RESPIRATORY BLOCK

Bronchial Asthma

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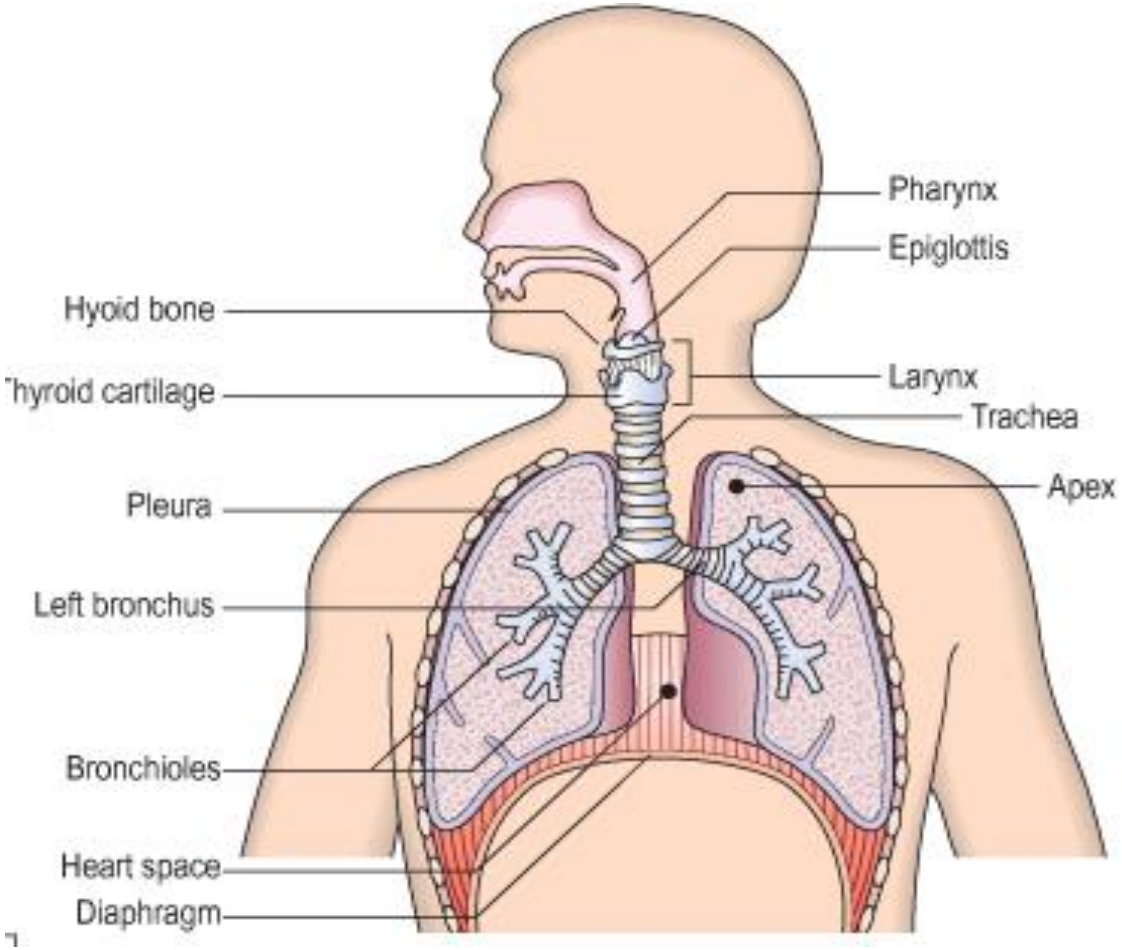
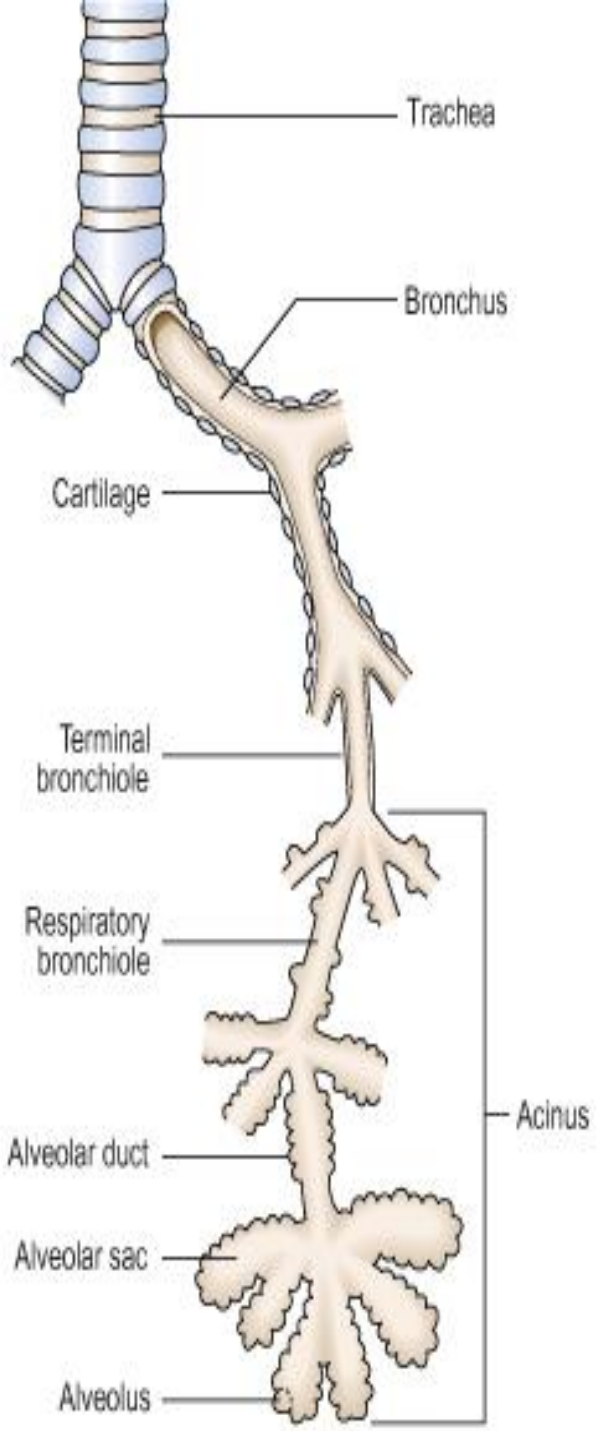
Feb 2017

Objectives

- Define asthma as an episodic, reversible bronchoconstriction caused by increased responsiveness of the tracheobronchial tree to various stimuli.
- Know that asthma is divided into two basic types:
  - 1. Extrinsic or atopic allergic
  - 2. Intrinsic asthma.
- Understanding the morphological changes (gross and microscopic) seen in the lungs in cases of severe asthma.

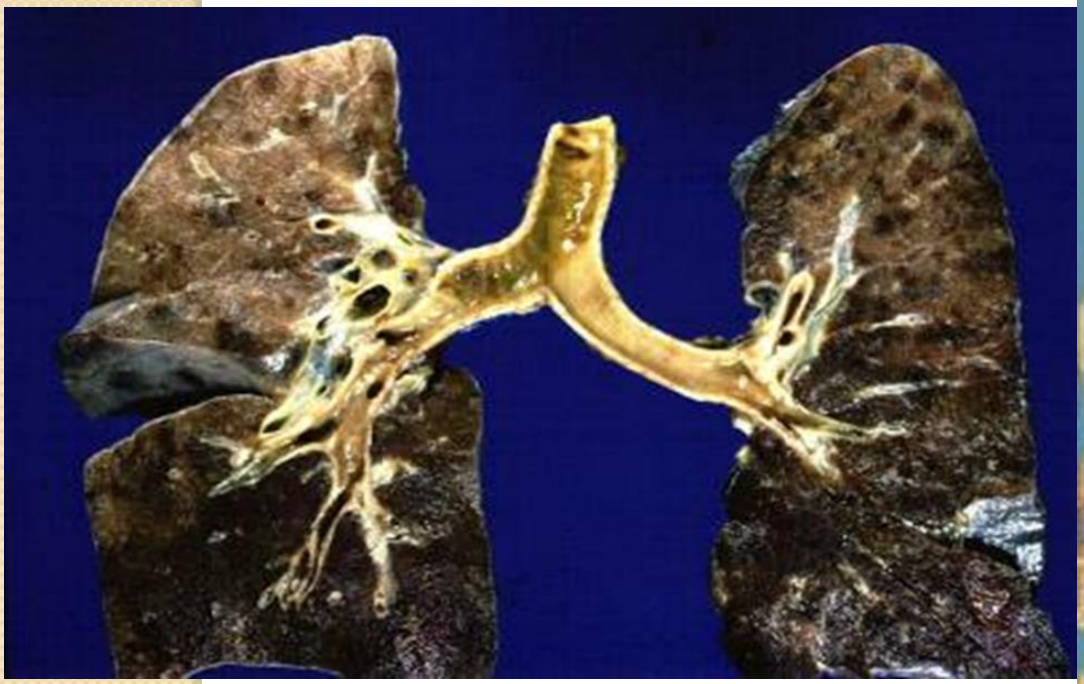
INTRODUCTION TO THE RESPIRATORY TRACT





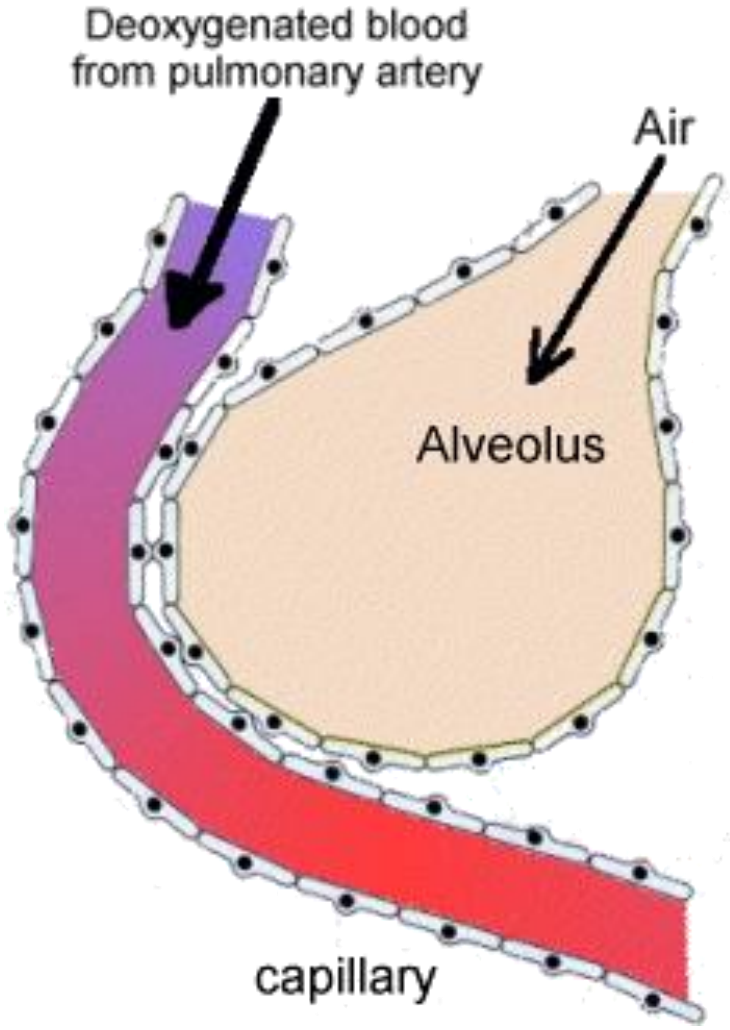
- The right and left **main bronchi** divide into **lobar bronchi**.
- The lobar bronchi divide into **tertiary/segmental bronchi,** each of which supplies a bronchopulmonary segment.
- The segmental bronchi divide **into primary bronchioles** which divide into **terminal bronchioles** and then divide into **respiratory bronchioles,** which go on to divide into **alveolar ducts.**
- Each alveolar duct divides into five or six **alveolar sacs**.
- The alveolar sacs are made up of **alveoli**. The alveolus is the basic anatomical unit of gas exchange in the lung.
- Beyond terminal bronchiole gas exchange occurs
- The distal airspaces are kept open by elastic tension in alveolar walls

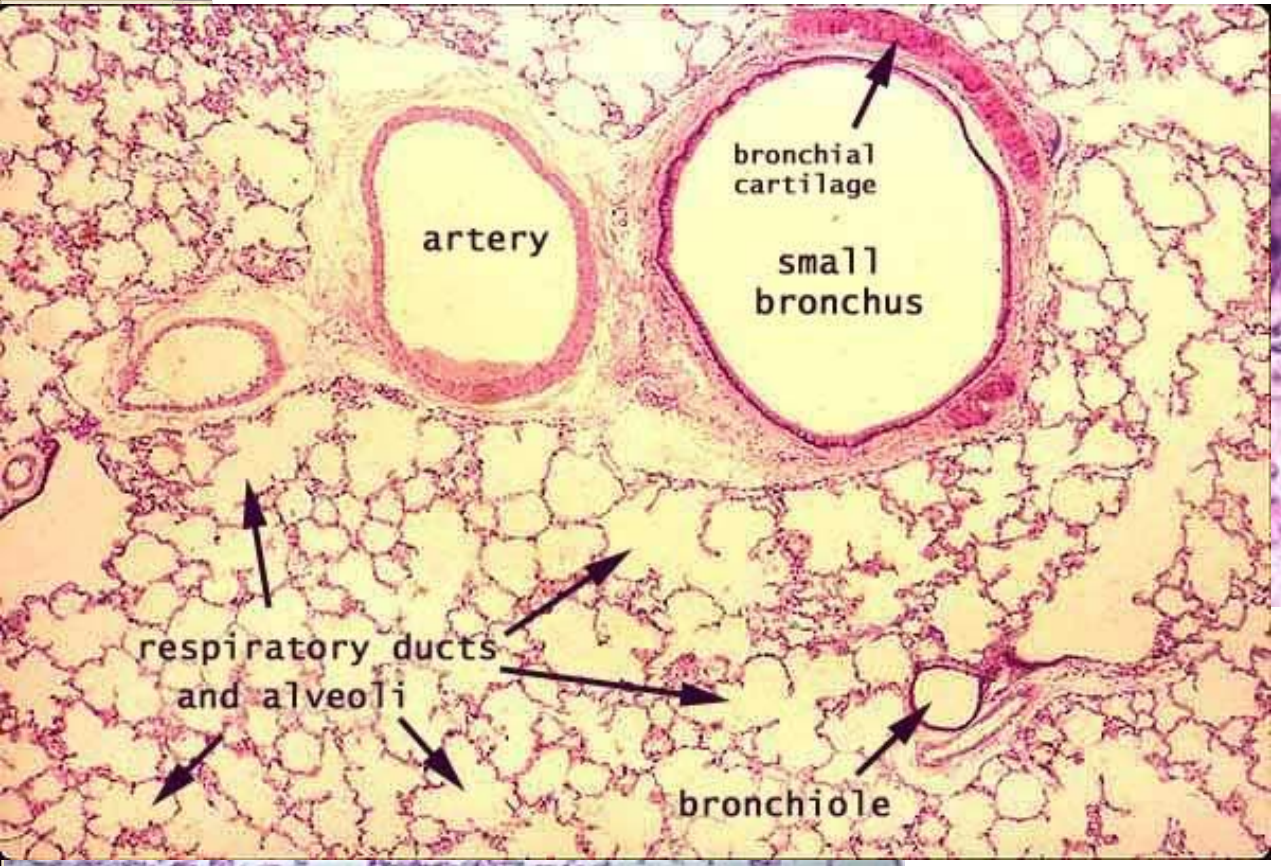
normal lung

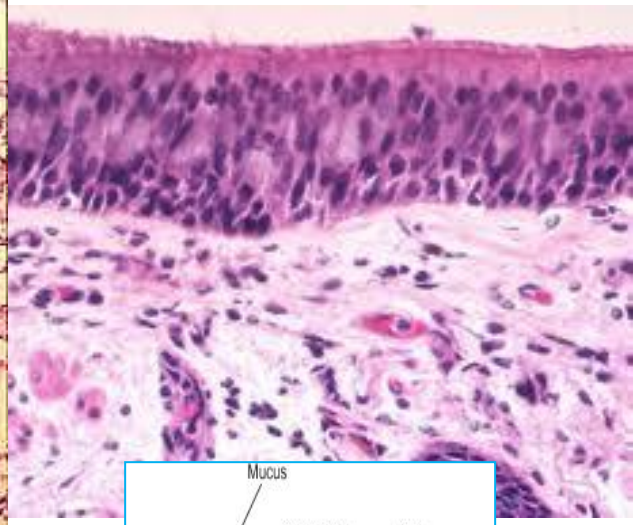


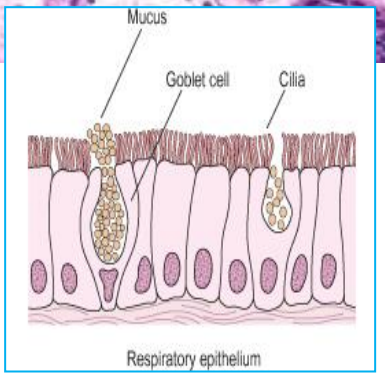
Function of lungs….

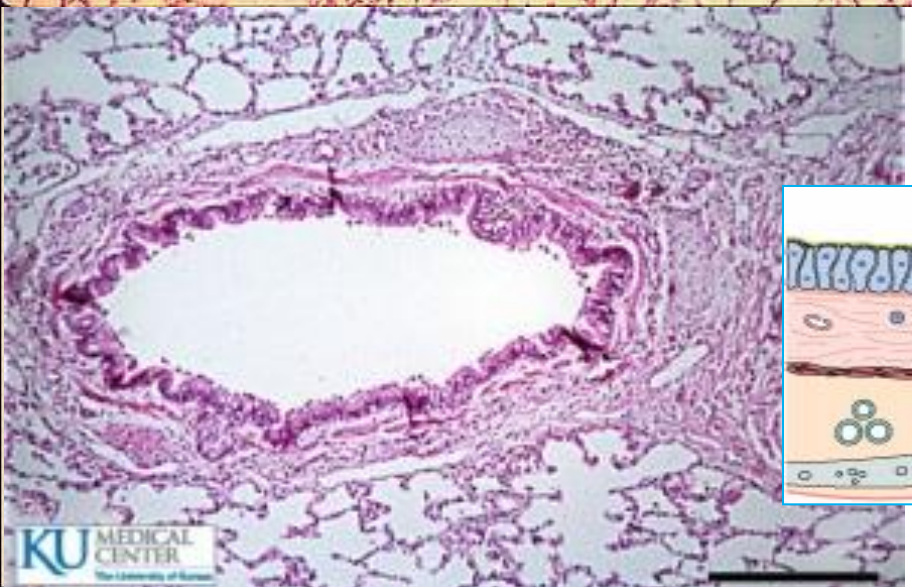
- Gas exchange (O2, CO2)
  - Depends on compliance (stretchability) of lungs
  - Can only occur in alveoli that are *both* ventilated and perfused

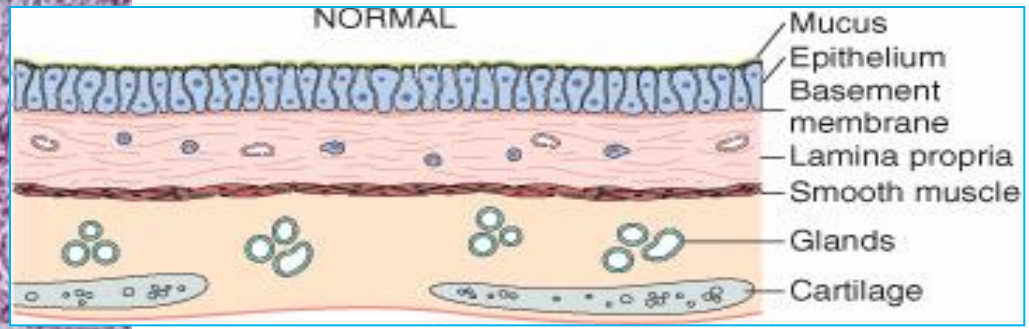



bronchial cartilage
artery
small bronchus
respiratory ducts and alveoli
bronchiole



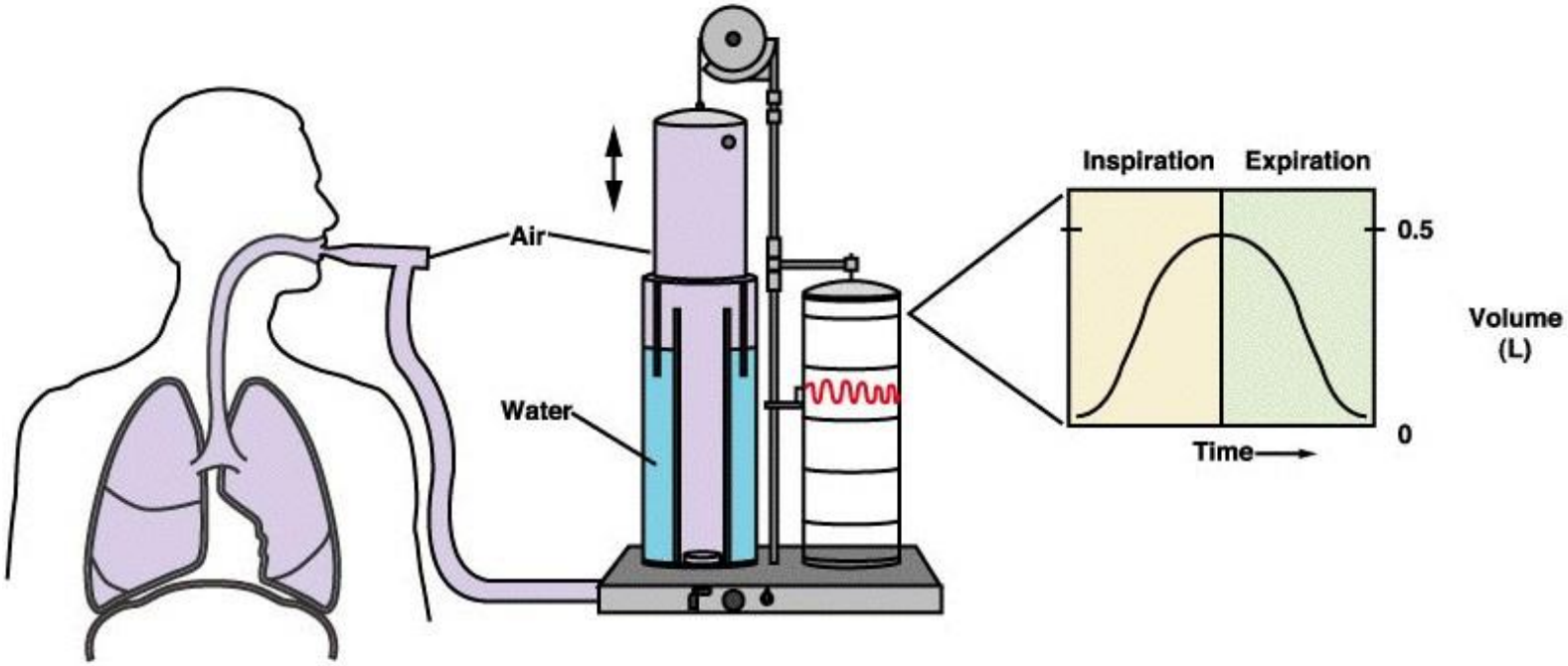

Mucus
Goblet cell
Cilia
Respiratory epithelium

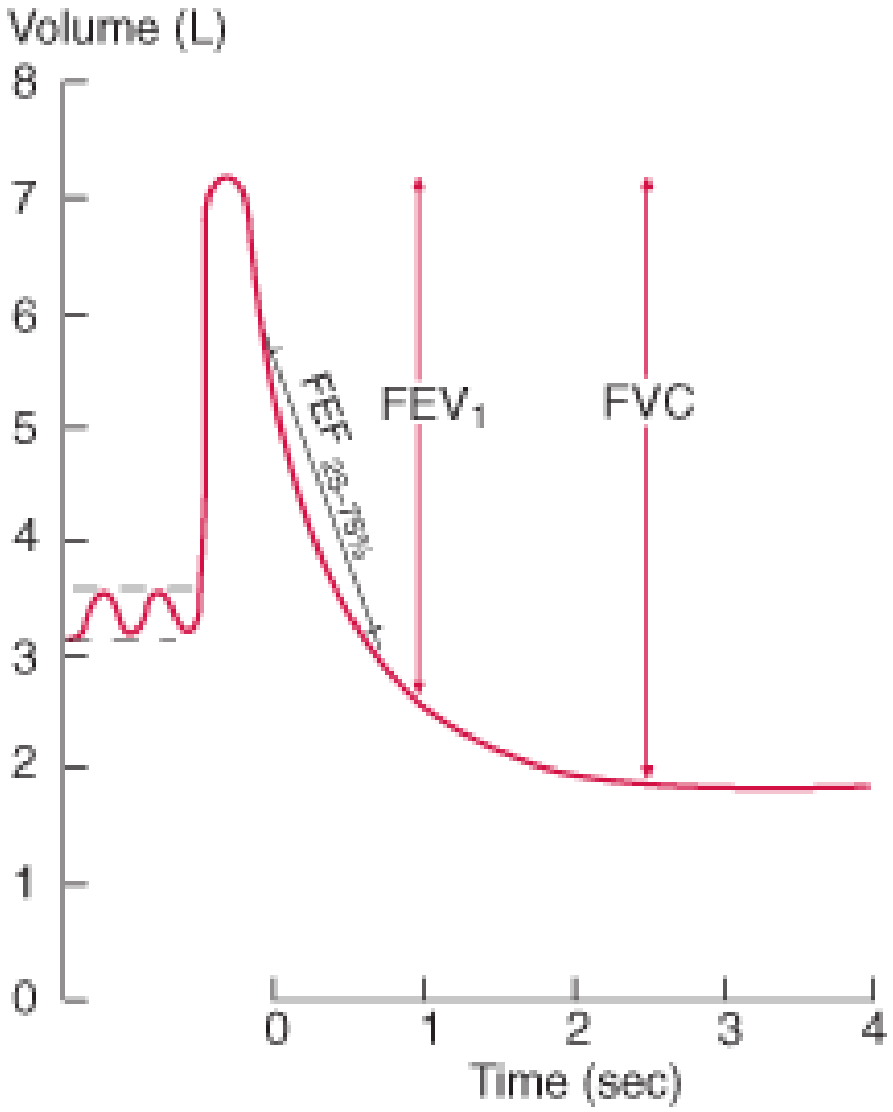

KU MEDICAL CENTER


NORMAL
Mucus
Epithelium
Basement membrane
Lamina propria
Smooth muscle
Glands
Cartilage

Spirometer

- is an equipments used for measuring the volume of air inspired and expired by the lungs (Pulmonary Function Tests)




Volume (L)
8
7
6
5
4
3
2
1
0
FEF 25–75%
FEV1
FVC
0
1
2
3
4
Time (sec)

Spirometry (pulmonary physiology)

- Forced expiratory volume (FEV1): volume of air blown out forcibly in 1 second. A function of large airways. Dependent on body size.

- Vital capacity (VC): total volume of expired air.

- Diffusing capacity or Transfer factor of the lung for carbon monoxide (D_{LCO} or T_{LCO}): absorption of carbon monoxide in one breath (gas exchange). It is dependent on the concentration of blood haemoglobin, which has a strong affinity for CO and it assesses the ability of the lungs to exchange gas efficiently.

Classification of Lung Disease based on distinctive clinical and physiological features:

1. **Obstructive lung diseases**:

- Is a category of respiratory disease characterized by airway obstruction due to partial or complete obstruction at any level from trachea to respiratory bronchioles. It is generally characterized by inflamed and easily collapsible airways, obstruction to airflow and problems exhaling.
- Pulmonary function test: decreased FEV1 and decreased FEV1/VC.

2. **Restrictive lung diseases**:

- Are a category of diseases that restrict lung expansion, resulting in a decreased total lung capacity, increased work of breathing, and inadequate ventilation and/or oxygenation.
- Both forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) are reduced, however the FEV1/VC is normal to high. The Tco is decreased. The expiratory flow rate is near normal.

Types of Obstructive Lung Diseases

(diffuse)

Common symptoms in lung disease

- Dyspnea: difficulty with breathing
- Cough
- Hemoptysis

1) Bronchial Asthma

2) Chronic obstructive pulmonary disease (COPD). It is also known as Chronic obstructive airway disease (COAD) or Chronic obstructive lung disease (COLD). They are of two types:

   a) Chronic bronchitis

   b) Emphysema

3) Bronchiectasis

BRONCHIAL ASTHMA

Asthma is an increased irritability of the bronchial tree with paroxysmal narrowing of the airways, which may reverse either spontaneously or after treatment with bronchodilators.

DEFINITION

BRONCHIAL ASTHMA (BA)

- It is a chronic relapsing inflammatory obstructive lung disease characterized by hyper-reactive airways.

- It is reversible bronchoconstriction/spasm characterized by hyper-irritability of the airways due to increased responsiveness of the tracheobronchial tree to various stimuli.

DEFINITION

BRONCHIAL ASTHMA (BA)

- It is a triad of:
  1. Intermittent and reversible airway obstruction (bronchospasm, oedema and mucous plugging)
  2. Chronic bronchial inflammation with eosinophils
  3. Bronchial smooth muscle cell hypertrophy and hyper-reactivity
- Primarily targets the bronchi and terminal bronchioles
- Most common chronic respiratory disease in children.
  - More common in children than adults

Asthma animation:
https://www.youtube.com/watch?v=7EDo9pUYvPE

Types

Bronchial asthma (BA):

It has been divided into two basic types:

1. Extrinsic asthma.
2. Intrinsic asthma.

Sometimes extrinsic and intrinsic can co-exist in the same patient

Extrinsic (atopic, allergic) Asthma 70%

- Initiated by type I hypersensivity reaction induced by exposure to extrinsic antigen/allergens e.g. food, pollen, dust, etc.
- Subtypes include:

a) atopic (allergic)asthma.
b) occupational asthma.
c) allergic bronchopulmonary aspergillosis.

- Develop early in life

Intrinsic (non-atopic) Asthma 30%

- Initiated by diverse, non-immune mechanisms e.g. infections, drugs like aspirin, pollutants, inhaled chemical irritants, cold, stress and exercise.
- No personal or family history of allergic reaction.
- Develop later in life

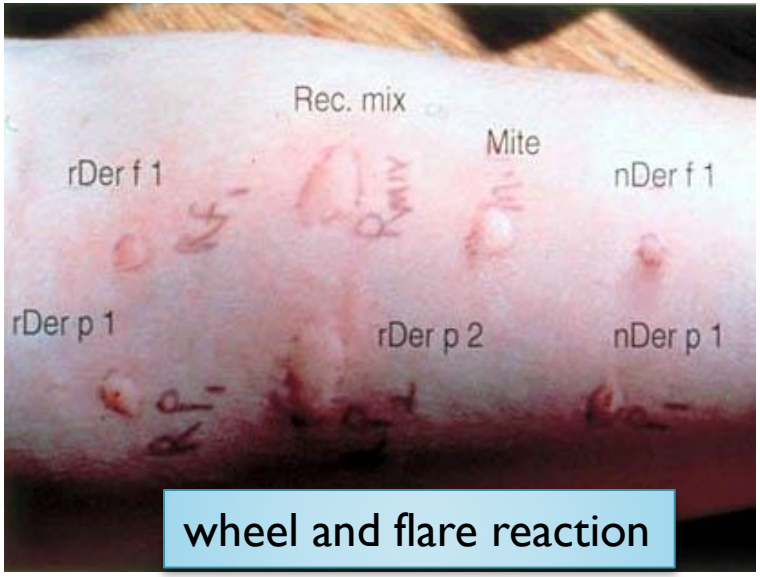
Extrinsic/ Allergic BA

- Other names:
  - allergic asthma
  - immune mediated asthma
  - atopic asthma
  - reaginic asthma.
- Bronchospasm is induced by inhaled antigens, usually in children with a personal or family history of allergic disease
- Symptoms are brought about by IgE mediated type I hypersensitivity reaction to inhaled allergens.
- Serum levels of IgE and eosinophils usually are elevated.

Extrinsic/ Allergic BA

- Atopic (allergic) asthma is the most common type and begins in childhood
- Other allergic manifestation may be present: allergic rhinitis, urticaria, eczema or hay fever.
- Skin test with antigen is positive and results in an immediate wheel and flare reaction


eczema



wheel and flare reaction

Intrinsic / Non-Atopic/ Idiosyncratic BA (non-immune mediated asthma)

- Intrinsic asthma is a disease of adults in which the bronchial hyper-reactivity is precipitated by a variety of factors unrelated to immune mechanisms.
- It has an unknown basis.
- Symptoms are precipitated by non allergic factors such as inhaled irritants/pollutants (e.g. sulfur dioxide, ozone), medication (e.g. aspirin) or infection (viruses).
- Positive family history is uncommon.
- Serum IgE – normal.
- No other associated allergies.
- Skin test – negative.
- Subtypes:

1. Drug-induced asthma (aspirin or nonsteroidal drug sensitivity).
2. Occupational asthma(fumes, dusts, gases)

Pathogenesis of Bronchial Asthma

The pathophysiology of asthma is complex and involves the following components:

1. **Chronic airway inflammation**
2. **Intermittent airflow obstruction**. Airflow obstruction can be caused by a variety of changes, including acute bronchoconstriction, airway edema, chronic mucous plug formation, and airway remodeling
3. **Bronchial hyper-responsiveness** causes exaggerated bronchoconstriction.

   The degree of airway hyper-responsiveness generally correlates with the clinical severity of asthma.

Pathogenesis of Bronchial Asthma

- Principal cells in asthma: **mast cells, eosinophils, epithelial cells, macrophages, and activated T lymphocytes (TH2 subset) and neutrophils.**
- T lymphocytes play an important role in the regulation of airway inflammation through the release of numerous cytokines
- The pathogenetic mechanisms have been best studied in atopic asthma

Pathogenesis of Bronchial Asthma using type I IgE-mediated Atopic Asthma as a model

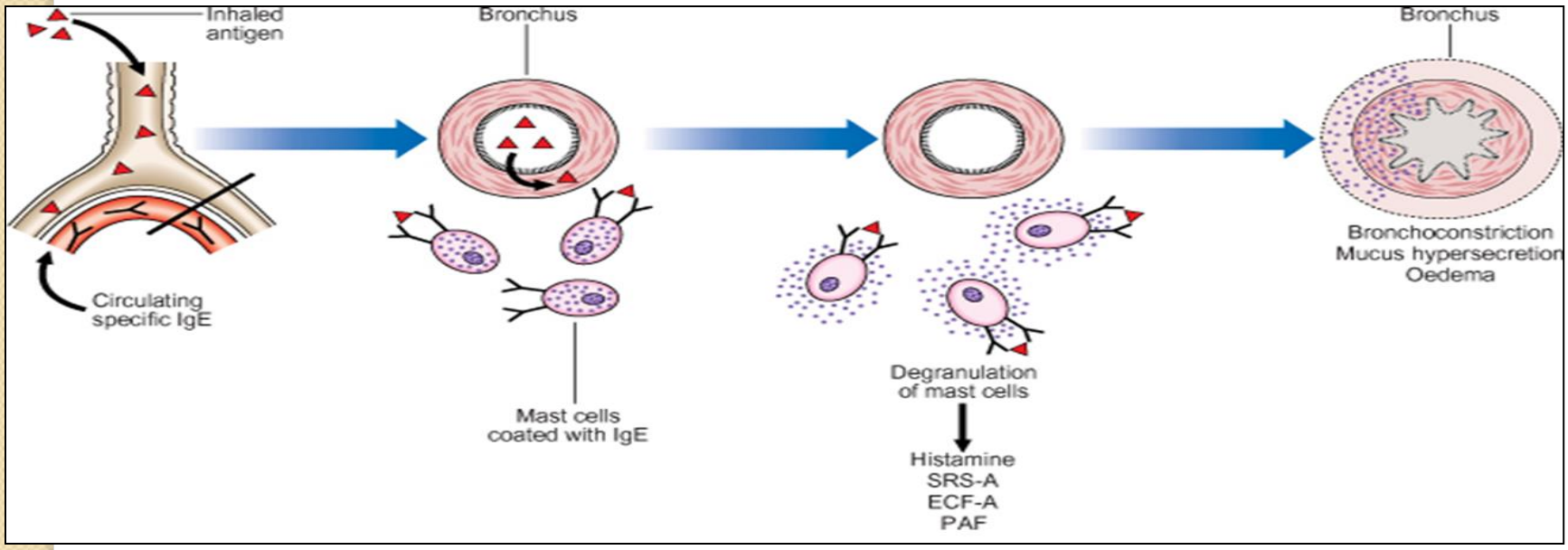
- First there is initial sensitization or priming: first time exposure to an inhaled allergen which stimulates induction of Th2-type T cells (CD4 T_H2) to produce cytokines(interleukin IL- 4, IL-5 and IL-13)
  - IL-4 plays a role in cross-linking of immunoglobulins in B lymphocytes, promote production of IgE and mast cells.
  - IL-5 stimulates production and activation (recruitment) of eosinophils.
  - IL-13 is needed for IgE formation.
- And then there is subsequent re-exposure to the allergen will leads to an IgE mediated reaction.
- This IgE-mediated reaction to inhaled allergens elicits:

  1. an acute response (within minutes)
  2. a late phase reaction (after 4-8 hours)

Pathogenesis of Bronchial Asthma using type I IgE-mediated Atopic Asthma as a model

Acute-phase response

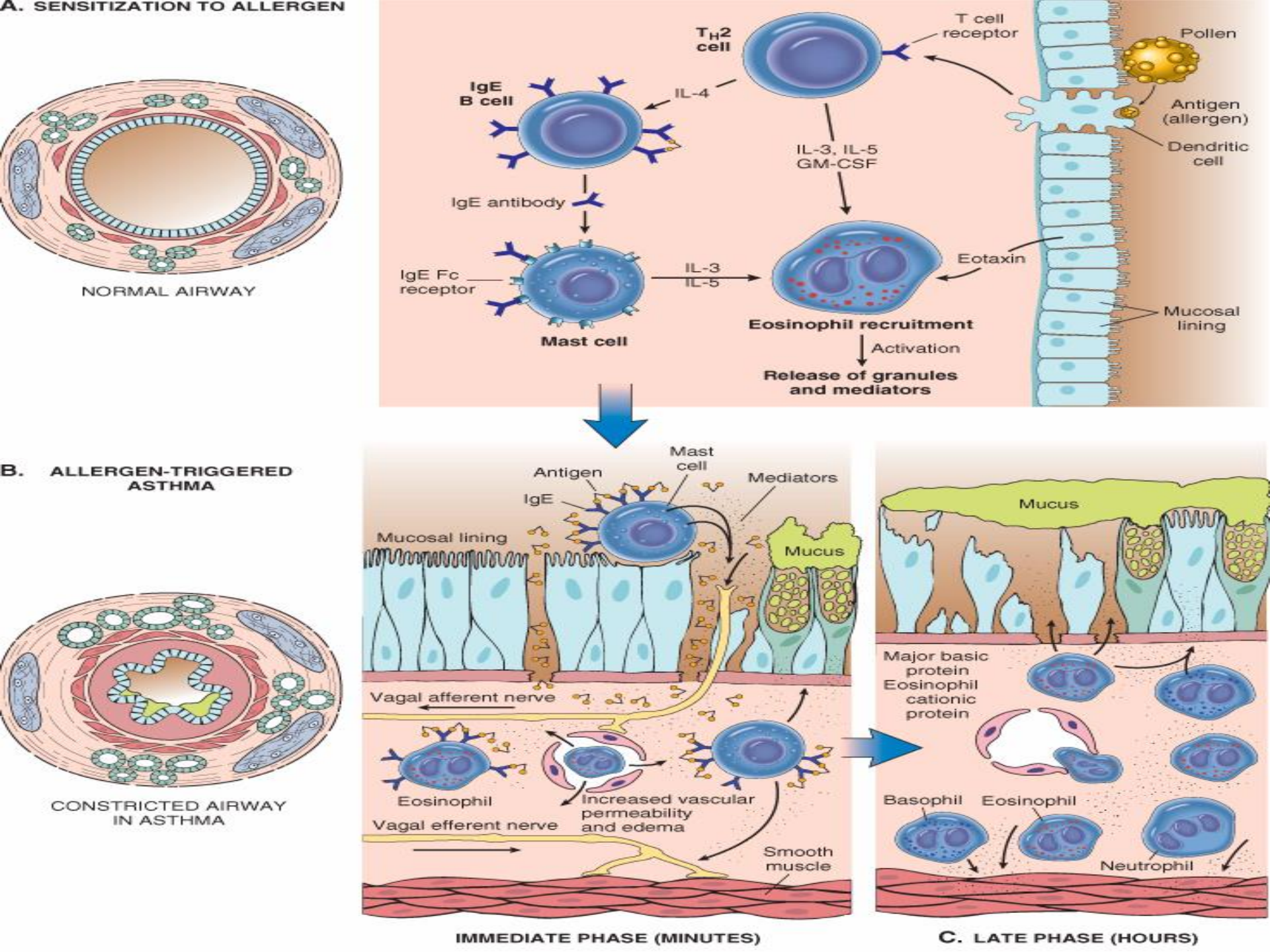
- Begin 30 to 60 minutes after inhalation of antigen/aeroallrgens(e.g. allergens, drugs, cold, exercise).
- The exposure results in the stimulation and degranulation of mast cells, eosinophils, and basophils with the release of inflammatory mediators from these cells and also from activated macrophages. The released mediators induce bronchoconstriction/spasm, increased vascular permeability, inflammation and injury of the bronchial walls and bronchial epithelium and excess mucous secretion.



Pathogenesis of Bronchial Asthma using Atopic Asthma as a model

Late phase reaction/ late asthmatic response:

- Lead to airway edema
- Occurs 6-24 hours following allergen exposure.
- The arrival of leukocytes at the site of mast cell degranulation leads to release of more mediators to activate more mast cells
- Discharge of eosinophil granules releases major basic protein, eosinophilic cationic protein and eosinophil peroxidase into the bronchial lumen. These substances are toxic to epithelial cells and cause epithelial cell damage and further impair mucociliary function.
- Eotaxin is secreted by injured bronchial mucosal lining cells and helps in the eosinophils recruitment
- Moreover, chemotactic factors like leukotriene B_4, eosinophil chemotactic factor and PAF recruit more eosinophils, neutrophils and platelets to the bronchial wall
- The vicious circle continues and prolongs and amplifies the asthmatic attack.
- All these factors amplify and sustain injury without additional antigen.


A. SENSITIZATION TO ALLERGEN
NORMAL AIRWAY
T_H2 cell
T cell receptor
Pollen
IgE B cell
IL-4
Antigen (allergen)
Dendritic cell
IL-3, IL-5 GM-CSF
IgE antibody
IgE Fc receptor
IL-3 IL-5
Eotaxin
Mucosal lining
Mast cell
Eosinophil recruitment
Activation
Release of granules and mediators
B. ALLERGEN-TRIGGERED ASTHMA
CONSTRICTED AIRWAY IN ASTHMA
Antigen
IgE
Mast cell
Mediators
Mucosal lining
Mucus
Vagal afferent nerve
Eosinophil
Increased vascular permeability and edema
Vagal efferent nerve
Smooth muscle
IMMEDIATE PHASE (MINUTES)
Mucus
Major basic protein
Eosinophil cationic protein
Basophil
Eosinophil
Neutrophil
C. LATE PHASE (HOURS)

Inflammatory Mediators of Bronchial Asthma using Atopic Asthma as a model

- Inflammatory mediator produced are :
  - Leukotrienes C4, D4 & E4 (induce bronchospasm, vascular permeability & mucous production)
  - Prostaglandins D2, E2, F2 (induce bronchospasm and vasodilatation)
  - Histamine from the mast cells (induce bronchospasm and increased vascular permeability)
  - Platelet-activating factor (cause aggregation of platelets and release of histamine)
  - Mast cell tryptase (inactivate normal bronchodilator).
  - Tumor necrosis factor (amplify the inflammatory response)
  - Eotaxin: is secreted by bronchial mucosal lining cells and helps in the eosinophils recruitment

Effects of Inflammatory Mediators

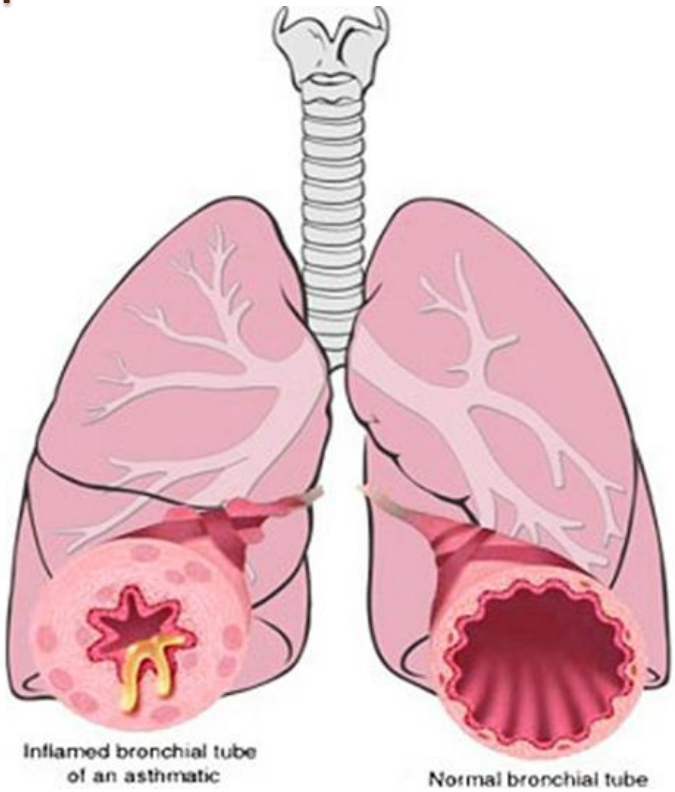
(1) smooth muscle contraction, bronchospasm

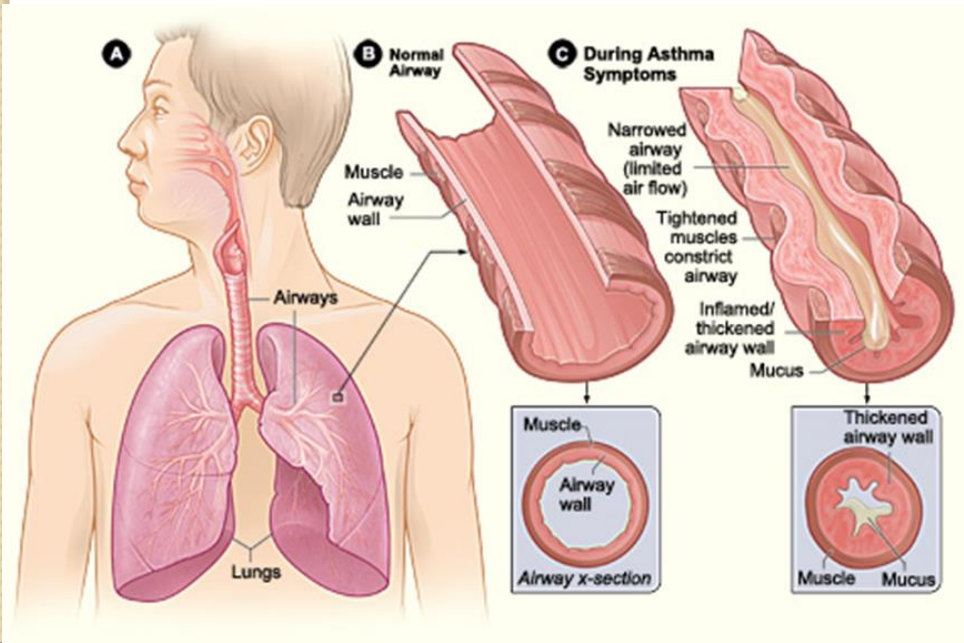
(2) mucous secretion

(3) increased vascular permeability and edema.

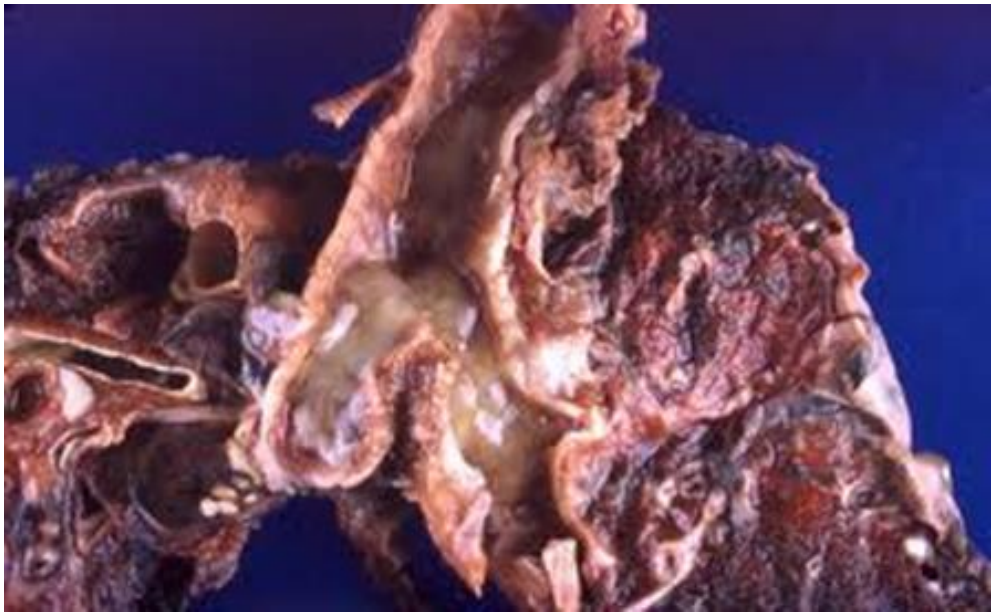
Morphology of Asthma: the pathologic findings are similar in both types BA

- Grossly: - lung over distended (over inflation), occlusion of bronchi and bronchioles by thick mucous.
- the bronchi have thickened walls with narrowed lumina and generally are filled with plugs of mucus in acute attack



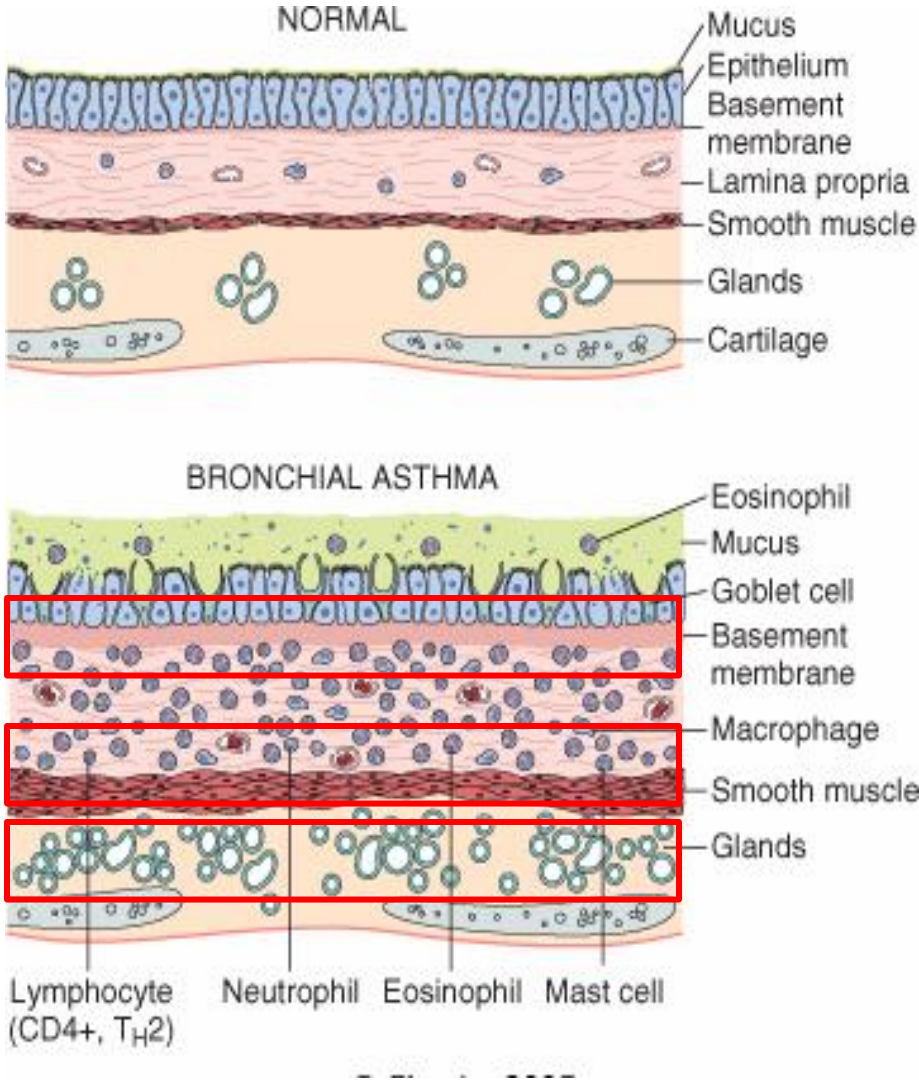


Mucus plugs



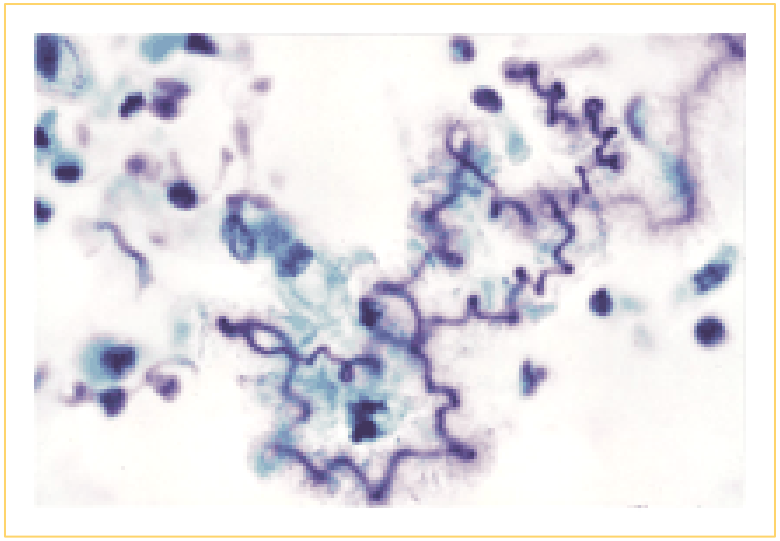
Morphology of Asthma

- Histologic finding:
  - Thick Basement Membrane.
  - Edema and inflammatory infiltrate in bronchial wall.
  - mucous contain Curschmann spirals, eosinophil and Charcot-Leyden crystals.
  - Submucosal glands increased.
  - Hypertrophy of the bronchial wall muscle.



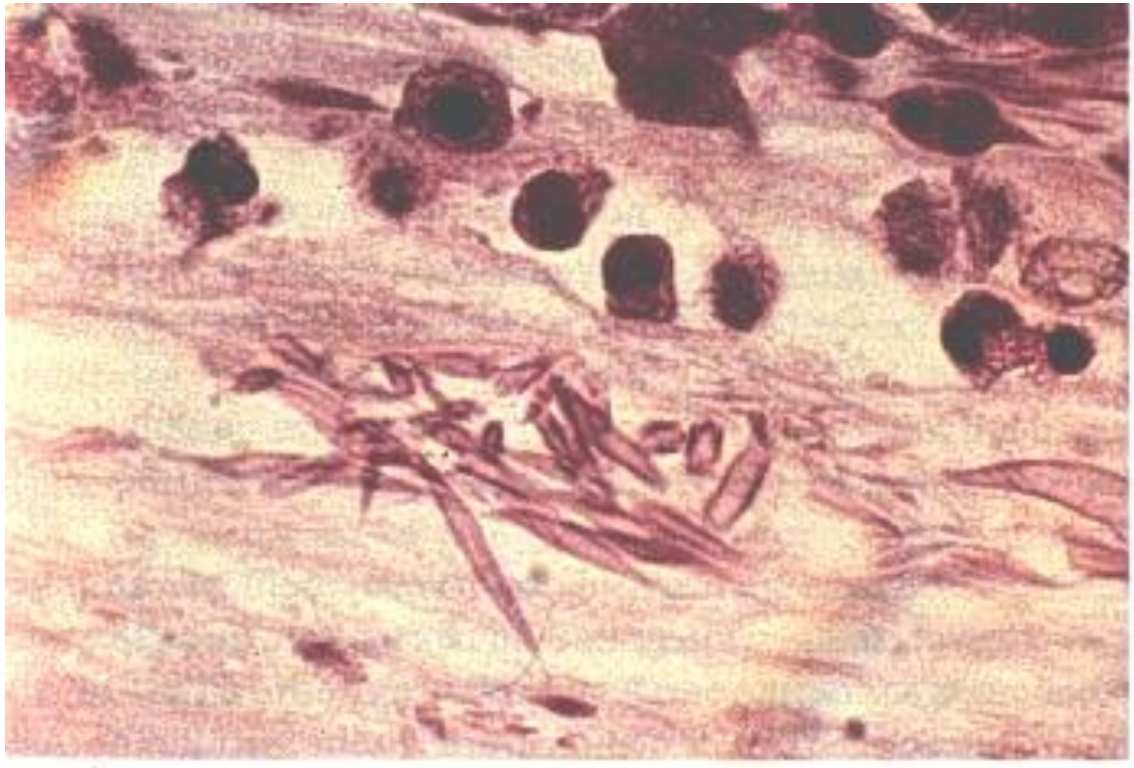
Curschmann spirals

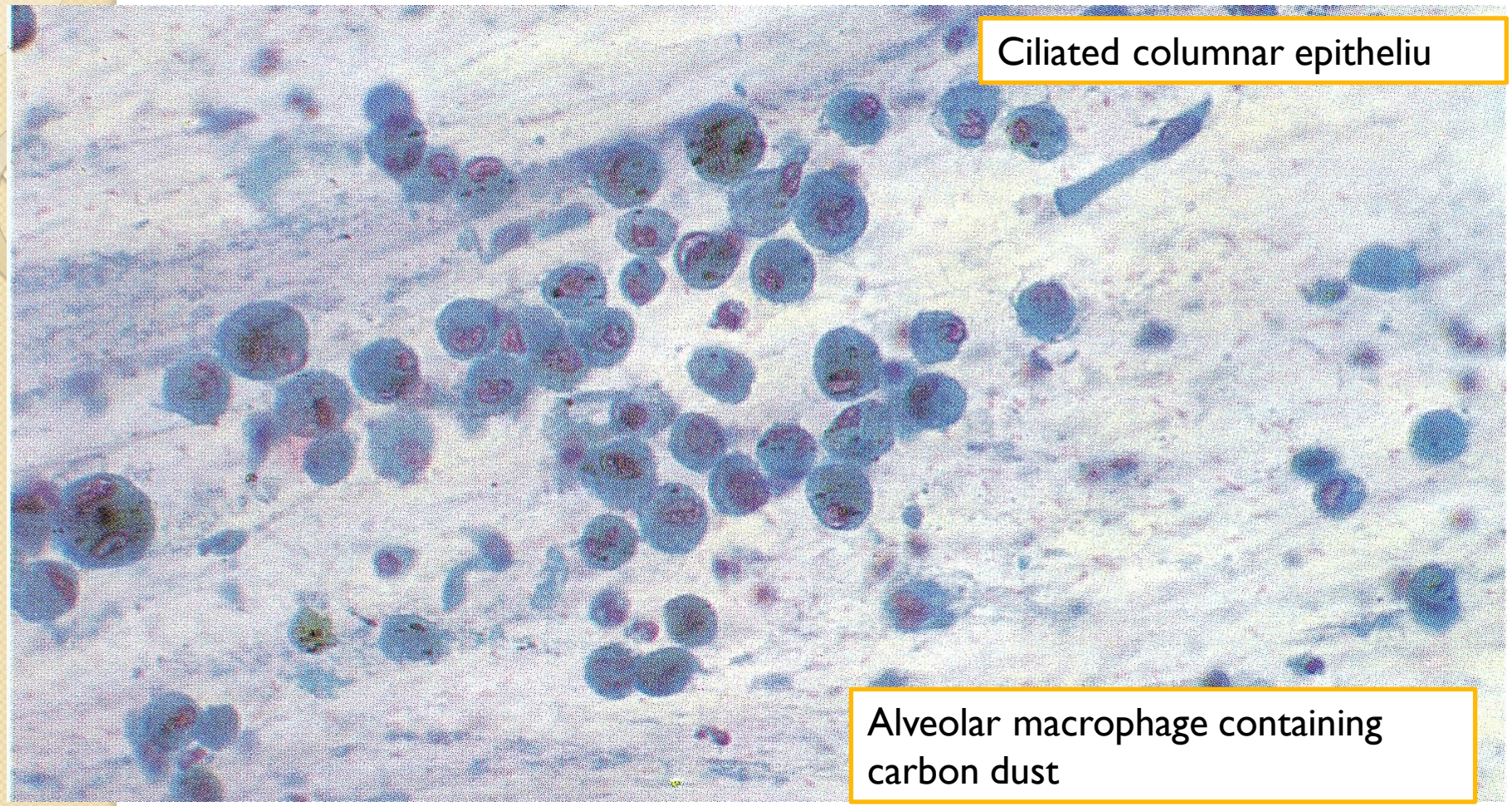
- Coiled, basophilic plugs of mucus formed in the lower airways and found in sputum and tracheal washings



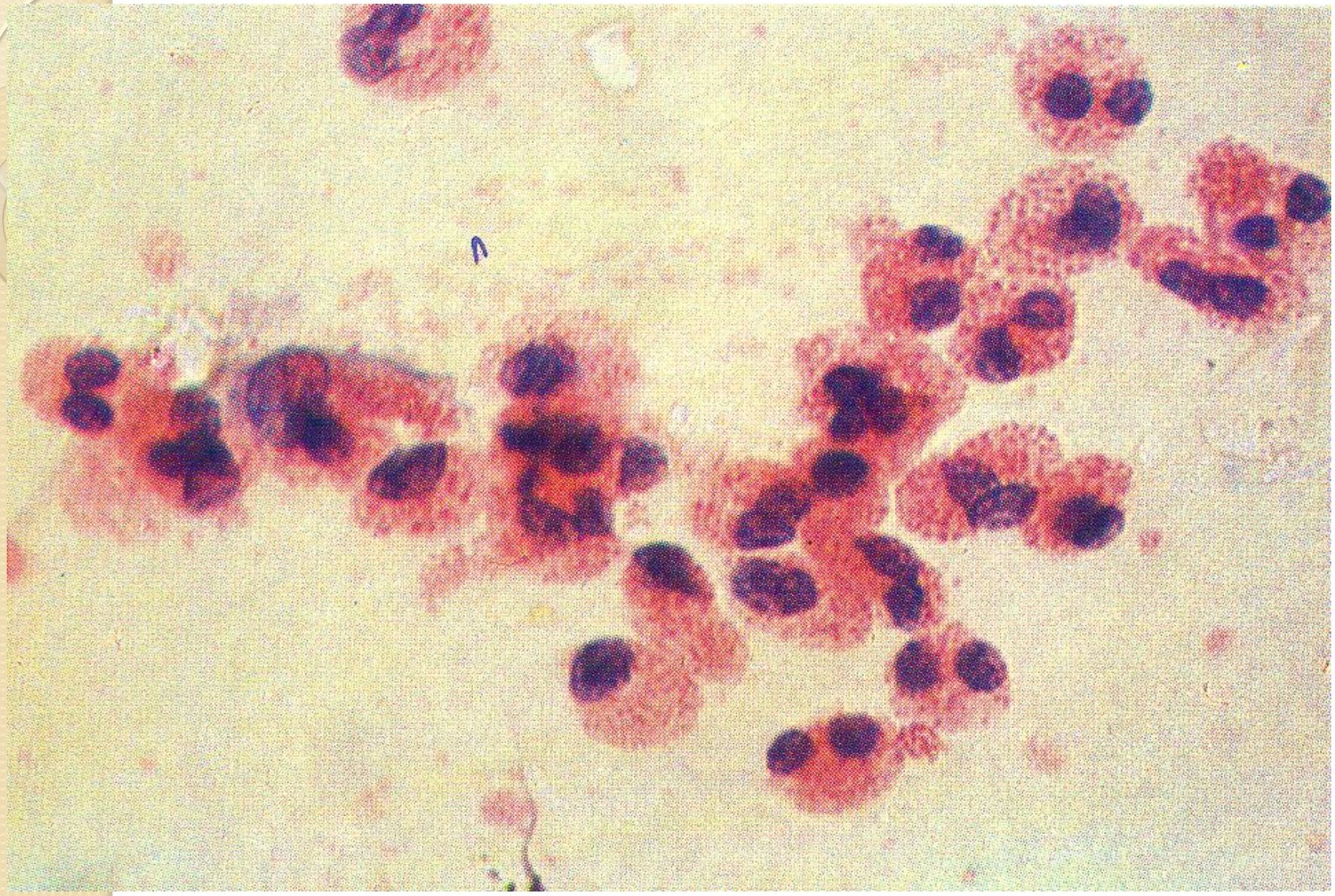
Charcot-Leyden crystals.

- Eosinophilic needle-shaped crystalline structures.

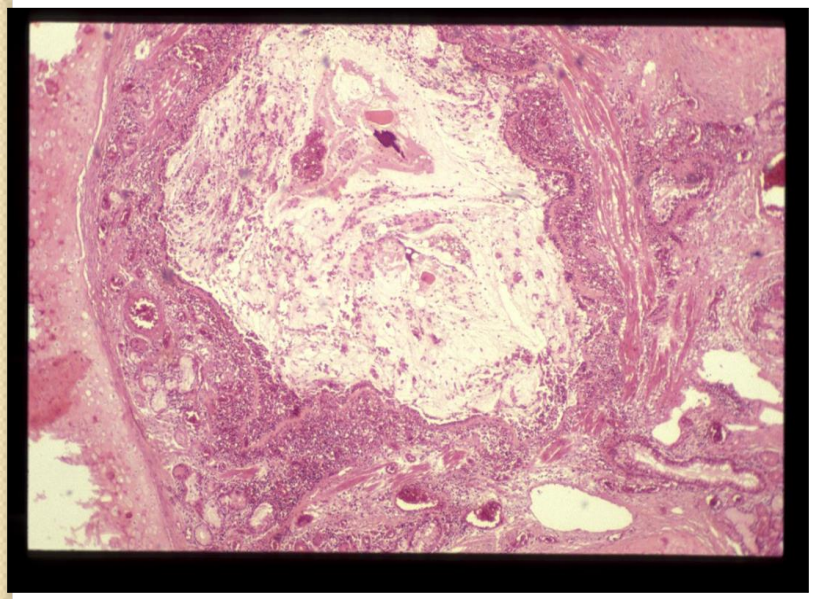


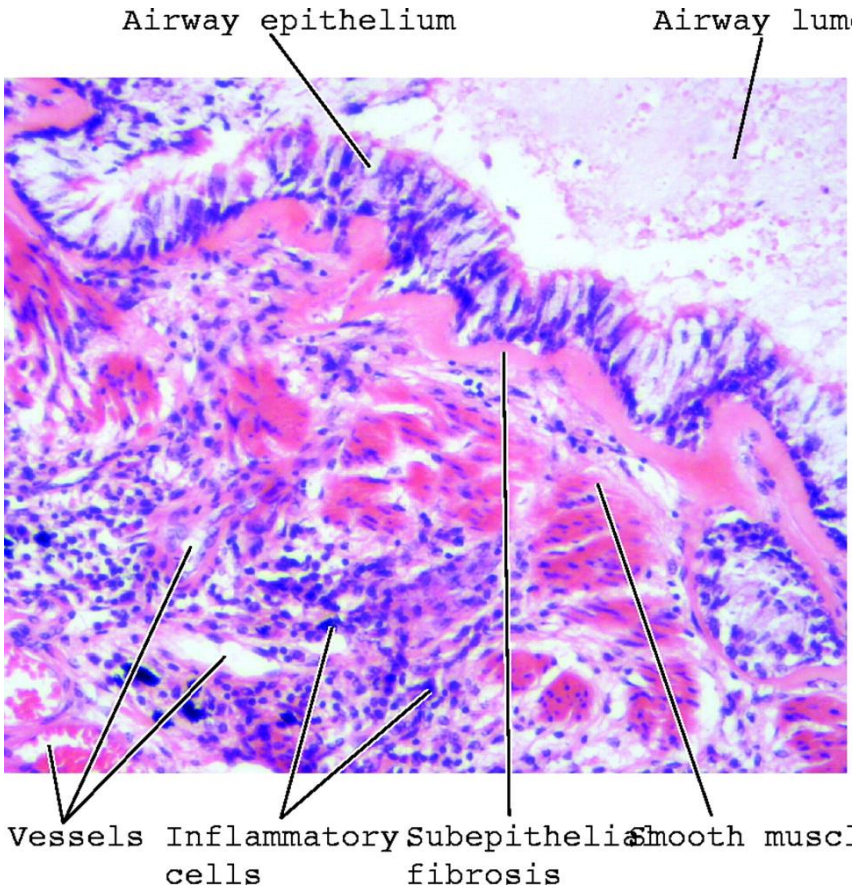


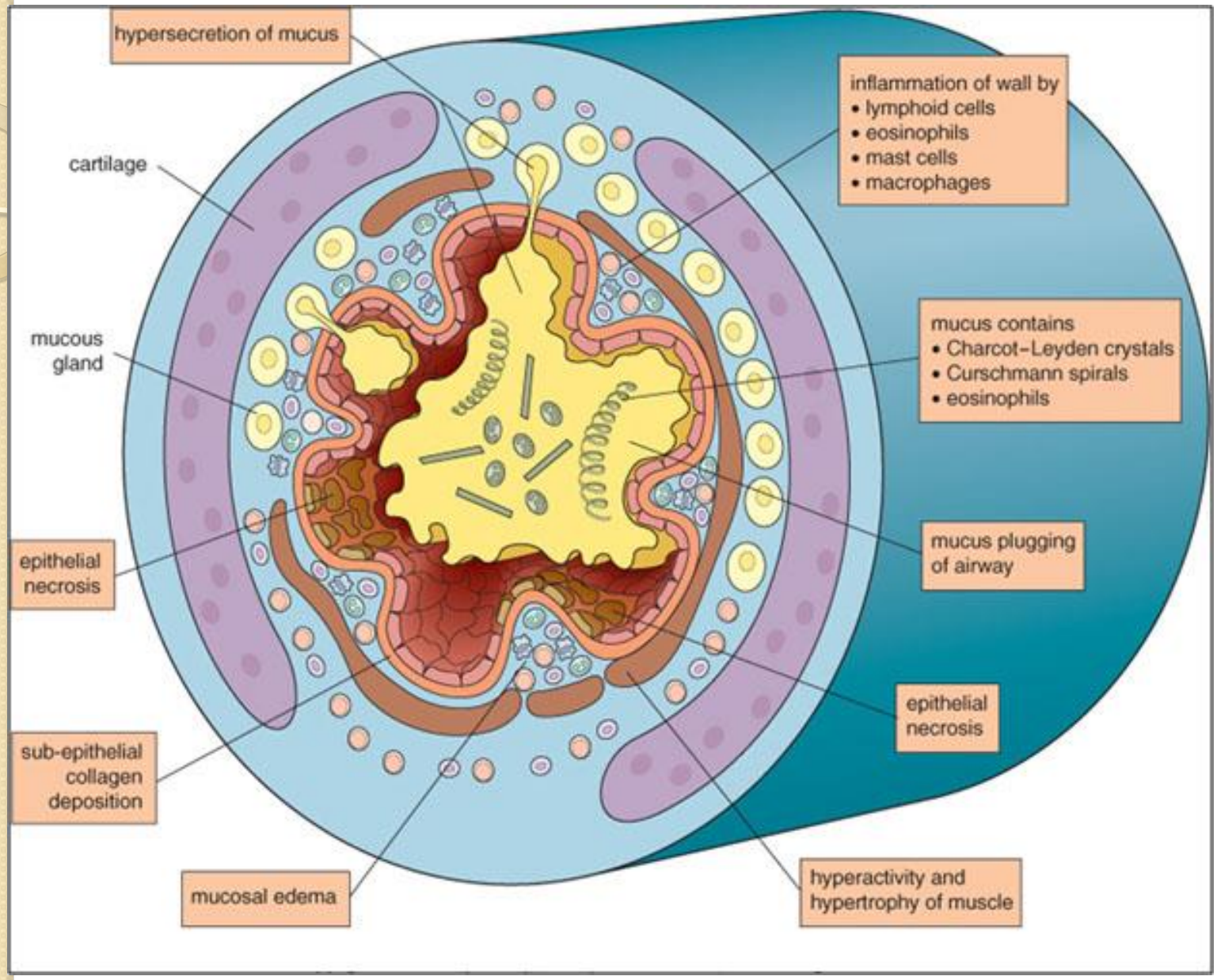
Composition of satisfactory specimen : Sputum



Eosinophils from a case of Bronchial Asthma



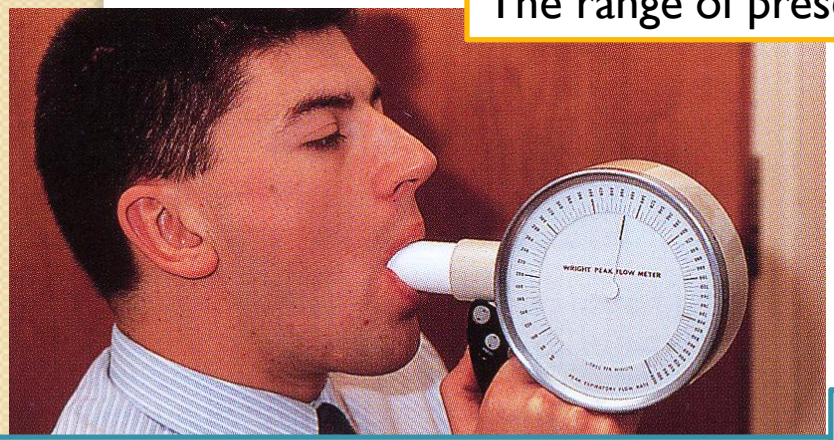

Airway epithelium
Airway lum
Vessels
Inflammatory cells
Subepithelial fibrosis
Smooth muscl


hypersecretion of mucus
cartilage
mucous gland
epithelial necrosis
sub-epithelial collagen deposition
mucosal edema
inflammation of wall by
• lymphoid cells
• eosinophils
• mast cells
• macrophages
mucus contains
• Charcot–Leyden crystals
• Curschmann spirals
• eosinophils
mucus plugging of airway
epithelial necrosis
hyperactivity and hypertrophy of muscle

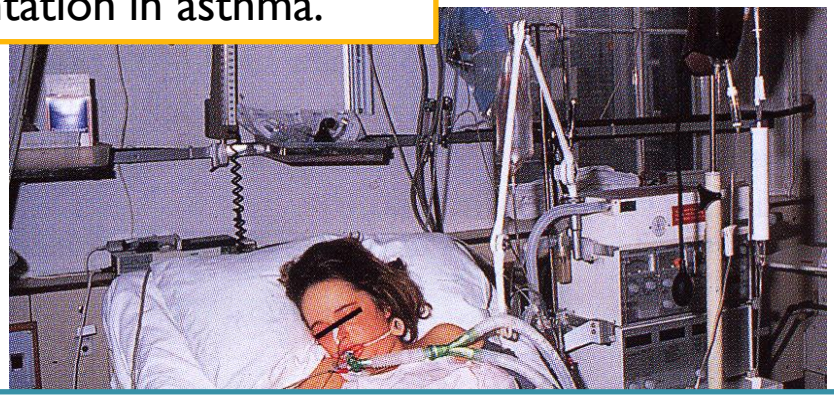
CLINICAL COURSE of BA

- The clinical manifestations vary from occasional wheezing to paroxysms of dyspnea and respiratory distress.
- In a classic asthmatic attack there is **dyspnea, cough, difficult expiration, progressive hyperinflation of lung and mucous plug in bronchi**. This may resolve spontaneously or with treatment.
- Nocturnal cough
- Increased anteroposterior diameter, due to air trapping and increase in residual volume
- Status asthmaticus – severe cyanosis and persistent dyspnea, may be fatal

The range of presentation in asthma.



This patient was found incidentally to have a degree of reversible airways obstruction during a routine medical examination.



medical emergency with acute severe breathlessness, diagnosed as a case of status asthmaticus which required immediate intensive care including intermittent positive-pressure ventilation.

STATUS ASTHMATICUS

- It is the most severe form of asthma. It refers to severe bronchoconstriction that does not respond to the drugs that usually abort the acute attack. There is severe acute paroxysm of respiratory distress.
- This situation is potentially serious and requires hospitalization. Patients in status asthmaticus have hypoxemia and often hypercapnia.
- In particularly severe episodes the ventilatory functions may be so impaired so as to cause severe cyanosis and even death.
- They require oxygen and other pharmacologic interventions.
- It may persists for days and even weeks.

COMPLICATIONS OF ASTHMA

- **Airway remodeling**: some persons with long standing asthma develop permanent structural changes in the airway with hypertrophy of muscle, thickened BM and increased glands. These result in progressive loss of lung function with increase airflow obstruction and airway responsiveness.
- **Superimposed infection** i.e. pneumonia
- **Chronic bronchi**tis (i.e.Asthmatic bronchitis: chronic bronchitis with superimposed asthma)
- **Emphysema, pneumothorax and pneumomediastinum**
- **Bronchiectasis**
- **Respiratory failure** requiring intubation in severe exacerbations i.e. status asthmaticus
- In some cases **cor pulmonale and heart failure** develop.

Prognosis

- Approximately half the children diagnosed with asthma in childhood outgrow their disease by late adolescence or early adulthood and require no further treatment.
- Patients with poorly controlled asthma develop long-term changes over time (i.e. with airway remodeling). This can lead to chronic symptoms and a significant irreversible component to their disease.
- Many patients who develop asthma at an older age also tend to have chronic symptoms.

Prognosis

- Remission—approximately 50% of cases of childhood asthma resolve spontaneously but may recur later in life; remission in adult-onset asthma is less likely.

- Mortality—death occurs in approximately 0.2% of asthmatics. Mortality is usually (but not always) preceded by an acute attack and about 50% are more than 65 years old.

Prevention

- Control of factors contributing to asthma severity. Exposure to irritants or allergens has been shown to increase asthma symptoms and cause exacerbations.

- Clinicians should evaluate patients with persistent asthma for allergen exposures and sensitivity to seasonal allergens. Skin testing results should be used to assess sensitivity to common indoor allergens.

- All patients with asthma should be advised to avoid exposure to allergens to which they are sensitive.

Asthma: Summary:

Episodic attacks of bronchoconstriction

Types

- Extrinsic asthma: Type 1 Hypersensitivity reaction, IgE, childhood, family Hx of allergy.
- Intrinsic asthma: associated e intake of aspirin, exercise, cold induced. No Hx of allergy

Morphology

- Hypertrophy of bronchial smooth muscle & hyperplasia of goblet cells e eosinophils, thickened basement membrane
- Mucous plug e Curschmann spirals & Charcot-Leyden crystals.

Complication

- Superimposed infection
- Chronic bronchitis
- Pulmonary emphysema
- Status asthmaticus