Pathology of Asthma

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Bronchial Asthma

- Definition: chronic, relapsing inflammatory lung disorder characterised by reversible bronchoconstriction. The airways are hyperreactive owing to increased responsiveness of the tracheobronchial tree to various stimuli.

Pathogenesis

- 2 major components.
- Chronic airway inflammation
- Bronchial hyperresponsiveness

- The inflammation involves many cell types & numerous mediators.

- Best studied is Atopic asthma hence much information is from this form of asthma.

- Types of asthma: Atopic asthma, non-atopic asthma, drug-induced asthma & Occupational Asthma.

Atopic Asthma

- Most common and begins in childhood.
- Disease triggered by environmental antigens e.g. dust, pollen, animal excreta, food, temperature change, potentially any.
- There is a genetic link: A positive family history is common
- A positive family history of atopy, allergic rhinitis, urticaria and eczema.

- There is genetic predisposition: areas of interest and research are – antigen presentation (HLA complex), T-cell activation, cytokine production regulation & receptors for bronchodilators.
- To test predisposed individuals are skin test is done to elicit Type I IgE hypersensitivity reaction.

Pathogenesis

- In airways, hypersensitivity reaction set in motion by:
  - Initial sensitisation to inhaled antigens (allergens).
  - Inhaled allergens stimulate Th2-type T cells to release cytokines: IL-4 & IL-5.
- These cytokines promote IgE production by B cells, growth of mast cells (IL-4) & growth & activation of eosinophils (IL-5).
- IgE mediated reaction to inhaled allergens elicits an *acute response* & a *late-phase reaction.*

Pathogenesis

- Reaction to airborne antigens occurs first on sensitized mast cells on the mucosal surface.
- Resultant mediator release opens mucosal inter-cellular tight junctions.
- Opening of inter-cellular tight junctions enhances penetration of antigens to sub mucosal mast cells.
- In addition, stimulation of subepithelial vagal (parasympathetic) receptors by inflammatory mediators & cytokines provokes bronchoconstriction via central & local reflexes.
- All these occur within minutes of exposure to allergen. Termed *acute* or *immediate* response.
- Acute response characterised by: bronchoconstriction, oedema, mucus secretion & hypotension (severe).
- Mast cells release cytokines causing recruitment of neutrophils, monocytes, lympocytes, basophils and eosinophils. Arrival of these inflammatory cells set the scene for late-phase reaction that can occur 4-8 hrs later, & may persists for 12-24 hrs.

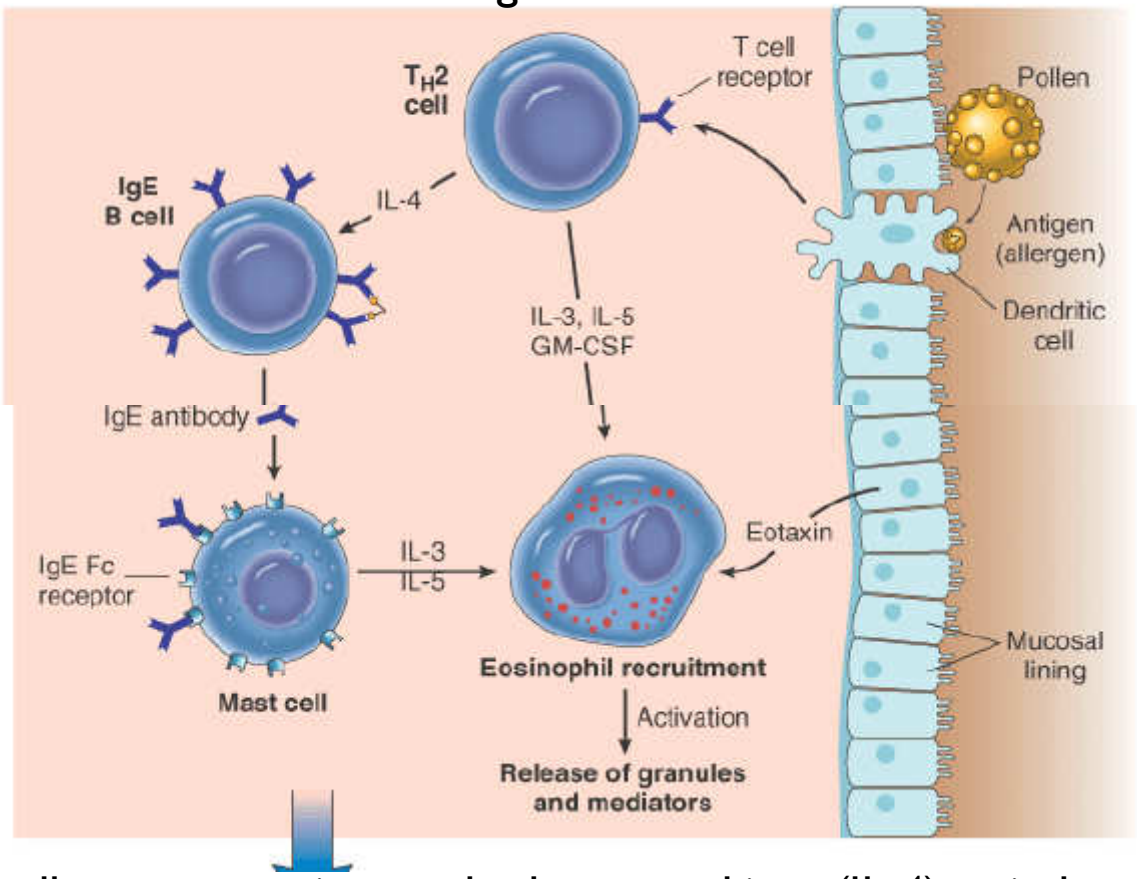
Pathogenesis – Late Phase Reaction

- Second wave of mediator release produce the late phase reaction.
- Late phase reaction mediated
  - by leucocytes recruited by chemotactic factors & cytokines release from mast cells in the acute phase reaction.
  - Inflammatory cells already present in asthmatics (recurrent attacks), vascular endothelium & airway epithelial cells.
- Epithelial cells produce wide variety of cytokines in response to infectious antigens.

Late Phase Reaction Mediators

- Eotaxin – produced by airway epithelial cells.
  - Potent chemoattractant and activator of eosinophils.
- Major basic protein (eosinophils) causes epithelial damage and airway constriction.
- Leukotrienes – C4, D4 & E4.
  - Cause bronchoconstriction, increased vascular permeability & increase mucus secretion.
- Histamine (bronchoconstrictor), PGD2 (bronchoconstriction & Vasodilation), PAF (plt aggregation & histamine & serotonin release from plt granules).
- Interleukins, TNF, chemokines (e.g. eotaxin), neuropeptides, NO, bradykinin and endothelins.

Sensitization to inhaled allergen.

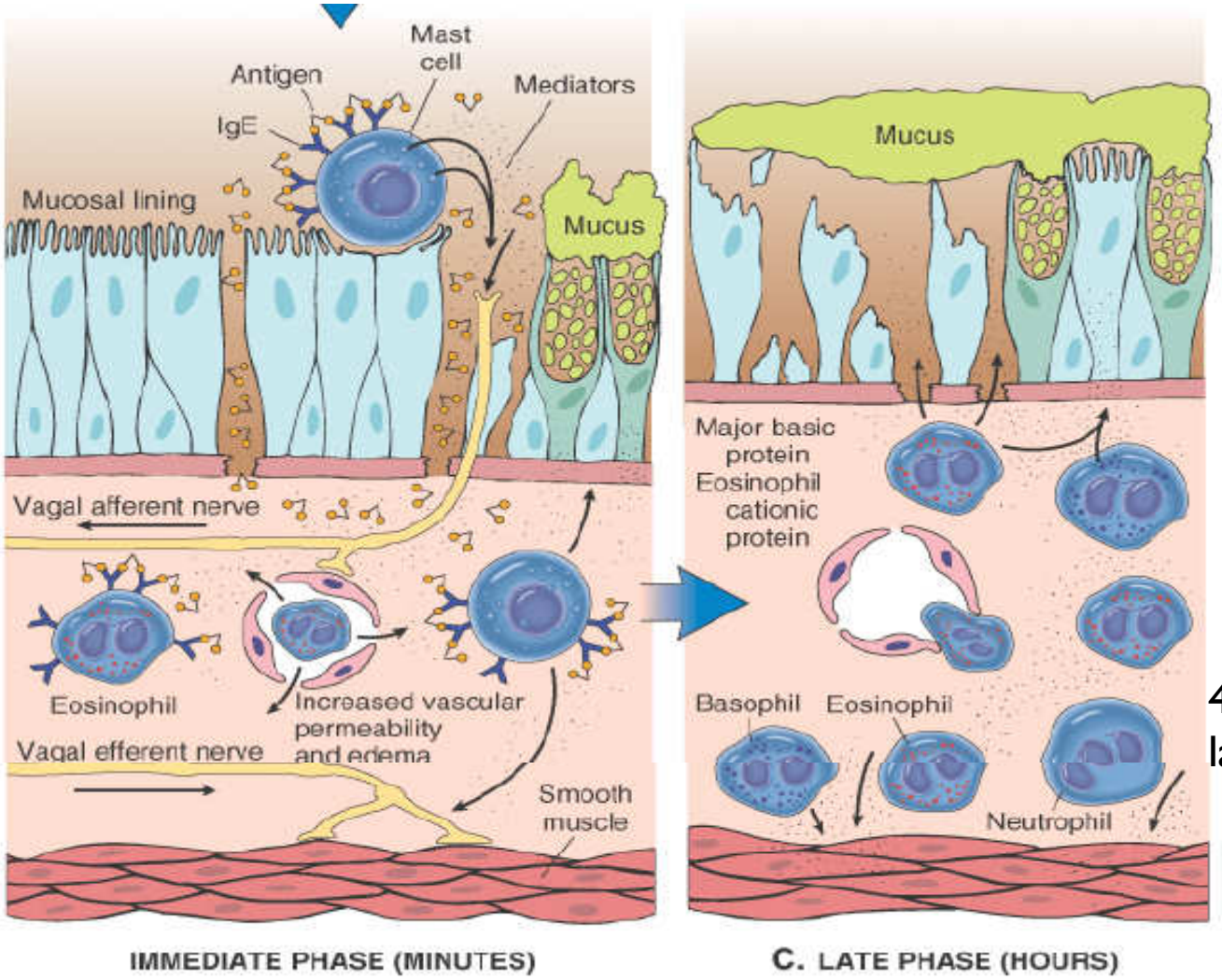


Dendritic cells process antigen and present to T cells via HLA system

T cells process antigen and release cytokines (IL-4) to induce B cell to produce IgE.

IgE is then bound to Fc receptors of basophils and tissue mast cells
Re-exposure of Ag activates Mast cells to release mediators

Ref: Robins Pathological Basis of Diseases, 7th Ed



4-8 hrs later

On re-exposure, allergen reacts with bound IgE resulting in cytolysis & degranulation of basophils & tissue mast cells. This rxn requires cross-linking of adjacent IgE molecules on mast cell surface. Degranulation results in release of pre-formed inflammatory mediators.

Non-Atopic Asthma

- Frequently triggered by viruses that cause respiratory infections (rhinovirus, parainfluenza virus).
- Normal IgE levels.
- Positive family history uncommon.
- No associated allergies.
- Skin test are usually negative.

Non-atopic Asthma: Pathogenesis

- ?hyperirritability of bronchial tree to virus infection and subsequent inflammation.
- Current theory: virus induced inflammation of respiratory mucosa lowers threshold of subepithelial vagal receptors to irritants.
- Inhaled air pollutants can also contribute to chronic airway inflammation & hyperreactivity.

Drug-Induced Asthma

- Several drugs are known to induce asthma.
- Aspirin sensitive asthma occur in individuals with recurrent allergic rhinitis and nasal polyps.
- Highly sensitive to small doses of aspirin. Can occur with urticaria.
- Probably does this by inhibiting cyclooxygenase pathway of AA metabolism without affecting lipoxygenase route, favoring synthesis of bronchoconstrictor leukotrienes.

Occupational Asthma

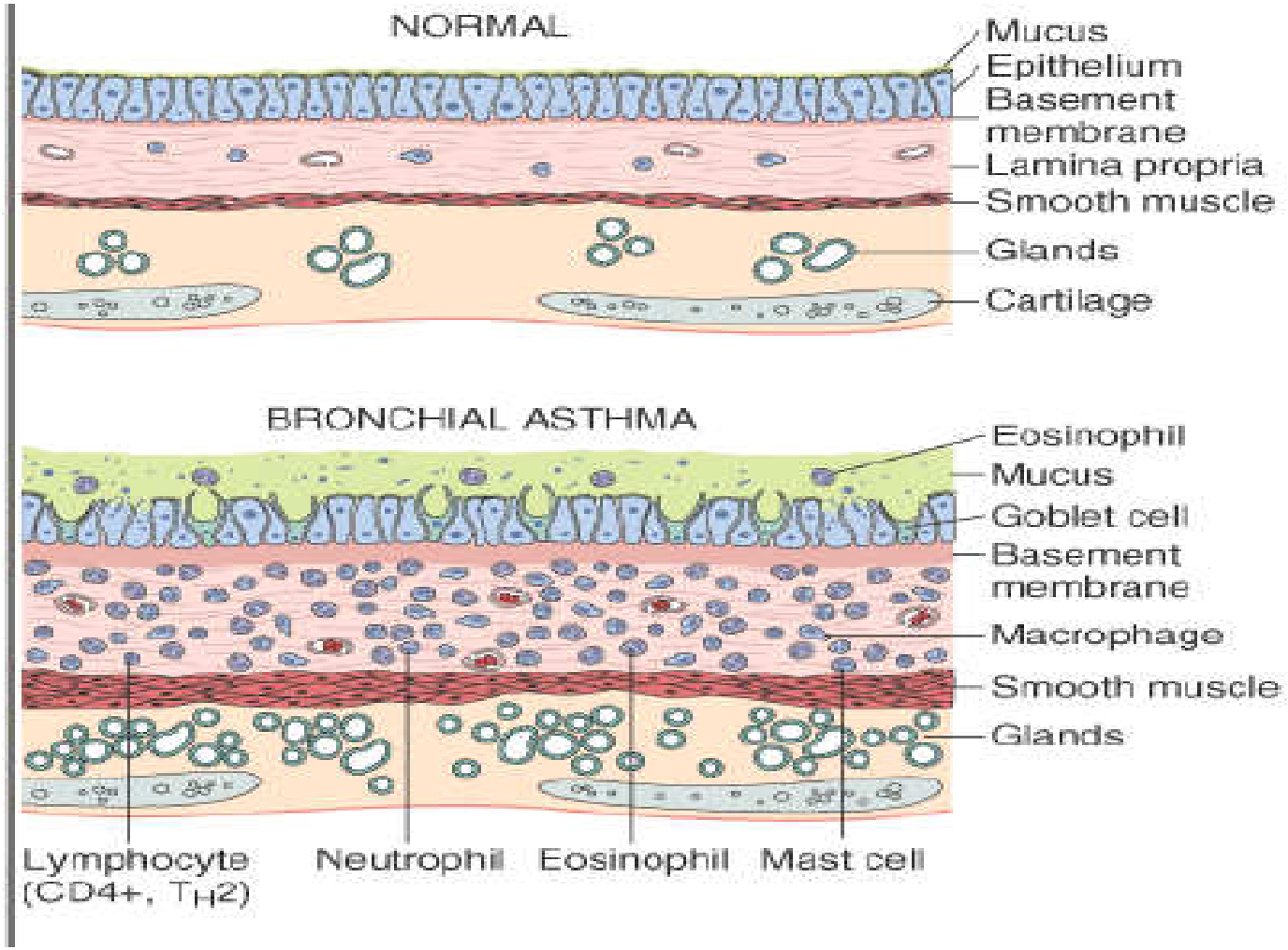
- This form stimulated by fumes (epoxy resins, plastics), organic or chemical dusts (wood, cotton, platinum), gases, (toluene).
- Other chemicals – formaldehyde, penicillin products.
- Minute amounts required to induce attack.
- Occurs after repeated exposure.
- Underlying mechanism vary – according to stimulus.
- IgG mediated reactions – direct liberation of bronchoconstrictor substances and hypersensitivity.

Morphology - airway

- Macro:
- Overdistended due to overinflation.
- Small areas of atelectasis.
- Occlusion of bronchi and bronchioles by thick, tenacious mucus plugs.
- Essentially normal appearing lung.

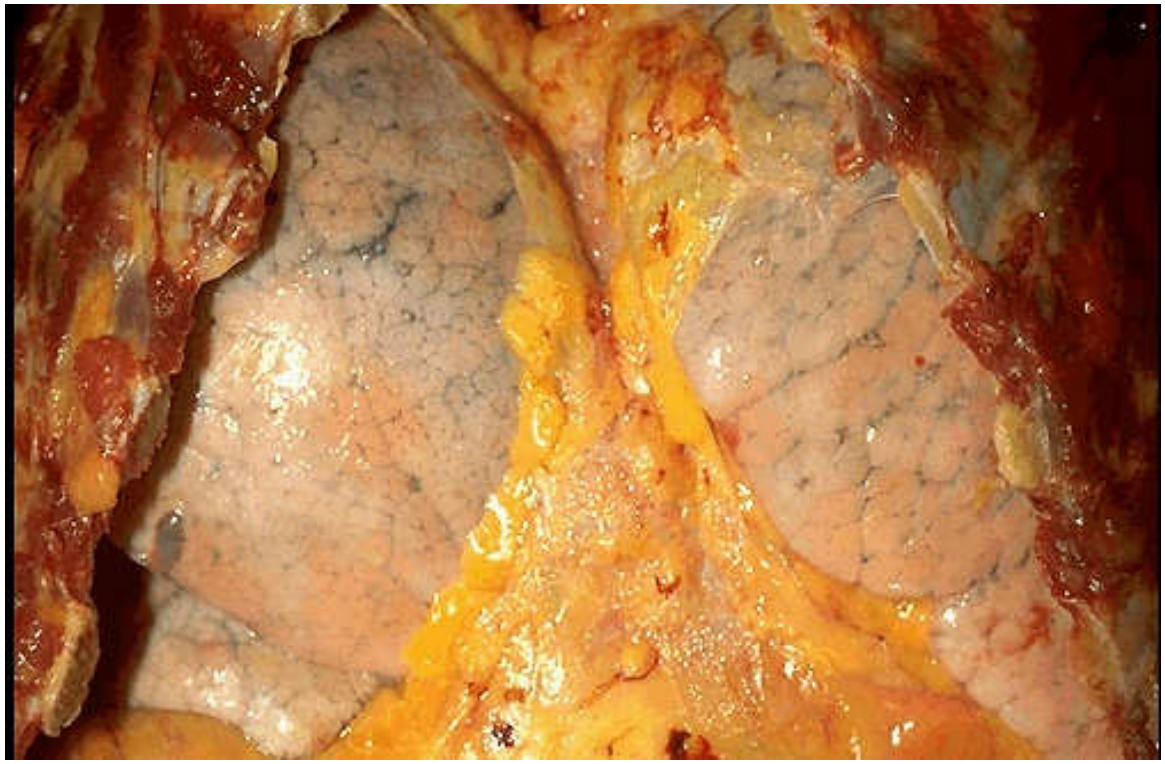
- Micro:
- Smooth muscle hypertrophy, mucus plugs, widened submucosa with inflammation predominantly eosinophils.
- Mucus plugs contain whorls of shed epithelium referred to as Curschmann's spirals.
- Numerous eosinophils, Charcot-Leyden crystals present (collections of crystalloid made from eosinophil membrane protein).

Morphology in Asthma



Ref: Robins Pathological Basis of Diseases, 7th Ed.

Gross Pathology

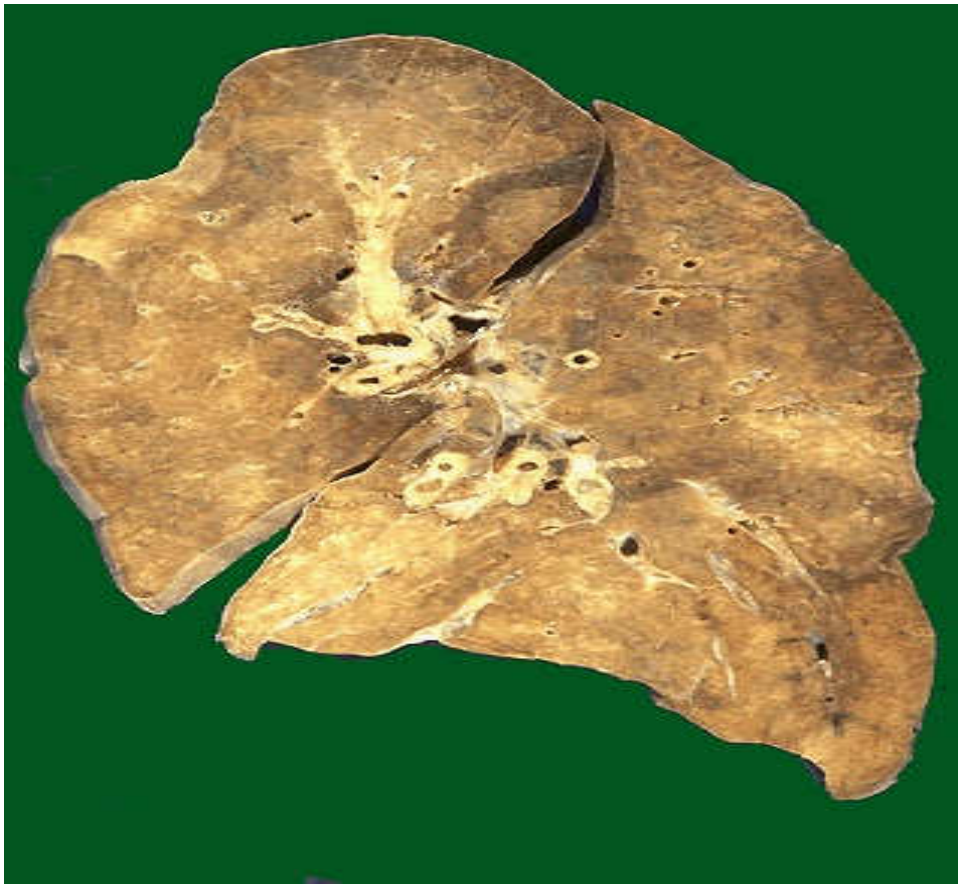


Normal appearance

hyperinflated

Ref: Internet Pathology laboratory, University of Utah

Gross Pathology



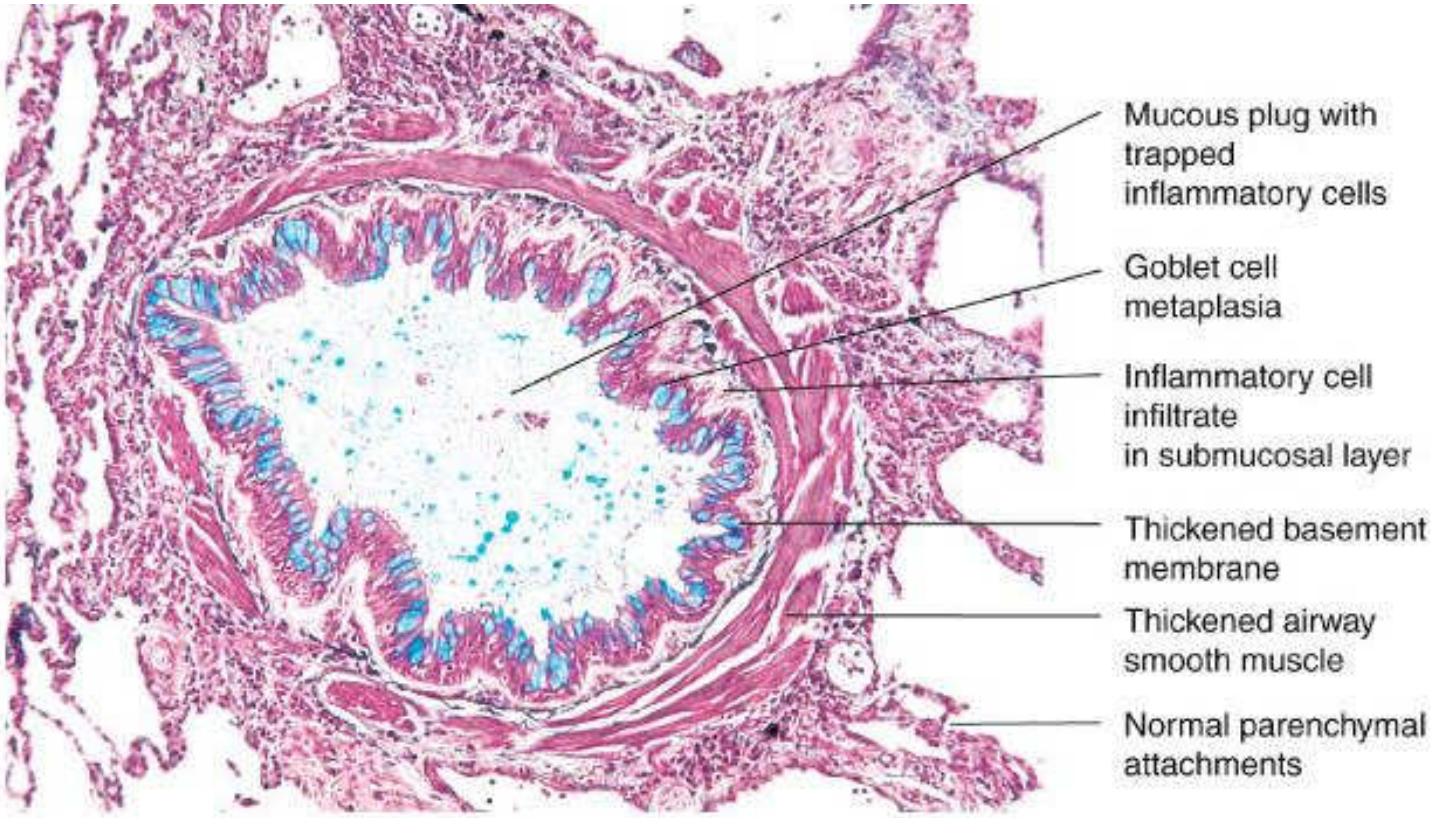
Cut section
normal

Ref: Internet Pathology laboratory, University of Utah

Mucus Plug

Ref: Internet Pathology laboratory, University of Utah

Histopathology



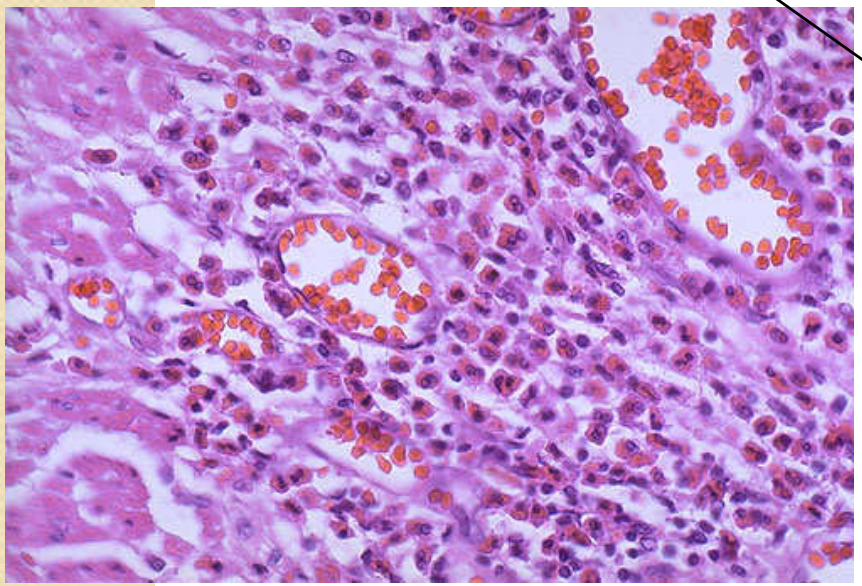
Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

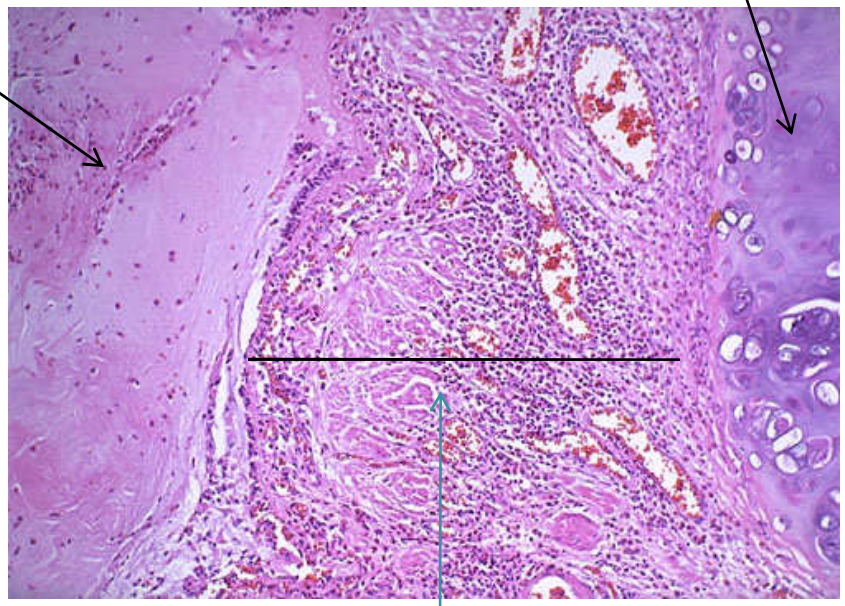
Image from: littledoctors.wordpress.com

Histopathology

Mucus plug in bronchial lumen

Bronchial cartilage

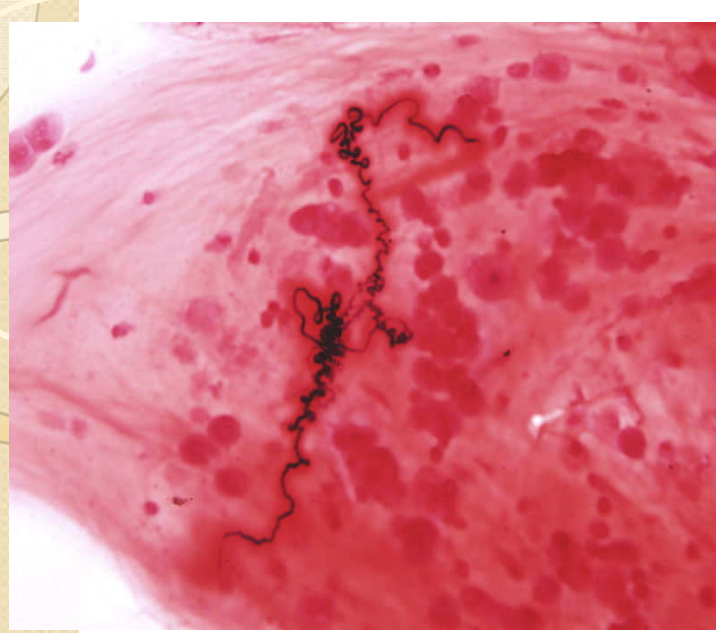




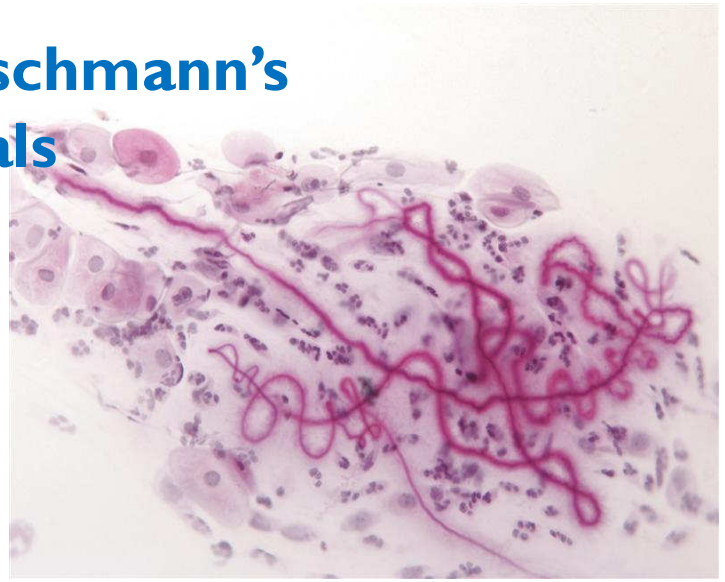
Inflammation – Eosinophils predominant & vascular congestion

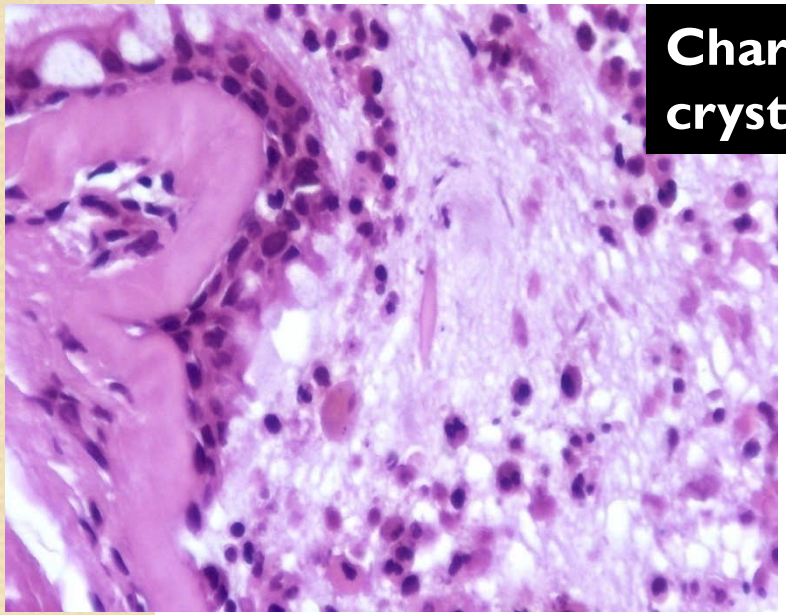
Widened submucosa: smoth muscle hypertrophy, oedema, inflammation, vascular congestion

Ref: Internet Pathology laboratory, University of Utah

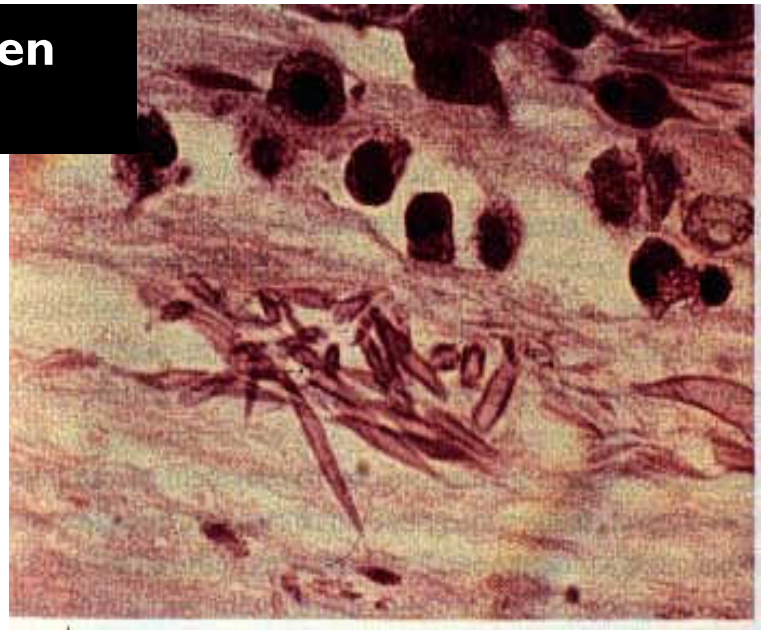


Curschmann's spirals





Charcoat-Leyden crystals



Ref: www.wikipedia.org

Clinical Course

- Asthma attack can last up to several hours followed by prolonged cough.
- Coughing up copious mucous secretions provide great relief.
- These symptoms may persist in low form (clinical classification).
- Severe form: Status asthmaticus can persists for days or weeks. Can cause severe hypoxia and death if not managed well.
- With appropriate therapy patient maintain good quality of life.
- Complications: emphysema, chronic persistent bronchitis, bronchiectasis or pneumonia, cor pulmonale & HF.

Diagnosis

- Usually clinical if acute.
- Chronic – Lung function tests, good history and examination.
- Sputum: eosinophils, Curschmann's spirals & Charcoat-Leyden crystals.
- Blood – increased eosinophils.

END

Main reference: Robins Pathological Basis of Disease.

Download seminar notes in PDF format at:

http://pathologyatsmhs.com/

Visit Internet Pathology Laboratory:
http://library.med.utah.edu/WebPath/