Clinical Pathological Correlation of Chronic Obstructive Pulmonary Disease (COPD)*

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The two most common forms of COPD, chronic bronchitis and pulmonary emphysema, will be briefly reviewed.

Etiology. The causes of COPD are not definitely known. However, there appears to be a statistically significant correlation between the incidence of COPD, cigarette smoking, and air pollution. This is especially true for chronic bronchitis. In some cases, genetic factors ($alpha_1$ – antitrypsin deficiency) may be responsible for development of COPD. This is called familial type of COPD or familial emphysema. Chronic irritation of the tracheobronchial tree is common to all cases of chronic bronchitis. Cigarette smoking appears to be the single most important factor in the development of chronic bronchitis. Heavy cigarette smokers appear to be affected to a greater extent than light smokers, and the symptoms are worse in patients who give a history of long cigarette smoking. However, not all cigarette smokers develop chronic bronchitis. Individual susceptibility may play a role in some people. The symptoms of smoking are greater if a person lives in a heavily polluted area and also if there is cold and damp weather.

The Incidence. It has been estimated that there are currently 15 million people suffering from COPD in the United States. The incidence of COPD is higher in industrial areas, especially among men who engage in dusty jobs, such as coal miners.

Mortality. In the United States in 1969, 35,000 died primarily from chronic bronchitis and pulmonary emphysema. In 65,000 cases chronic bronchitis and pulmonary emphysema contributed to the demise of the patients. Since 1950, the death rate from emphysema has doubled every five years. The federal government pays more than $200,000,000 annually to respiratory cripples.

Definition. Chronic bronchitis is a clinical syndrome which is characterized by productive cough on most days during at least three months a year for two or more successive years. There is chronic productive cough without known specific causes such as tuberculosis or chronic suppurative lung disease. It is more common in males.

There is excessive mucous production with hypertrophy and hyperplasia of the mucous secreting glands including the Goblet cells. Bronchial mucous glands are normally located in the bronchi which contain cartilage in their wall. Hypertrophy of the gland size can be measured as a gland to wall ratio, and this is called the Reid Index. In normal people over the age of four years, this falls below one-third. In children under the age of four years, the ratio is a little higher.

A high Reid Index is very suggestive of chronic bronchitis, but there is no close correlation between clinical chronic bronchitis and the degree of mucous gland hypertrophy and hyperplasia. There is also an overlap of the Reid Index between bronchitis and nonbronchitis.

Clinical and Functional Manifestations of Chronic Bronchitis. The cardinal manifestation of chronic bronchitis is productive cough. There is in general a history of 20–30 years of cigarette smoking. The disease in general has a slow onset. In the beginning, patients attribute the cough to cigarette smoking. The so-called "cigarette cough" is an early sign of

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bronchitis. In many patients there is also an associated chronic sinusitis. The cough may disappear if smoking is stopped early enough.

The activity of cilia in the bronchial tree is inhibited by tobacco smoke. As a result of this, movement of mucous blanket is reduced significantly. The mucous glands and Goblet cells are stimulated and they produce more mucous. The result will be chronic cough and expectoration.

Excessive mucous production increases the tendency to infection which causes further hypersecretion. There develops a vicious cycle of excessive mucous secretion, infection, and more hypersecretion results. Tobacco smoke also causes bronchoconstriction which may aggravate the symptoms of bronchitis.

Normally the lower respiratory tract is essentially sterile. This is primarily due to cough reflexes, mucociliary, and alveolar macrophagic activity that eliminates bacteria or foreign particles that may have been inhaled during inspiration.

In chronic bronchitis many organisms can be isolated from the sputum which may be responsible for acute exacerbations. However, viruses probably are responsible to a great extent for the acute episodes in chronic bronchitis.

Following viral infections, as a result of damage to bronchial mucous, growth of bacteria may be encouraged. Diplococcus pneumoniae and Hemophilus influenzae appear to be important organisms; however, sometimes Staphylococcus aureus and the Friedlander's bacillus may be responsible for acute infection. Some patients trace the beginning of symptoms to some acute episode of infection such as bronchopneumonia.

In general there is fluctuation in the manifestations during the course of the disease. Symptoms become worse after exposure to cold, damp, or foggy weather or to irritants. However, during the end-stage of the disease the patients are, more or less, continuously symptomatic. Death secondary to pneumonia, congestive heart failure, or acute respiratory failure may occur 15 to 30 years after the beginning of symptoms. In a typical bronchitic, sputum is usually mucoid which becomes mucopurulent during acute bronchopulmonary infections.

Dyspnea may also occur during episodes of acute bronchoconstriction secondary to infections, irritants, and so forth. It may also indicate development complicating pulmonary emphysema. Intermittent wheezing may also be present.

Dyspnea, cough, and wheezing may awaken the patient, and the picture may be confused with paroxysmal nocturnal dyspnea due to left-sided heart failure. But in bronchitis the symptoms are generally improved by expectoration of sputum. The body weight of these patients is generally normal or heavy.

Arterial gas abnormalities are quite common. Many patients have hypoxemia alone. CO_2 retention takes place late in the course of the disease or during acute episodes of bronchopulmonary infection.

When hypoxemia and respiratory acidosis are present, pulmonary hypertension develops which may result in cor pulmonale.

There is a high incidence of erythrocytosis resulting from hypoxemia. Many patients later in the course of the disease have florid appearance and cyanosis. Because of increased incidence of congestive heart failure and cyanosis, the patients are called "Blue Bloaters."

The amount of airway obstruction will influence the physical signs. In advanced stages, the thoracic cage is in the inspiratory position. There is kyphosis of the dorsal spine. The anteroposterior diameter of the chest increases. There is excessive use of accessory respiratory muscles. The degree of scalene muscle contraction may give an idea about the extent of airway obstruction. In general, the breath sounds are normal. Ronchi are present in most patients.

In the early stages of chronic bronchitis and pulmonary emphysema, there is a significant degree of involvement of the small airways. It should be emphasized that small airways (2 mm or less in diameter) are only responsible for approximately 15 to 20% of the total airway resistance; thus, marked increases in peripheral or small airways will not be detected by the conventional tests such as FEV_1 (forced expiratory volume in one second) or MMFR (maximum mid expiratory flow rate).

In the early stages of these conditions, frequency-dependent dynamic compliance studies and alveolar-arterial O_2 tension gradient, A–a P_{O_2}, may detect pulmonary dysfunction. For clinical purposes, however, simple spirometric studies with measurements of FVC (forced vital capacity), FEV_1 and MMFR are satisfactory.

Improvements in flow rates after administration of bronchodilating agents indicate the presence of partially reversible obstruction.

In established chronic bronchitis, there is over-expansion of the lungs with enlargement of

residual volume and FRC (functional residual capacity). VC (vital capacity) is either normal or decreased. The total lung capacity may be normal or increased. The ratio between FEV_1 and FVC, and the maximal mid expiratory flow rate are reduced.

Radiologic Findings. In simple or uncomplicated chronic bronchitis, the chest x-ray may be normal. There may be over-expansion of the lungs and the diaphragm may be depressed.

Some cases would show "tram lines" or parallel shadows and prominence of the lung markings mainly at the bases. Prominence of the main pulmonary artery may suggest pulmonary hypertension. Bronchograms may demonstrate tiny diverticulum-like shadows in the large bronchi. Irregularity of the caliber of segmental and subsegmental bronchi is frequently seen.

Pulmonary Emphysema. Pulmonary emphysema is accurately defined in morphologic terms only. It is defined by increase beyond normal in the size of air spaces distal to the terminal bronchioles, with destruction of the walls of these air spaces. It is a destructive process. There is reduction in elastic retractive force of the lungs.

The portion of the lung distal to the terminal bronchiole is called acinus, and it contains respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli. It is in this area that gas exchange takes place. For this reason, acinus is considered as the basic functioning unit of the lungs which is analogous to the nephron of the kidney.

In panacinar emphysema, there is involvement of the entire acinus. In centriacinar emphysema, only those alveoli near the center of the acinus are affected. The centriacinar type is more common in the upper two-thirds, and the panacinar is roughly uniform, commonly affecting the basal regions of the lungs.

Many patients have both types of emphysema together; however, centriacinar is much more common than panacinar and is in general associated with chronic bronchitis and chronic respiratory irritation. Dr. W. M. Thurlbeck found panacinar as often in women as men, while the centriacinar was more common in men.

Emphysema is more common in patients with bronchitis than in nonbronchitics. There is also a higher incidence of emphysema in patients with extensive bronchiectasis. This is also true in other chronic inflammatory diseases of the lungs, especially when both lungs are diffusely affected. On the other hand, emphysema is rarely found in the postmortem studies of the lungs of patients with bronchial asthma.

Clinical and Functional Manifestations. The main symptom of emphysema is dyspnea which has an insidious onset and becomes manifested on exertion. Dyspnea gradually increases, and in advanced stages, ordinary daily activities may induce severe shortness of breath.

Cough may be absent or insignificant during the early course of the disease. Episodes of severe dyspnea and wheezing may occur, usually during acute bronchopulmonary infections or after exposure to irritants. In general, the body weight is below normal, and loss of weight is common in emphysematous patients.

The anteroposterior diameter of the chest is increased. Breath sounds are distant. The heart sounds are frequently inaudible. They may be heard easily in the epigastric area. There is a higher incidence of peptic ulcer disease in patients with emphysema. The exact cause of this is unknown at the present time.

Airway resistance is increased especially during expiration. Static compliance of the lungs is greater than normal. However, frequency dependent compliance studies are generally abnormal. Residual volume, FRC, and TLC (total lung capacity) are frequently elevated. VC may be normal or reduced due to increased RV and FRC. There is obstruction to airflow. FEV_1, MMFR, and MVV (maximal voluntary ventilation) are diminished.

X-ray Findings. In mild pulmonary emphysema the chest x-ray may be normal. In some cases there is x-ray evidence of over-expansion of the lungs which is a nonspecific finding that is seen in cases of diffuse bronchial obstruction such as bronchial asthma and chronic bronchitis. If, in addition to over-expansion, there is marked reduction or absence of peripheral vascular markings associated with engorged hilar pulmonary vessels and blebs bullae, presence of underlying emphysema is almost certain. The heart shadow is usually long and narrow.

Arterial gas studies reveal only mild abnormalities at least during early stages of the disease. Patients attempt to maintain a relatively normal P_{O_2} and P_{CO_2}. Because of this, these patients are called "Pink Puffers." The incidence of cor pulmonale is less frequent in Pink Puffers as compared with Blue Bloaters.

There are two primary factors responsible for

TABLE 1.

MAIN MANIFESTATIONS OF PURE CHRONIC BRONCHITIS OR PULMONARY EMPHYSEMA

	(Blue Bloater) Chronic Bronchitis	(Pink Puffer) Pulmonary Emphysema
Cough	++++	±
Dyspnea	±	++++
Body Weight	normal or heavy	thin
Arterial Gas Abnormalities	++++	+
Cor Pulmonale	++++	+(Terminally)
Erythrocytosis	++++	+
Breath Sounds	normal	diminished

±: Insignificant
+: Increase
++++: Significant increase

the development of pulmonary hypertension in patients with COPD: 1) Functional or reversible factors due to hypoxemia and hypercapnia, 2) Irreversible factors due to loss or occlusion of pulmonary capillaries.

Functional factors are mainly responsible, and they play a major role in the production of pulmonary hypertension. Since there are in general more disturbed arterial gas tensions in bronchitis, incidence of pulmonary hypertension and cor pulmonale are higher in bronchitics.

In over 90% of the cases of COPD, patients have combined chronic bronchitis and pulmonary emphysema. Some of these patients have predominantly chronic bronchitis and some predominantly pulmonary emphysema. However, a very small percentage of these patients would only have either chronic bronchitis or pure pulmonary emphysema.

TABLE 2.

CAUSES OF ACUTE RESPIRATORY FAILURE IN COPD

1. Bronchopulmonary infections.
2. Heavy sedation and anesthesia.
3. Improper use of oxygen.
4. Pulmonary edema and congestion.
5. Thoracotomy, abdominal surgery.
6. Atelectasis or pneumothorax.
7. Dehydration.
8. Pulmonary embolism.
9. Severe episode of air pollution.

TABLE 3.

THE FINDINGS THAT MAY INDICATE POOR PROGNOSIS IN COPD

1. Recent significant weight loss.
2. Persistent tachycardia at rest.
3. Presence of cor pulmonale.
4. FEV_1 less than 750 ml.
5. Persistent severe hypoxemia and hypercapnia.
6. Marked reduction in pulmonary diffusion capacity.

If manifestations due to pure chronic bronchitis or emphysema are appreciated, one may have some opinion as to symptoms and signs primarily related to either chronic bronchitis or pulmonary emphysema (Table 1). It has been shown that chronic bronchitis does not necessarily always lead to pulmonary emphysema nor does pulmonary emphysema always lead to chronic bronchitis.

Table 2 shows causes of acute respiratory failure in patients who have chronic respiratory failure with COPD. Finally, Table 3 shows factors that may indicate poor prognosis in patients with COPD.

Comment. There are currently 15 million people affected with COPD in the United States. It appears that once the disease is well established or advanced, the ultimate course cannot be altered significantly. Emphasis should be given upon prophylactic measures. Discouragement of cigarette smoking is probably the most important means to reduce the incidence of COPD.

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