PATHOLOGY

RESPIRATORY SYSTEM

SHEET NO. 2

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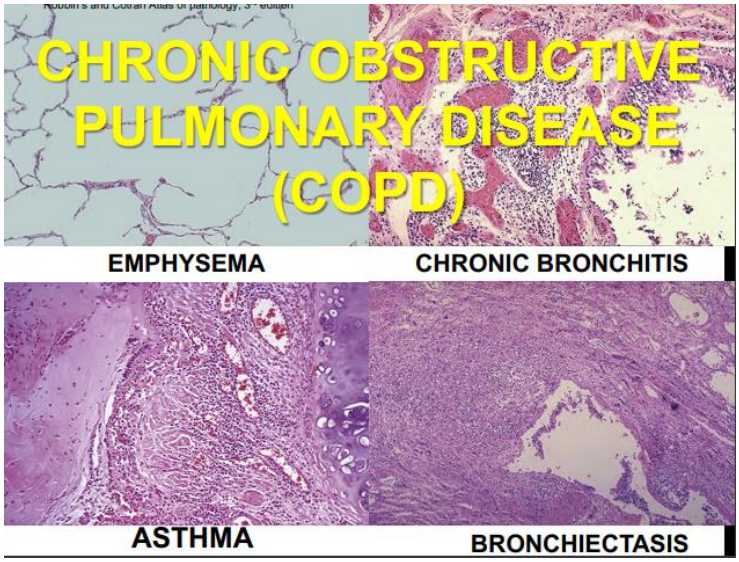
Obstructive lung diseases

- They're diffuse lung diseases.
- They include four main entities: Emphysema, chronic bronchitis, asthma, bronchiectasis.
- There's usually an overlap between the signs, symptoms and presentation of the patient that has COPD. Which means that even though each of these diseases has its own morphologic features, the overlap between them is common. You could see a patient with features of emphysema and features of chronic bronchitis or asthma; this is a common combination in these patients. Because they also share the predisposing factors like smoking, so the patient lies within the spectrum of COPDs.



- **It's hard to get the air OUT**
- **It's hard to EXHALE**

Air is accumulating in lungs, so it is trapped.

- **Lungs are hyperinflated**

• Total lung capacity: (TLC) is the volume of air in the lungs upon the maximum effort of inspiration.

Could be normal or elevated because of partial or total obstruction.

• lung compliance is a measure of the lung's ability to stretch or expand. Remember the rubber band.

Chronic obstructive pulmonary disease (COPD):

• defined by the WHO as "a common, preventable and treatable obstructive disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities caused by exposure to noxious particles or gases."

- They share predisposing factors and outcomes and they're considered irreversible-long term-.

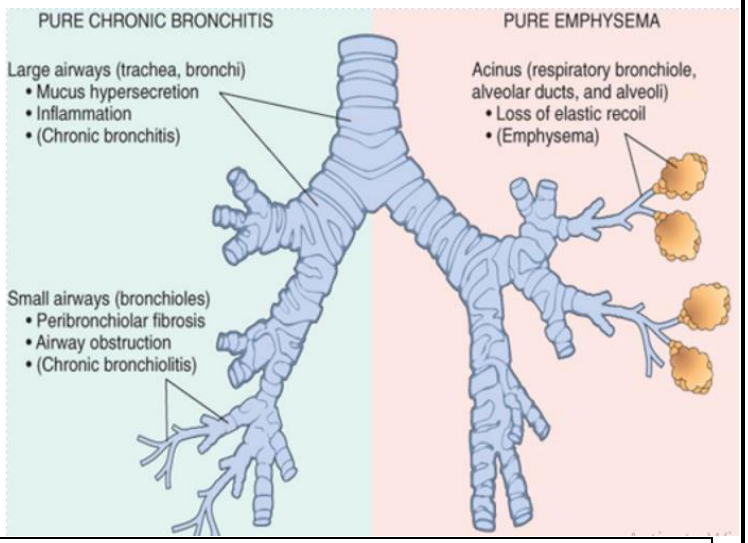
• 4th leading cause of death in the world

• There is a strong association between heavy cigarette smoking and COPD.

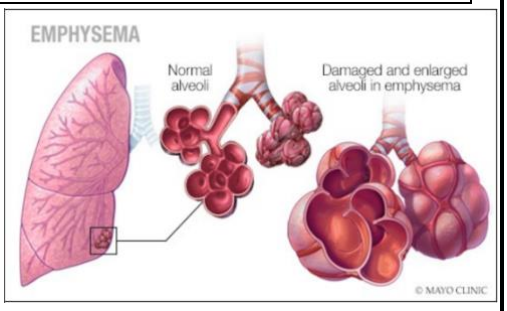
• 35% to 50% of heavy smokers develop COPD.

• 80% of COPD is attributable to smoking.

- Notice the anatomic distribution of chronic bronchitis and emphysema
  in severe cases of both, small airways are affected (chronic bronchiolitis because both diseases are associate with transudate and inflammation. For example, smoking initiates inflammation by inducing injury (remember inflammation process) then it will lead to peribronchiolar fibrosis and airway obstruction.
- Definition:
  They are both irreversible.



Chronic bronchitis	Emphysema
Large airways(trachea, main bronchi)	Acinus (respiratory bronchiole, alveolar ducts and alveoli)
Need to have typical clinical features (clinically defined) ex. Productive cough that persists for 3 months for consecutive 2 years. No need for radiology and other findings. History is enough.	Clinical history, morphologic features, radiology findings and pulmonary function tests are needed to confirm the diagnosis.



1. EMPHYSEMA

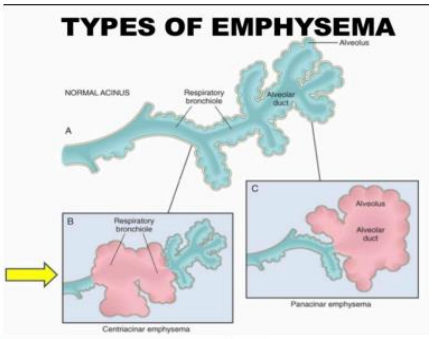
• **Permanent** (irreversible) enlargement of the airspaces **distal** to the terminal bronchioles (acinus) with destruction of their walls.

• Subtle but functionally important small airway fibrosis → significant contributor to airflow obstruction.

• Classified according to its anatomic distribution:

(1) centriacinar, (2) panacinar, (3) distal acinar, and (4) irregular

- **CENTRIACINAR (CENTRILOBULAR) EMPHYSEMA.**



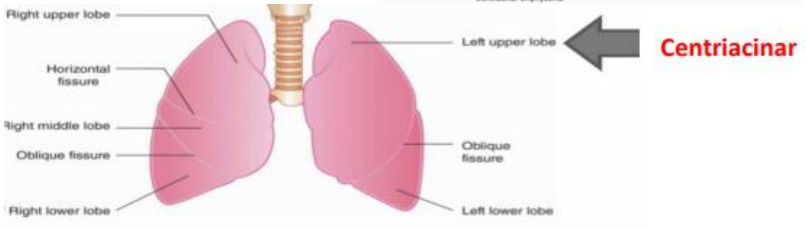
• the most common form > 95% of clinically significant cases.
Irregular emphysema is common but it is clinically insignificant.

• It occurs predominantly in heavy smokers with COPD.

• the central or proximal parts of the acini, formed by respiratory bronchioles, are affected, whereas distal alveoli are spared.

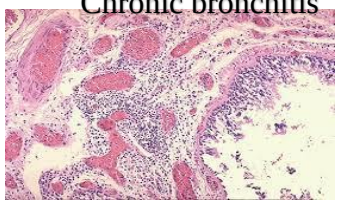
• both emphysematous and normal airspaces exist within the same acinus and lobule.

• The lesions are more common and more pronounced in the upper lobes, particularly in the apical segments.



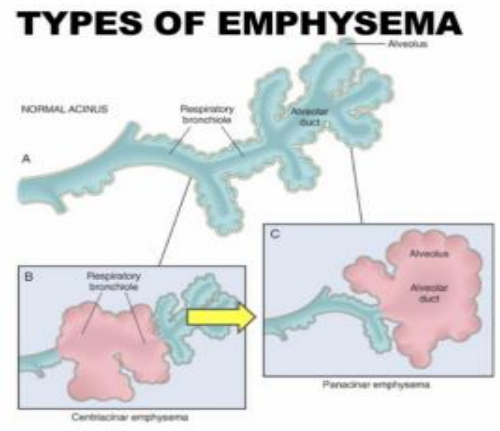
• In severe centriacinar emphysema, the distal acinus may also be involved, making differentiation from panacinar emphysema difficult.

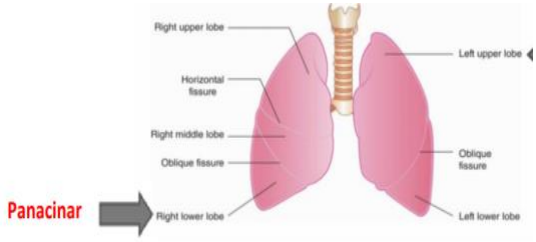
Chronic bronchitis



- Strongly associated with tobacco smoking so it is associated with chronic bronchitis.

- **PANACINAR (PANLOBULAR) EMPHYSEMA.**
  • is associated with α1-antitrypsin deficiency. Affects the liver and respiratory system.
  • exacerbated by smoking.
  • the acini are uniformly enlarged from the level of the respiratory
  • bronchiole to the terminal blind alveoli
  • tends to occur more commonly in the lower zones and in the anterior margins of the lung, and it is usually most severe at the bases.



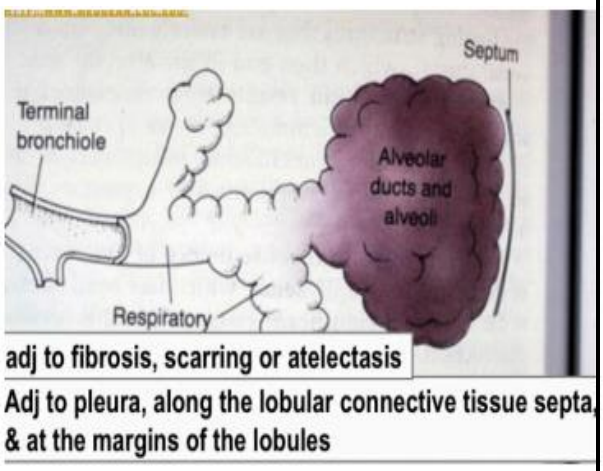


- **DISTAL ACINAR (PARASEPTAL) EMPHYSEMA.**

• underlies many cases of spontaneous pneumothorax in young adults. Because of the formation of blebs and bullae.

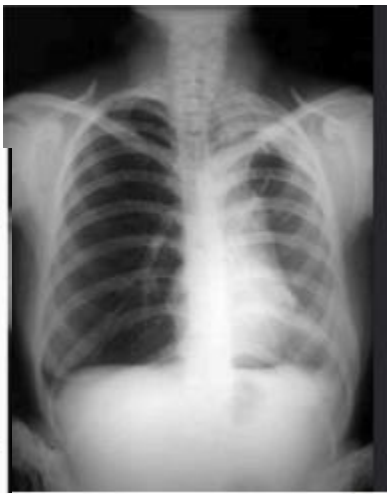
• the proximal portion of the acinus is normal, and the distal part is predominantly involved.

• The emphysema is more striking adjacent to the pleura, along the lobular connective tissue septa, and at the margins of the lobules.

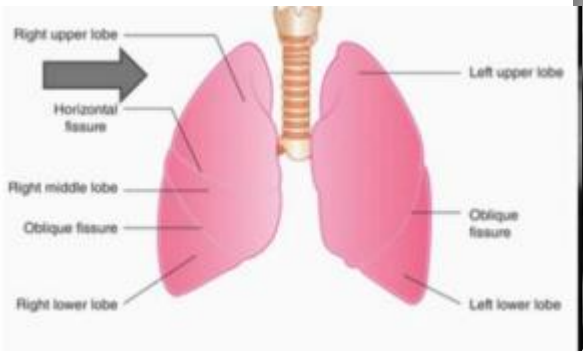


• It occurs adjacent to areas of fibrosis, scarring, or atelectasis and is usually

• more severe in the upper half of the lungs.



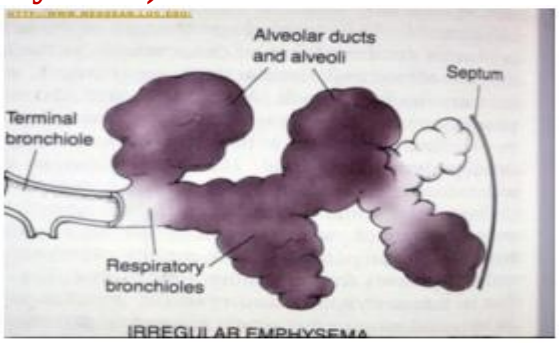
- Clinical presentation: ruptured bullae.



• The characteristic finding is multiple enlarged airspaces, ranging from < 0.5 cm to >2.0 cm in diameter, which sometimes form cyst-like structures.

- Chest X-Ray: loss of lung markings/ vasculature, mediastinum is shifted to the contralateral side.

Airspace enlargement with fibrosis (irregular emphysema).



• the acinus is irregularly involved,

• almost invariably associated with scarring.

• occurs in small foci and is clinically insignificant. Clinically asymptomatic. Discovered in autopsy.

QUESTION: - (Clues, Answer)

A 20-year-old, previously healthy gentleman is jogging one morning when he falls to the ground. He suddenly becomes markedly short of breath. in ER no breath sounds audible over the Rt side of the chest. A CXR shows shift of the mediastinum from right to left. A chest tube is inserted on the right side, and air rushes out. Which of the following underlying diseases is most likely to have produced this complication?

A. Centriacinar emphysema

B. Chronic bronchitis

C. Distal acinar emphysema.

D. Panlobular emphysema

PATHOGENESIS

Clinically significant emphysema is largely confined to smokers and to patients with α1-antitrypsin deficiency,

1- **Toxic injury and inflammation:**

• Inhaled cigarette smoke and other noxious particles →damage respiratory epithelium and cause inflammation

• leukotriene B4, interleukin [IL]-8, TNF are increased. which will eventually recruit neutrophils → they will release cytokines.

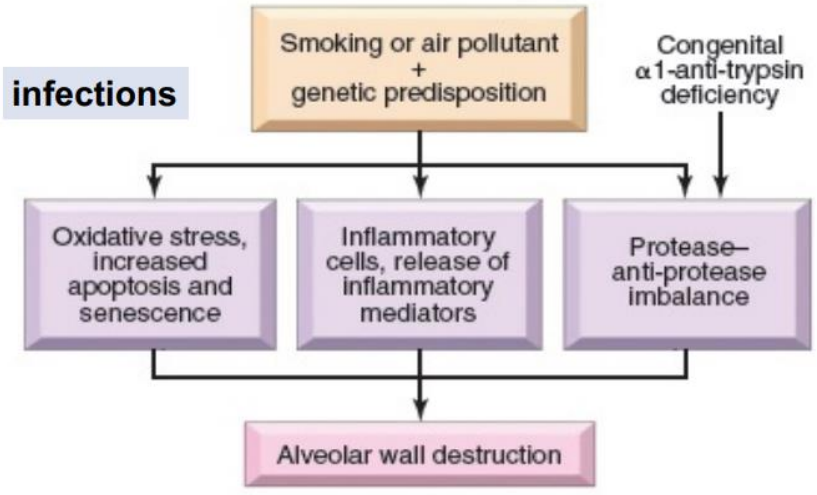


Fig. 13.6 Pathogenesis of emphysema. See text for details.

• These mediators are released by resident epithelial cells and macrophages and attract inflammatory cells from the circulation and amplify the inflammatory process. Then cause alveolar wall destruction.

2- Protease-antiprotease imbalance.

• Several proteases are released from the inflammatory cells and epithelial cells that break down connective tissue components.

• In patients who develop emphysema, there is a relative deficiency of protective antiproteases

• patients with a genetic deficiency of the antiprotease α1- antitrypsin have a markedly enhanced tendency to develop emphysema that is compounded by smoking.

• About 1% of all patients with emphysema have this defect.

• α1-Antitrypsin, normally present in serum, tissue fluids, and macrophages, is a major inhibitor of proteases (particularly elastase) secreted by neutrophils during inflammation.

• any injury like that induced by smoking → increases the activation and influx of neutrophils into the lung → local release of proteases(in the absence of α1-antitrypsin activity) →excessive digestion of elastic tissue →emphysema.

3- Oxidative stress.

• Substances in tobacco smoke, alveolar damage, and inflammatory cells all produce oxidants → tissue damage, endothelial dysfunction, and inflammation.

• **Infection.**

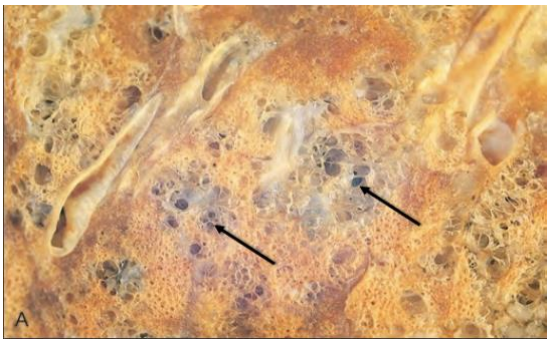
• It's not an initiating factor in the tissue destruction

• But bacterial and/or viral infections may acutely exacerbate existing disease. Will add more to the destruction and obstruction.

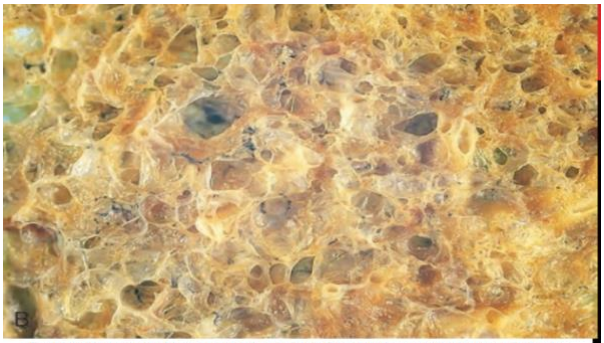
MORPHOLOGY

Macroscopic: **Advanced emphysema→ voluminous lungs**

Centriacinar emphysema: Central areas show**:** marked emphysematous of cystically dilated damage (arrows) surrounded by relatively spared alveolar spaces.



Panacinar emphysema: no preserved acini.



Panacinar emphysema involving the entire pulmonary lobule.

• **Microscopic examination of the lung:**

• abnormally large alveoli are separated by thin septa with only focal centriacinar fibrosis. With respiratory bronchioles around it.

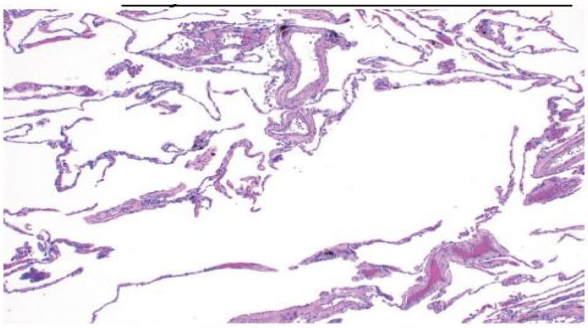


Figure 13.5 ROBBINS BASIC PATHOLOGY, 10TH EDITION

EMPHYSEMA, PRESENTATION:

• Symptoms do not appear until at least 1/3 of the functioning pulmonary parenchyma is damaged.

*extensive, needs genetic or predisposing factors like smoking or alpha 1 antitrypsin deficiency.

• **Dyspnea**: appears first, beginning insidiously but progressing steadily

• Weight loss; common

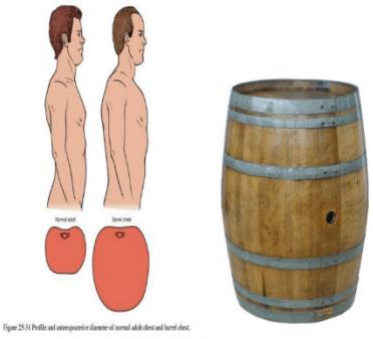
• barrel-chested

• prolonged expiration

• sitting forward in a hunched-over Position

• breathes through pursed lips

• Hyperventilation



• adequate oxygenation of Hemoglobin especially at rest and prominent dyspnea → "pink puffers." No cyanosis and CO2 retention.

• Cough and wheezing if Coexistent asthma & chronic bronchitis.

CONDITIONS RELATED TO EMPHYSEMA

These conditions are associated with lung overinflation or focal emphysematous change.

• Compensatory hyperinflation:

• Compensatory dilation of alveoli in response to loss of lung substance elsewhere. {normal healthy lung]

Example: hyper-expansion of residual lung parenchyma following surgical removal of a diseased lung. {due to a tumor or congenital defect correction surgery}.

• Obstructive overinflation:

• Lung expands because air is trapped within it.

•A common cause is subtotal obstruction by a tumor or foreign object.

• Can be Life-threatening emergency if distends sufficiently to compress the remaining normal lung.

• **Obstructive overinflation:**

Overinflation in obstructive lesions occurs either because:

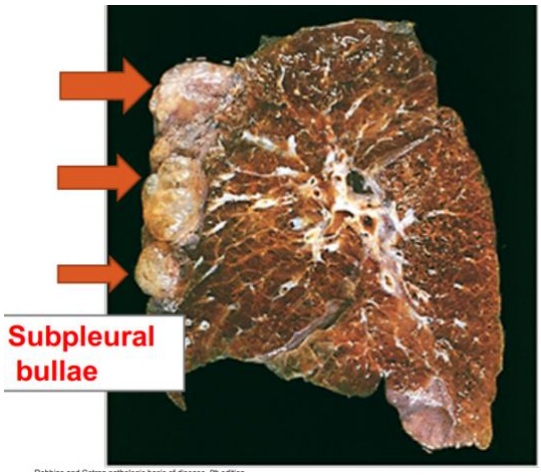
1. the obstructive agent acts as ball valve, allowing air to enter on inspiration while preventing its exodus on expiration
   or
2. because collaterals bring in air behind the obstruction. (collaterals consist of the pores of Kohn and other direct accessory bronchioloalveolar connections (the canals of Lambert).

• Bullous emphysema:

• Any form of emphysema, most are subpleural

• Large subpleural blebs or bullae

- mostly associated with distal acinar and paraseptal emphysema types.
- The airspaces should be 0.5 – 2 cm or more.



• Pneumothorax if rupture

- **interstitial emphysema:**
  - Due to entrance of air into the connective tissue stroma of the lung, mediastinum, or subcutaneous tissue.

Outcome:

• Decreased capillary bed area due to:

- ✓ Destruction of alveolar walls
- ✓ Compression of the respiratory bronchioles and lung vasculature by the enlarged airspaces (bullae and blebs) in advanced disease.
- ✓ Inflammatory changes in small airways

• Decreased capillary bed area→ hypoxia

• Hypoxia-induced pulmonary vascular spasm →gradual development of secondary pulmonary hypertension→ in 20-30% right-sided congestive heart failure (cor pulmonale).

Prognosis:

• Poor prognosis is associated with development of secondary pulmonary hypertension →cor pulmonale and congestive heart failure.

• Death from emphysema is related to either respiratory failure or right-sided heart failure.

II. CHRONIC BRONCHITIS

Defined clinically as Persistent productive cough for AT LEAST 3 consecutive months in AT LEAST 2 consecutive years in the absence of any other identifiable cause.

• 90% **cigarette smokers**; air pollutants also contribute.

• chronic bronchitis is one end of the spectrum of COPD, with emphysema being the other.

• When chronic bronchitis persists for years:

• decline in lung function, leading to cor pulmonale

• cause atypical metaplasia and dysplasia of the respiratory epithelium, providing a rich soil for cancerous transformation.

• In early stages airflow is not obstructed.

• May coexist with hyper-responsive airways with intermittent bronchospasm and wheezing→ asthmatic bronchitis.

Pathogenesis

The primary factor in the genesis of chronic bronchitis is exposure to irritating inhaled substances such as tobacco smoke (90%of pt) and dust from grain, cotton, and silica.

• **Hypersecretion of mucus**:

• The earliest feature of chronic bronchitis

• beginning in the large airways. (trachea and bronchi)

• cigarette smoking, other air pollutants:

- ➢ hypertrophy of submucosal glands in the trachea and bronchi.
- ➢ increase in goblet cells in the epithelial surfaces of smaller bronchi and bronchioles.

• **Acquired cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction.**

- ✓ smoking leads to acquired CFTR dysfunction →secretion of abnormal dehydrated mucus →increases the severity of chronic bronchitis.

• Inflammation

- ✓ Due to the Inhalants
- ✓ Acute and chronic inflammatory responses involving neutrophils, lymphocytes, and macrophages without eosinophils
- ✓ Long-standing inflammation and fibrosis involving small airways (small bronchi and bronchioles, less than 2 to 3 mm in diameter) →chronic airway obstruction.

• Infection

- ✓ Infection does not initiate chronic bronchitis but is probably significant in maintaining it
- ✓ Produces acute exacerbations.

• **airflow obstruction in chronic bronchitis** results from:

1. **Small airway disease chronic bronchiolitis**: results in early and **mild airflow obstruction**. Induced by mucus plugging of the bronchiolar lumen, inflammation, and bronchiolar wall fibrosis

2. **Coexistent emphysema**: The cause of **significant airflow obstruction.**

Morphology

Macroscopic:

• Mucosal lining is hyperemic and swollen (due to the accumulation of edema fluid).

• Layers of mucinous or mucopurulent secretions (the smaller bronchi and bronchioles also may be involved and filled with secretions)

Microscopic:

- ✓ The red star represents the lumen.
- ✓ The yellow star represents the mucous glands.
- ✓ Squamous metaplasia of lung epithelium is one of the adaptive mechanisms to protect the respiratory epithelium in smokers.

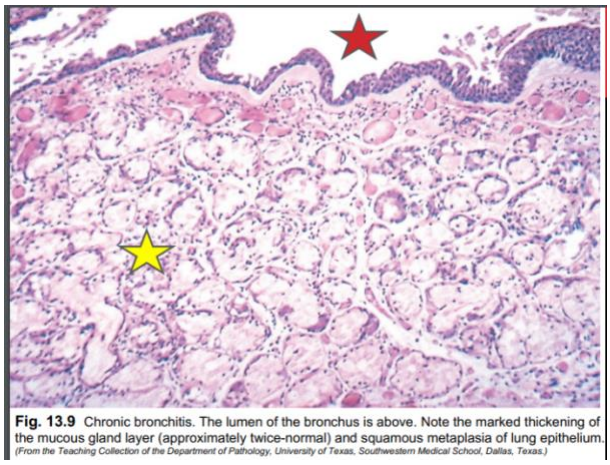


Fig. 13.9 Chronic bronchitis. The lumen of the bronchus is above. Note the marked thickening of the mucous gland layer (approximately twice-normal) and squamous metaplasia of lung epithelium. *(From the Teaching Collection of the Department of Pathology, University of Texas, Southwestern Medical School, Dallas, Texas.)*

• The characteristic features are:

- ➢ Mild chronic inflammation of the airways (predominantly lymphocytes)
- ➢ Enlargement (hyperplasia) of the mucus-secreting glands of the trachea and bronchi
- ➢ Squamous metaplasia and dysplasia of the bronchial epithelium
  - • Changes of emphysema often co-exist

• **Chronic bronchiolitis (small airway disease)** characterized by marked narrowing of the bronchioles due to goblet cell metaplasia, mucous plugging, inflammation, and submucosal fibrosis

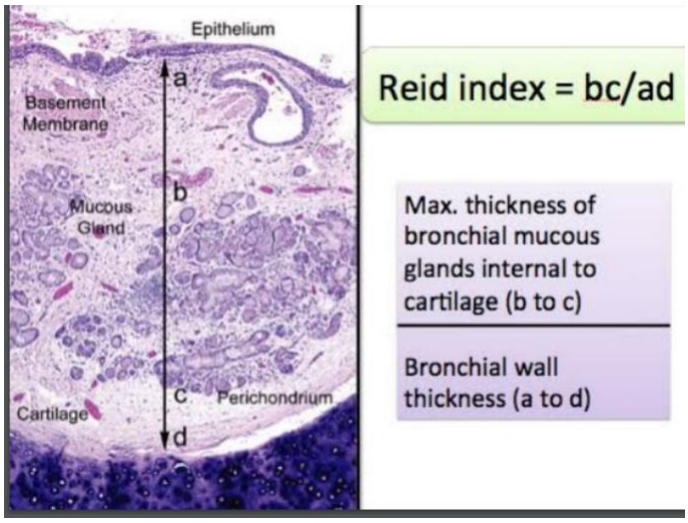
• **Bronchiolitis obliterans:** happens in severe cases when there is complete obliteration of the lumen due to fibrosis

• The increase in the size of mucus glands (hyperplasia) is assessed by the (Reid index).

• **Reid index**: is the ratio of the thickness of the mucous gland layer to the thickness of the wall between the epithelium and the cartilage

• Normal Reid index is 0.4

• **<u>Reid index is increased in chronic bronchitis</u>**, usually in proportion to the severity and duration of the disease.



CLINICAL FEATURES:

• The cardinal symptom is **<u>persistent cough with production of sparse sputum</u>**

• For many years no respiratory functional impairment is present, but eventually dyspnea on exertion develops.

• Long-standing severe chronic bronchitis commonly leads to cor pulmonale and cardiac failure.

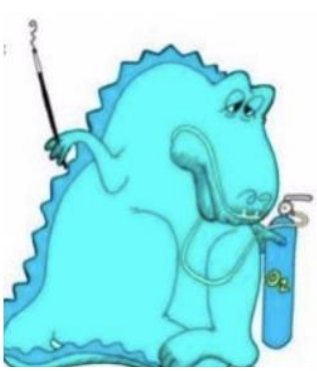
• Chronic bronchitis and COPD patients show frequent exacerbations, rapid disease progression, and poorer outcomes than emphysema alone.

OUTCOME:

• Progressive disease is marked by the development of pulmonary hypertension, cardiac failure, recurrent infections; and ultimately respiratory failure

• Death may also result from further impairment of respiratory function due to superimposed acute infections

THE OTHER END OF THE SPECTRUM: EMPHYSEMA WITH PRONOUNCED CHRONIC BRONCHITIS AND A HISTORY OF RECURRENT INFECTIONS.



• **Less dyspnea** (because the obstruction happens later in the disease process)

• absence of increased respiratory drive →**hypoxic and cyanotic**.

• For unclear reasons, patients with chronic bronchitis tend to be obese hence the designation **"blue bloaters"** →carbon dioxide retention, hypoxia, and cyanosis.

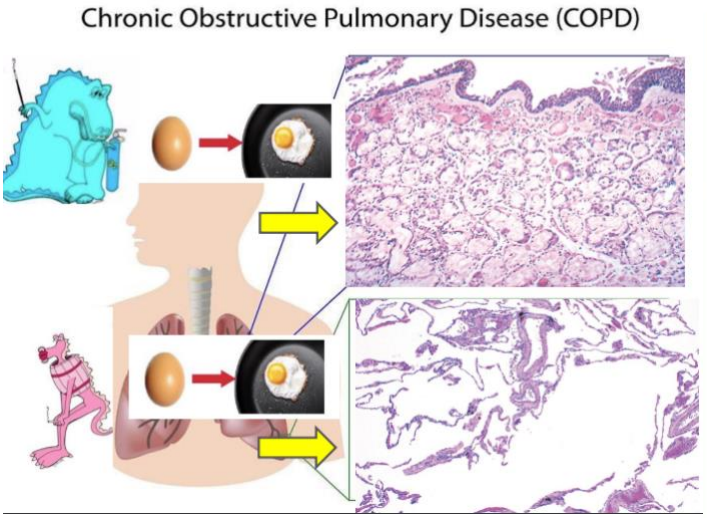


Table 15-4 Emphysema and Chronic Bronchitis

	Predominant Bronchitis	Predominant Emphysema
Age (yr)	40-45	50-75
Dyspnea	Mild; late	Severe; early
Cough	Early; copious sputum	Late; scanty sputum
Infections	Common	Occasional
Respiratory insufficiency	Repeated	Terminal
Cor pulmonale	Common	Rare; terminal
Airway resistance	Increased	Normal or slightly increased
Elastic recoil	Normal	Low
Chest radiograph	Prominent vessels; large heart	Hyperinflation; small heart
Appearance	Blue bloater	Pink puffer

These are extra☺

These two tables are taken from Robbins Pathology to help you revise this lecture.

SUMMARY

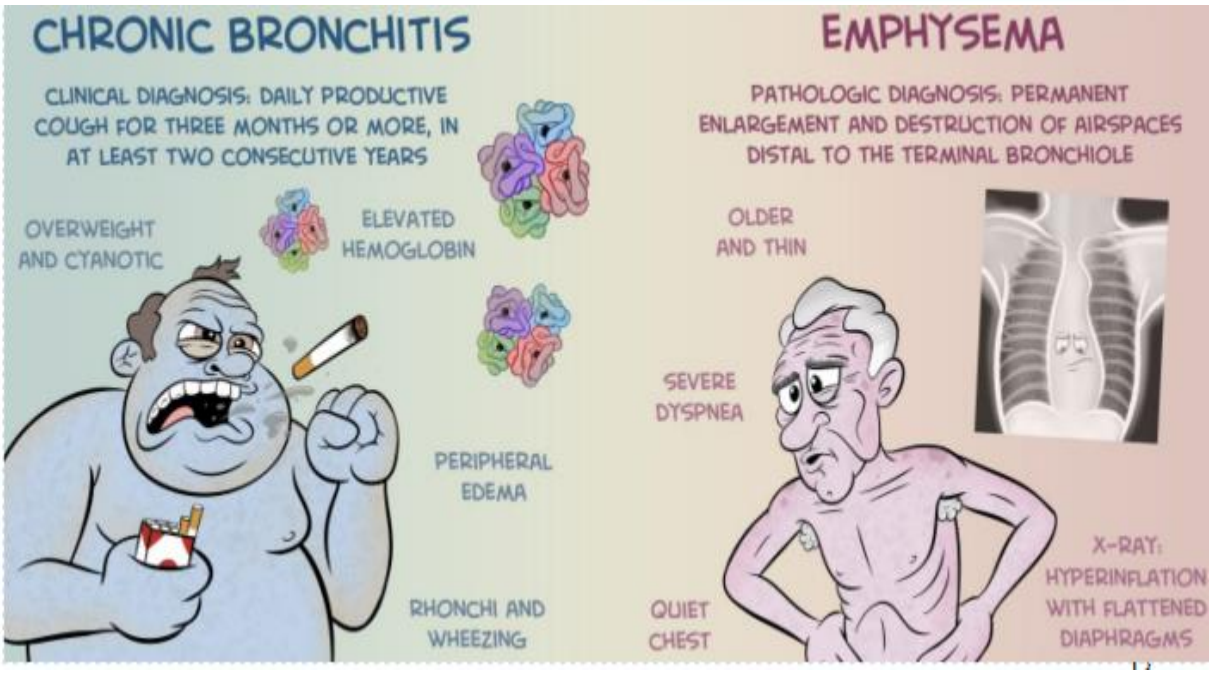
EMPHYSEMA

- Emphysema is a chronic obstructive airway disease characterized by enlargement of air spaces distal to terminal bronchioles.
- Subtypes include centriacinar (most common: smoking-related), panacinar (seen in α_1-anti-trypsin deficiency), distal acinar, and irregular.
- Smoking and inhaled pollutants cause ongoing accumulation of inflammatory cells, which are the source of proteases such as elastases that irreversibly damage alveolar walls.
- Patients with uncomplicated emphysema present with increased chest volumes, dyspnea, and relatively normal blood oxygenation at rest ("pink puffers").
- Most patients with emphysema also have signs and symptoms of concurrent chronic bronchitis, since cigarette smoking is a risk factor for both.

SUMMARY

CHRONIC BRONCHITIS

- Chronic bronchitis is defined as persistent productive cough for at least 3 consecutive months in at least 2 consecutive years.
- Cigarette smoking is the most important underlying risk factor; air pollutants also contribute.
- Chronic airway obstruction largely results from small airway disease (chronic bronchiolitis) and coexistent emphysema.
- Histologic examination demonstrates enlargement of mucus-secreting glands, goblet cell metaplasia, and bronchiolar wall fibrosis.



Good luck