PATHOLOGY

SHEET NO. 3

RESPIRATORY SYSTEM

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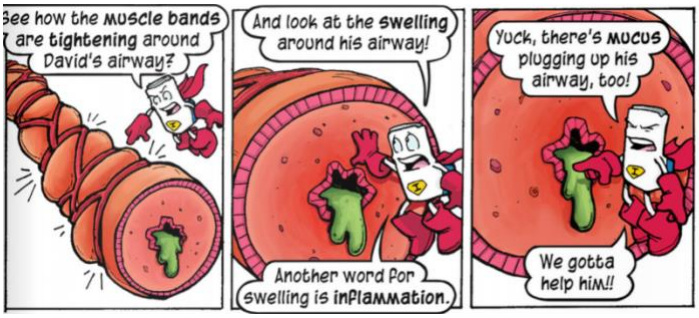
Asthma

Asthma is a chronic inflammatory disorder of the airways that causes recurrent episodes of **wheezing, dyspnea (shortness of breath), chest tightness and cough**, especially at night and/or early in the morning. Its **hallmarks** are:

1. **Intermittent** (not continuous) and **reversible** (not permanent) airway obstruction [bronchospasm].
2. Chronic bronchial inflammation with **eosinophil** infiltration.
3. Bronchial smooth muscle cell **hypertrophy and hyper-reactivity.**
4. Increased **mucus secretion**.



The third hallmark occurs with repeated attacks (not from the first or second ones)

✳ **Major Factors** contributing to the development of asthma are:

1. Genetic predisposition to type 1 hypersensitivity (atopy).
2. Acute and chronic airway inflammation.
3. Bronchial hyper-responsiveness to a variety of stimuli.

✳ Asthma can be **triggered** by exposure to different stimuli such as:

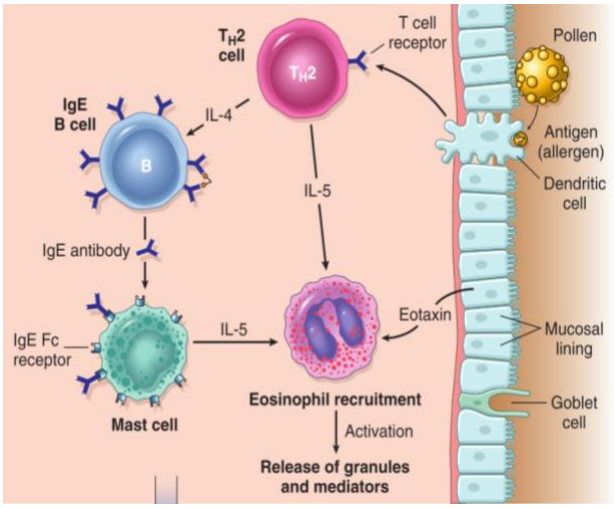
- Respiratory infections (especially viral).
- Airborne irritants (smoke and fumes).
- Cold air.
- Stress.
- Exercise.

✳ Pathogenesis

This figure shows the initial airway response after exposure to inhaled allergen **for the first time**.
The allergen(antigen) will be recognized by antigen-presenting cells (APCs) like dendritic cells in the epithelial lining of the bronchial wall, resulting in type 2 helper T (T_H2) cell activation which starts releasing inflammatory mediators.

Examples of these mediators and their functions:

- ✓ IL-4 and IL-13 stimulate IgE production
- ✓ L-5 activates eosinophils
- ✓ IL-13 stimulates mucus production

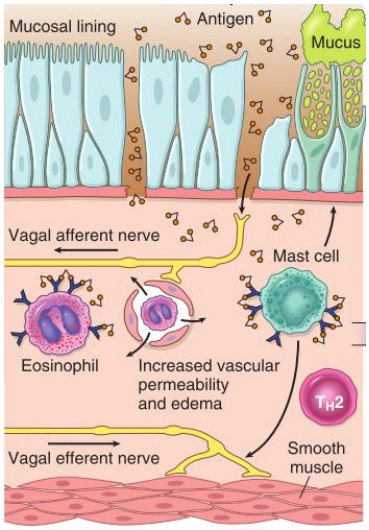


IgE coats submucosal mast cells, which in the re-exposure to the same allergen release their granule contents and secrete cytokines and other mediators.

- There is NO mast cell degranulation in the **first** exposure.
- Usually there is NO symptoms in first exposure.

In case of re-exposure to the same allergen, Mast cell-derived mediators produce two waves of reaction: 1. early (immediate) phase 2. late phase

✳ Early-phase reaction

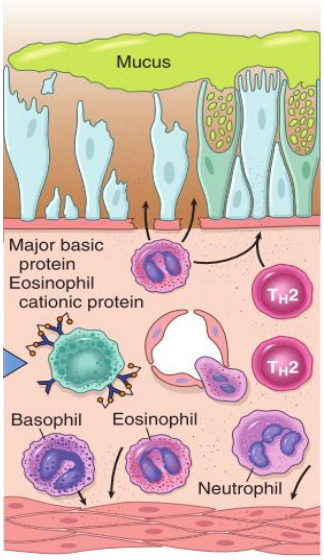


Triggered by Ag-induced cross-linking of IgE bound to Fc receptors on mast cells. Mast cells release preformed mediators that directly and via neuronal reflexes induce:

1. Bronchoconstriction.
2. Increased mucus production.
3. Vasodilation (↑ vascular permeability).
4. Recruitment of leukocytes.

- The early phase takes minutes after the exposure.

✳ Late-phase reaction



- The late-phase reaction is inflammatory in nature.

Inflammatory mediators → stimulate epithelial cells to produce chemokines (including eotaxin, a potent chemoattractant and activator of eosinophils) → recruitment of TH2 cells, eosinophils, and other leukocytes to the site of reaction → amplifying an inflammatory reaction that is initiated by resident immune cells.

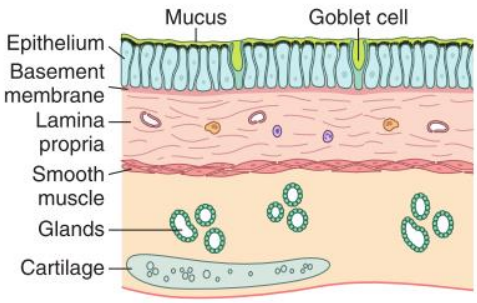
This figure shows leukocytes recruited to the site of the reaction including neutrophils, eosinophils, basophils, lymphocytes and monocytes, which all will initiate the late-phase reaction.

- Eosinophils release major basic proteins and eosinophil cationic proteins that cause damage to the epithelium.

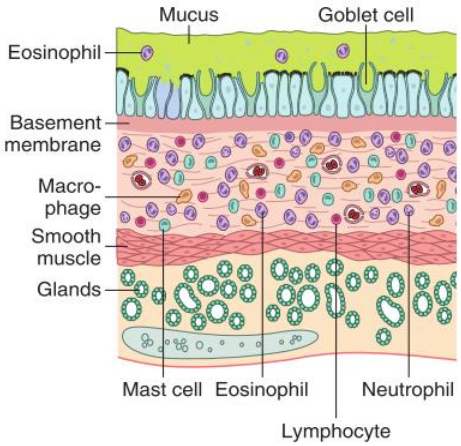
Repeated bouts of inflammation lead to structural changes in the bronchial wall that are collectively referred to as **airway remodeling**. These changes include:

1. Hypertrophy of bronchial smooth muscle
2. Hypertrophy in mucus glands
3. Increased vascularity
4. Deposition of subepithelial collagen

A. Normal airway



B. Airway in asthma



(A and B) Comparison of a normal airway and an airway involved by asthma. The asthmatic airway is marked by:

1. accumulation of mucus in the bronchial lumen secondary to an increase in the number of mucus-secreting goblet cells in the mucosa.
2. hypertrophy of submucosal glands.
3. intense chronic inflammation due to the recruitment of eosinophils (mainly), macrophages, and other inflammatory cells.
4. thickened basement membrane (due to fibrosis and collagen deposition).
5. hypertrophy and hyperplasia of smooth muscle cells.

TYPES OF ASTHMA

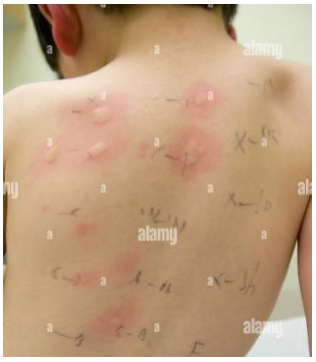
1 Atopic asthma

- The most common type.
- Classic example of type 1 IgE–mediated hypersensitivity reaction.
- beginning in childhood with a positive family history of atopy and/or asthma.
- Attacks are preceded by allergic rhinitis, urticaria, or eczema.
- Attacks are triggered by allergens in dust, pollen, animal dander, or food, or by infections.

* The mechanism of action mentioned in the previous page.

Diagnosis:

1. Skin test with the antigen: Immediate wheal-and-flare reaction (eg; skin prick test is the most common test).
   How is it performed? Tiny drops of the allergen are put on the back, then a needle is used to break the skin underneath each drop. Now, in case someone is allergic, a red, itchy rash will appear especially at the site of the needle break.



2. Serum radioallergosorbent tests (RASTs): blood test using radioimmunoassay to detect specific IgE antibodies.

2 Non-atopic asthma

- No evidence of allergen sensitization (not mediated by type 1 hypersensitivity reaction).
- Negative skin test.
- A positive family history of asthma is less common.
- Common triggers:
  - **a.** viral respiratory infections (rhinovirus, parainfluenza virus)
  - **b.** inhaled air pollutants (sulfur dioxide, ozone, nitrogen dioxide)
- The mechanism isn't well understood.
- 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

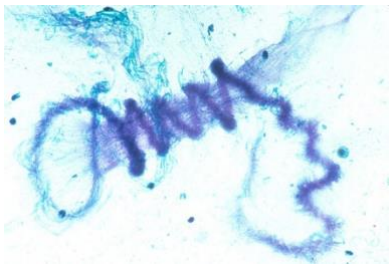
- Aspirin is the most striking example.
  - present with recurrent rhinitis, nasal polyps, urticaria, and bronchospasm.
- The precise pathogenesis is unknown but is likely to involve some abnormality in prostaglandin metabolism stemming from the inhibition of cyclooxygenase by aspirin.

4 Occupational asthma

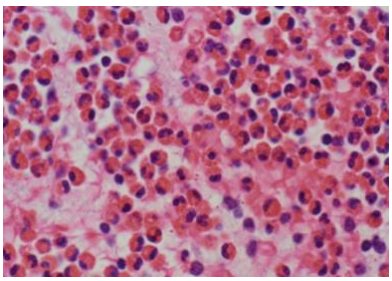
- Asthma attacks usually develop after repeated exposure to the antigen at the workplace.
- Triggered by fumes (plastics), organic and chemical dusts (wood, cotton, platinum), gases (toluene), and other chemicals.

✳ Morphology

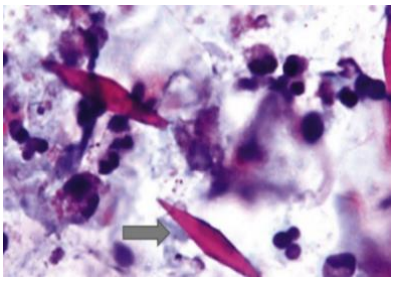
1. Occlusion of bronchi and bronchioles by thick mucus plugs.
2. Mucous plugs contain whorls of shed epithelium called **Curschmann Spirals** in sputum.
3. Eosinophils are the characteristic inflammatory cells in asthma.
4. **Charcot-Leyden crystals**: crystalloids made up of the eosinophil protein galectin-10.
5. Airway remodeling.



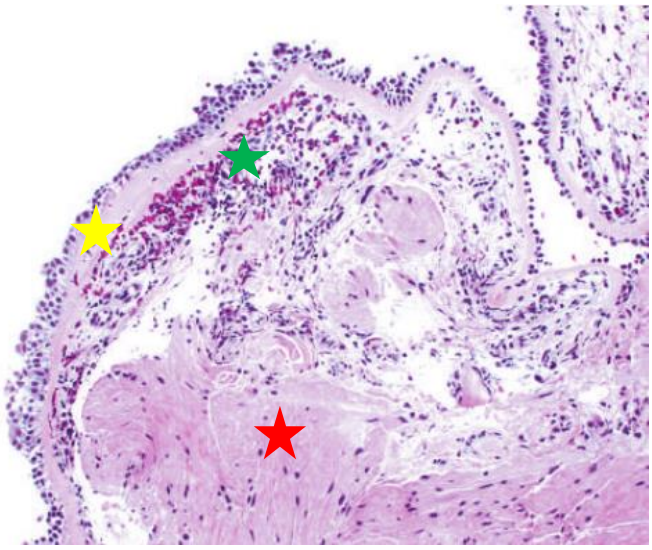
Curschmann spirals



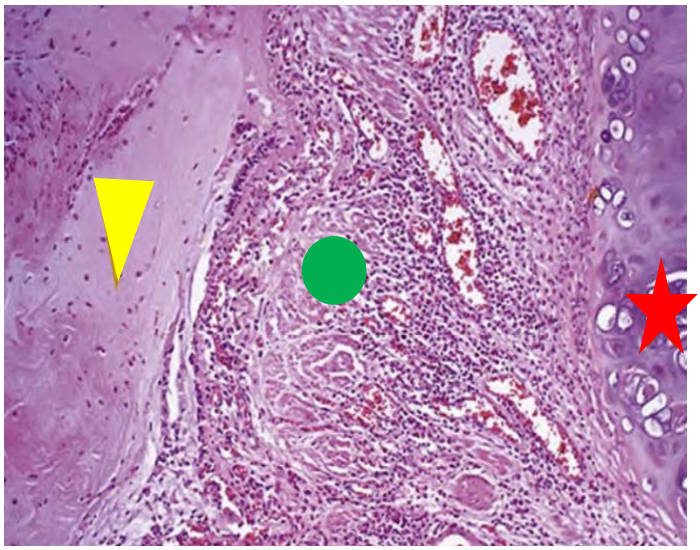
Eosinophils



Charcot-Leyden crystals



Yellow: Sub-basement membrane fibrosis (collagen deposition).
Green: Eosinophil inflammation.
Red: Smooth muscle hyperplasia.



Yellow: Lumen stuffed with mucus.
Green: muscle hyperplasia + edema + Eosinophil inflammation.
Red: Bronchial cartilage.

✳ Clinical features

1. Dry coughing: Becomes worse at night and early morning.
2. Wheezing: Whistling sound especially during expiration.
3. Chest tightness: It feels like something is squeezing or sitting on the chest
4. Dyspnea: shortness of breath/inability to breathe properly (due to bronchospasm).

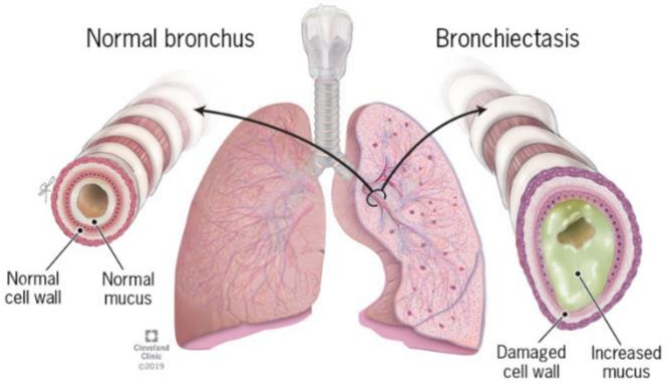
- Status asthmaticu: A severe paroxysm that does not respond to therapy and persists for days or weeks. It is associated with hypercapnia (increased carbon dioxide in the bloodstream), acidosis and severe hypoxia which could be fatal.

✳ Management

1. Anti-inflammatory drugs (glucocorticoids).
2. Bronchodilators (beta-adrenergic drugs).
3. Leukotriene inhibitors.

Bronchiectasis

Permanent (irreversible) dilation of bronchi and bronchioles caused by destruction of smooth muscle and supporting elastic tissue.
[remember emphysema is permanent dilation of the airways distal to the terminal bronchioles].
It is not a primary disorder, as it always occurs **secondary** to persistent infection or obstruction.
Typically results from or is associated with chronic necrotizing infections.



Clinically: cough and expectoration of copious amounts of purulent sputum.
(Purulent sputum is off-white, yellow or green, and opaque. It indicates the presence of large numbers of white blood cells and cellular debris (pus)).
Diagnosis: appropriate history and radiographic demonstration of bronchial dilation.

✳ Pathogenesis

Two intertwined processes contribute to bronchiectasis:

1. **OBSTRUCTION:** Impairs the clearance of mucus secretions, providing a favorable environment for superimposed infection. This causes inflammatory damage to the bronchial wall and accumulation of exudate, which further distend the airways leading to irreversible dilation
2. **PERSISTENT NECROTIZING INFECTION** in the bronchi or bronchioles may lead to poor clearance of secretions. The accumulation of secretions results in obstruction and inflammation associated with peribronchial fibrosis and traction on the bronchi, which also leads to irreversible dilation.

The conditions that most commonly predispose to bronchiectasis include:

Bronchial obstruction:

- By tumors, foreign bodies, and impaction of mucus OR as a complication of atopic asthma and chronic bronchitis.
- Bronchiectasis is localized.

Congenital or hereditary conditions:

- Cystic fibrosis
  - widespread severe bronchiectasis
  - Due to obstruction caused by abnormally viscid mucus and secondary infections.
- Immunodeficiency states
  - Due to recurrent bacterial infections
  - localized or diffuse

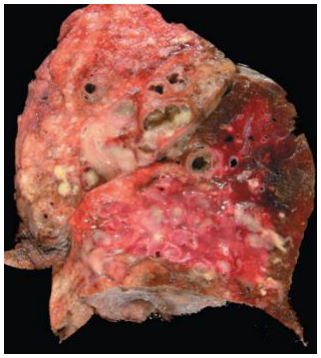
- Primary ciliary dyskinesia (immotile cilia syndrome)
  - Rare autosomal recessive disorder → abnormalities of cilia → inability to clear the mucus → persistent infections.
  - It is associated with bronchiectasis and sterility in males.

Necrotizing, or suppurative, pneumonia

- particularly with virulent organisms such as Staphylococcus aureus or Klebsiella spp.

✳ Morphology

1 Macroscopic:



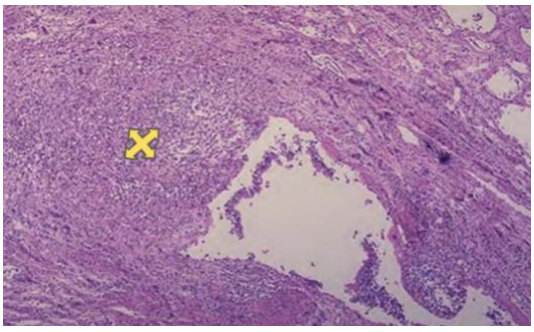
- Lower lobes bilaterally (The most common location to be affected).
- It is most severely involved in distal bronchi and bronchioles.
- The airways may be dilated to as much as four times their usual diameter.

This image shows a gross appearance of a lung of a cystic fibrosis patient with bronchiectasis. The bronchi are markedly dilated and filled with purulent mucus.

2 Microscopic:

The histologic findings vary with the activity and chronicity of the disease.

- **In full-blown active cases:**
  - Intense acute and chronic inflammatory exudate within the walls of the bronchi and bronchioles → desquamation of lining epithelium and extensive ulceration.
  - Typically mixed flora is cultured from the sputum including: staphylococcus, streptococcus, pneumococcus, enteric organizers and aerobic bacteria.
- **When healing occurs:**
  - The lining epithelium may regenerate completely however the injury cannot be fully reversed.
  - Abnormal dilation and scarring (permeant).
  - Fibrosis of bronchial and bronchiolar walls.
  - Peribronchiolar fibrosis.
  - Abscess formation in some cases.



This image shows bronchiectasis. Necrotizing inflammation in the center has dilated the bronchus to the degree that you cannot see the mucosal lining because it is mostly desquamated.

✳ Clinical features

1. severe, persistent cough with mucopurulent sputum.
2. dyspnea, rhinosinusitis, and hemoptysis

3. symptoms are episodic
4. precipitated by URTI.
5. severe widespread bronchiectasis: significant obstructive ventilatory defects, hypoxemia, hypercapnia, pulmonary hypertension, and cor pulmonale.

✳ Clinical case

A 45-year-old gentleman smoked two packs of cigarettes per day for 20 yrs. For the past 4 years, he has had a chronic cough with copious mucoid expectoration. During the past year, he has had multiple respiratory tract infections. He has also developed difficulty breathing, tightness of the chest, and audible wheezing. His breathing difficulty is relieved by inhalation of a beta-adrenergic agonist and disappears after the chest infection has resolved. Which of the following pathologic conditions is most likely responsible for his clinical condition?

A) Alpha 1-Antitrypsin deficiency with pan lobular emphysema
B) Centrilobular emphysema with cor pulmonale
C) Chronic asthmatic bronchitis
D) Cystic fibrosis with bronchiectasis

Answer: c

Table 13.1 Disorders Associated With Airflow Obstruction: The Spectrum of Chronic Obstructive Pulmonary Disease

Clinical Entity	Anatomic Site	Major Pathologic Changes	Etiology	Signs/Symptoms
Chronic bronchitis	Bronchus	Mucous gland hypertrophy and hyperplasia, hypersecretion	Tobacco smoke, air pollutants	Cough, sputum production
Bronchiectasis	Bronchus	Airway dilation and scarring	Persistent or severe infections	Cough, purulent sputum, fever
Asthma	Bronchus	Smooth muscle hypertrophy and hyperplasia, excessive mucus, inflammation	Immunologic or undefined causes	Episodic wheezing, cough, dyspnea
Emphysema	Acinus	Air space enlargement, wall destruction	Tobacco smoke	Dyspnea
Small airway disease, bronchiolitis*	Bronchiole	Inflammatory scarring, partial obliteration of bronchioles	Tobacco smoke, air pollutants	Cough, dyspnea

*Can be present in all forms of obstructive lung disease or by itself.

SUMMARY

ASTHMA

- Asthma is characterized by reversible bronchoconstriction caused by airway hyperresponsiveness to a variety of stimuli.
- Atopic asthma most often is caused by a T_H2 and IgE-mediated immunologic reaction to environmental allergens and is characterized by early-phase (immediate) and late-phase reactions. The T_H2 cytokines IL-4, IL-5, and IL-13 are important mediators. Non-T_H2 inflammation also has roles in atopic asthma that are being defined.
- Triggers for nonatopic asthma are less clear but include viral infections and inhaled air pollutants, which also can trigger atopic asthma.
- Eosinophils are key inflammatory cells found in almost all subtypes of asthma; eosinophil products (such as major basic protein) are responsible for airway damage.
- Airway remodeling (sub-basement membrane thickening and hypertrophy of bronchial glands and smooth muscle) adds an irreversible component to the obstructive disease.