Doctor.021

no.1

RS PATHOLOGY

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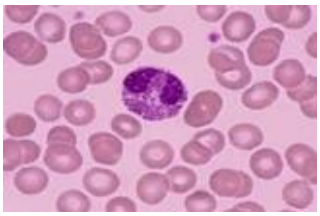
Asthma

- **Chronic inflammatory disorder of the airways.**
- **Causes recurrent episodes of wheezing, Dyspnea, chest tightness and cough particularly at night and/or early in the morning.**

  Click to hear the wheezing sound.
  Click to hear a patient with dyspnea.

- **Its hallmarks are:**



  a) **Intermittent and reversible** (not continuous nor permanent) airway **obstruction (bronchospasm),**
  b) **Chronic bronchial inflammation with eosinophils,**
  c) **Bronchial smooth muscle cell hypertrophy and hyper-reactivity.**
  d) **increased mucus secretion.**

- **MAJOR FACTORS:**
  - ✓ **Genetic predisposition to type I hypersensitivity (atopy).**
  - ✓ **Acute and chronic airway inflammation.**
  - ✓ **Bronchial hyperresponsiveness to a variety of stimuli.**

- **CAN BE TRIGGERED BY:**
  - ✓ **Respiratory infections (especially viral).**
  - ✓ **Airborne irritants (smoke, fumes).**
  - ✓ **Cold air.**
  - ✓ **Stress.**
  - ✓ **Exercise.**

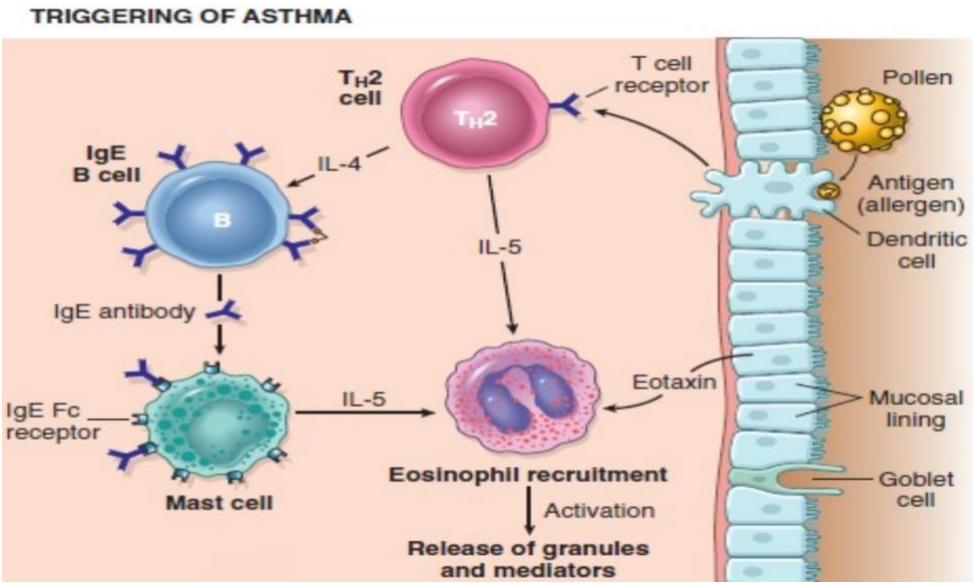
Q: Asthma is an irreversable obstructive airway disease:

- True
- False ✓

Q: Choose the correct statement:

- Asthma is a restrictive lung disease.
- The destruction of airways is characteristic in asthma.
- Asthma is a reversible airway disease. ✓

Asthma pathogenesis



The above figure shows the **initial airway response** after exposure to one of the inhaled allergens **for the first time**. The allergen or the antigen will be recognised by antigen -presenting cells or dendritic cells in the epithelial lining. As a result, T-helper lymphocytes will be activated and start releasing inflammatory mediators, resulting in **IgE production and eosinophils** activation and recruitment.

- ✓ **IL-4 and IL-13, for example, stimulate the IgE production.**
- ✓ **IL-5 activates the eosinophils.**
- ✓ **IL-13 stimulates the mucus production**.

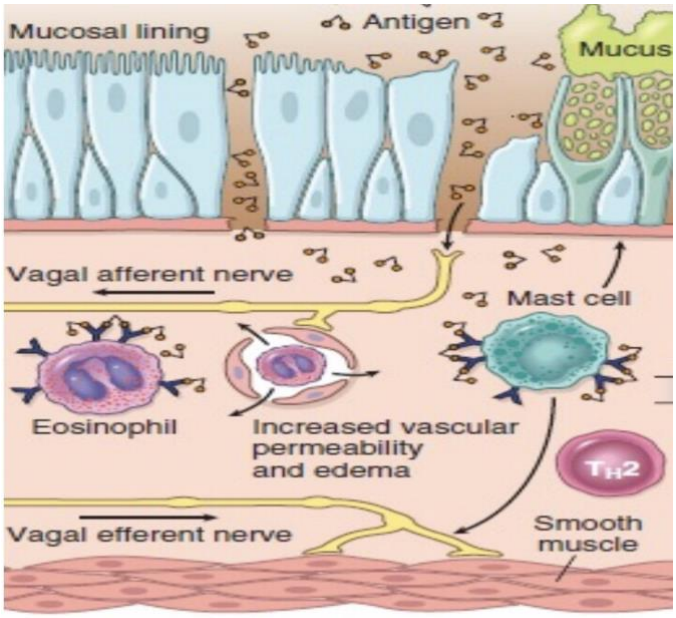
The IgE coats the submucosal mast cells. Upon the re-exposure of the mast cells to the same allergen or antigen, two waves of reaction happen: one is the **early or immediate phase,** and the other is the **late phase.**

- **The early-phase reaction is dominated by:**
  - ✓ **Bronchoconstriction** triggered by mediators released from mast cells, including **histamine, prostaglandin D2, leukotrienes** (e.g. **leukotriene C4, D4, and E4**), and by the **reflux neural pathways.**
  - ✓ **increased mucus production.**
  - ✓ **vasodilation.**

• This figure highlights the **early phase reaction.** **Immediate reaction → on re-exposure to an antigen.**

• This reaction is triggered by Ag-induced cross-linking of IgE that is already bound toFC receptors on mast cells.

• Mast cells release previously performed mediators that directly and via neuronal reflexes induce: bronchospasm, increased vascular permeability, mucus production, and recruitment of leukocytes.

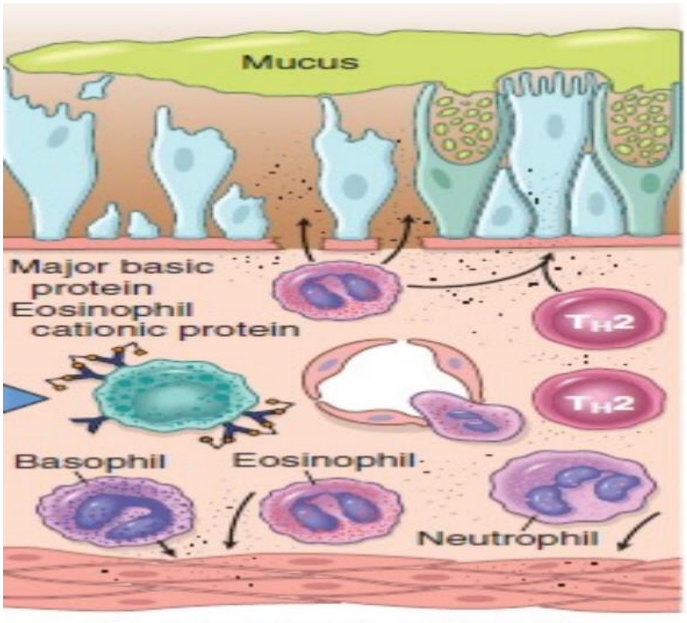


D IMMEDIATE PHASE (MINUTES)

• The late-phase reaction is inflammatory:
Inflammatory mediators → stimulate epithelial cells to produce chemokines (eotaxin: a potent chemoattractant and activator for eosinophils) **→ recruit TH2 cells** (T-helper type 2 lymphocytes)**, eosinophils, and other leukocytes → amplifying the inflammatory reaction.**

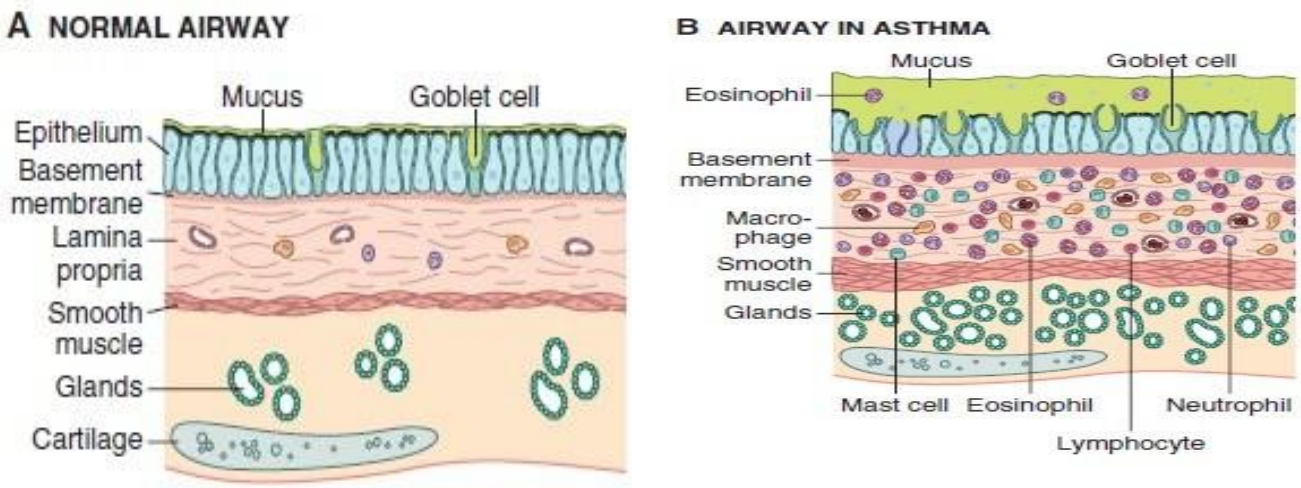
• Leukocytes recruited to the site of reaction (neutrophils, eosinophils, and basophils; lymphocytes and monocytes) → release mediators → initiate the late phase of asthma.

• Eosinophils release major basic protein and eosinophil cationic protein that cause damage to the epithelium.



E LATE PHASE (HOURS)

- **Repeated bouts of inflammation lead to structural changes in the bronchial wall → called airway remodeling, including:**
  - ✓ **hypertrophy of bronchial smooth muscle.**
  - ✓ **hypertrophy of Mucus glands.**
  - ✓ **increased vascularity.**
  - ✓ **deposition of subepithelial collagen.**

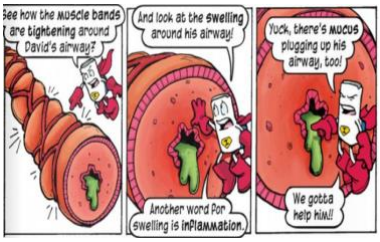


The figure above shows a comparison between a normal airway and an airway in asthma.

- Airway in asthma: there is a green layer of mucus overlying the surface epithelium. Asthmatic airways are marked by **accumulation of mucus in the bronchial lumen,** usually this happens secondary to the increased number of the mucus-secreting goblet cells in the mucosa and hypertrophy of the submucosal glands (remember the remodeling). The mucosa here is seen just below this thick layer of mucus and shows a lot of mucus-secreting goblet cells, also, the the basement membrane beneath the epithelium is thickened with intense chronic inflammation composed of eosinophils, macrophages, and other inflammatory cells, with smooth muscles hypertrophy and hyperplasia along with hypertrophy of submucosal glands.

- So, the **airways in patients with asthma** shows the following:
  - ✓ **Increased number of mucus-secreting goblet cells.**
  - ✓ **Hypertrophy of submucosal glands.**

- ✓ **Accumulation of mucus in the bronchial lumen.**
- ✓ **Thickened basement membrane.**
- ✓ **Intense chronic inflammation.**
- ✓ **Hypertrophy and hyperplasia of smooth muscle cells.**



Q: Choose the right statement:

- The initial airway response after exposure to the Inhaled allergens for first time starts with the recognition of the antigen by antigen presenting cells on surface mucosa. ✓
- The initial airway response after exposure to the Inhaled allergens for first time starts with bronchoconstriction and wheezes.
- The initial airway response after exposure to the Inhaled allergens for first time starts with the degranulation of the mast cells and release of preformed mediators.

Q: Choose the right statement:

- Upon re-exposure to the same antigen IgE production and eosinophil activation and recruitment follows.
- Upon re-exposure to the same antigen an inflammatory phase reaction follows.
- Upon re-exposure to the same antigen degranulation of the mast cells and release of preformed mediators follows. ✓

Q: Choose the right statement:

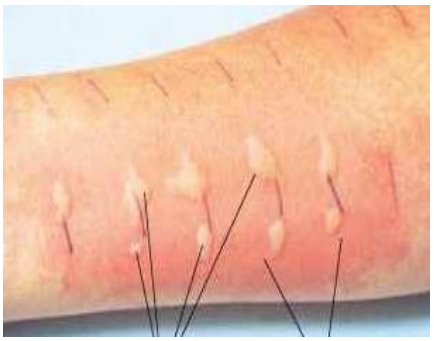
- The first wave of reaction upon re-exposure is dominated by release of inflammatory mediators.
- The first wave of reaction upon re-exposure is dominated by bronchoconstriction, increased mucus production, and vasodilation. ✓
- The first wave of reaction upon re-exposure is dominated by airway remodeling.

TYPES OF ASTHMA

1. ATOPIC ASTHMA:

- **The most common.**
- **Classic example of type I IgE–mediated hypersensitivity reaction.**
- **Beginning in childhood.**
- **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** (the material that shed from animal feathers)**, food, or by infections.**
- Initial **exposure to the antigen → excessive activation of type 2 helper cells → Cytokines production →**
  - ✓ **IL-4 and IL-13 stimulate IgE production.**
  - ✓ **IL-5 activates eosinophils.**
  - ✓ **IL-13 also stimulates mucus production.**
- **IgE coats submucosal mast cells → upon re-exposure → release of Mast cell–derived mediators → produce two waves of reaction:**
  1. **Early (immediate) phase of reaction.**
  2. **Late phase of reaction.**
- Atopic asthma can be diagnosed by two tests:

1. Skin test with the antigen: immediate wheal-and-flare reaction (eg; skin prick test and it's the most common allergy skin test). How is it done?



1. We get series of tiny drops of the allergen on the patient's back (or forearm).
2. Then quick needle pricks are made underneath each drop.
3. If the patient is allergic to that antigen, redness and itchiness will result especially at the needle prick sites.

2. Serum radioallergosorbent tests (RASTs): a blood test using radioimmunoassay to detect specific IgE antibodies, to determine the substances a subject is allergic to.

Click here to watch a video about the difference between skin testing and blood tests for allergies.

2. NON-ATOPIC ASTHMA

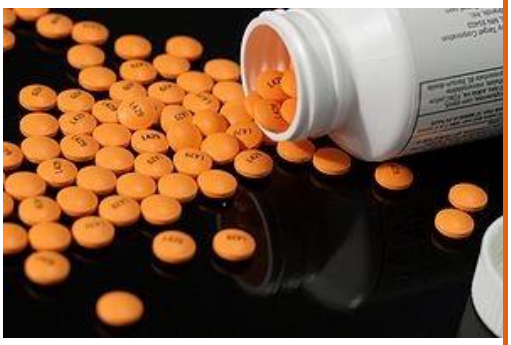
- **No evidence of allergen sensitization.**
- **Negative skin test.**
- **A positive family history of asthma is less common.**
- **Triggered by:**
  - **viral respiratory infections (rhinovirus, parainfluenza virus).**
  - **inhaled air pollutants (sulfur dioxide, ozone, nitrogen dioxide).**

Although the connection between those exposures and the non-atopic asthma is not well understood, the ultimate humeral and cellular mediators of the airway obstruction are the same to both topic and non-atopic variants of asthma, so they are treated in a similar way.

3. DRUG-INDUCED ASTHMA

- Several drugs can provoke asthmatic attacks; however, aspirin is the most important example.
- **Eg: Aspirin induced asthma →**
  - **present with recurrent rhinitis, nasal polyps, urticaria, and bronchospasm.**

- **The precise pathogenesis is unknown → involve some abnormality in prostaglandin metabolism from inhibition of cyclooxygenase by aspirin.**



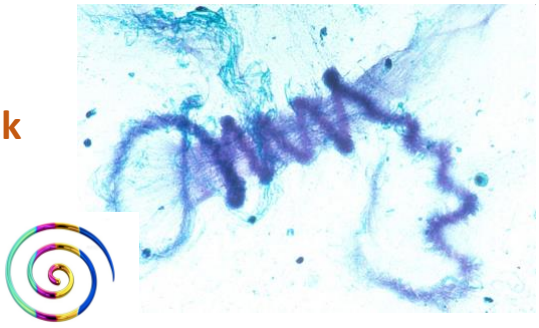
4.OCCUPATIONAL ASTHMA

- **Triggered by fumes (epoxy resins, plastics), organic and chemical dusts (wood, cotton, platinum), gases (toluene),** animal substances **and other chemicals.**
- **Asthma attacks usually develop after repeated exposure to the antigen.**
- **Examples include: farmers, animal handlers, manufacturers of foam mattresses, bakers, food processors, cotton workers and manufacturers of metals.**

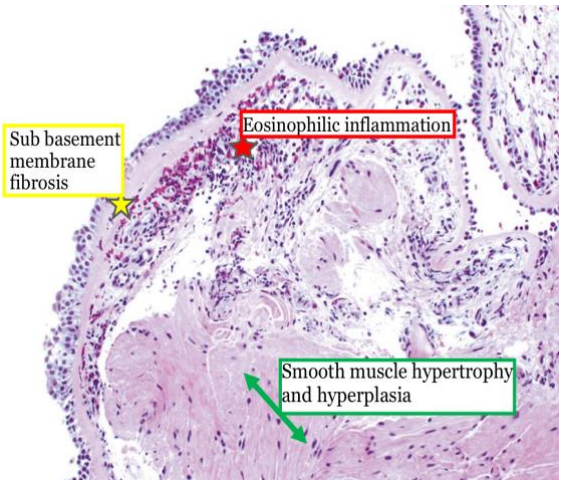
Click here to read more about occupational asthma.

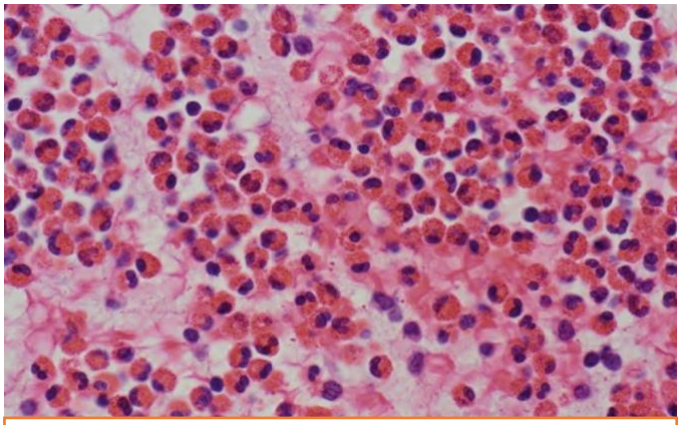
Q: A positive family history of atopy or asthma is common in **atopic asthma**.
Drug induced asthma can be triggered by **aspirin**, for example.
Asthma attacks developing after repeated exposure to the antigen in the workplace is called **occupational asthma**.

Morphology of asthma

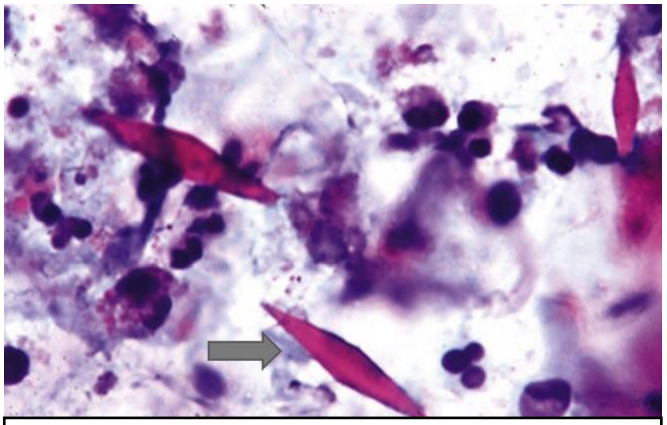


- **Occlusion of bronchi and bronchioles by thick mucous plugs** (the most striking finding).
- **Mucous plugs contain whorls of shed epithelium called Curschmann spirals.**
- **The figure to the right shows a bronchial biopsy from an asthmatic patient showing the following:**
  - **Sub basement membrane fibrosis.**
  - **Eosinophilic inflammation.**
  - **Smooth muscle hypertrophy and hyperplasia.**





• **Eosinophils are the characteristic inflammatory cells in asthma.**



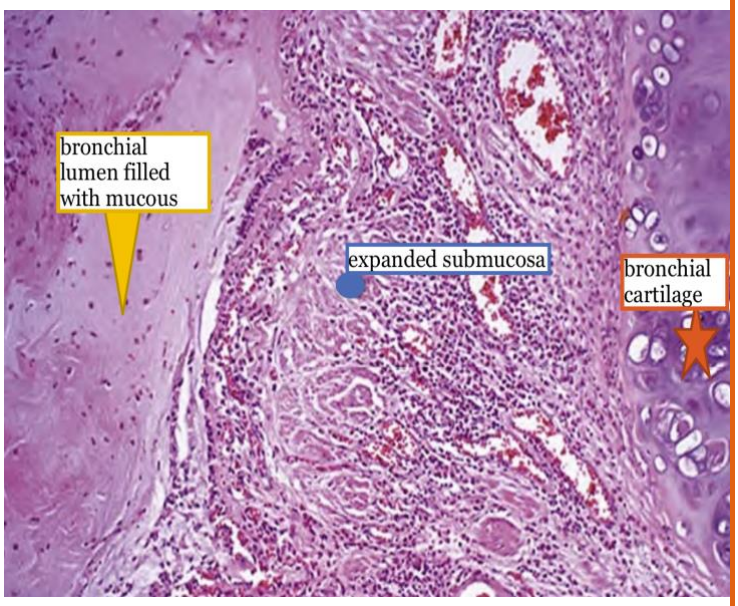
• **Charcot-Leyden crystals: crystalloids made up of the eosinophil protein galectin-10.**

• **Airway remodeling** (the characteristic morphologic changes in asthma)**, including:**

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

• **In fatal** severe advanced **cases → distension of lungs,** due to the air trapping with small areas of atelectasis.

This figure shows a predominantly expanded submucosa which lies between the bronchial cartilage (the red star) and the bronchial lumen here it is filled with mucous (yellow arrowhead), **the submucosa is widened by smooth muscle hypertrophy, edema and inflammatory cells (mainly eosinophils).**



Q: The mucous plugs in asthmatic patient contain whorls of shed epithelium called **Curschmann Spirals.**
Eosinophils are the characteristic.
inflammatory cells in asthma patients. Charcot-Leyden crystals are another finding and represent crystalloids made up of the eosinophil protein **galectin-10.**

Clinical features:

An attack of asthma is caractarised by the following:

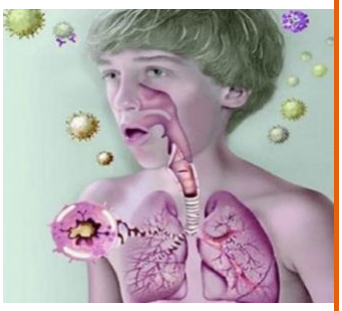
- **Cough**, worse at night or early morning.
- **Wheezing**, a whistling sound especially during expiration, sometimes it can be heard easily even without a stethoscope.
- **Chest tightness**, the patient may feel something is squeezing or stitting on their chest.
- **Shortness of breath or dyspnea**, patients can't catch their breath or breathe deeply enough.

Asthma is usually associated with difficulty in expiration, each asthmatic attack may last from one to several hours and subsides either spontaneously or with therapy.
The intervals between the attacks are free from the respiratory difficulties, remember asthma is reversible except in advanced severe cases.
Click for another video about the wheezing sound.

Status asthmaticus:

A severe paroxysm that does not respond to therapy, this type of attacks persists for days or weeks. Maybe associated with hypercapnia, acidosis, and severe hypoxia, it is fatal in some patients.

*From google: hypercapnia is too much CO2 in the blood.



Management of asthma

- **Standard therapies include:**
  - **Anti-inflammatory drugs (glucocorticoids).**
  - **Bronchodilators (beta-adrenergic drugs).**
  - **Leukotriene inhibitors,** which are potent bronchoconstrictors! however those agents can block specific immune mediators such as IL-4 and IL-5, this effect can be helpful in some patients.

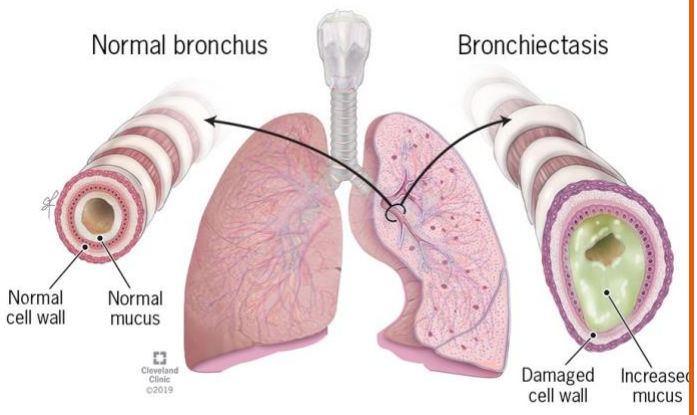
We finished taking about asthma, now we will talk about another disease which is Bronchiectasis.

Bronchiectasis

• **Permanent dilation of bronchi and bronchioles caused by destruction of smooth muscle and the supporting elastic tissue. It is an irreversible dilution.** (You can compare it to emphysema which is defined as permanent dilation of the airways distal to the terminal bronchioles, the difference here is that the destruction of smooth muscle and elastic tissue is not primary by itself, but rather related to a primary process such as persistent infection or obstruction).

• **Typically results from or is associated with chronic necrotizing infections.**

• **It is not a primary disorder, as it always occurs secondary to persistent infection or obstruction.**



Q: Regarding bronchiectasis, one of the following statements is correct:

- Restrictive disease.
- Irreversible. ✓
- Primary process.
- Affects the acini.

• **Clinically: cough and expectoration of copious amounts of purulent sputum** which usually contains white blood cells, cellular debris, dead tissue and mucus, it is typically yellow or green and can be seen in cases of bronchiectasis and lung abscess.

• **Diagnosis: appropriate history and radiographic demonstration of bronchial dilation.**

• Pathogenesis of bronchiectasis:

Two intertwined processes contribute to bronchiectasis:

- ✓ **Obstruction.**
- ✓ **Chronic infection.**

• **Obstruction** (by a foreign body for example) → **impairs clearance of secretions** results in its accumulation providing a favourable environment for infections → **superimposed infection** so the secretions and the bronchial wall are infected now, and this induces an inflammatory reaction → **inflammatory damage to the bronchial wall + the accumulating exudate → airways distention** (even further) → **irreversible dilation.**

• **Persistent necrotizing infection in the bronchi or bronchioles → poor clearance of secretions, obstruction** by the accumulation of secretions, **and inflammation with peribronchial fibrosis and bronchial walls damage → irreversible dilation.**

• The conditions that most commonly predispose to bronchiectasis include (primary disorders for bronchiectasis):

1. **Bronchial obstruction:**
   - **By tumors, foreign bodies, and impaction of mucus OR as a complication of atopic asthma and chronic bronchitis.**
   - **Bronchiectasis is localized** to the obstructed lung segment.

2. **Congenital or hereditary conditions:**

- Cystic fibrosis:

- **Widespread severe bronchiectasis.**
- **Due to obstruction caused by abnormally viscid mucus and secondary infections.**
  Remember CF affects RS and GI, the body produces thick and sticky mucus that may block the lungs and obstruct the pancreas.

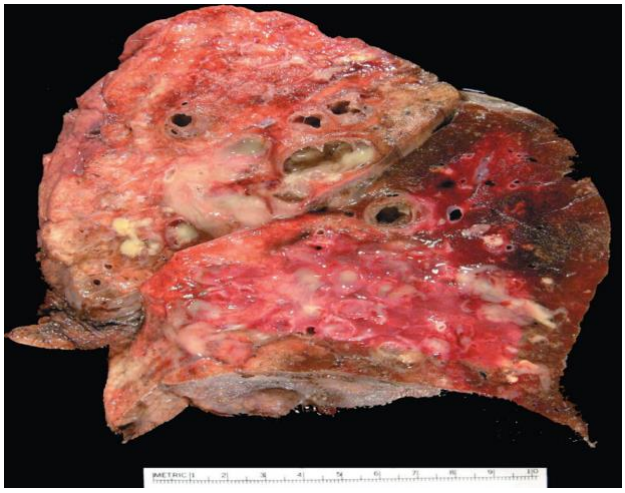
- **Immunodeficiency states:**
  - **Due to recurrent bacterial infections.**
  - **Localized or diffuse.**
- **Primary ciliary dyskinesia (immotile cilia syndrome):**
  - **Rare autosomal recessive disorder → abnormalities of cilia** (impaired clearance) **→ persistent infections.**
  - **Bronchiectasis + sterility in males.**

3. **Necrotizing, or suppurative, pneumonia:**
   - **Particularly with virulent organisms such as Staphylococcus aureus or Klebsiella spp.**

• Morphology and macroscopy of bronchiectasis:

- **Lower lobes bilaterally** particularly the vertical air passages.
- **Most severe involvement in distal bronchi and bronchioles.**
- **The airways may be dilated to as much as four times their usual diameter.**

This picture shows a lung with bronchiectasis in a patient with cystic fibrosis who underwent lung reconstruction for transplantation.
It is a markedly dilated bronchi filled with purulent mucus.



• Morphology and microscopy of bronchiectasis:

The histologic findings vary with the activity and the 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** (due to the severe inflammation).
  - **Mixed flora are cultured from the sputum,** the usual organisms include: staphylococcus, streptococcus, pneumococcus, enteric organisms and anaerobic bacteria.

- **When healing occurs:**
  - **The lining epithelium may regenerate completely;** however, the injury usually cannot be repaired completely, and **abnormal dilation and scarring** persists.
  - **Fibrosis of bronchial, bronchiolar walls and peribronchiolar fibrosis** (in chronic cases). In some cases, the necrosis destroys the bronchial and bronchiolar walls producing an abscess cavity.
  - **Abscess formation in some cases** (by the destruction of the bronchial and bronchiolar walls by the necrosis).

This figure shows the histological findings in bronchiectasis. At the centre there is an extensive necrotizing inflammation to the degree where you cannot see the mucosal lining clearly (it is mostly desqamated).

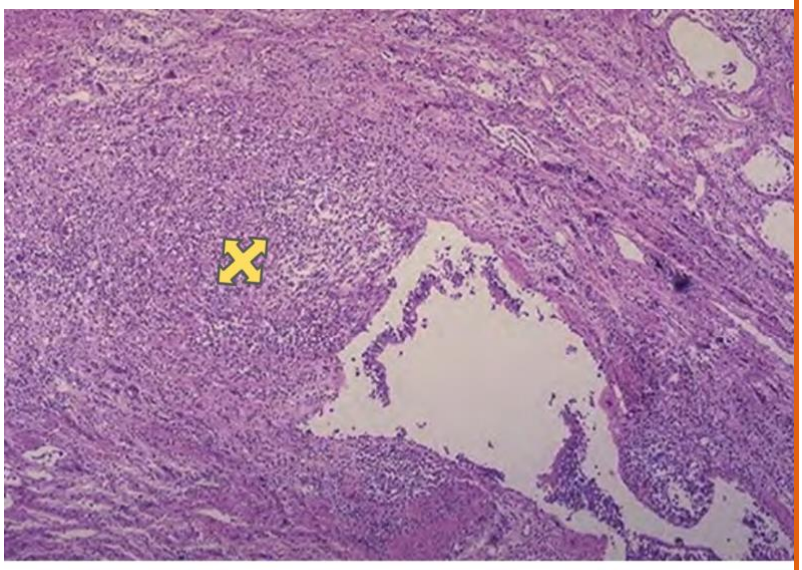


Figure 5-34 **Bronchiectasis, microscopic** dilated bronchus in which the mucosa an bronchial wall are not seen clearly because of the necrotizing inflammation with tissu destruction.

Clinical features of bronchiectasis:

- **Severe, persistent cough with expectoration of mucopurulent sputum.**
  - **Other symptoms: dyspnea, rhinosinusitis, and hemoptysis.**
- **Symptoms are episodic.**
- **Precipitated or induced by URTI.**
- **Severe widespread bronchiectasis: may lead to significant obstructive ventilatory defects, hypoxemia, hypercapnia, pulmonary hypertension, and cor pulmonale.**

However, with current treatment the outcomes have been improved and severe complications of bronchiectasis such as brain abscess and cor pulmonale are less frequent.

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.

Test bank:

- **Regarding the pathogenesis of atopic asthma one of the following statements is correct:**

A) the initial response upon first exposure is associated with type-1 helper lymphocyte activation.

B) IL-4 & IL-5 are secreted from alveolar macrophages during the early phase response.

C) phago-lysosomal maturation arrest is essential in the pathogenesis during early phase

D) Eotaxin is a potent chemoattractant and activator of eosinophils in late phase.
E) early phase is triggered by antigen induced cross-linking of IgG bound to receptor on mast cells.

- **Regarding bronchiectasis, one of the following statements is CORRECT:**

A) It's a primary inherited pulmonary disease.
B) considered as reversible obstructive pulmonary disease.
C) Alveolar sacs are the most involved part.
D) Heals with complete resolution and no fibrosis.
E) patient present with cough and purulent sputum

- **Wrong about bronchiectasis:**

Diagnosis is only through biopsy.

ANS: D, E

Lippincott questions:

5 A 28-year-old woman with cystic fibrosis presents with increasing shortness of breath and production of abundant foul-smelling sputum. The sputum in this patient is most likely associated with which of the following pulmonary conditions?

(A) Atelectasis
(B) Bronchiectasis
(C) Empyema
(D) Pneumothorax
(E) Pyothorax

5 **The answer is B: Bronchiectasis.** Bronchiectasis refers to the irreversible dilation of bronchi, which is caused by the destruction of the muscular and elastic elements of bronchial walls. Bronchiectasis is often localized to a segment of the lung distal to mechanical obstruction of a bronchus by a variety of lesions, including tumors, inhaled foreign bodies, mucous plugs (e.g., cystic fibrosis and asthma), and compressive lymphadenopathy. Nonobstructive bronchiectasis is usually a

27 An 8-year-old girl is brought into the physician's office in mild respiratory distress. She has a history of allergies to cats and wool, and her parents state that she has recurrent episodes of upper respiratory tract infections. Physical examination shows expiratory wheezes, use of accessory respiratory muscles, and a hyperresonant chest to percussion. Analysis of arterial blood gases discloses respiratory alkalosis, and the peripheral eosinophil count is increased. What is the appropriate diagnosis?

(A) Acute bronchiolitis
(B) Asthma
(C) Cystic fibrosis
(D) Kartagener syndrome
(E) Usual interstitial pneumonia

27 **The answer is B: Asthma.** Asthma is a chronic lung disease caused by increased responsiveness of the airways to a variety of stimuli. Patients typically have paroxysms of wheezing, dyspnea, and cough. Acute episodes of asthma may alternate with asymptomatic periods or they may be superimposed on a background of chronic airway obstruction. The consensus hypothesis attributes bronchial hyperresponsiveness in asthma to an inflammatory reaction to diverse stimuli, either extrinsic (e.g., pollen) or intrinsic (e.g., exercise). Extrinsic asthma is typically a childhood disease, whereas intrinsic asthma usually begins in adults. The other choices do not lead to wheezing and eosinophilia.
Diagnosis: Asthma