Team 435

PATHOLOGY

As a doctor you should know what can threaten your patient's life
should know what makes your patient suffers from pain

That's why you study pathology

Lecture 1,2

Lecture one: (Asthma)

Objectives:

A- Understanding asthma as an episodic, reversible bronchoconstriction caused by increased responsiveness of the tracheobrachial tree to various stimuli.

B- Knowing that asthma is divided into two basic types: extrinsic or atopic allergic and intrinsic asthma.

C- Understanding the morphological changes seen in the lungs in cases of severe asthma.

Contents:

1- Definitions of asthma as one of the chronic obstruction airway diseases.

2- Types and pathogenesis of extrinsic (immune) asthma and extrinsic (non-immune) asthma.

3- Clinical presentation and pathological changes seen in the bronchial tree in cases of asthma.

4- Complications of asthma: superimposed infection, chronic bronchitis and pulmonary emphysema.

5- Definition and manifestation of status asthmaticus.

Lecture two: (Obstructive lung diseases)

Objectives:

A- Understand that this group of disorders is characterized by an increase in resistance to airflow, owing to partial or complete obstruction at any level of the bronchial/ bronchiolar.

B- Know that the major obstructive disorders are chronic bronchitis, emphysema, asthma and bronchiectasis.

C- Is aware that the symptom common to all these disorders is 'dyspnea' (difficulty in breathing) but each have their own clinical and anatomical characteristics.

D- Chronic bronchitis and emphysema almost always coexist.

Contents:

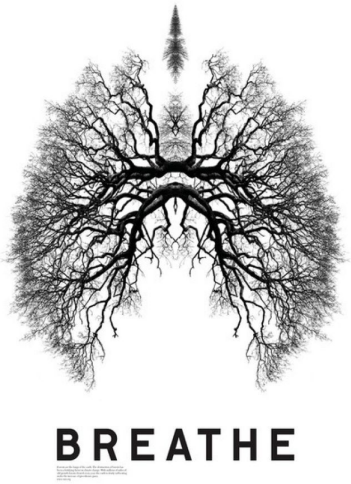
A- Chronic bronchitis: definition, clinical presentation, role of cigarette smoking and air pollution, pathological changes and complications with special emphasis on cor pulmonale.

B- Emphysema: definition and clinical characteristics. Types of emphysema including centrilobular emphysema, panacinar emphysema (deficiency of alpha one antitrypsin), paraseptal and irregular emphysema.

C- Complications of emphysema with special emphasis on interstitial emphysema and pneumothorax.

D- Bronchiectasis: definition, predisposing factors, kartagener's syndrome (primary ciliary dyskinesia) and pathological features of bronchiectasis.

Introduction



You can skip it if you're already familiar with the normal anatomy & histology of the lungs

Normal Anatomy:

The major function of the lung is to replenish oxygen and excrete carbon dioxide from blood. It depends on:

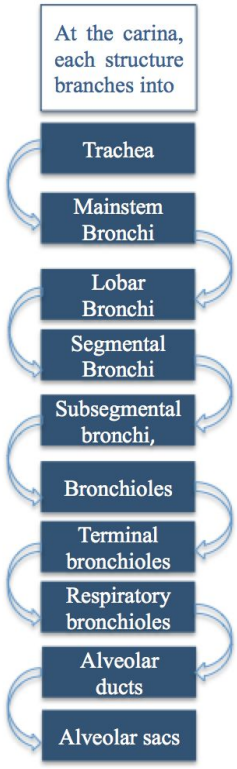
- Compliance of the lungs.
- Can only occur in alveoli that are both ventilated and perfused.

The air conducting passages consist of:

- The nasal cavities.
- Paranasal sinuses.
- Nasopharynx.
- Oropharynx
- Tracheobronchial tree.
- Hypopharynx (epiglottis and larynx)

➔ The pulmonary arteries follow the airways while the pulmonary veins run through the connective tissues septa.

Dr. AlRikabbi's Note: Wall of alveoli has pores (pores of Kohn) which are surrounded by a large number of capillaries; this is why we have blood gases exchange at this level (through the pores and capillaries).



➔ Lymphatic channels are present along the bronchovascular structures but are also found in the pleura and connective tissue septa.

Dr. Maha Arafah's note: In normal lung we can see the bronchial tree until mid hilum and pleural surface, during abnormal dilation we see the tree till the periphery.

Histology:

With the exception of the oropharynx and portions of the nasopharynx and hypopharynx (which are lined by squamous epithelium), the upper respiratory tract and the large airways are lined by pseudostratified ciliated columnar epithelium interspersed with mucus-secreting goblet cells and neuroendocrine cells.

Mucus–secreting glands lie beneath the epithelial surface and the cartilaginous plates help to maintain patency.

Cartilage, submucosal glands and goblet cells are lost at the level of the bronchioles which are lined by ciliated cuboidal epithelium and Clara cells (which secrete a non-mucoid watery substance that contains lysozyme and immunoglobulins).

The majority of the alveolar surface is lined by the type I pneumocytes which are interspersed with the surfactant-producing Type II (cuboidal/ granular) pneumocytes.

The interstitium contains:

- Collagen - Elastin - Mast cells
- Occasional inflammatory cells & connective tissue cells (primarily smooth muscle & fibroblasts).

Dr. Rikabbi's note: The interstitium of the lung is the basement membrane in the alveolar wall and the blood vessels which are lining one side of the alveoli. It's the connective tissue between the alveoli and the vessels.

Alveolar macrophages that are derived from blood monocytes are loosely attached to the alveolar wall or lie free within the alveolar space.

Dr. Maha Arafah's note: The Alveoli are lined by squamous flat cells and a thin layer of basement membrane, because it needs the space for gas exchange.

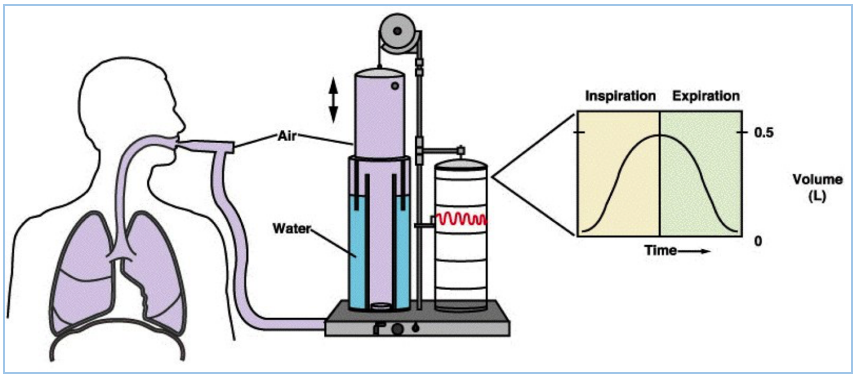
+ Any condition which destroys the alveoli like emphysema will ruin the function of the lung.
+ Surfactant keeps the alveoli open without collapse

Remember: There are multiple primary lung diseases that can broadly be divided into those primarily affecting:

- The airways. - The interstitium. - The pulmonary vascular system.

Note that a disease in one compartment often causes secondary alterations of morphology and function in other areas.

Spirometer: An equipment used for measuring the volume of air inspired and expired by the lungs (Pulmonary Function Tests).



- 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.

Dr. Maha Arafah's note: Function of the lung we use the spirometer and its important to help differentiate between different lung diseases (COPD & RPD)

- FVC= forced vital capacity.

Rikkabi's note:

Best way to study a disease is by defining the disease and also by clinical investigation (how patient present) , pathological investigation (the pathology of the disease), aetiology (by bacteria if present)

Diffuse pulmonary diseases can be classified into two categories:

1. **Restrictive Lung Diseases (Discussed in detail next lecture).**

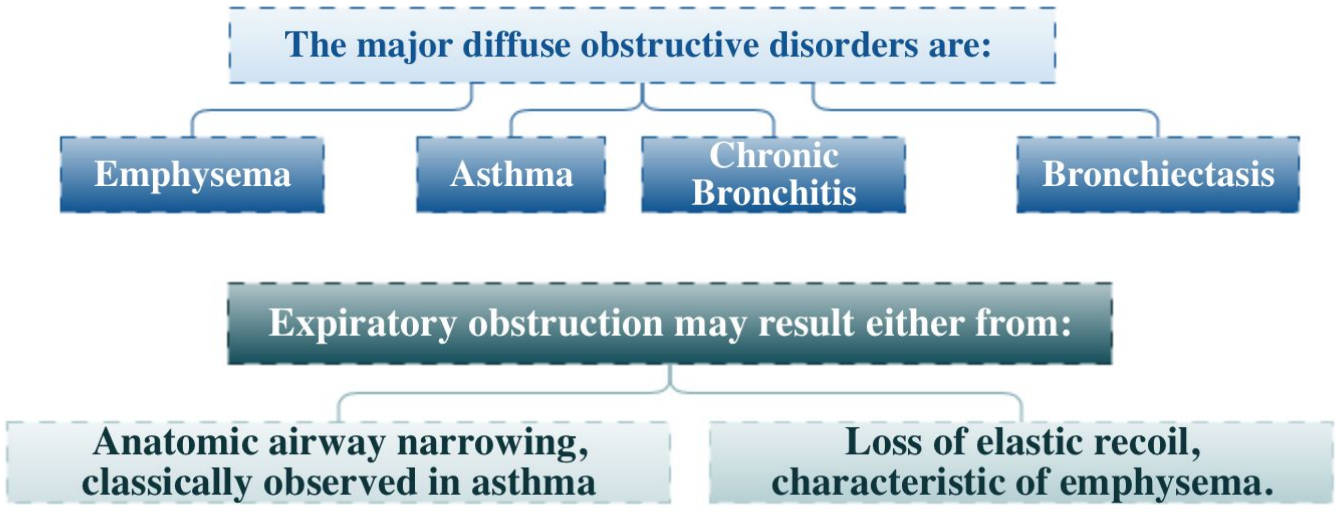
   - Are a category of diseases that restrict lung parenchymal expansion, resulting in a decreased total lung capacity, increased work of breathing, and inadequate ventilation and/or oxygenation.
   - Both forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) are reduced, however the FEV1/VC is normal to high. The expiratory flow rate is near normal.
   - Occur in:
     - Chest wall disorder.
     - Acute or chronic, interstitial and infiltrative parenchymal fibrotic diseases or skeletal abnormalities such as kyphoscoliosis

2. **Chronic Obstructive Pulmonary Disease (COPD).**

   General considerations:

   1. COPD is a group of disorders characterized by airflow 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.
   2. Characteristics include a marked decrease in the forced expiratory volume (FEV_1), but force vital capacity (FVC) is either normal or slightly decreased.
   3. COPD is often contrasted with restrictive pulmonary disease.
   4. A common symptom to these disorders is dyspnea.

Dr. Rikabbi's Note:
COPD : the diseases which affects the trunks (bronchi and bronchioles and sometimes the trachea & the conducting system). Doesn't affect the interstitial or the parenchyma of the lungs.



Pathologic Findings in Chronic Obstructive Pulmonary Disease:

Name of Disorder:	Pathologic Findings:
Bronchial Asthma	- Bronchial smooth muscle hypertrophy. - Hyperplasia of bronchial submucosal glands and goblet cells. - Airways plugged by viscid mucus containing Curschmann spirals, eosinophils and Charcot-leyden crystals. Dr. Maha Arafa's notes: - Causes bronchospasm - Majority of asthma is due to inhaled antigens - Extrinsic asthma most commonly studied - In between attacks patient is normal
Chronic Bronchitis	Hyperplasia of bronchial submucosal glands leading to increased Reid index: ratio of the thickness of the gland layer to that if the bronchial wall.
Pulmonary Emphysema	- Abnormal dilation of air spaces with destruction of alveolar walls. - Reduced lung elasticity.
Bronchiectasis	Abnormally dilated bronchi which are filled with mucus and neutrophils. Inflammation and necrosis of bronchial walls and alveolar fibrosis.

Table 12–2 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

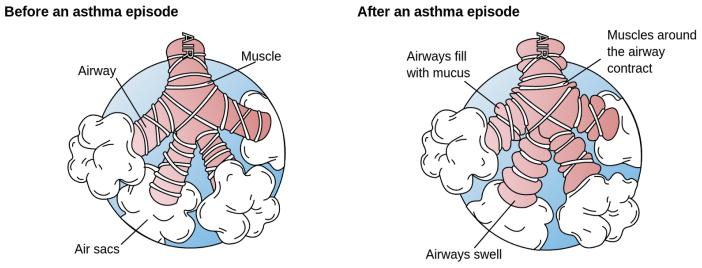
*Can be present in all forms of obstructive lung disease or by itself.

Common symptoms in lung disease: Dyspnea (difficulty with breathing), cough, hemoptysis.

Bronchial Asthma: *Click Here*

A chronic inflammatory disorder of the airways that causes recurrent (relapsing) episodes of reversible bronchoconstriction caused by increased responsiveness of the tracheobronchial tree to various stimuli.

Dr.AlRikabbi's Note: *we can also say that It is an episodic, reversible, chronic, obstructive airway disease characterized by attacks of bronchospasm " "*



Symptoms:

- Wheezing. " "

  Dr. AlRikabbi's Note: Bronchospasm makes narrowing of the respiratory tracts. This narrowing is responsible for dyspnea but also responsible for the second major symptoms we see in asthma, which is wheezing. Wheezing is different as sometimes the patient complains from it, some you can only hear using the stethoscope, some you can hear from a short distance and some you can hear from a long distance.

- Breathlessness. " *Dyspnea" -" " - "shortness of breath"*

  Dr. AlRikabbi's Note: It occurs in many diseases either lung or cardiac diseases. First thing to do when somebody has got dyspnea is to put the patient in the right category: belongs to respiratory system OR cardiac system. The answer is known by taking good history and examination as well as understanding the pathophysiology.

- Chest tightness.

- Chronic nonproductive cough (dry and does not produce sputum).

  Dr. AlRikabbi's Note: Happens sometimes; cough is not a principle symptom. Sometimes patients cough and sometimes they produce mucous (frothy) sputum. *If it is complicated asthma and the patient has inflammation he will produce purulent sputum, develop bronchitis, secondary bronchitis with infection.*

  Particularly at night and/or early in the morning.

Note: Some of the stimuli that trigger attacks in patients would have little or no effect in persons with normal airways.

Dr. AlRikabbi's Note: This disease is episodic, it comes in attacks (comes and goes) and it is reversible BUT sometimes it is NOT like this. Sometimes it lasts more than few minutes or hours; at times it lasts for days or even weeks.

Sometimes the patient dies from complications; in this case the patient suffered from acute medical emergency: "Status asthmaticus" " ":

It is an acute medical emergency which is caused by very severe and prolonged attacks of bronchial asthma which does not respond to ordinary treatments *(like avoiding factors causing the attack and irritating the bronchial tree)*.

As "Status asthmaticus" is prolonged and the patient has dyspnea, hypoxemia, lower Po_2 , higher Pco_2 , confusion and not responding (because of severe hypoxemia). It can lead to death. Such patient should NOT be treated in the house; they should be treated in the accident and emergency unit and intensive care unit when needed. We see a lot of these patients especially in the time of sand storms.

The hallmarks of the disease are:

- Intermittent and **reversible airway obstruction.**
- **Chronic bronchial inflammation with eosinophils in particular.**
- Bronchial smooth muscle cell **hypertrophy** and **hyperreactivity.**
- **Increased mucus secretion.**

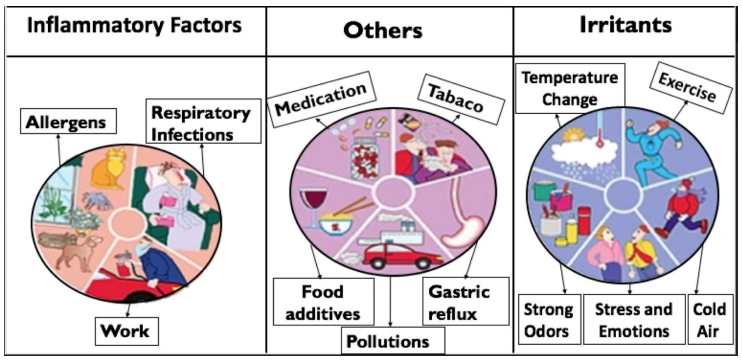
Note: Many cells play a role in the inflammatory response other than eosinophils such as, mast cells, macrophages, lymphocytes, neutrophils and epithelial cells.

Types of asthma:

Note: Asthma may be categorized into two basic types which are:

- (Extrinsic) Atopic (evidence of allergen sensitization, often in a patient with a history of allergic rhinitis, eczema)
- (Intrinsic) Nonatopic.

In either type, episodes of bronchospasm can be triggered by diverse mechanisms, such as:
The subgroups may differ in etiology, immunopathology and response to treatment.



1. **Extrinsic (immune, atopic) asthma:**

It is mediated by a **type I hypersensitivity response** involving IgE bound to mast cells (IgE-mediated). The disease begins in childhood and usually in patients with a family history of allergy.

- ➔ The **most common** type of asthma.
- ➔ Asthmatic attacks are often preceded by allergic rhinitis, urticaria, or eczema.
- ➔ The disease is triggered by environmental antigens, such as dusts, pollen, animal dander, and foods.
- ➔ Infections can also trigger atopic asthma.

Dr. AlRikabbi's Note: It means the person has atopy which is increased inherited susceptibility to develop allergic diseases and allergic reactions. Those people have many allergic reactions like Eczema. These allergic reactions may come and go. *"May go after many years, may not go away, may go away and the person will develop another allergy because he is atopic (he has susceptibility)".*
Some babies are presented with red faces which are itchy and irritating; they might have "congenital asthma" or "congenital eczema".
This person is prone to develop:
*Bronchial asthma *Allergic conjunctivitis *Allergic rhinosinusitis
* Those people who have atopic bronchial asthma develop asthmatic attacks because of exposure to sand storms or a certain smell, or certain food, or dust from carpets, or the smell of the grass, or animal dander etc.
* It is more common in children and young people.

Diagnosis:

- **Skin test** with the offending antigen is positive and results in an immediate wheal-and- flare reaction.
- **Serum radioallergosorbent tests (RASTs)** that identify the presence of IgE specific for a panel allergens.

2. **Intrinsic (non-immune) asthma:**

Includes asthma associated with **chronic bronchitis** as well as other asthma variants such as **exercise or cold-induced asthma**. It usually begins in adult life and is not associated with a history of allergy.

- ➔ Do not have evidence of allergen sensitization, and skin test results usually are negative.
- ➔ Respiratory infections due to viruses (e.g., rhinovirus, parainfluenza virus) and inhaled air pollutants (e.g., sulfur dioxide, ozone, nitrogen dioxide) are common triggers.
- ➔ Serum IgE levels are normal.

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.

	Extrinsic asthma	Intrinsic asthma
Definition	**Initiated by type one hypersensitivity reaction and used by exposure to an extrinsic allergen**	**Initiated by diverse, nonimmune mechanism. Stimuli are intrinsic to body.**
Age of presentation	**Childhood**	**Adult**
Family history	**Present**	**Absent**
Preceding allergic reactions	**present in form rhinitis, urticaria, eczema**	**Absent**
Allergens	**Present**	**Absent**
Drug hypersensitivity	**Absent**	**Present, aspirin**
Serum IgE level	**Increased**	**Normal**
Skin test	**Positive**	**Negative**
Emphysema	**Unusual**	**Common**
Associated bronchitis	**Absent**	**Present**
Examples	**Atopic/ allergic asthma, occupational asthma, allergic bronchopulmonary aspergillosis.**	**Aspirin ingestion, pulmonary infection especially viral, cold, inhaled irritants, stress, exercise**

3. **Drug-induced Asthma:**

Several pharmacologic agents provoke asthma, aspirin being the most striking example.

Note: 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 bronchospasm.

4. **Occupational Asthma:**

This form of asthma is stimulated by fumes (epoxy resins, plastics), organic and chemical dusts (wood, cotton, platinum), gases (toluene), and other chemicals.

❏ Asthma attacks usually develop after **repeated exposure** to the inciting antigen(s).

The Major Etiologic Factors of Asthma are:

- Genetic predisposition to type I hypersensitivity (atopy).
- Acute and chronic airway inflammation.
- Bronchial hyperresponsiveness to a variety of stimuli.
- Intermittent airflow obstruction that can be caused by a variety of changes, including acute bronchoconstriction, airway edema, chronic mucous plug formation, and airway remodeling.

Clinical Presentation:

There is:

- Bronchial asthma is related to increased sensitivity of air passages to stimuli, which leads to spasm in the bronchial muscular wall.
- Primarily targets the bronchi and terminal bronchioles.
- Most common chronic respiratory disease in children. More common in children than adults.
- Increased anteroposterior diameter, due to air trapping and increase in residual volume.

Note: *In the usual case,* attacks last from 1 to several hours and subside either spontaneously or with therapy, usually bronchodilators and corticosteroids.

The Morphologic Changes:

Described in persons who die of prolonged severe attacks (status asthmaticus) and in mucosal biopsy specimens of persons challenged with allergens.

Dr. Rikabbi's Note:

1- Wall changes:

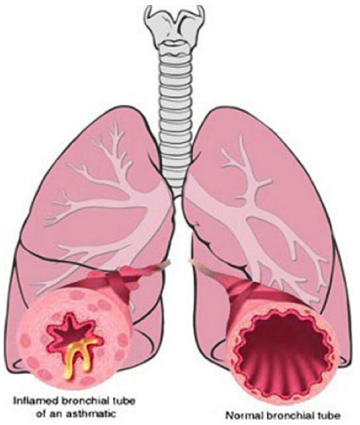
- Redness in bronchial tree.
- Mucosa is thick (edematous).
- Increased mucus secretion by the action of IL13 and 12.
- Increased number of bronchial glands and cells.
- Inflammatory cells in the wall (mast cells and eosinophils).
- Sub-Endothelial membrane fibrosis.
- Sometimes a thickness in basement membrane.

2- Changes in lumen: (examining a sputum sample):

- Alveolar macrophages that contain carbon particles (so, the patient could be a smoker or living in the city).
- Churchman spirals which causes thick sputum.
- Lots of eosinophils that may causes eczema.
- Charcot-Leyden crystals that can be obtained from biopsy or in sputum, and in tissues containing heavy amounts of eosinophils.

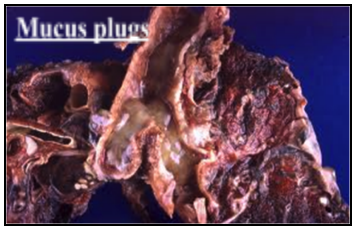
Gross:

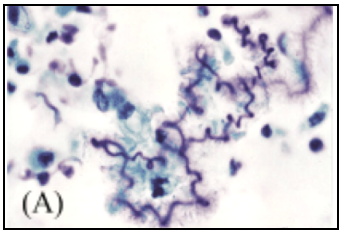
Hyperinflated lungs[1] + occlusion of bronchi and bronchioles by thick, tenacious mucous plugging of airways.(and there may be small areas of atelectasis[2])

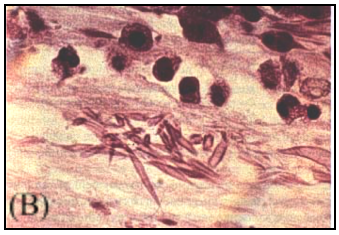


Why is there a hyperinflated lung?
The victim labors to get air into the lungs and then cannot get it out, so that there is progressive hyperinflation of the lungs with air trapped distal to the bronchi, which are constricted and filled with mucus and debris.

Microscopic:

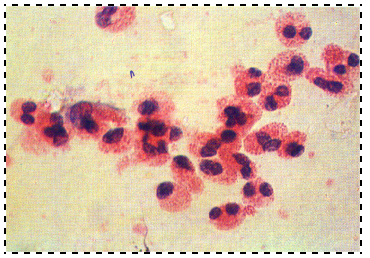






Spiral–shaped mucous plugs contain:

- ➔ **Curschmann spirals**[3]: 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. (B)
- ➔ **Eosinophilic infiltrate and proliferation.**
- ➔ **AIRWAY REMODELING:** These changes include: "Thickening of airway wall"
  - **Hypertrophy** of bronchial smooth muscle.
  - **Increased vascularity** in submucosa and **deposition of subepithelial collagen.**
  - Sub-basement membrane **fibrosis.**
  - **Thickening** and **hyalinization** of basement membranes
  - **Hyperplasia** of submucosal glands and goblet cells.
  - **Metaplasia** of the airway epithelium.



[1] فرط انتفاخ الرئتين

[2] Partial or complete collapse of the lung

[3] Sloughed epithelial cells in mucous cast in the shape of airways.

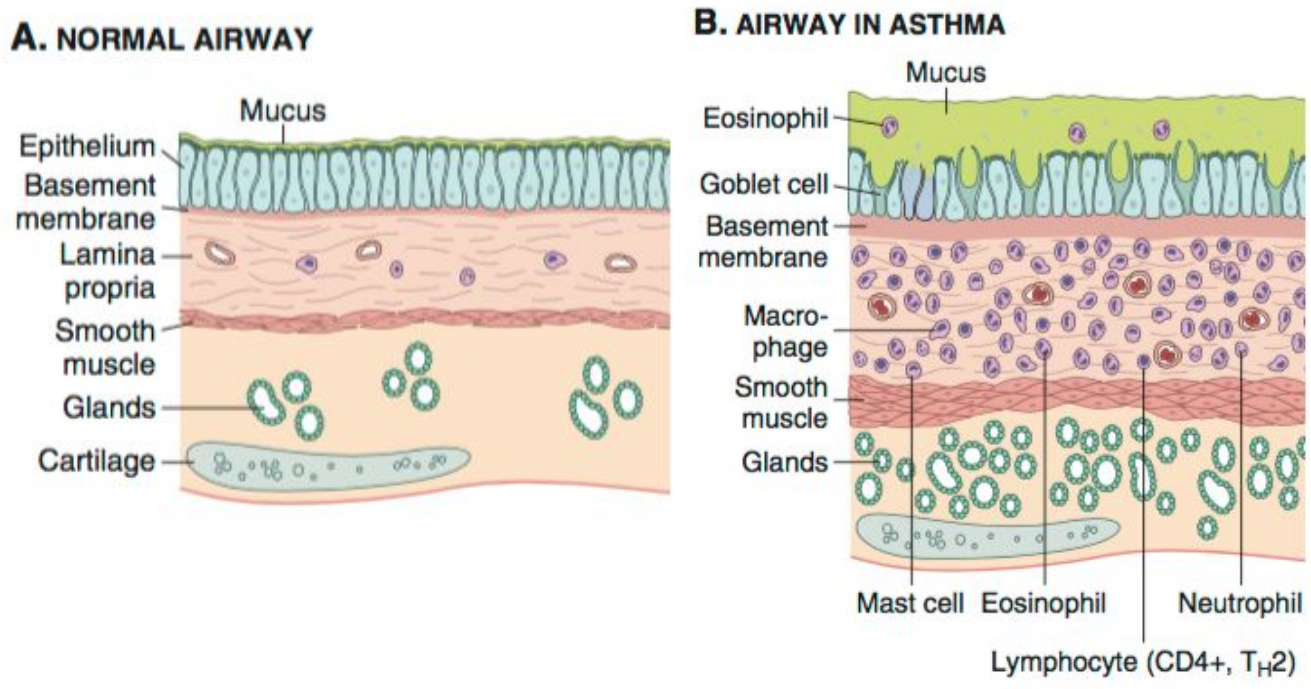
Pathogenesis of asthma: ***(Asthma Animation)***

Note:

- In nonatopic and drug-induced asthma, the mechanism is less well understood, but it is **NOT IgE mediated**.
- In atopic and occupational asthma, the disease process is a type I hypersensitivity reaction involves many cell types and numerous inflammatory mediators, but the role of type 2 helper T (TH2) cells may be critical to the pathogenesis of asthma.

  What is the difference between TH1 & TH2?
  - **TH1** in protective immunity.
  - **TH2** in allergic disease.
- The classic atopic form of asthma is associated with an excessive TH2 reaction against environmental antigens.

A and B, Comparison of a normal bronchus with that in a patient with asthma.
Note the accumulation of mucus in the bronchial lumen resulting from an increase in the number of mucus-secreting goblet cells in the mucosa and hypertrophy of submucosal glands.
In addition, there is intense chronic inflammation due to recruitment of eosinophils, macrophages, and other inflammatory cells.
Basement membrane underlying the mucosal epithelium is thickened, and smooth muscle cells exhibit hypertrophy and hyperplasia.



Steps of the pathogenesis:

1. **INITIAL SENSITIZATION** to an Inhaled antigen elicits:
   - ➔ TH2 to produce various cytokines which are:
     - ➔ **IL-4** (stimulates IgE production)
     - ➔ **IL-5** (activates eosinophils)
     - ➔ **IL-13** (stimulates mucus production and also promotes IgE production by B cells)

2. **ON REEXPOSURE TO ANTIGEN:** IgE bound to IgE receptor on mast cells ,these cells will release granule contents.

> What do we mean by reexposure?
> First time, our bodies only make IgE, as there are no symptoms. However the second time symptoms start to appear because our bodies have already made IgE before.

3. **After the degranulation of mast cells, the reaction occurs in two phases:**
   - **Phase1: the early stage (minutes):**
     - ➔ Bronchoconstriction (triggered by direct stimulation of subepithelial vagal receptors).
     - ➔ Increased mucus production.
     - ➔ Vasodilation.
   - **Phase2: the late phase (hours):** Responsible for the morphologic changes that occur in asthma
     - ➔ Inflammation, with activation of eosinophils (releases major basic protein & cationic protein into the bronchial lumen which are toxic to epithelial cells and cause epithelial cell damage which further impairs mucociliary function) neutrophils, and T cells. These cells Activated by chemotactic factors released during the early stage of asthma.
     - ➔ Epithelial cells produce chemokines that attract more Th2 cells and eosinophils (including eotaxin, a potent chemoattractant and activator of eosinophils). Thus amplifying the inflammatory reaction, without any additional antigen (allergen).
     - ➔ Repeated bouts of inflammation leads to structural changes in the bronchial wall, collectively referred to **AIRWAY REMODELING** (what do these changes include?? See the morphology).

4. A susceptibility locus for atopic asthma:

Note: Asthma is a complex genetic disorder in which multiple susceptibility genes interact with environmental factors to initiate the pathologic reaction.

A. On the long arm of chromosome 5 (5q):

At this loci there are several genes involved in regulation of **IgE synthesis** and mast cell and eosinophil growth and differentiation map.

These genes are responsible of the production of IgE in many ways. As you would imagine, a person overexpressing this gene would definitely be susceptible to asthma.

These genes include:

- **IL13** (genetic polymorphisms linked with susceptibility to the development of atopic asthma)
- **CD14** (single-nucleotide polymorphisms associated with occupational asthma)
- **Class II HLA alleles** (tendency to produce IgE antibodies)
- **IL-4 receptor gene** (atopy, total serum IgE level, and asthma).
- **β2- adrenergic receptor gene**

B. On the long arm of chromosome 20 (20q):

ADAM-33 (this controls airway remodeling)

Why? Because it regulates proliferation of bronchial smooth muscle and fibroblasts

5. Level of YKL-40[4] is a marker of asthma:

Chitinases and chitinase-like proteins play a role in Th2-type inflammation. Thus, they may be useful in diagnosing and monitoring of asthma.

[4] Chitinase family member with no enzymatic activity.

Complications of Asthma:

1. Superimposed infection i.e. pneumonia.
2. Chronic bronchitis.
3. Pulmonary emphysema and pneumomediastinum.
4. Pneumothorax (occurs when air leaks into the space between your lungs and chest wall. This air pushes on the outside of your lung and makes it collapse).
5. Airway remodeling.
6. Bronchiectasis.
7. Respiratory failure requiring intubation in severe exacerbations i.e. status asthmaticus.
8. 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.

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.

Dr. Maha Arafa's note:
Skin testing: Intradermal injection of the allergen and they watch it for half hour to an hour to see if there is any wheel and flare which will mean the person is allergic to that specific allergen that when we inject the skin with the allergen it will cause a reaction.

Inflammatory Mediators of Bronchial Asthma using Atopic Asthma as a model:

Inflammatory mediator produced are :

- Leukotrienes C4, D4 & E4 (induce bronchospasm, vascular permeability and 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)

The inflammatory mediators lead to:

1. Smooth muscle contraction, bronchospasm.
2. Mucous secretion.
3. Increased vascular permeability and edema.

Status asthmaticus:

It is the most severe form of asthma. It's a prolonged asthmatic attack that does not respond to therapy (which usually aborts the acute attack) and persists for days and even weeks.

- This situation is potentially serious and requires hospitalization.
- Patients in status asthmaticus have hypoxemia and often hypercapnia.
- They require oxygen (intermittent positive-pressure ventilation) and other pharmacologic interventions.

In particularly severe episodes the ventilatory functions may be so impaired so as to cause severe cyanosis and even death.

The associated: hypercapnia, acidosis, and severe hypoxia may be fatal, although in most cases the condition is more disabling than lethal.

Emphysema: (Permanent enlargement of all or part of the respiratory unit)

General Considerations, Definitions and Clinical Features:

A. Emphysema is abnormal permanent **dilation of air spaces** distal to the terminal bronchioles with destruction of alveolar walls without significant fibrosis .

B. The disease is strongly associated with cigarette smoking (which is a strong reason for this disease's coexistence with chronic bronchitis).

C. Emphysema is classified according to its anatomic distribution within the lobule; the **acinus** is the structure distal to terminal bronchioles, and a cluster of three to five acini is called a lobule. (Picture A)

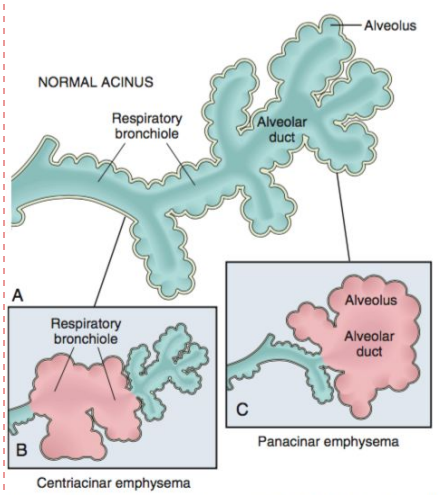
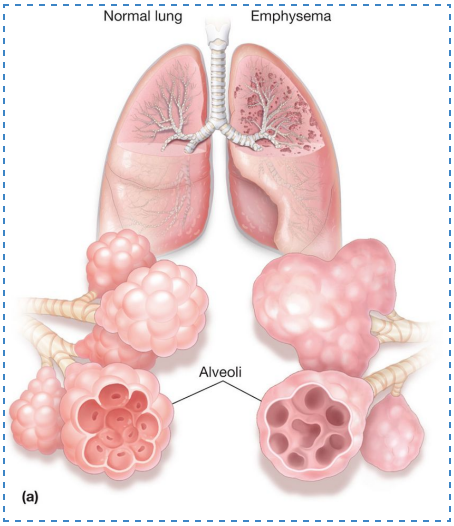
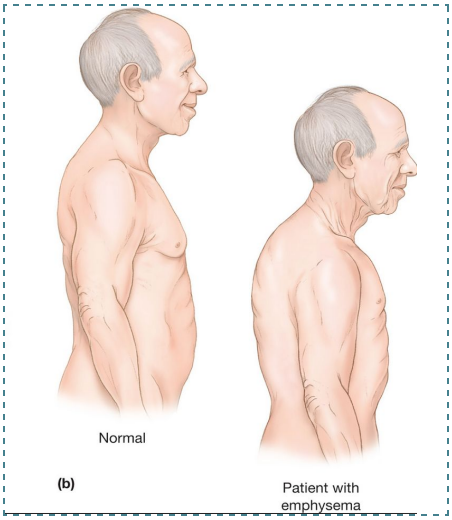


Figure 12–6 Major patterns of emphysema. **A,** Diagram of normal structure of the acinus, the fundamental unit of the lung. **B,** Centriacinar emphysema with dilation that initially affects the respiratory bronchioles. **C,** Panacinar emphysema with initial distention of all the peripheral structures (i.e., the alveolus and alveolar duct); the disease later extends to affect the respiratory bronchioles.

Clinical characteristics:

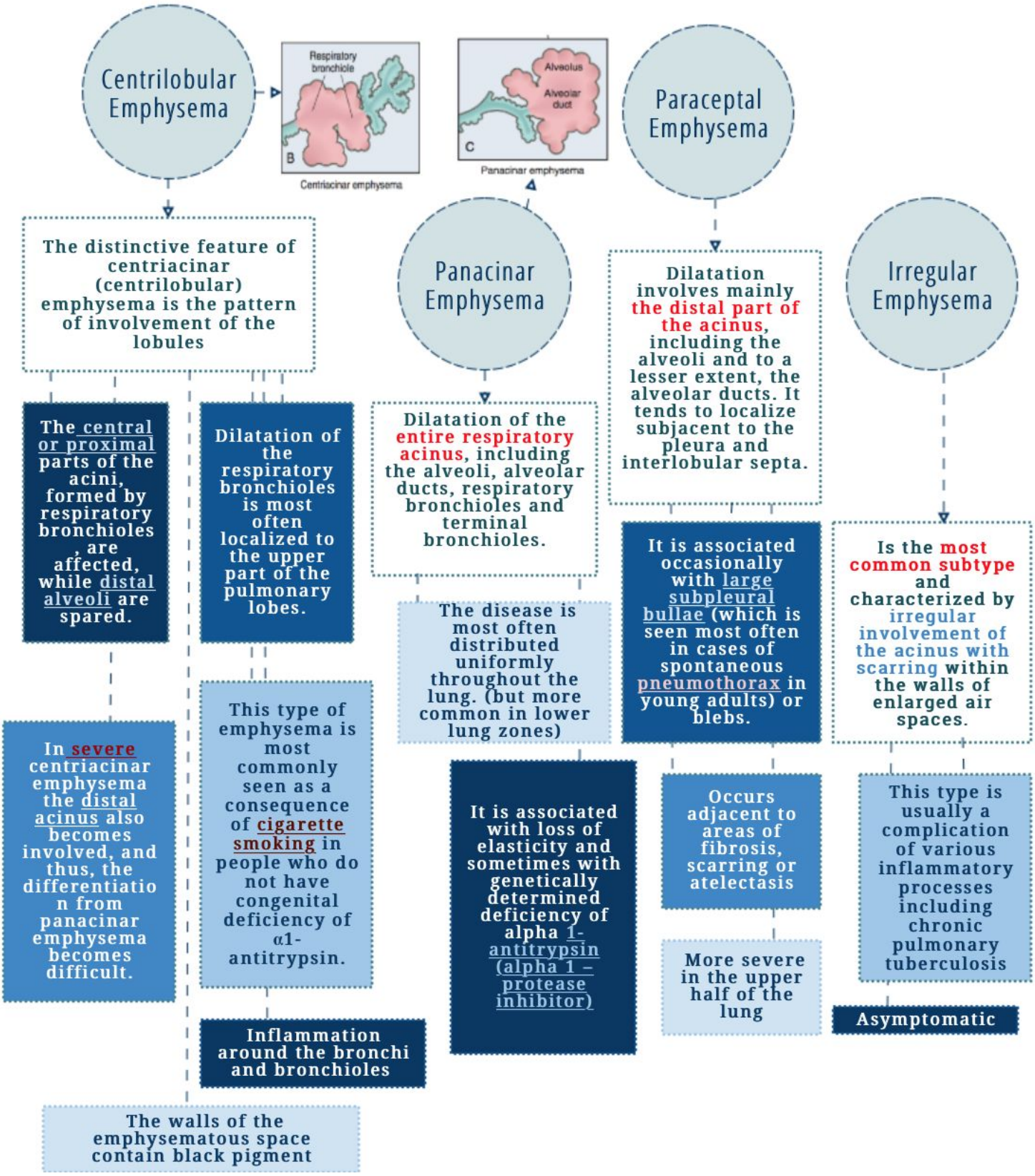
- Dyspnea usually is the first symptom; it begins insidiously but is steadily progressive.
- Cough and wheezing.
- Pulmonary function tests reveal reduced FEV1
- The disease appears as "holes" in the lung tissue.
- Emphysema Impairs Respiratory Function:
  - Diminished alveolar surface area for gas exchange (decreased Tco)
  - Loss of elastic recoil and support of small airways leading to tendency to collapse with obstruction.
- In patients with underlying chronic bronchitis or chronic asthmatic bronchitis, cough and wheezing may be the initial complaints.
- Weight loss is common and may be so severe as to suggest a hidden malignant tumor.
- Increased anteroposterior diameter if the chest (Barrell-chest), increased total vital capacity.
- Advanced: hypoxia, cyanosis, respiratory acidosis. Hypoxia and cyanosis occur when the patient has chronic bronchitis and a history of recurrent infections with purulent sputum. those patients often seek help after the onset of **cor pulmonale.**
- Patients are known as **pink puffers.** (because they always try to puff the air out)



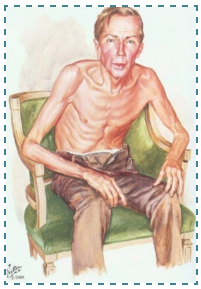


What is the person with emphysema presented with?
No cyanosis. Always try to puff the air out. The lung is expanded.

Types of Emphysema: Differentiated into different types depending on the parts it affects. Only the first two types cause clinically significant airway obstruction, with centriacinar emphysema being about 20 times more common than panacinar disease.



Why is emphysema considered to be an obstructive airway disease? Is there any mechanical obstruction?



Because emphysema affects the peripheral airways, it is not, anatomically speaking, an obstructive disease, and there is no mechanical obstruction. However, it is functionally an obstructive disease, because destruction of the wall of the air spaces prevents the elastic recoil that is necessary to push air out of the lungs. Thus, in effect, there is limitation of airflow, just as there would be if there were mechanical obstruction.

Complications:

A. Emphysema is often complicated by or coexistent with **chronic bronchitis.**

B. **Interstitial emphysema**, in which air spaces may enter into the interstitial tissues of the chest from a tear in the airways may sometimes occur.

C. Other complications of emphysema may include rupture of a surface bleb (markedly dilated and emphysematous alveolus) with resultant pneumothorax.

D. Death from emphysema is related to either:
   - ➢ Pulmonary failure, with respiratory acidosis, hypoxia, and coma
   - ➢ Right-sided heart failure (cor pulmonale).

Postulated Causes:

Emphysema may result from action of proteolytic enzymes such as elastase on the alveolar wall. Elastase can induce destruction of elastin unless neutralized by the antiproteinase-antielastase activities of alpha 1-antitrypsin which can be deficient in cases of emphysema.

A. **Cigarette smoking** increases number of neutrophils and macrophages in their alveoli, which are sources of elastase (an enzyme which destroys elastic fibers from the wall of alveoli). Smoking also Inhibits alpha 1 antitrypsin. Tobacco smoke contains reactive oxygen species with inactivation of anti-proteases.

B. **Hereditary alpha 1 antitrypsin deficiency** accounts for a small subgroup of cases of **panacinar emphysema.** It is caused by variants in the pi (proteinase inhibitor) gene, localized to chromosome 14.

Pathogenesis: (not completely understood)

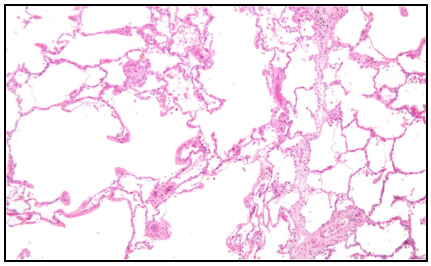
- ➔ Elastic tissue of the alveolar wall is broken down by action of proteolytic enzymes like protease (e.g.elastase).
- ➔ Normally there is a balance between protease and anti protease activity.
- ➔ Any condition that increases the neutrophils or macrophages in the lung will lead to release of protease enzyme which causes damage to the elastic tissue of the alveolar wall.
- ➔ Therefore one of the key mechanisms in emphysema is alveolar wall destruction which occurs due to excess proteases (elastase) activity coupled with low anti-protease level and inflammation (protease-antiprotease hypothesis)
  - ❑ Protease is produced by neutrophils and macrophages.
  - ❑ Alpha 1 antitrypsin is an anti-protease (anti-elastase) and it counter acts the protease. It is a major inhibitor of proteases secreted by neutrophils during inflammation. a1-antitrypsin is normally present in the serum, in tissue fluids and in macrophages.
- ➔ The protease-antiprotease hypothesis explains the effect of cigarette smoking in the production of centriacinar emphysema

Morphology:

Gross: The lungs are pale, voluminous.

Histologically:

- ➢ Thinning and destruction of alveolar walls creating large airspaces.
- ➢ Loss of elastic tissue.
- ➢ Reduced radial traction on the small airways.
- ➢ Alveolar capillaries is diminished.
- ➢ Accompanying bronchitis and bronchiolitis.



Dr. Rikabbi's Notes: In this disease the lung is "Sponge like" and there are spaces filled with air with different sizes.
How do we define this disease ? The definition of emphysema is a "pathological definition" not a clinical.

Definition: Abnormal dilatation of air spaces which are distal to the terminal bronchioles.

What could also lead to emphysema?

Air Pollution: the polluted air irritates the bronchial mucosa, they induce an inflammatory reaction, leading to chemotaxis of neutrophils and macrophages to the bronchial tree and spaces, they have enzymes and these enzymes called proteolytic. They will act on the connective tissue in those spaces and will destroy part of the alveolar wall. Which leads to dilatation.

- People who don't smoke have congenital emphysema.
- Congenital emphysema is rare, but acquired emphysema is common because of smoking.

Chronic Bronchitis: *Click Here*

Is one type of COPD (chronic obstructive pulmonary disease), which initially involves the large airways.

Clinical Presentation:

The clinical definition of chronic bronchitis is a **productive cough (with sputum) that occurs during at least 3 consecutive months over at least 2 consecutive years.**

Dr. Alrikkabi note:
In Chronic bronchitis we have two types of cough:
Dry cough: person only coughing and feel irritation no produce of sputum.
Wet cough: productive cough for period of 2 months in chronic bronchitis
Also when the sputum is yellow and green is it infected.

Note: Chronic bronchitis is defined on the basis of clinical features such as the presence of chronic and recurrent cough with excessive mucus secretion

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

➔ Some patients with chronic bronchitis may demonstrate hyper responsive airways with intermittent bronchospasm and wheezing.

Note: with progression, chronic bronchitis is complicated by pulmonary hypertension and cardiac failure.

➔ Chronic bronchitis is clearly linked to cigarette smoking (Common among smokers and urban dwellers age 40 - 65) and is also associated with air pollution, infection and genetic factors.

➔ It may lead to **cor pulmonale.** (diseases of the lung or pulmonary vasculature leads to pulmonary hypertension which leads to right ventricular dilation and hypertrophy (right heart failure).

➔ Increased sleepiness due to CO_2 narcosis.

➔ Can occur in several forms:

- Simple chronic bronchitis.
- Chronic mucopurulent bronchitis.
- Chronic asthmatic bronchitis.
- Chronic obstructive bronchitis.

➔ Hypercapnia and hypoxemia.

➔ Elevated red cell counts (secondary polycythemia) as a result of chronic hypoxemia.

➔ Cyanosis due to very poor oxygenation in severe cases.

➔ Patients with severe chronic bronchitis are termed blue bloaters.

Note: Recurrent infections and respiratory failure are constant threats

Note:

Chronic bronchitis and emphysema mostly coexist but can occur on their own. This is because the major cause —cigarette smoking, especially long-term, heavy tobacco exposure— is common to both disorders.

Etiology:

- Cigarette smoking is the most important underlying risk factor.
- Air pollutants.
- Genetic factors e.g. cystic fibrosis.
- Infection.

Pathological Changes: (Chronic irritation of inhaled substances or microbial infection leads to)

➔ Hypersecretion of mucus due to marked **hyperplasia of mucus-secreting submucosal glands,** beginning in the large airways.

➔ Environmental irritants such as cigarette smoking and air pollutants induce **hypertrophy of mucous glands** in the trachea and main bronchi, leading to a marked increase in mucin-secreting goblet cells in the surface epithelium of smaller bronchi and bronchioles.

Note: These irritants cause inflammation with infiltration of CD8+ lymphocytes, macrophages, and neutrophils. In contrast with asthma, there are no eosinophils in chronic bronchitis.

- As chronic bronchitis persists the small bronhi and bronchioles also get affected.
- Irreversible fibrosis may occur in chronically inflamed segmental bronchi and bronchioles.

➔ 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:

- Small airway disease (chronic bronchiolitis).
  Induced by goblet cell metaplasia with mucous plugging of the bronchiolar lumen, inflammation, and bronchiolar wall fibrosis
- Coexistent emphysema.

Note: In general, while small airway disease (AKA chronic bronchiolitis) is an important component of early and relatively mild airflow obstruction, chronic bronchitis with significant airflow obstruction is almost always complicated with emphysema

➔ It is postulated that many of the respiratory epithelial effects of environmental irritants (e.g., mucus hypersecretion) are mediated by local release of T cell cytokines such as IL-13.

➔ **Microbial infection** often is present but has a secondary role, chiefly by maintaining the inflammation and exacerbating symptoms.

Morphology:

Gross specimens:

➢ The mucosal lining of the larger airways usually is **hyperemic and swollen** by edema fluid.
➢ It often is covered by a layer of mucinous or mucopurulent secretion.

Histological examination:

- The diagnostic feature of chronic bronchitis in the trachea and larger bronchi is the **enlargement of the mucus-secreting gland**.
- Increased number of Goblet cells.
- Squamous metaplasia which can progress to dysplasia and even invasive carcinoma.
- Bronchiolar wall fibrosis and resultant narrowing of bronchioles.
- Injury to cilia with loss of ciliated epithelial cells
- Inflammation.

Biopsy is not needed for diagnosis.

How do these changes differ from the changes seen in a typical case of allergic asthma?

In typical allergic asthma, which also has mucous gland hyperplasia, the bronchial wall has an inflammatory infiltrate in which eosinophils are prominent. There is also hypertrophy and hyperplasia of smooth muscle cells in asthma.

How do the changes differ from those seen in bronchiectasis?

Infection-related destruction of the bronchial wall is the characteristic appearance of bronchiectasis.

Dr. Alrikkabi note:
In chronic bronchitis:
Mucus blocking the gas exchange so it is not normal so they can't excrete CO_2 normally
cyanosis in lips, fingers.
They use accessory muscles
Right ventricle pressure increased

Dr. Rikabbi's Notes:

How do we diagnose Chronic bronchitis? There are two major triggering factors for this disease:

1. Smoking. & Air pollution.
2. Productive cough with sputum.

So, any sudden change suggests there might be an "Infection" thus, we should do "Culture".
Other thing is **clinical examination:**
While you listen to the chest of the patient you listen to the effect of the disease on the bronchial tree.

What is this effect?

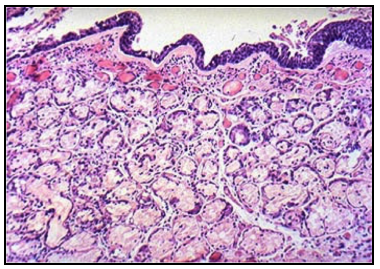
- He has a lot of mucopurulent substance in the lumen of those bronchi.
- And there's air coming and going, and it will produce a sound called "Wet crepitation"

The diagnosis of chronic bronchitis depends on:

1. The clinical history.
2. Listing to the chest
3. Culturing and sometimes X-ray of the chest.

The people who have this disease have:

- Lots of "Goblet cells" we refer to it as goblet cells metaplasia.
- Increase in the volume and the thickness bronchial mucus glands. Means, hypertrophy & hyperplasia of those glands.
- Chronic inflammatory cells infiltrate.



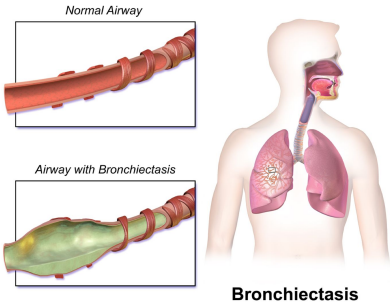
Mucosa : is ulcerated
Lumen : mucous has inflammatory cells, and maybe not.
And the thickness of the submucosal glands is increased, and this thickness we refer to it as the "red index"
Is the ratio between the thickness of the mucous glands to the entire thickness of the bronchial wall.
These people have "mucous plugs" in their bronchial tree, therefore the gas exchange is abnormal.
They can't get rid of BCOT . therefor will increased. Then will lead to "Cyanosis"
Chronic bronchitis leads to increase pressure in heart "Right ventricle" , abnormalities in blood gases, respiratory failure or acidosis .

Bronchiectasis: NOTE:Suffix: -ectasis = Dilation

It is the permanent and abnormal dilation of bronchi and bronchioles caused by destruction of the muscle and the supporting elastic tissue. Resulting from or associated with chronic infection with inflammation and necrosis of the bronchial wall.

It represents the end stage of a variety of pathologic processes that cause destruction of the bronchial wall.

Dr. Alrikkabi note:
Difference between bronchiole and bronchi is the cartilage presents in bronchi not in bronchioles



Commonly predisposing factors:

NOTE: It's not a primary disease **BUT** rather secondary disease.
Bronchiectasis is a result of chronic inflammation compounded by an inability to clear mucoid secretions. Conditions commonly associated with Bronchiectasis are as follows:

1. **Bronchial obstruction: can be either**
   - **Localized to the obstructed lung segment:**
     Most often by tumor, foreign bodies, or occasionally mucus impaction(انحشار).
   - **Generalized:**
     Complicate atopic asthma and chronic bronchitis.

2. **Congenital or hereditary conditions—for example:-**

- **Cystic fibrosis** (This is widespread, an important & serious complication):
  Caused by the secretion of abnormally viscid mucus, thus predisposing to infections of the bronchial tree. (builds up in the lungs and digestive tract).

  What is cystic fibrosis?

  - An inherited disease.
  - It is one of the most common chronic lung diseases in children and young adults, and may result in early death.
  - It may lead to bronchiectasis.
- **Immunodeficiency states:**

  It's likely to develop because of an increased susceptibility to repeated bacterial infections
- **Congenital bronchiectasis.**
- **Intralobar sequestration of the lung.**
- **Kartagener syndrome:** (The disease is rarely a manifestation of it).

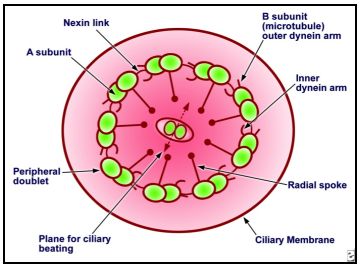
  ➔ It is a rare autosomal recessive disorder, which is caused by structural abnormalities of the mobility of respiratory, auditory and sperm cilia resulting in the failure to clear sputum that is referred to as **primary ciliary dyskinesia**.

  ➔ In this condition, there is a structural defect in dynein arms of the cilia which can be seen by electron microscopy.

  ➔ Male infertility is an important manifestation of ciliary dyskinesia (reduce mobility of spermatozoa.).

  ➔ Patient develop bronchiactasis, sinusitis and situs invertus sometimes with hearing loss and male sterility.

  What is Dynein?
  A type of ATPase, provides energy for microtubule sliding and the longitudinal displacement of adjacent microtubular doublets, resulting in ciliary bending.



  ➔ Impaired ciliary activity predisposes to infection in the sinuses and bronchi and disturbs embryogenesis, sometimes resulting in situs inversus[5].

  ➔ Lack of ciliary activity interferers with bronchial clearance of mucus.

3. **Chronic necrotizing infections, suppurative pneumonia or chronic sinusitis accompanied by postnasal drip:**

   Caused by TB, staphylococci or mixed infection.

Dr. Alrikkabi note:
Not all bronchiectasis is acquired, some of it is congenital e.g.: Immotile cilia syndrome (ciliary dyskinesia) :structural immortality in cilia.

[5] أَحْشاءٌ مَقْلوبَةِ المَوضِع

Pathogenesis:

Any of the previously mentioned conditions can cause damage to the airways resulting in impaired mucociliary clearance, mucus stasis and accumulation which in turn further makes the airways susceptible to microbial colonization.

- ❏ The persistence of the pathology with superadded infection leads to a "vicious circle" of inflammation and tissue damage.
- ❏ Inflammation results in progressive destruction of the normal lung architecture, in particular the elastic fibres of bronchi.
- ❏ Neutrophils are thought to play a central role in the pathogenesis of tissue damage that occurs in bronchiectasis.

> **Note:**
> - Two processes are crucial[6] and intertwined in the pathogenesis of bronchiectasis. Which are: ***obstruction*** and ***chronic persistent infection***. (how????)

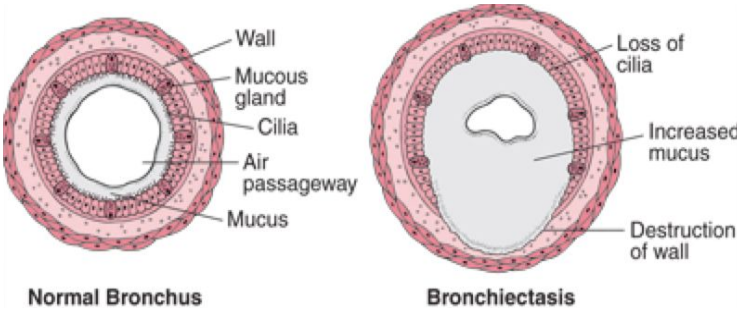
> **Note:** It requires two components, infection and obstruction, each one of which can occur first and start the disease process.

1. **Obstruction**→ hampers[7] normal clearance mechanisms (prevents the airways from clearing mucus, mucus help to remove inhaled dust, bacteria, and other small particles) (so secondary infection soon follows) → The resultant inflammatory damage to the bronchial wall and the accumulating exudate further→ leading to irreversible dilation (Bronchiectasis).
2. **Chronic persistent infection**→ Overtime, The resultant inflammatory damage to the bronchial wall and the accumulating exudate further→ leading to weakening and irreversible dilation (Bronchiectasis).

Morphology of bronchiectasis:

Gross:

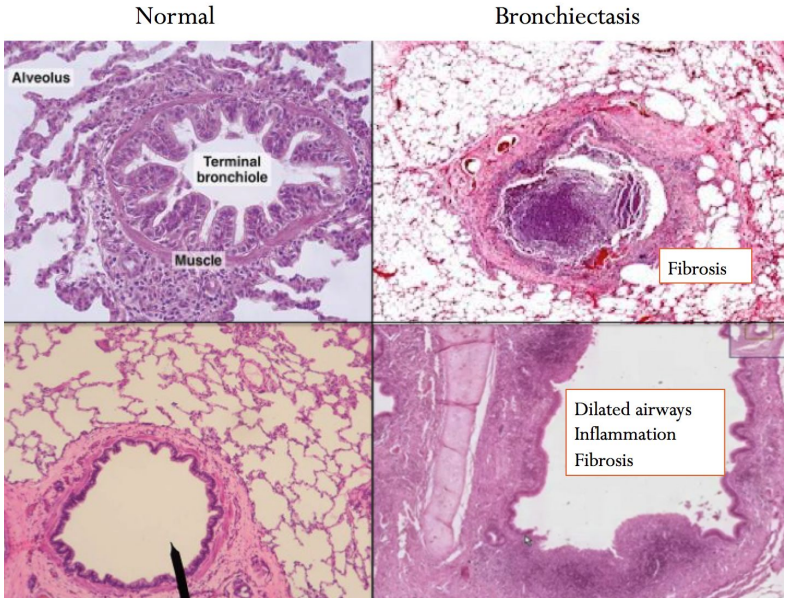
- Dilation of airways, usually involving lower lobes (right side more often than left) bilaterally (vertical airways). with airways almost extending to the pleural surface.
- Acute and chronic inflammation (neutrophils, lymphocytes, histiocytes and plasma cells)
- Necrosis and ulceration in the wall of the bronchi and bronchioles with loss of cilia, squamous metaplasia and fibrosis.



[6] مصيريه
[7] عرقل

Microscopic:

Appearance depends upon stage, inflammatory infiltrate, and tissue destruction.



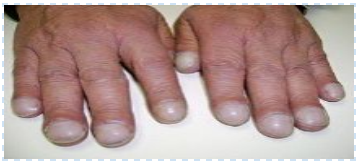
Clinical presentation of bronchiectasis

Symptoms:

Dyspnea, chronic cough (dry, or with large amounts of copious purulent foul smelling sputum production), fever . Hemoptysis is common.

Signs:

Clubbing of the fingers[8] (i.e., pulmonary osteoarthropathy), hypoxemia, and hypercapnia[9]



Complications of bronchiectasis

- Persistent Hemoptysis[10] with potentially life-threatening hemorrhage.
- If severe, obstruction of pulmonary function develops.
- **Rarely,** pulmonary hypertension, metastatic brain abscess formation (from recurrent pulmonary infection), amyloidosis.

[8] زياده في سماكة اللحم تحت الأظافر.
[9] فرط ثنائي أكسيد الكربون في الدم.

[10] The coughing up of blood.

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قال صلى الله عليه وسلم: من سلك طريقاً يلتمس به علماً سهل الله له به طريقاً إلى الجنة.

دعواتنا لكم بالتوفيق.