

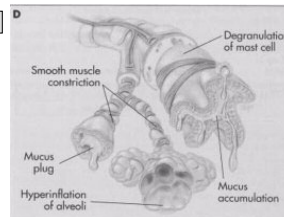
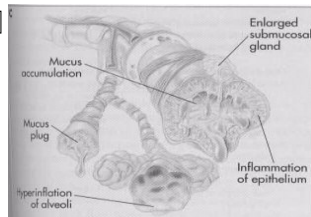
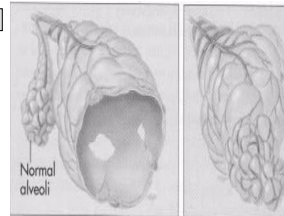
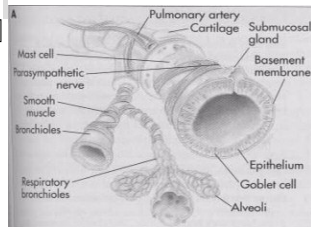
# Lung diseases

May 19, 2005

## Obstructive pulmonary diseases

- They are characterized by airway obstruction that is worse with expiration.
- Either more force (i.e., use of accessory muscles of expiration) is required to expire a given volume of air or emptying of the lungs is slowed or both.
- The unifying symptom of obstructive disease is dyspnea, the unifying sign is wheezing.
  
- The most common obstructive diseases are asthma, chronic bronchitis and emphysema.
- Because many individuals have both bronchitis and emphysema, they are often called COPD

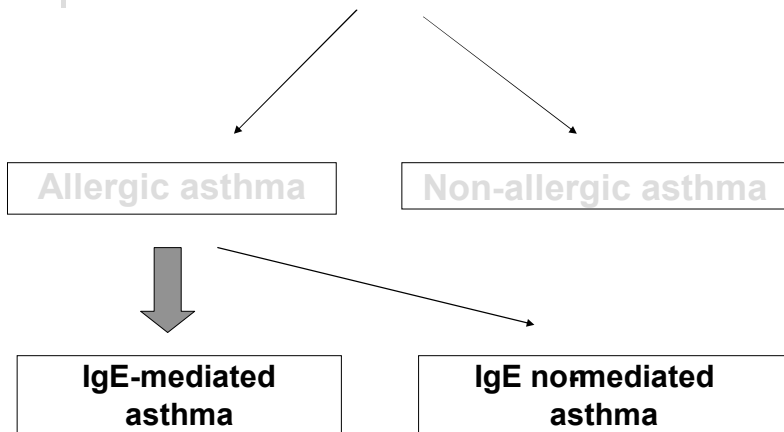
## Airway obstruction caused by emphysema, chronic bronchitis, and asthma



## Asthma bronchiale

- Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.
  
- The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning.
  
- These episodes are usually associated with widespread but variable airway obstruction that is often reversible either spontaneously or with treatment.

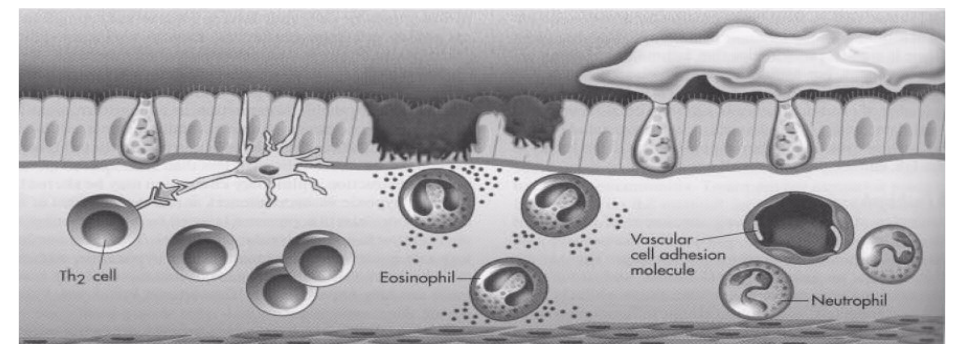
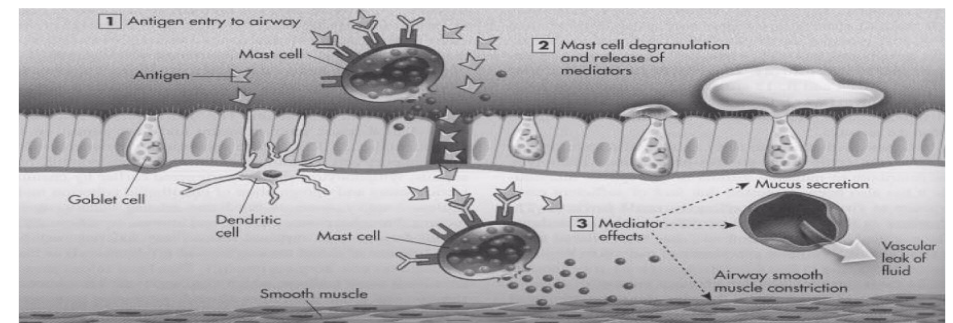
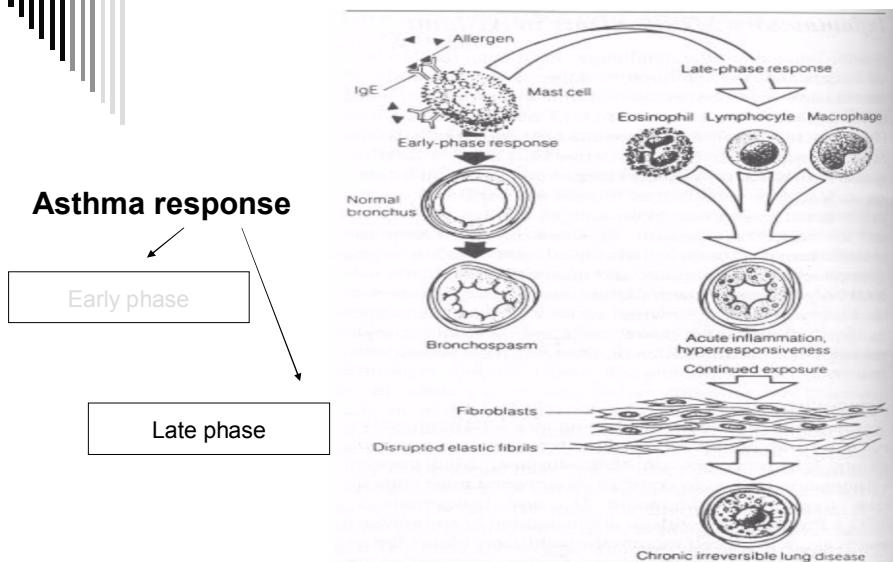
## Types of asthma



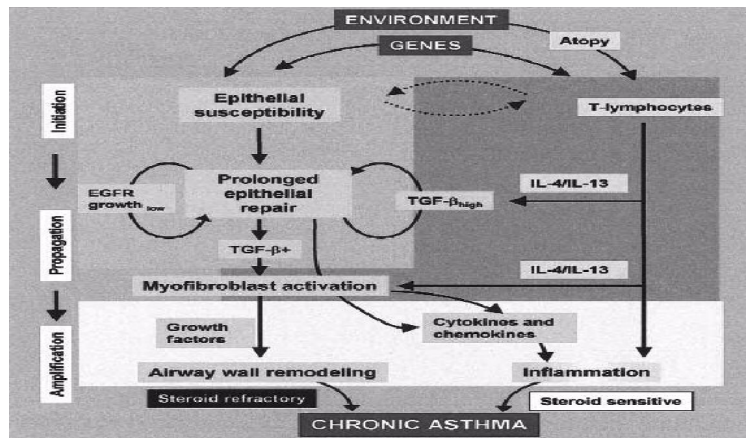
## Asthma classification based on severity

- Mild intermittent
- Mild persistent
- Moderate persistent
- Severe persistent

## Asthma response



## Paradigma of asthma pathogenesis



## Asthma – clinical manifestations

- During full remission
  - Individuals are asymptomatic and pulmonary function tests are normal.
- During partial remission
  - There are no clinical symptoms but pulmonary function tests are abnormal
- During attacks
  - Individuals are dyspneic and respiratory effort is marked
  - Breath sounds are decreased except for considerable wheezing, dyspnea, non-productive coughing, tachycardia and tachypnea occur

## Asthma - pulmonary function

- Spirometry shows decreases in expiratory flow rate, forced expiratory volume (FEV), and forced vital capacity (FVC)
- FRC and total lung capacity (TLC) are increased.
- Blood gas analysis shows hypoxemia with early respiratory alkalosis or late respiratory acidosis.

## Treatments

### Goals:

- To reverse of acute attacks
- To control recurrent attacks
- To reduce bronchial inflammation and the associated hyperreactivity
- + elimination of allergens (if it is possible)

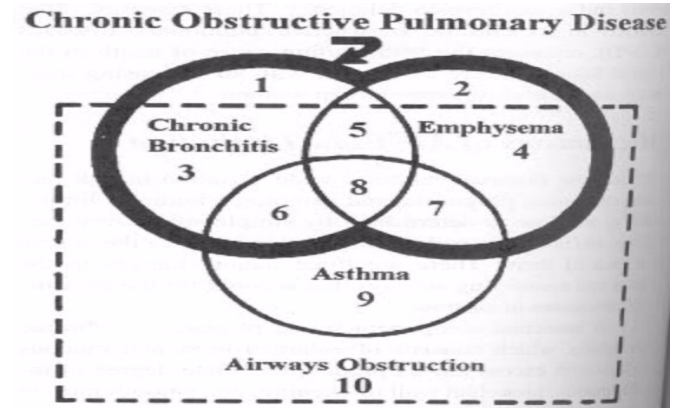
### Drugs:

- Allergen's immunotherapy
- Bronchodilator (Beta agonists, Anticholinergic agents, Theophylline)
- Immunosuppressant (corticosteroids)
- Others (Leukotriene modifiers, antihistamine, e.g.)

## Chronic obstructive pulmonary disease (COPD)

- COPD is defined as pathologic lung changes consistent with emphysema or chronic bronchitis.
- It is syndrome characterized by abnormal tests of expiratory airflow that do not change markedly over time, and without a reversible response to pharmacological agents.
- 5-20% adult population
- Most frequently in men
- The fifth leading cause of death

The complex, heterogenous overlapping of the three primary diagnoses include under diseases of air flow limitation is present on the next picture:



## 1. Chronic bronchitis

Chronic bronchitis is defined as hypersecretion of mucus and chronic productive cough that continues for at least 3 months of years for at least 2 consecutive years.

Incidence is increased in smokers (up to twentyfold) and even more so in workers exposed to air pollution.

It is a major health problem for the elderly population. Repeated infections are common.

## Chronic bronchitis - etiology

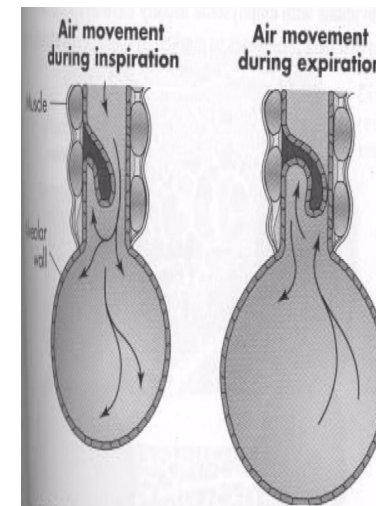
- It is primarily caused by cigarette smoke, both active and passive smoking have been implicated
- Other risk factors:
  - profesional exposition
  - air pollution
  - repeated infections of airways
  - genetics



## Chronic bronchitis - morphology

- Inspired irritants not only increase mucus production but also increase the size and number of mucous glands and goblet cells in airway epithelium
- The mucus produced is thicker and more tenacious than normal. This sticky mucus coating makes it much more likely that bacteria, such as H. influenzae and S. pneumoniae, will become embedded in the airway secretions, there they reproduce rapidly.
- Ciliary function is impaired, reducing mucus clearance further. The lung's defense mechanisms are therefore compromised, increasing susceptibility to pulmonary infection and injury.
- The bronchial walls become inflamed and thickened from edema and accumulation of inflammatory cells.

- Initially chronic bronchitis affects only the larger bronchi, but eventually all airways are involved.
- The thick mucus and hypertrophied bronchial smooth muscle obstruct the airways and lead to closure, particularly during expiration, when the airways are narrowed.
- The airways collapse early in expiration, trapping gas in the distal portions of the lung.
- Obstruction eventually leads to ventilation-perfusion mismatch, hypoventilation (increased PaCO<sub>2</sub>) and hypoxemia.



## Chronic bronchitis – clinical manifestations

- Individuals usually have a productive cough („smoker’s cough“) and evidence of airway obstruction is shown by spirometry
- Bronchitis patients are often described as „blue bloaters“ due to their tendency to exhibit both hypoxemia and right heart failure with peripheral edema in spite of only moderate obstructive changes on pulmonary functional tests.
- Acute episodes (e.g. after infection) result in marked hypoxemia that leads to polycythemia and cyanosis (blueness) associated with an increase in pulmonary artery pressure, impairing right ventricular function, and significant jugular venous distension and ankle edema (bloating)

**Table 32-4** Clinical Manifestations of Chronic Obstructive Lung Disease

Clinical Manifestations	Bronchitis	Emphysema
Productive cough	Classic sign	Late in course with infection
Dyspnea	Late in course	Common
Wheezing	Intermittent	Minimal
History of smoking	Common	Common
Barrel chest	Occasionally	Classic
Prolonged expiration	Always present	Always present
Cyanosis	Common	Uncommon
Chronic hypoventilation	Common	Late in course
Polycythemia	Common	Late in course
Cor pulmonale	Common	Late in course

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## Chronic bronchitis – evaluation and treatment

- Diagnosis is made on the basis of physical examination, chest radiograph, pulmonary function tests and blood gas analyses
  - The best „treatment“ is prevention, because pathological changes are not reversible.
  - If the individuals stops smoking, disease progression can be halted
  - Therapy: - bronchodilators
    - expectorans
    - chest physical therapy
    - steroids
    - antibiotics
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## Chronic bronchitis: low-flow oxygen therapy

- It is administered with care to individuals with severe hypoxemia and CO<sub>2</sub> retention
  - Because of the chronic elevation of PaCO<sub>2</sub>, the central chemoreceptors no longer act as the primary stimulus for breathing.
  - This role is taken over by the peripheral chemoreceptors, which are sensitive to changes in PaO<sub>2</sub>.
  - Peripheral chemoreceptors do not stimulate breathing if the PaO<sub>2</sub> is much more than 60 mmHg.
  - Therefore, if oxygen therapy causes PaO<sub>2</sub> to exceed 60 mmHg, the stimulus to breathe is lost, PaCO<sub>2</sub> increases, and apnea results.
  - If inadequate oxygenation cannot be achieved without resulting in respiratory depression, the individual must be mechanically ventilated)
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## 2. Emphysema

- It is abnormal permanent enlargement of gas-exchange airways (acini) accompanied by destruction of alveolar walls and without obvious fibrosis.
  - In emphysema, obstruction results from changes in lung tissues, rather than mucus production and inflammation, as in chronic bronchitis.
  - The major mechanism of airflow limitation is loss of elastic recoil.
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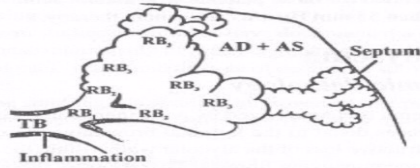
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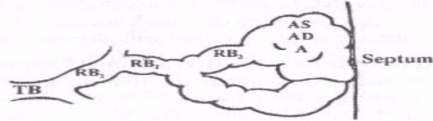
## Types of emphysema

- Three distinctive types of alveolar destruction have been described, according to the portion of the acinus first involved with disease:
    - 1) Centrilobular (centriacinar):
      - septal destruction occurs in the respiratory bronchioles and alveolar ducts, usually in the upper lobes of the lung. The alveolar sac (alveoli distal to the respiratory bronchiole) remains intact. It tends to occur in smokers with chronic bronchitis.
    - 2) Panacinar (panlobular):
      - It involves the entire acinus with damage more randomly distributed and involving the lower lobes of the lung. It tends to occur in patients with  $\alpha$ 1-antitrypsin deficiency.
    - 3) Distal acinar (subpleural):
      - It is typically seen in a young adult with a history of a spontaneous pneumothorax.
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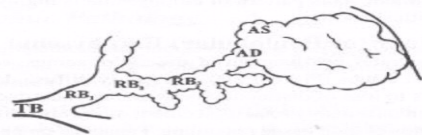
### A. Centrilobular Emphysema



### B. Panacinar Emphysema



### C. Distal Acinar Emphysema



## Types of emphysema

### □ Primary emphysema:

- it is commonly linked to an inherited deficiency of the enzyme  $\alpha$ 1-antitrypsin that is a major component of  $\alpha$ 1-globulin, a plasma protein.

- Normally it inhibits the action of many proteolytic enzymes.

- Individuals with deficiency of this enzyme (AR) have an increased likelihood of developing emphysema because proteolysis in lung tissues is not inhibited.

### □ Secondary emphysema:

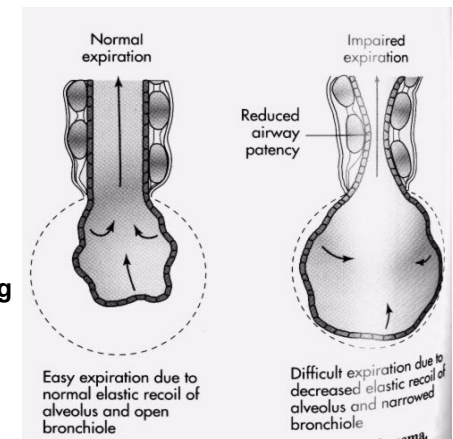
- It is also caused by an inability of the body to inhibit proteolytic enzymes in the lung. It results from an insult to the lungs from inhaled toxins, such as cigarette smoke and air pollution.

## Pathophysiology of emphysema

- Emphysema begins with destruction of alveolar septa
- It is postulated that inhaled oxidants, such as those in cigarette smoke and air pollution, tip the normal balance of elastases (proteolytic enzymes) and antielastases (such as  $\alpha$ 1-antitrypsin) such that elastin is destroyed at an increased rate
- Expiration becomes difficult because loss of elastic recoil reduces the volume of air that can be expired passively.
- Hyperinflation of alveoli causes large air spaces (bullae) and air spaces adjacent to pleura (blebs) to develop.
- The combination of increased RV in the alveoli and diminished caliber of the bronchioles causes part of each inspiration to be trapped in the acinus.

## Mechanisms of air trapping in emphysema

- Damaged or destroyed alveolar walls no longer support and hold open the airways, and alveoli lose their property of passive elastic recoil.
- Both of the se factors contribute to collapse during expiration.



## Emphysema – clinical manifestations

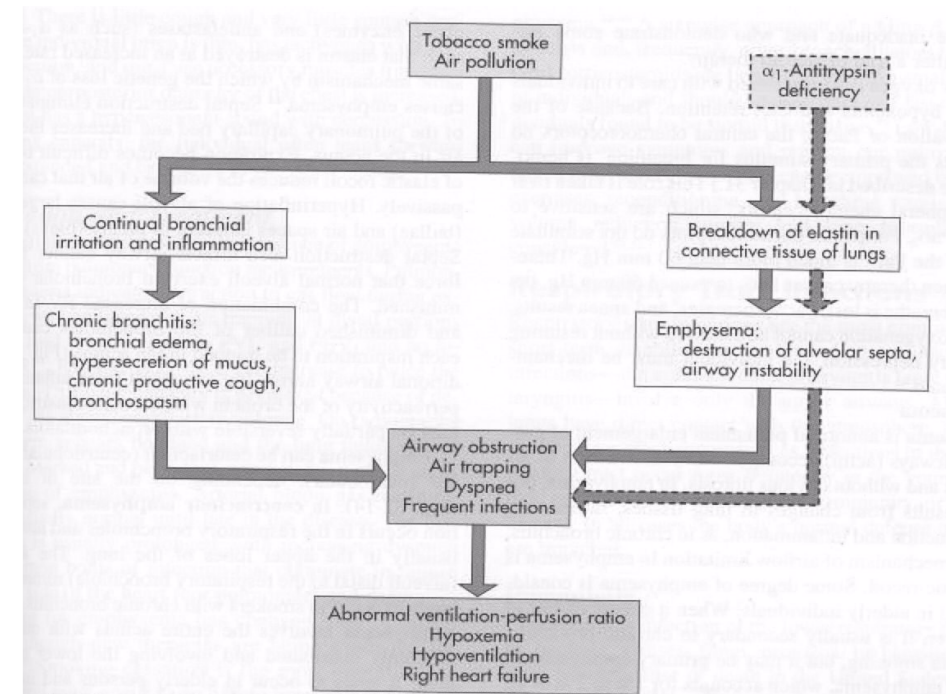
- Patients with emphysema are able to maintain a higher alveolar minute ventilation than those with chronic bronchitis. Thus they tend to have a higher PaO<sub>2</sub> and lower PaCO<sub>2</sub> and have classically been referred to as „pink puffers“
- Physical examination often reveals a thin, tachypneic patient using accessory muscles and pursed lips to facilitate respiration. The thorax is barrel-shaped due to hyperinflation.
- There is little cough and very little sputum production (in „pure“ emphysema)

## Emphysema – evaluation

- **Pulmonary function tests:**
  - indicate obstruction to gas flow during expiration
  - airway collapse and air trapping lead to a decrease in FVC and FEV<sub>1</sub> and an increase in FRC, RV, and TLC.
  - diffusing capacity is decreased because destruction of the alveolocapillary membrane
- **Arterial blood gas measurements are usually normal until late in the disease**

## Emphysema – approach to therapy

- Smoking cessation is the most important intervention
- Inhaled anticholinergic agents
- β<sub>2</sub>-adrenergic agonists
- Steroids
- Low-flow oxygen therapy in selected individuals
- Lung transplant can be considered

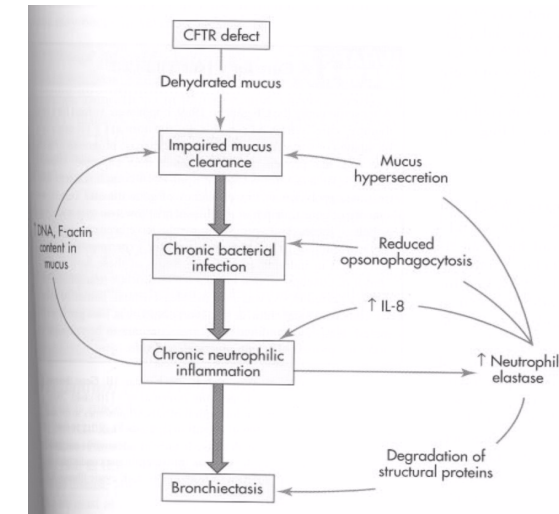




## Cystic fibrosis (mucoviscidosis)

- It is AR inherited disorder that results from defective epithelial ion transport
- On simplistic level, CF is associated with abnormal secretions that may cause obstructive problems within the respiratory, digestive and reproductive tracts.
- The CF gene has been localized on chromosome 7  
↓  
its mutation result in the abnormal expression of the protein cystic fibrosis transmembrane regulator (CFTR) = chloride channel present on the surface of many cells (airways, bile ducts, pancreas, sweat ducts, vas deferens)

## Pathogenesis of cystic fibrosis lung diseases



## Cystic fibrosis – clinical manifestations

- The most common manifestations are respiratory and gastrointestinal.
- Respiratory symptoms include:  
persistent cough or wheeze and recurrent or severe pneumonia  
Physical signs include barrel chest and digital clubbing.
- Gastrointestinal manifestations include:  
meconium ileus at birth, failure to thrive, and malabsorptive symptoms, such as frequent loose and oily stools
- Male with CF are typically infertile (98%)
- May be liver disease or diabetes mellitus

## Cystic fibrosis – evaluation and treatment

- The standard method of diagnosis is the sweat test, which will reveal sweat chloride concentration in excess of 60 mEq/L.
- Genotyping for CFTR mutation (above 800 variations)
- Treatment:
  - chest physical therapy
  - bronchodilators
  - antibiotics
  - pancreatic enzymes, vitamins

## Interstitial lung diseases

- There are a large number of diseases that affect the interstitium of the lung



it is connective tissue present between the alveolar epithelium and capillary endothelium

- Some of these diseases have known etiology, e.g. occupational diseases
- Others are diseases of unknown etiology
  - most frequent of these are idiopathic pulmonary fibrosis (diffuse interstitial fibrosis), pulmonary fibrosis associated with collagen-vascular diseases, and sarcoidosis.

## Nozological units

### Idiopathic pulmonary fibrosis

- Diseases unknown etiology, non-specific fibrotic change in lung. The diagnosis is to some extent one of exclusion.

### Sarcoidosis

- One of the most common. It is multi-system granulomatous disease that involves lung, lymph nodes, salivary glands, and liver. Specific type is called erythema nodosum

### Occupational interstitial diseases

- Exposure to occupational and environmental inhalants for a long time can lead to develop lung disease. Workers in industries with heavy exposure to silica dust, asbestos particles, and welding fumes are generally aware of the risk of their occupation.

## Occupational diseases

	<i>Aspergillus</i>

## Clinical manifestations

### Subjective symptoms

- dyspnoe
- cough

### Objective signs

- tachypnoe
- crackles
- clubbing
- cyanosis
- cor pulmonale

### Laboratory findings

- Decrease PaO<sub>2</sub>
- normal PaCO<sub>2</sub>
- ECG- cor pulmonale
- Spirometry - restrictive pattern (↓VC, normal ratio FEV1/FVC)
- Decrease diffusion capacity of the lung for carbon monoxide

## Therapy

- It depends on etiology (if it is known)
- Stopping the occupational exposure
- Antibiotics
- Diseases of unknown etiology (sarcoidosis, idiop. pulmonary fibrosis) corticosteroids
- Oxygen therapy

## Pulmonary edema

It is excess water (fluid) in the lung

- The normal lung contains very little water or fluid. It is kept dry by lymphatic drainage and a balance among capillary hydrostatic pressure, capillary oncotic pressure, and capillary permeability
- In addition, surfactant lining the alveoli repels water, keeping fluid from entering the alveoli.

## Pulmonary edema - pathogenesis

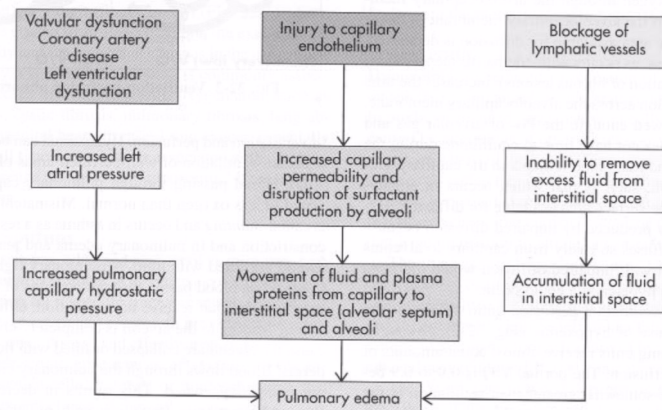


FIG. 32-3 Pathogenesis of pulmonary edema.

## Classification of pulmonary edema

- 1) **High pressure (hydrostatic, cardiogenic) edema**
  - It is associated with elevated capillary hydrostatic pressure
- 2) **Low pressure (high permeability, noncardiogenic) edema**
  - It refers to conditions in which hydraulic filtration coefficient is elevated and osmotic reflection coefficient is reduced

interstitial edema x alveolar edema

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## Effects of pulmonary edema

### □ Pulmonary vascular pressure and volume

In cardiogenic edema the increase in left atrial pressure is reflected passively in a retrograde direction to the pulmonary veins, capillaries, and arteries. This increase in pulmonary vascular pressure produces an increase in pulmonary blood volume.

In permeability edema the passive increase in vascular volume is absent but the fundamental process of lung injury releases substances which may produce pulmonary vasoconstriction leading to increased pulmonary artery pressure despite normal left atrial pressure.

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### □ Pulmonary blood flow redistribution

Cardiogenic edema is associated with a redistribution of blood flow in the lungs such that the lung bases, which normally receive the highest blood flow, experience a decrease in blood flow while the apices, which normally receive the least amount of flow, experience an increase in blood flow.

Perfusion redistribution becomes relevant in gas exchange. Perfusion of the pulmonary capillaries in an edema-filled alveolus has the effect of a right-to-left shunt since venous blood which is not exposed to alveolar air is admixed with oxygenated blood from nonedematous alveoli.

Vasodilator therapy for congestive heart failure, while improving cardiac function, usually increases the severity of hypoxemia by reversing pulmonary blood flow redistribution.

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### □ Lung compliance

Interstitial edema produces a reduction in lung compliance which increases the elastic work the muscles must do to achieve a given tidal volume.

Furthermore, even small amounts of edema fluid interfere with surfactant function, leading to increased surface tension, alveolar instability, and alveolar collapse.

In cardiogenic edema the increase in pulmonary blood volume causes a further increase in lung stiffness.

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### □ Airway resistance (AR)

There are several factors increasing airway resistance:

- 1) A reduction in lung volume produces an increase in airway resistance
  - 2) Edema in the bronchovascular sheath produces compression of small airways
  - 3) Fluid in the airways combined with edema of the bronchial mucosa narrows the lumen and increases AR.
  - 4) Reflex bronchospasm which occurs in some patients with congestive heart failure – „cardiac asthma“
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**Oxygenation**

Alveolar edema produces a right-to-left shunt, which has the same effect on arterial PO<sub>2</sub> as an anatomic shunt.

**Acid-base balance**

- mild forms of pulmonary edema stimulate interstitial „J“ receptors in the lung, leading to hyperventilation and respiratory alkalosis.
  - More severe forms increasing the work of breathing lead to relative hypoventilation and respiratory acidosis.
  - In cardiogenic edema while the metabolism of the respiratory muscles is increased, cardiac dysfunction leads to decreased blood flow, resulting in reduced tissue PO<sub>2</sub>, anaerobic metabolism, and metabolic acidosis.
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## Therapy

The treatment is based on pathophysiologic consequences and on pathogenic mechanisms:

- Oxygen and respiratory support**
  - Acid-base balance**
  - Reduce pulmonary capillary pressure  
(increase plasma oncotic pressure)**
-