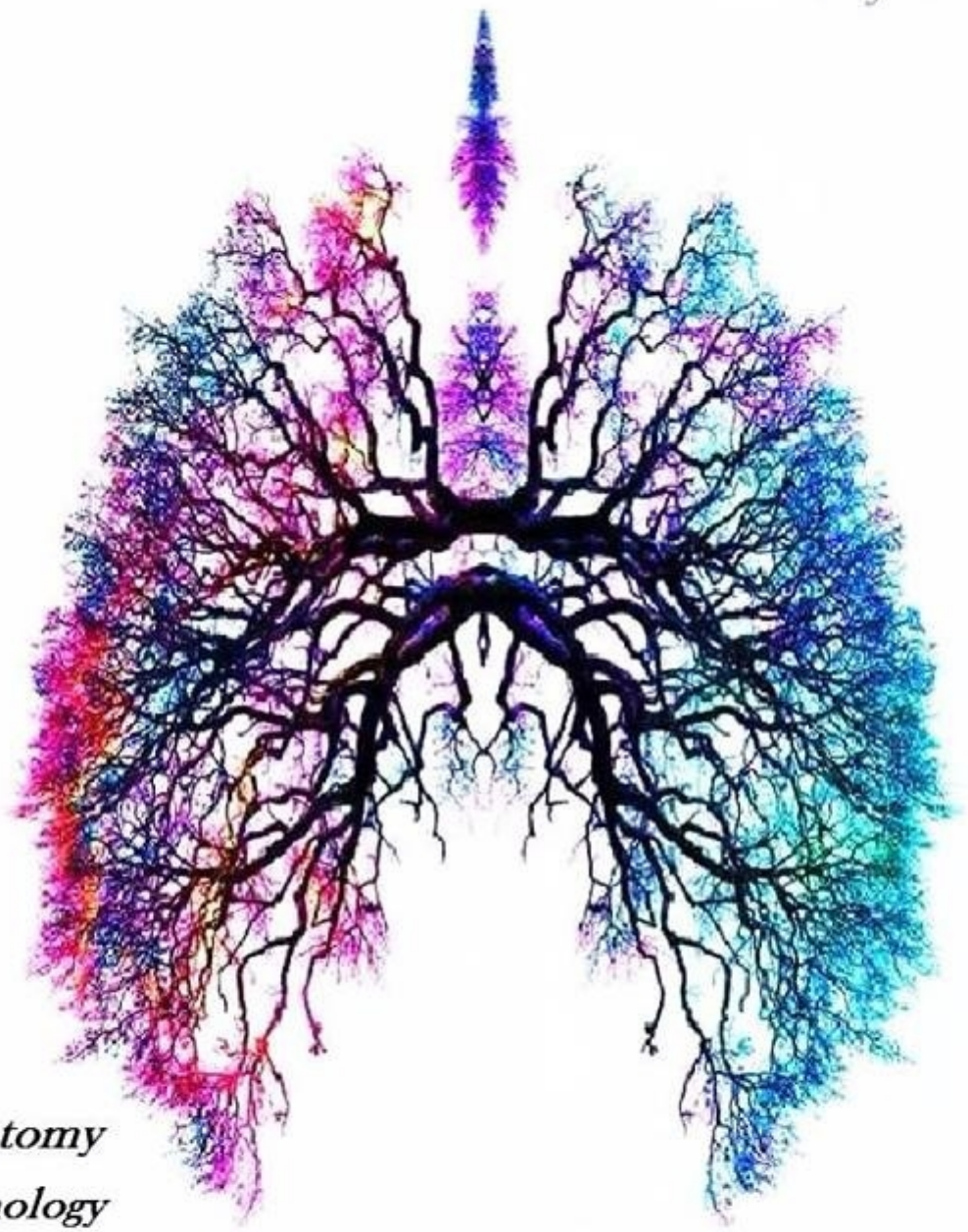
RESPIRATORY SYSTEM

Cover by: Aseil Khatib



- ○ Anatomy
- ● Pathology
- ○ Physiology
- ○ Pharmacology
- ○ Microbiology
- ○ PBL

Dr Name: Fatimah Obeidat

Lecture # 3

Sheet ☐

Slide ■

Other ☐

2. Chronic Bronchitis

- Is common among cigarette smokers and urban dwellers
- The diagnosis of chronic bronchitis is made on clinical grounds:
- It is defined by the presence of a persistent productive cough for at least 3 consecutive months in at least 2 consecutive years.

Note

-In early stages of the disease, the productive cough raises mucoid sputum, but airflow is not obstructed.

- Some patients with chronic bronchitis may have hyper-responsive airways with intermittent bronchospasm and wheezing.

- A subset of bronchitic patients, especially heavy smokers, develop chronic outflow obstruction, usually with associated emphysema

PATHOGENESIS

- The distinctive feature of chronic bronchitis is hypersecretion of mucus, beginning in the large airways.
- Although the single most important cause is cigarette smoking, other air pollutants, such as sulfur dioxide and nitrogen dioxide, may contribute.

- These environmental irritants

a. Induce hypertrophy of mucous glands in the trachea and main bronchi,

b. Marked increase in mucin-secreting goblet cells in the surface epithelium of smaller bronchi and bronchioles.

C. Infiltration of CD8+ lymphocytes, neutrophils but no eosinophils

- It is postulated that many of the respiratory epithelial effects of environmental irritants (mucus hypersecretion) are mediated by local release of T-cell cytokines such as IL-13.
- The transcription of the mucin gene *MUC5AC* in bronchial epithelium is a consequence of exposure to tobacco smoke.

Note

- 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 –(chronic bronchiolitis) is** induced by:

a. Goblet cell metaplasia with mucous plugging of the bronchiolar lumen,

b. Inflammation,

c. Bronchiolar wall fibrosis,

(2) **Coexistent emphysema**

.

Note

- Small airway disease (chronic bronchiolitis) is an important component of early and relatively mild airflow obstruction,
- Significant airflow obstruction is almost always caused by emphysema - chronic bronchitis with

MORPHOLOGY

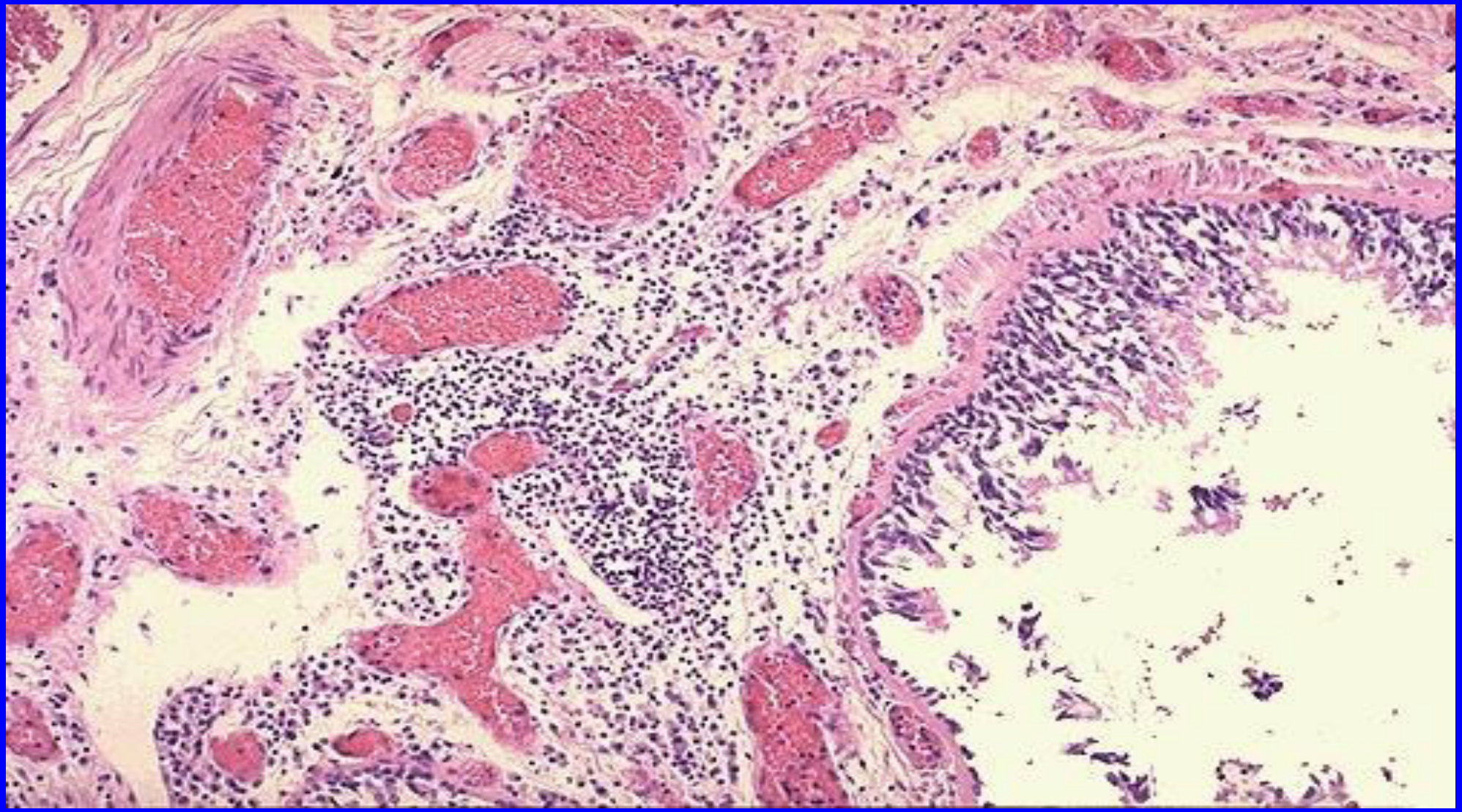
Gross:

- Hyperemia and swelling of the mucosal lining of the large airways.
- The mucosa of bronchi is covered by a layer of mucinous or mucopurulent secretions

On histologic examination

- Enlargement of the mucus-secreting glands in trachea and large bronchi.
- The magnitude of the increase in size is assessed by the ratio of the thickness of the submucosal gland layer to that of the bronchial wall (the Reid index-normally 0.4).

Chronic bronchitis



- Inflammatory cells, largely mononuclear but sometimes admixed with neutrophils, are frequently present in variable density in the bronchial mucosa .

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- It is the submucosal fibrosis that leads to luminal narrowing and airway obstruction.
- Changes of emphysema often co-exist

Clinical Features

- In patients with chronic bronchitis, a prominent cough and the production of sputum may persist indefinitely without ventilatory dysfunction
- Some patients develop significant COPD with outflow obstruction.

- This clinical syndrome is accompanied by hypercapnia, hypoxemia, and (in severe cases) cyanosis (hence the term "blue bloaters").
- With progression, chronic bronchitis is complicated by pulmonary hypertension and cardiac failure .
- Recurrent infections and respiratory failure are constant threats.

3. Asthma

- Asthma is a chronic inflammatory disorder of the airways that causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and/or early in the morning.

The hallmarks of the disease are

1. Intermittent and reversible airway obstruction,
2. Chronic bronchial inflammation with eosinophils,
3. Bronchial smooth muscle cell hypertrophy and hyperreactivity,
4. Increased mucus secretion.

1. Atopic Asthma

- This is the most common type of asthma,
- Usually beginning in childhood,
- Is a classic example of type I IgE-mediated hypersensitivity reaction

- A positive family history of atopy and/or asthma is common,
- Asthmatic attacks are often preceded by allergic rhinitis, urticaria, or eczema.
- The disease is triggered by environmental antigens, such as dusts, pollen, and foods

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- A skin test with the offending antigen results in an immediate wheal-and-flare reaction.
- Atopic asthma also can be diagnosed based on serum radioallergosorbent tests (RASTs) that identify the presence of IgE specific for a panel of allergens.

2. Non-Atopic Asthma

- No evidence of allergen sensitization,
- Skin test results usually are negative.
- A positive family history of asthma is less common.

d. Respiratory infections due to viruses (e.g., rhinovirus, parainfluenza virus) and inhaled air pollutants (e.g., sulfur dioxide,) are common triggers.

- It is thought that virus-induced inflammation of the respiratory mucosa lowers the threshold of the subepithelial vagal receptors to irritants.

Note:

-Although the connections are not well understood, the ultimate humoral and cellular mediators of airway obstruction (e.g., eosinophils) are common to both atopic and nonatopic variants of asthma, so they are treated in a similar way.

3. 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.

PATHOGENESIS

- The major etiologic factors of asthma are:

1. Genetic predisposition to type I hypersensitivity (atopy)
2. Acute and chronic airway inflammation,
3. and bronchial hyperresponsiveness to a variety of stimuli.

- **Role of type 2 helper T (T_H2) cells may be critical to the pathogenesis of asthma.**
- The classic atopic form of asthma is associated with an excessive T_H2 reaction against environmental antigens.

- Cytokines produced by T_H2 cells account for most of the features of asthma

a. IL-4 stimulates IgE production,

b. IL-5 activates eosinophils,

c. IL-13 stimulates mucus production and also promotes IgE production by B cells

4. 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

- Early reaction is dominated by

a. Bronchoconstriction, triggered by direct stimulation of subepithelial vagal receptors

b. Increased mucus production and

c. Vasodilation.

The late-phase reaction consists of inflammation, with

a. Activation of eosinophils, neutrophils, and T cells.

b. Epithelial cells are activated to produce chemokines that promote recruitment of more T_H2 cells and eosinophils (including eotaxin, a potent chemoattractant and activator of eosinophils),

- Repeated bouts of inflammation lead to structural changes in the bronchial wall, referred to as **airway remodeling.**
- These changes include

1. Hypertrophy of bronchial smooth muscle and mucus glands,
2. Deposition of subepithelial collagen, which may occur as early as several years before initiation of symptoms.

MORPHOLOGY

- The morphologic changes in asthma have been described in persons who die of prolonged severe attacks (status asthmaticus) and in mucosal biopsies of persons challenged with allergens

Gross:

- The most striking macroscopic finding is occlusion of bronchi and bronchioles by thick, mucous plugs.

Mucus plug of Asthma

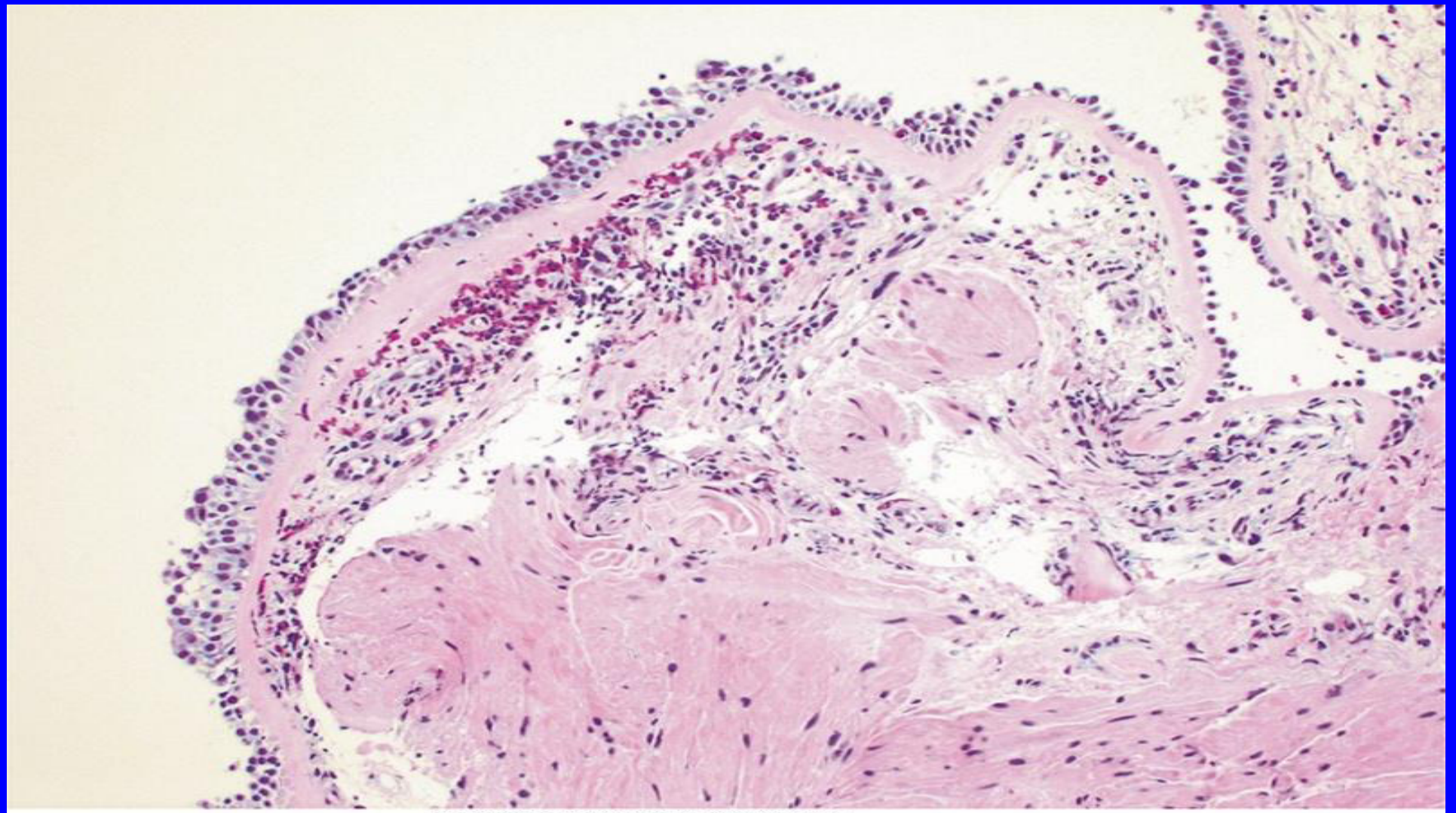
Histologically,

a. The mucous plugs contain whorls of shed epithelium (Curschmann spirals).

b. Numerous eosinophils

c. Charcot-Leyden crystals (collections of crystalloids made up of eosinophil proteins) in the mucus.

Asthma



Airway remodeling," include

a. Thickening of airway wall Sub-basement membrane fibrosis

b. Increased vascularity in submucosa

c. An increase in size of the submucosal glands and goblet cell metaplasia of the airway epithelium

d- Hypertrophy and/or hyperplasia of the bronchial muscle- this is the basis for the novel therapy of bronchial thermoplasty, which involves controlled delivery of thermal energy during bronchoscopy; this reduces the mass of smooth muscles which in turn reduces airway hyperresponsiveness)

- Asthma is a complex genetic disorder in which multiple susceptibility genes interact with environmental factors to initiate the pathologic reaction.
- There is significant variation in the expression of these genes and in the combinations of polymorphisms that effect the immune response or tissue remodeling.

A..One of the susceptibility loci is on the 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:

1. *IL13* (genetic polymorphisms linked with susceptibility to the development of atopic asthma)
2. , CD14

2. and IL-4 receptor gene (atopy, total serum IgE level, and asthma).

B. Another important locus is on 20q where ADAM-33 that regulates proliferation of bronchial smooth muscle and fibroblasts is located; this controls airway remodeling.

Clinical Features

- An attack of asthma is characterized by severe dyspnea with wheezing; the chief difficulty lies in expiration.
- The victim labors to get air into the lungs and then cannot get it out, so that there is progressive hyperinflation

- Intervals between attacks are characteristically free from overt respiratory difficulties, but persistent, subtle deficits can be detected by spirometry.
- Occasionally a severe paroxysm occurs that does not respond to therapy and persists for days and even weeks (*status asthmaticus*).
- The associated hypercapnia, acidosis, and severe hypoxia may be fatal, although in most cases the condition is more disabling than lethal

4.Bronchiectasis

- Is the permanent dilation of bronchi and bronchioles caused by destruction of the muscle and the elastic tissue, resulting from or associated with chronic necrotizing infections.
- It is not a primary disease but secondary to persisting infection or obstruction caused by a variety of conditions.

- Once developed, it gives rise to a characteristic symptom complex dominated by cough and expectoration of copious amounts of purulent sputum.
- Diagnosis depends on an appropriate history along with radiographic demonstration of bronchial dilation.

The Predisposing conditions include:

1. Bronchial obstruction and common causes are :

a- Tumors, foreign bodies, and impaction of mucus.

- With these conditions, the bronchiectasis is localized to the obstructed lung segment.

b- Bronchiectasis can also complicate atopic asthma and chronic bronchitis.

2. Congenital or hereditary conditions

a. In *cystic fibrosis*, widespread severe bronchiectasis results from obstruction secretion of abnormally viscid mucus so predisposing to infections of the bronchi.

b. In *immunodeficiency states*- immunoglobulin deficiencies, localized or diffuse bronchiectasis develop due to increased susceptibility to bacterial infections.

c. Kartagener syndrome is an autosomal recessive disorder associated with bronchiectasis and sterility in males due to structural abnormalities of the cilia that impair mucociliary clearance in the airways, leading to persistent infections, and reduce the mobility of sperms

3. *Necrotizing,* or *suppurative, pneumonia,* particularly with *Staphylococcus aureus* or *Klebsiella* spp., may predispose affected patients to development of bronchiectasis.

Note: Posttuberculosis bronchiectasis continues to be a significant cause of morbidity in endemic areas.

PATHOGENESIS of bronchiectasis:

- Two processes are crucial in pathogenesis : obstruction and chronic infection and either of these may come first.
- Normal clearance mechanisms are hampered by obstruction, so secondary infection soon follows conversely, chronic infection over time causes damage to ; bronchial walls, leading to weakening and dilation.

1- For example, obstruction caused by a primary lung cancer or a foreign body impairs clearance of secretions, providing substrate for superimposed infection and the resultant inflammatory damage to the bronchial wall and the accumulating exudate further distend the airways, leading to irreversible dilation.

2- Conversely, a persistent necrotizing inflammation in the bronchi or bronchioles may cause obstructive secretions, inflammation in the wall (with peribronchial fibrosis and traction on the walls), and eventually the train of events .

Bronchiectasis

Kumar et al: Robbins Basic Pathology, 9e.

- **MORPHOLOGY**

- Bronchiectasis usually affects the lower lobes bilaterally,

- When caused by tumors or foreign bodies the involvement may be localized to a single segment and the most severe involvement is in the more distal bronchi and bronchioles.

Gross:The airways may be **dilated** to as much as four times their usual diameter and on gross examination of the lung 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

Histologic findings

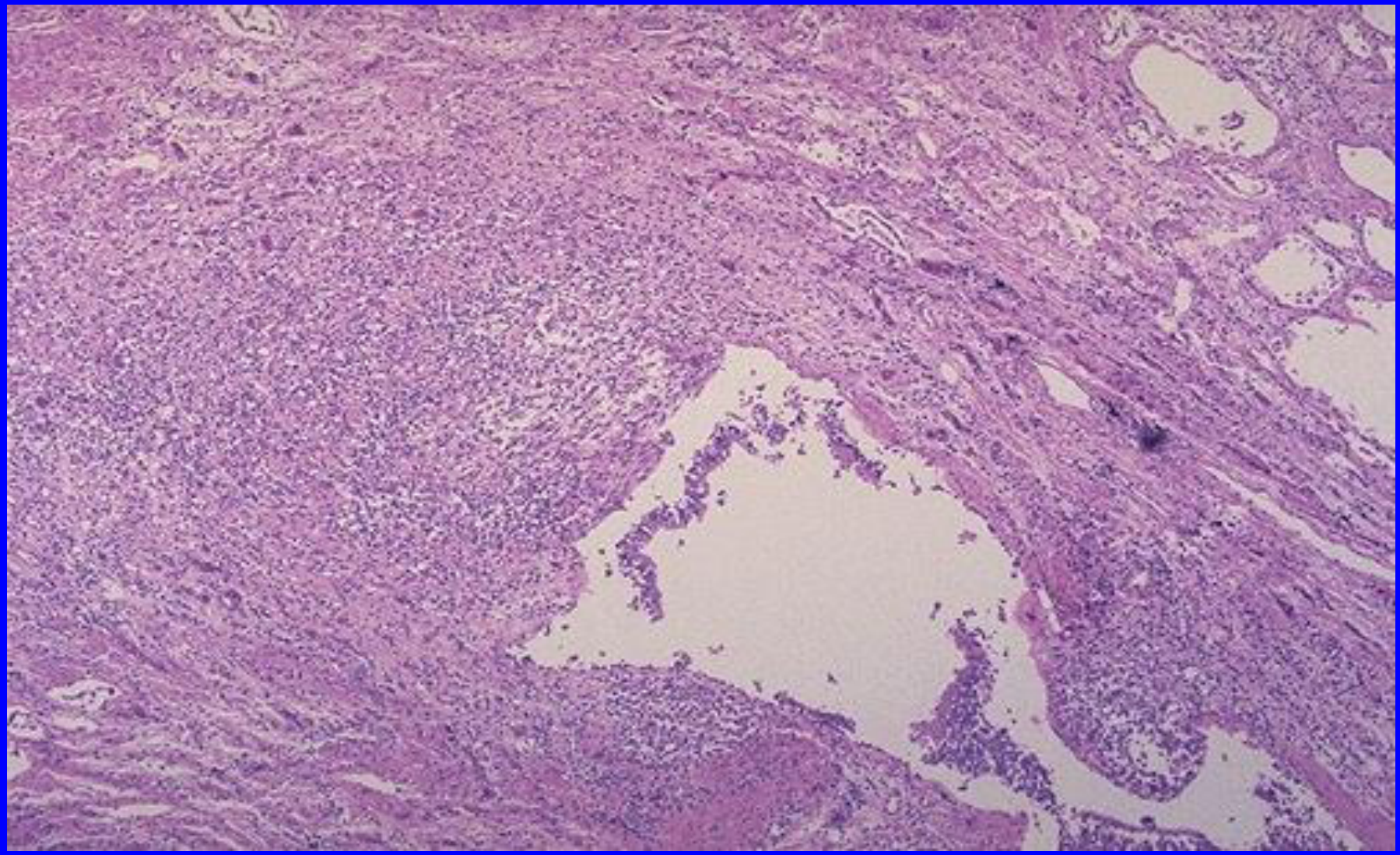
1. In the full-blown active case

a. An intense acute and chronic inflammatory exudate within the walls of the bronchi and bronchioles

b. Desquamation and ulceration of lining epithelium.

c. a **mixed** flora can be cultured from the involved bronchi,

Bronchiectasis



- When healing occurs,

a. The lining epithelium may regenerate completely; however, usually so much injury has occurred that abnormal dilation and scarring persist.

b- Fibrosis of the bronchial and bronchiolar walls and peribronchiolar fibrosis develop in more chronic cases.

c. In some instances, the necrosis destroys the bronchial or bronchiolar walls resulting in the formation of an abscess c avity within which a fungus ball may develop.

Clinical Features

- Consist of severe, persistent cough with expectoration of mucopurulent, sometimes fetid, sputum.
- The sputum may contain flecks of blood; frank hemoptysis can occur.

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- Symptoms often are episodic and are precipitated by upper respiratory tract infections or the introduction of new pathogenic agents.
- Clubbing of the fingers may develop

Complications of bronchiectasis

1- In cases of severe, widespread bronchiectasis, significant obstructive ventilatory defects are usual, with hypoxemia, hypercapnia, pulmonary hypertension, and (rarely) cor pulmonale.

2- Metastatic brain abscesses

3- Reactive amyloidosis

Airway remodeling," include

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