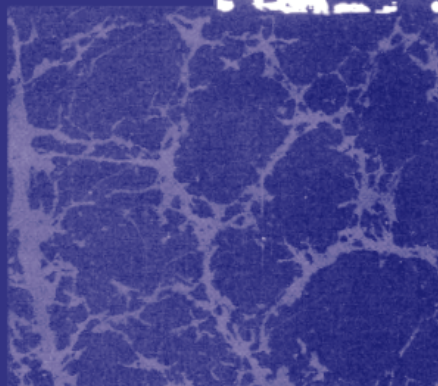
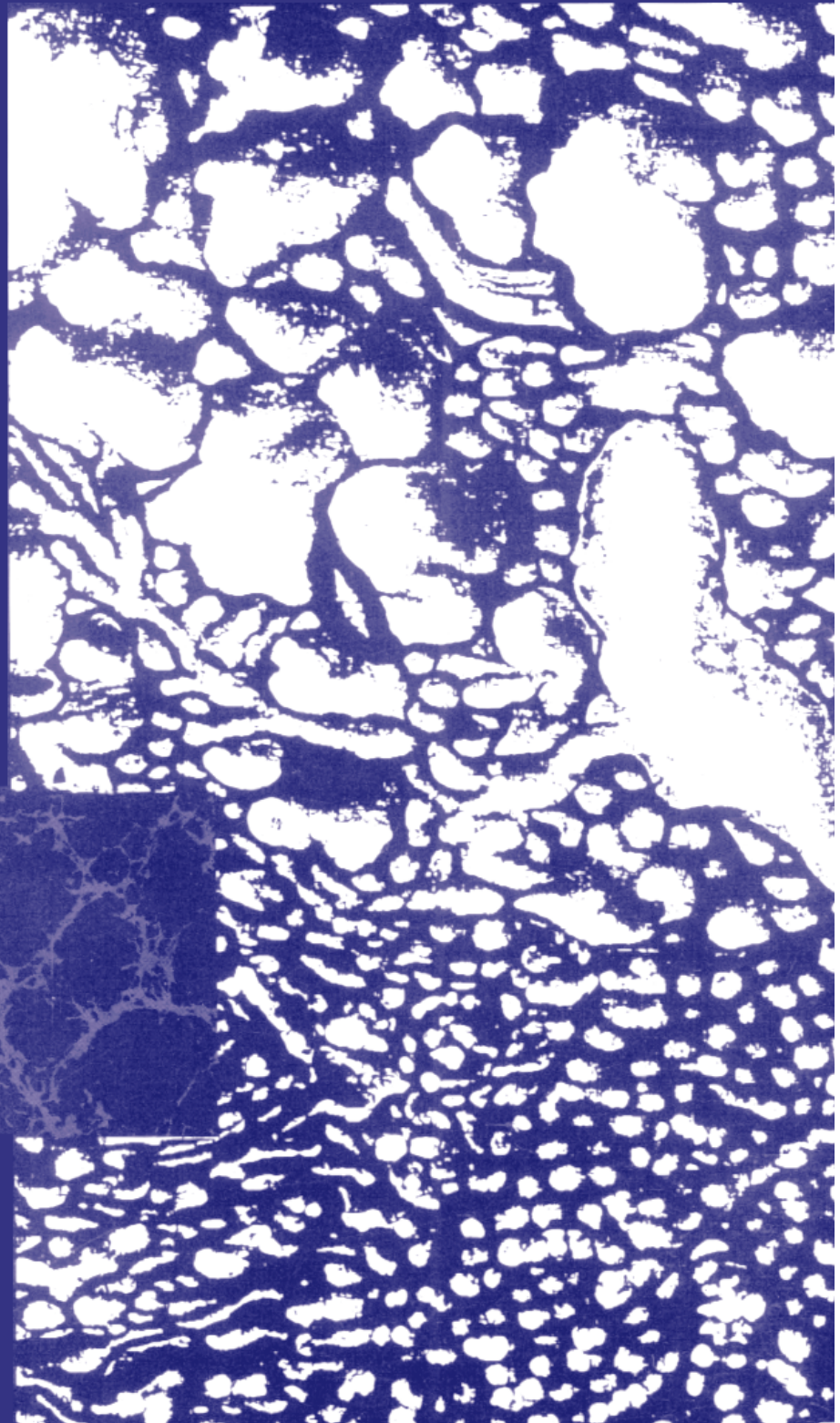


# Chronic Obstructive Pulmonary Disease



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National Heart, Lung,  
and Blood Institute

Front cover: Drawing of the common features of the lung from a COPD patient. Upper area shows emphysematous changes; note large airspaces. Lower right is normal. (Reprinted from *Chronic Obstructive Pulmonary Disease, 5th Edition, 1977, p.17*, by courtesy of the American Lung Association.

Inset: Shows elastic fibers in normal lung tissue. (Reprinted from *Chronic Obstructive Lung Disease: Biology in Health and Disease, 1978, pg. 48* by courtesy of Marcel Dekkar, Inc.

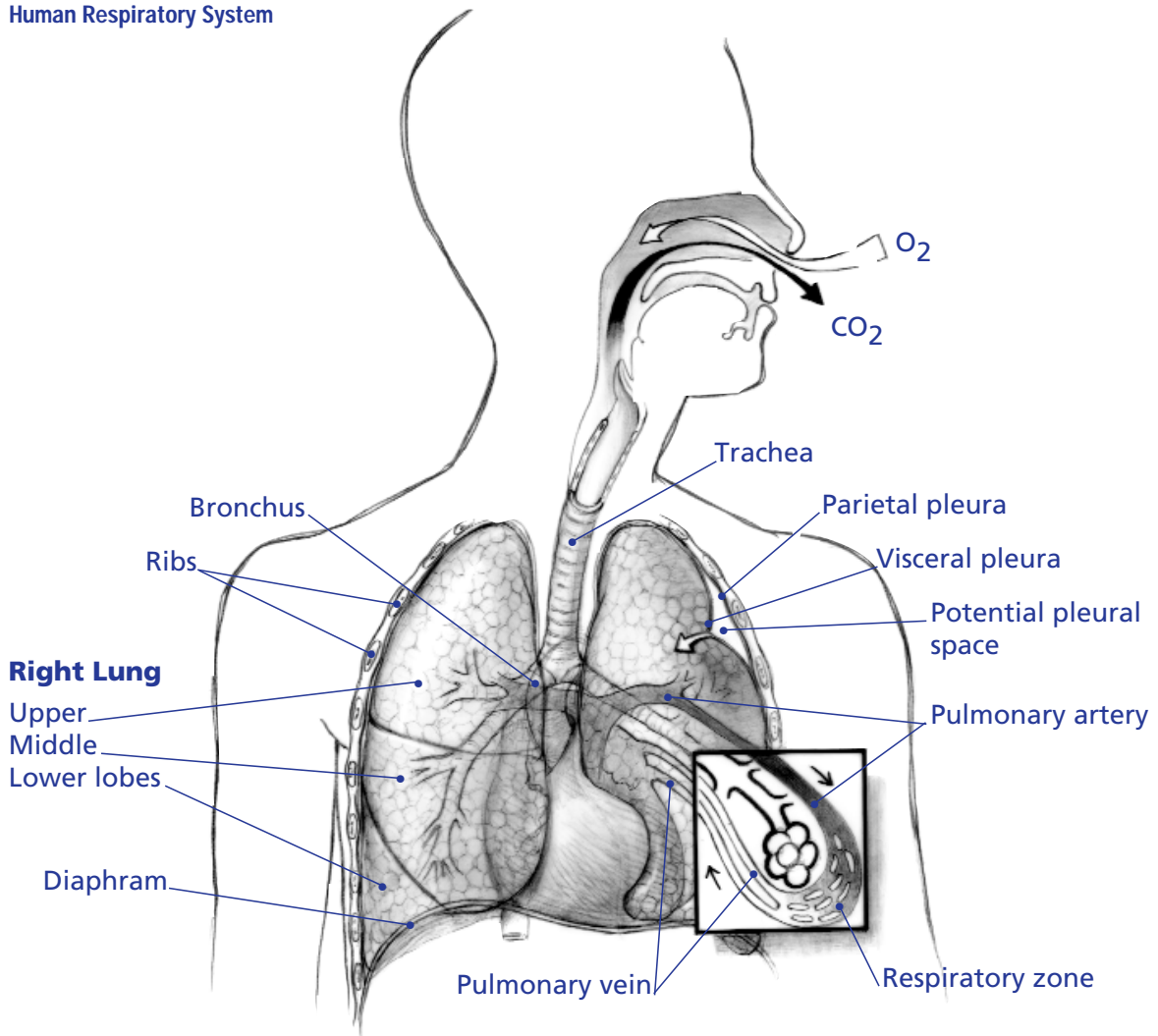


Prepared by  
Division of Lung Diseases and  
Office of Prevention, Education, and Control  
National Heart, Lung, and Blood Institute

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# Human Respiratory System



## What Is Chronic Obstructive Pulmonary Disease?

Chronic obstructive pulmonary disease (COPD), also called chronic obstructive lung disease, is a term that is used for two closely related diseases of the respiratory system: *chronic bronchitis* and *emphysema*. In many patients these diseases occur together, although there may be more symptoms of one than the other. Most patients with these diseases have a long history of heavy cigarette smoking.

**Cigarette smoking is the most important risk factor for COPD.**

COPD gets gradually worse over time. At first there may be only a mild shortness of breath and occasional coughing. Then a chronic cough develops with clear, colorless sputum. As the disease progresses, the cough becomes more frequent and more and more effort is needed to get air into and out of the lungs. In later stages of the disease, the heart may be affected. Eventually death occurs when the function of the lungs and heart is no longer adequate to deliver oxygen to the body's organs and tissues.

Cigarette smoking is the most important risk factor for COPD; it would probably be a minor health problem if people did not smoke. Other risk factors include age, heredity, exposure to air pollution at work and in the environment, and a history of childhood respiratory infections. Living in low socioeconomic conditions also seems to be a contributing factor.

More than 13.5 million Americans are thought to have COPD. It is the fifth leading cause of death in the United States. Between 1980 and 1990, the total death rate from COPD increased by 22 percent. In 1990, it was estimated that there were 84,000 deaths due to COPD, approximately 34 per 100,000 people. Although COPD is still much more

common in men than women, the greatest increase in the COPD death rate between 1979 and 1989 occurred in females, particularly in black females (117.6 percent for black females vs. 93 percent for white females). These increases reflect the increased number of women who smoke cigarettes.

**Between 1979 and 1989, COPD death rate increased more in females than in males, particularly in black females.**

COPD attacks people at the height of their productive years, disabling them with constant shortness of breath. It destroys their ability to earn a living, causes frequent use of the health care system, and disrupts the lives of the victims' family members for as long as 20 years before death occurs.

In 1990, COPD was the cause of approximately 16.2 million office visits to doctors and 1.9 million hospital days. The economic costs of this disease are enormous. In 1989, an estimated \$7 billion was spent for care of persons with COPD and another \$8 billion was lost to the economy by lost productivity due to morbidity and mortality from COPD.

### **What Are Chronic Bronchitis and Emphysema?**

*Chronic bronchitis*, one of the two major diseases of the lung grouped under COPD, is diagnosed when a patient has excessive airway mucus secretion leading to a persistent, productive cough. An individual is considered to have chronic bronchitis if cough and sputum are present on most days for a minimum of 3 months for at least 2 successive years or for 6 months during 1 year. In chronic bronchitis, there also may be narrowing of the large and small airways making it more difficult to move air in and out of the lungs. An estimated 12.1 million Americans have chronic bronchitis.

**People with familial emphysema have a hereditary deficiency of a blood component called alpha-1-antitrypsin, resulting in the loss of a lung structural protein, elastin.**

In *emphysema* there is permanent destruction of the alveoli, the tiny elastic air sacs of the lung, because of irreversible destruction of a protein in the lung called *elastin* that is important for maintaining the strength of the alveolar walls. The loss of elastin also causes collapse or narrowing of the smallest air passages, called bronchioles, which in turn limits airflow out of the lung. The number of individuals with emphysema in the U.S. is estimated to be 2 million.

In the general population, emphysema usually develops in older individuals with a long smoking history. However, there is also a form of emphysema that runs in families. People with familial emphysema have a hereditary deficiency of a blood component, alpha-1-protease inhibitor, also called alpha-1-antitrypsin (AAT). The number of Americans with this genetic deficiency is quite small, probably no more than 70,000. It is estimated that 1 in 3,000 newborns have a genetic deficiency of AAT, and 1 to 3 percent of all cases of emphysema are due to AAT deficiency.

The destruction of elastin that occurs in emphysema is believed to result from an imbalance between two proteins in the lung—an enzyme called elastase which breaks down elastin, and AAT which inhibits elastase. In the normal individual, there is enough AAT to protect elastin so that abnormal elastin destruction does not occur. However, when there is a genetic deficiency of AAT, the activity of the elastase is not inhibited and elastin degradation occurs unchecked. If individuals with a severe genetic deficiency of alpha-1-protease inhibitor smoke, they usually have symptoms of COPD by the time they reach early middle age. Deficiency of alpha-1-protease inhibitor can be detected by blood tests available through hospital laboratories. People from families in which relatives have developed

emphysema in their thirties and forties should be tested for AAT deficiency. If a deficiency is found, it is critical for these people not to smoke.

**Some scientists believe that “smoker’s emphysema,” also results from an imbalance between elastin-degrading enzymes and their inhibitors.**

Some scientists believe that nonfamilial emphysema, usually called “smoker’s emphysema,” also results from an imbalance between elastin-degrading enzymes and their inhibitors. The elastase-AAT imbalance is thought to be a result of the effects of smoking, rather than inherited as in familial emphysema. Some evidence for this theory comes from studies on the effect of tobacco smoke on lung cells. These studies showed that tobacco

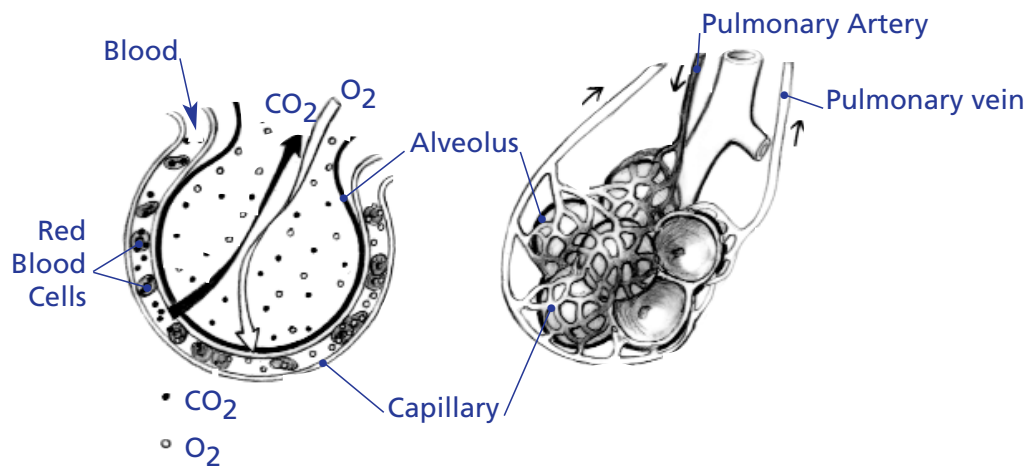
smoke stimulates excess release of elastase from cells normally found in the lung. The inhaled smoke also stimulates more elastase-producing cells to migrate to the lung which in turn causes the release of even more elastase. To make matters worse, oxidants found in cigarette smoke inactivate a significant portion of the elastase inhibitors that are present, thereby decreasing the amount of active antielastase available for protecting the lung and further upsetting the elastase-antielastase balance.

Scientists believe that, in addition to smoking-related processes, there must be other factors that cause emphysema in the general population since only 15 to 20 percent of smokers develop emphysema. The nature and role of these other factors in smokers’ emphysema are not yet clear.



## What Goes Wrong With the Lungs and Other Organs in Chronic Obstructive Pulmonary Disease?

The most important job that the lungs perform is to provide the body with oxygen and to remove carbon dioxide. This process is called *gas exchange*, and the normal anatomy of the lungs serves this purpose well. The lungs contain 300 million alveoli whose ultrathin walls form the gas exchange surface. Enmeshed in the wall of each of these air sacs is a network of tiny blood vessels, the capillaries, which bring blood to the gas exchange surface. When a person inhales, air flows from the nose and mouth through large and small airways into the alveoli. Oxygen from this air then passes through the thin walls of the inflated alveoli and is taken up by the red blood cells for delivery to the rest of the body. At the same time, carbon dioxide leaves the blood and passes through the alveolar walls into the alveoli. During exhalation, the lung pushes the used air out of the alveoli and through the air passages until it escapes from the nose or mouth.



### Gas Exchange

Inhaled air travels through the airways to the alveoli. Blood is pumped out of the heart through the pulmonary arteries to a network of capillaries that surround the alveoli. The oxygen of the inhaled air diffuses out of the alveoli into the blood while carbon dioxide in the blood moves into the alveoli to be exhaled. The oxygen-rich blood is returned to the heart through the pulmonary veins.



Normal Airway



Bronchitic Airway



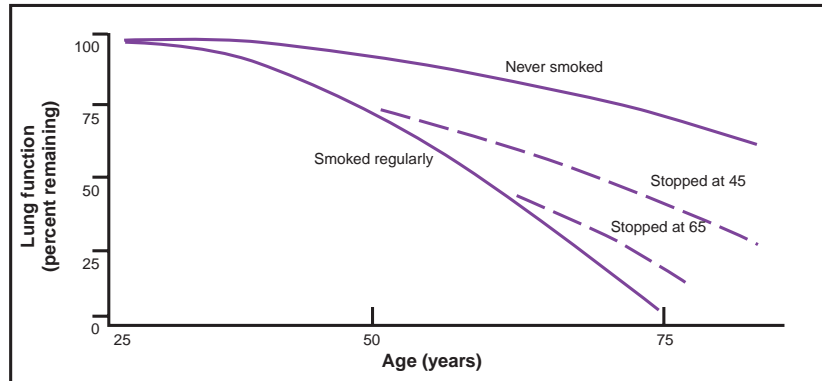
Emphysematous Airway

When COPD develops, the walls of the small airways and alveoli lose their elasticity. The airway walls thicken, closing off some of the smaller air passages and narrowing larger ones. The passageways also become plugged with mucus. Air continues to get into alveoli when the lung expands during inhalation, but it is often unable to escape during exhalation because the air passages tend to collapse during exhalation, trapping the “stale” air in the lungs. These abnormalities create two serious problems which affect gas exchange:

- Blood flow and air flow to the walls of the alveoli where gas exchange takes place are uneven or mismatched. In some alveoli there is adequate blood flow but little air, while in others there is a good supply of fresh air but not enough blood flow. When this occurs, fresh air cannot reach areas where there is good blood flow and oxygen cannot enter the bloodstream in normal quantities.
- Pushing the air through narrowed obstructed airways becomes harder and harder. This tires the respiratory muscles so that they are unable to get enough air to the alveoli. The critical step for removing carbon dioxide from the blood is adequate alveolar airflow. If airflow to the alveoli is insufficient, carbon dioxide builds up in the blood and blood oxygen diminishes. Inadequate supply of fresh air to the alveoli is called *hypoventilation*. Breathing oxygen can often correct the blood oxygen levels, but this does not help remove carbon dioxide. When carbon dioxide accumulation becomes a severe problem, mechanical breathing machines called respirators, or ventilators, must be used.

Pulmonary function studies of large groups of people show that lung function—the ability to move air into and out of the lungs—declines slowly with age even in healthy nonsmokers. Because healthy nonsmokers have excess lung

**Age-related change in the lung function and effect of smoking and smoking cessation.**



Adapted from 1984 Surgeon General's Report.

**In smokers, lung function tends to worsen much more rapidly than in nonsmokers.**

capacity, this gradual loss of function does not lead to any symptoms. In smokers, however, lung function tends to worsen much more rapidly. If a smoker stops smoking before serious COPD develops, the rate at which lung

function declines returns to almost normal. Unfortunately, because some lung damage cannot be reversed, pulmonary function is unlikely to return completely to normal.

COPD also makes the heart work much harder, especially the main chamber on the right side (right ventricle) which is responsible for pumping blood into the lungs. As COPD progresses, the amount of oxygen in the blood decreases which causes blood vessels in the lung to constrict. At the same time many of the small blood vessels in the lung have been damaged or destroyed as a result of the disease process. More and more work is required from the right ventricle to force blood through the remaining narrowed vessels. To perform this task, the right ventricle enlarges and thickens. When this occurs the normal rhythm of the heart may be disturbed by abnormal beats. This condition, in which the heart is enlarged because of lung problems, is called *cor pulmonale*. Patients with *cor pulmonale* tire easily and have chest pains and palpitations. If an additional strain is placed on the lungs and heart by a normally minor illness

such as a cold, the heart may be unable to pump enough blood to meet the needs of other organs. This results in the inability of the liver and kidneys to carry out their normal functions which leads to swelling of the abdomen, legs, and ankles.

Another adjustment the body makes to inadequate blood oxygen is called *secondary polycythemia*, an increased production of oxygen-carrying red blood cells. The larger than normal number of red blood cells is helpful up to a point; however, a large overpopulation of red cells thickens the blood so much that it clogs small blood vessels causing a new set of problems. People who have poor supply of oxygen usually have a bluish tinge to their skin, lips, and nailbeds, a condition called *cyanosis*.

Too little oxygen and too much carbon dioxide in the blood also affect the nervous system, especially the brain, and can cause a variety of problems including headache, inability to sleep, impaired mental ability, and irritability.

### **What Is the Course of Chronic Obstructive Pulmonary Disease?**

Daily morning cough with clear sputum is the earliest symptom of COPD. During a cold or other acute respiratory tract infection, the coughing may be much more noticeable and the sputum often turns yellow or greenish. Periods of wheezing are likely to occur especially during or after colds or other respiratory tract infections. Shortness of breath on exertion develops later and progressively becomes more pronounced with severe episodes of breathlessness (*dyspnea*) occurring after even modest activity.

A typical course of COPD might proceed as follows. For a period of about 10 years after cigarette smoking begins, symptoms are usually not very noticeable. After this, the patient generally starts developing a chronic cough with the production of a small amount of sputum. It is unusual to develop shortness of breath during exertion below the age of 40, after which it becomes more common and may be well developed by the age of 50. However, although all COPD patients have these symptoms, not all cigarette smokers develop a notable cough and sputum production, or shortness of breath.

**Daily morning cough with clear sputum is the earliest symptom of COPD.**

Most patients with COPD have some degree of reversible airways obstruction. It is therefore likely that, at first, treatment will lead to some improvement or stability in lung function. But as COPD progresses, almost all signs and symptoms except cough and sputum production tend to show a gradual worsening. This trend can show fluctuations, but over the course of 4 or 5 years, a slow deterioration becomes evident.

Repeated bouts of increased cough and sputum production disable most patients and recovery from coughing attacks may take a long time. Patients with severe lung damage sleep in a semi-sitting position because they are unable to breathe when they lie down. They often complain that they awaken during the night feeling “choked-up,” and they need to sit up to cough.

Survival of patients with COPD is closely related to the level of their lung function when they are diagnosed and the rate at which they lose this function. Overall, the median survival is about 10 years for patients with COPD who have lost approximately two-thirds of their normally expected lung function at diagnosis.

## How Is Chronic Obstructive Pulmonary Disease Detected?

Researchers are still looking for accurate methods to predict a person's chances of developing airway obstruction. None of the current ways used to diagnose COPD detects the disease before irreversible lung damage occurs. While many measures of lung function have been developed, those most commonly used determine: 1) air-containing volume of the lung (lung volume), 2) the ability to move air into and out of the lung, 3) the rate at which gases diffuse between the lung and blood, and 4) blood levels of oxygen and carbon dioxide.

Lung volumes are measured by breathing into and out of a device called a *spirometer*. Some types of spirometers are very simple mechanical devices which record volume changes as air is added to or removed from them. Other kinds are more sophisticated and use various types of electronic equipment to determine and record the volume of air moved into and out of the lungs. The three volume measures most relevant to COPD are forced vital capacity (FVC), residual volume (RV), and total lung capacity (TLC). The *forced vital capacity* is the maximum volume of air which can be forcibly expelled after inhaling as deeply as possible.

Use of a spirometer for lung function testing.



Not all of the air in the lungs is removed when measuring the vital capacity. The amount remaining is called the *residual volume*. The *total lung capacity* is the combination of the forced vital capacity and residual volume. While most of

**It is necessary to compare the results of several different tests to make a correct diagnosis of COPD.**

the measured lung volumes or capacities change to some degree with COPD, residual volume usually increases quite markedly. This increase is the result of the weakened airways collapsing before all the normally expired air can leave the lungs. The increased residual volume makes breathing even more difficult and labored.

Because COPD results in narrowed air passages, a measure of the rate at which air can be expelled from the lungs can also be used to determine how severe the narrowing has become. In this test, the *forced vital capacity maneuver*, the patient is asked to inhale as deeply as possible, and on signal, exhale as completely and as rapidly as possible. The volume of air exhaled within 1 second is then measured. This value is referred to as the *forced expiratory volume in 1 second* (FEV<sub>1</sub>). When FEV<sub>1</sub> is used as an indicator of lung function, the average rate of decline in patients with chronic obstructive lung disease is observed to be two to three times the normal rate of 20-30 milliliters per year. This volume may also be expressed in terms of the percent of the vital capacity which can be expelled in 1 second. As COPD progresses, less air can be expelled in 1 second. A greater than expected annual fall in FEV<sub>1</sub> is the most sensitive test for COPD and a fairly good predictor of disability and early death.

Another measure of lung function is called *diffusing capacity*. For this, a more complicated test determines the amount of gas which can move in a given period of time from the alveolar side of the lung into the blood. A number of conditions can cause the diffusing capacity to decrease. However,

in COPD the decrease is the result of the destruction of alveolar walls which leads to a significant decrease in surface area for diffusion of oxygen into the blood.

Because the primary function of the lung is to remove carbon dioxide from the blood and add oxygen, another indicator of pulmonary function is the blood levels of oxygen and carbon dioxide. As chronic obstructive pulmonary disease progresses, the amount of oxygen in the blood decreases and carbon dioxide increases.

In most cases, it is necessary to compare the results of several different tests in order to make the correct diagnosis, and to repeat some tests at intervals to determine the rate of disease progression or improvement. Measurement of FEV<sub>1</sub> and FEV<sub>1</sub>/FVC ratio should be a routine part of the physical examination of every COPD patient. It is hoped that current research will result in more accurate and earlier measures for detecting lung destruction and diminished function.

### **How Is Chronic Obstructive Pulmonary Disease Treated?**

Although there is no cure for COPD, the disease can be prevented in many cases. And, in almost all cases the disabling symptoms can be reduced. Because cigarette smoking is the most important cause of COPD, not smoking almost always prevents COPD from developing, and quitting smoking slows the disease process.

**There is no cure for COPD at present, but the disease is usually preventable.**

If the patient and medical team develop and adhere to a program of complete respiratory care, disability can be minimized, acute episodes prevented, hospitalizations reduced, and some early deaths avoided. On the other hand, none of



the therapies has been shown to slow the progression of the disease, and only oxygen therapy has been shown to increase the survival rate.

**Home oxygen therapy can improve survival of COPD patients.**

*Home oxygen therapy* can improve survival in patients with advanced COPD who have *hypoxemia*, low blood oxygen levels. This treatment can improve a patient's exercise tolerance and ability to perform on psychological tests which reflect different aspects of brain function and muscle coordination. Increasing the concentration of oxygen in blood also improves the function of the heart and prevents the development of cor pulmonale. Oxygen can also lessen sleeplessness, irritability, headaches, and the overproduction of red blood cells. Continuous oxygen therapy is recommended for patients with low oxygen levels at rest, during exercise, or while sleeping. Many oxygen sources are available for home use; these include tanks of compressed gaseous oxygen or liquid oxygen and devices that concentrate oxygen from room air. However, oxygen is expensive with the cost per patient running into several hundred dollars per month, depending on the type of system and on the locale.

*Medications* frequently prescribed for COPD patients include:

- *Bronchodilators* help open narrowed airways. There are three main categories: *sympathomimetics* (isoproterenol, metaproterenol, terbutaline, albuterol) which can be inhaled, injected, or taken by mouth; *parasympathomimetics* (atropine, ipratropium bromide); and *methylxanthines* (theophylline and its derivatives) which can be given intravenously, orally, or rectally.

- *Corticosteroids or steroids* (beclomethasone, dexamethasone, triamcinolone, flunisolide) lessen inflammation of the airway walls. They are sometimes used if airway obstruction cannot be kept under control with bronchodilators, and lung function is shown to improve on this therapy. Inhaled steroids given regularly may be of benefit in some patients and have few side effects.
- *Antibiotics* (tetracycline, ampicillin, erythromycin, and trimethoprim-sulfamethoxazole combinations) fight infection. They are frequently given at the first sign of a respiratory infection such as increased sputum production with a change in color of sputum from clear to yellow or green.
- *Expectorants* help loosen and expel mucus secretions from the airways.
- *Diuretics* help the body excrete excess fluid. They are given as therapy to avoid excess water retention associated with right-heart failure. Patients taking diuretics are monitored carefully because dehydration must be avoided. These drugs also may cause potassium imbalances which can lead to abnormal heart rhythms.

**Use of metered-dose inhaler.** (Courtesy of Boehringer Ingelheim Pharmaceutical, Inc.)



- *Digitalis* (usually in the form of digoxin) strengthens the force of the heartbeat. It is used very cautiously in patients who have COPD, especially if their blood oxygen tensions are low, because they are vulnerable to abnormal heart rhythms when taking this drug.
- *Other drugs* sometimes taken by patients with COPD are tranquilizers, pain killers (meperidine, morphine, propoxyphene, etc.), cough suppressants (codeine, etc.), and sleeping pills (barbiturates, etc.). All these drugs depress breathing to some extent; they are avoided whenever possible and used only with great caution.

A number of combination drugs containing various assortments of sympathomimetics, methylxanthines, expectorants, and sedatives are marketed and widely advertised. These drugs are undesirable for COPD patients for several reasons. It is difficult to adjust the dose of methylxanthines without getting interfering side effects from the other ingredients. The sympathomimetic drug used in these preparations is ephedrine, a drug with many side effects and less bronchodilating effect than other drugs now available. The combination drugs often contain sedatives to combat the unpleasant side effects of ephedrine. They also contain expectorants which have not been proven to be effective for all patients and may have some side effects.

*Bullectomy*, or surgical removal of large air spaces called *bullae* that are filled with stagnant air, may be beneficial in selected patients. Recently, use of lasers to remove bullae has been suggested.

*Lung transplantation* has been successfully employed in some patients with end-stage COPD. In the hands of an experienced team, the 1-year survival in patients with transplanted lungs is over 70 percent.

*Pulmonary rehabilitation* programs, along with medical treatment, are useful in certain patients with COPD. The goals are to improve overall physical endurance and generally help to overcome the conditions which cause dyspnea and limit capacity for physical exercise and activities of daily living. General exercise training increases performance, maximum oxygen consumption, and overall sense of well-being. Administration of oxygen and nutritional supplements when necessary can improve respiratory muscle strength. Intermittent mechanical ventilatory support relieves dyspnea and rests respiratory muscles in selected patients. Continuous positive airway pressure (CPAP) is used as an adjunct to weaning from mechanical ventilation to minimize dyspnea during exercise. Relaxation techniques may also reduce the perception of ventilatory effort and dyspnea. Breathing exercises and breathing techniques, such as pursed lips breathing and relaxation, improve functional status.

*Keeping air passages reasonably clear* of secretions is difficult for patients with advanced COPD. Some commonly used methods for mobilizing and removing secretions are the following:

**Exercise helps COPD patients maintain maximum fitness.**



- *Postural bronchial drainage* helps to remove secretions from the airways. The patient lies in prescribed positions that allow gravity to drain different parts of the lung. This is usually done after inhaling an aerosol. In the basic position, the patient lies on a bed with his chest and head over the side and his forearms resting on the floor.
- *Chest percussion* or lightly clapping the chest and back, may help dislodge tenacious or copious secretions.
- *Controlled coughing* techniques are taught to help the patient bring up secretions.
- *Bland aerosols*, often made from solutions of salt or bicarbonate of soda, are inhaled. These aerosols thin and loosen secretions. Treatments usually last 10 to 15 minutes and are taken three or four times a day. Bronchodilators are sometimes added to the aerosols.

### **How Can Patients With Chronic Obstructive Pulmonary Disease Cope Best With Their Illness?**

In most instances of COPD, some irreversible damage has already occurred by the time the doctor diagnoses the disease. At this point, the patient and the family should learn as much as possible about the disease and how to live with it. The goals, limitations, and techniques of treatment must be understood by the patient so that symptoms can be kept under control, and daily living can proceed as normally as possible. The doctor and other health care providers are good sources of information about COPD education programs. Patients and family members can usually take part in educational programs offered at a hospital or by a local branch of the American Lung Association.

Patients with COPD can help themselves in many ways. They can:



- Stop smoking. Many programs are available to help smokers quit smoking and to stay off tobacco. Some programs are based on behavior modification techniques; others combine these methods with nicotine gum or nicotine patches as aids to help smokers gradually overcome their dependence on nicotine.
- Avoid work-related exposures to dusts and fumes.
- Avoid air pollution, including cigarette smoke, and curtail physical activities during air pollution alerts.
- Refrain from intimate contact with people who have respiratory infections such as colds or the flu and get a one-time pneumonia vaccination (polyvalent pneumococcal vaccination) and yearly influenza shots.
- Avoid excessive heat, cold, and very high altitudes. (Note: Commercial aircraft cruise at high altitudes and maintain a cabin pressure equal to that of an elevation of 5,000 to 10,000 feet. This can result in hypoxemia for some COPD patients. However, with supplemental oxygen, most COPD patients can travel on commercial airlines.)
- Drink a lot of fluids. This is a good way to keep sputum loose so that it can be brought up by coughing.
- Maintain good nutrition. Usually a high protein diet, taken as many small feedings, is recommended.

- Consider “allergy shots.” COPD patients often also have allergies or asthma which complicate COPD.

Of all the avoidable risk factors for COPD, smoking is by far the most significant. Cessation of smoking is the best way to decrease one’s risk of developing COPD.

### **What Types of Research on Chronic Obstructive Pulmonary Disease Is the National Heart, Lung, and Blood Institute Supporting?**

The National Heart, Lung, and Blood Institute (NHLBI) is supporting a number of research programs on COPD with the following objectives: 1) to understand its underlying causes, 2) to develop methods of early detection, 3) to improve treatment, and 4) to help patient's and their families better manage the disease.

A study completed several years ago examined the use of oxygen therapy for people who, because of COPD, cannot get enough oxygen into their blood by breathing air. This study has determined that continuous oxygen therapy is more beneficial in extending life than giving oxygen only for 12 hours at night.

Another clinical study compared inhalation therapy using a machine which administers medication to the lungs by intermittent positive pressure breathing (IPPB) with one that delivers the medicine by relying on the patient's own breathing. Although home use of IPPB machines is widespread, previous studies had not been able to show conclusively whether they were effective. In this study, 985 ambulatory patients with COPD were randomly assigned to a treatment group which received a bronchodilator aerosol solution by IPPB, or to a control group which received the medication via a compressor nebulizer. The only difference between the two groups was the positive pressure applied by the IPPB. There was no statistically significant difference between the two treatment groups in numbers of deaths, frequency and length of hospitalization, change in lung function tests, or in measurements of quality of life. This study suggests that the use of IPPB devices may be unnecessary.



An intervention trial called the Lung Health Study, which began in 1983, has enrolled approximately 6,000 smokers in a study to determine whether an intervention program incorporating smoking cessation and use of inhaled bronchodilators (to keep air passages open) in men and women at high risk of developing COPD can slow the decline in pulmonary function compared to a group receiving usual care. When this study is completed, it should help to determine the extent to which identification and treatment of asymptomatic subjects with early signs of obstructive lung disease would be useful as a preventive health measure. In addition, the study will test some of the current theories about behavior and smoking cessation. Early results indicate that cigarette smoking may be more harmful to women than to men. Furthermore, smoking cessation results in greater weight gain in women than in men, and to avoid weight gain women are less likely to quit smoking and more likely to revert to their smoking habit.

Because familial emphysema results from a deficiency of AAT in affected individuals, efforts to minimize the risk of emphysema have been directed at increasing the circulating AAT levels either by promoting or increasing the production of AAT within the individual, or augmenting it from the outside. One strategy for improving the production of AAT is by pharmacological means (e.g., by administration of drugs such as danazol or estrogen/progesterone combinations), but this has not been found to be effective. Genetic engineering to correct the defective gene or introduce the functional gene in the deficient individuals is being attempted by several NHLBI-supported investigators. The normal gene for AAT as well as the mutant genes causing AAT deficiency have been characterized and cloned, and animal models carrying the mutant gene have been developed. The resulting animals displayed many of the physical and histologic changes seen in human neonatal AAT deficiency. These studies should provide the

groundwork for future development of gene replacement therapy for AAT deficiency.

In the meantime, attention is being focused on AAT augmentation therapy for familial emphysema. Studies have shown that intravenous infusion of AAT fractionated from blood is safe and biochemically effective, that is, the needed blood levels of AAT can be maintained by the continued administration of AAT at appropriate intervals.

Because of the practical and fiscal limitations to mounting a clinical trial for establishing the clinical efficacy of AAT augmentation therapy for emphysema, the NHLBI sponsored a national registry of patients with AAT deficiency to assess the natural history of severe AAT deficiency and to examine whether the disease course is altered by the augmentation therapy. This program is enrolling, at various medical centers both in the U.S. and Europe, at least 1,000 adult patients with AAT deficiency satisfying certain other eligibility criteria. The patients will be followed for 3 to 5 years (chest x rays, lung function, blood and urine analysis, etc.) at one of 37 participating clinical centers. The evaluation of the data and the release of the conclusions are expected by early 1995.

Methods to treat emphysema before it becomes disabling remain an important research objective of programs supported by NHLBI. Since it is believed that either excess protease (elastase), or too little useful antiprotease, can lead to development of the disease, scientists have also been attempting to use other approaches to develop animal models which will mimic the human condition of inherited alpha-1-protease inhibitor deficiency and using such models to test if natural or synthetic antiproteases can be used safely to prevent development of emphysema-like lesions in these animals. If found safe and effective in animals, these agents can be tried in humans. ■

## **For More Information**

Additional information on COPD can be obtained from:

National Heart, Lung, and Blood Institute  
Division of Lung Diseases  
Two Rockledge Center  
6701 Rockledge Drive  
MSC 7952  
Suite 10018  
Bethesda, MD 20892-7952

## Glossary

<b>Aerosol</b>	A solution of a drug that is made into a fine mist for inhalation.
<b>Airway obstruction</b>	A narrowing, clogging, or blocking of the passages that carry air to the lungs.
<b>Alpha-1-antitrypsin</b>	(See alpha-1-protease inhibitor.)
<b>Alpha-1-protease inhibitor</b>	A substance in blood transported to the lungs that inhibits the digestive activity of trypsin and other proteases which digest proteins. Deficiency of this substance is associated with emphysema.
<b>Alveoli</b>	Tiny sac-like air spaces in the lungs where transfer of carbon dioxide from blood into the lungs and oxygen from air into blood takes place.
<b>Bronchi</b>	Larger air passages of the lungs.
<b>Bronchiole</b>	Finer air passages of the lungs.
<b>Bronchoconstriction</b>	Tightening of the muscles surrounding bronchi, the tubes that branch from the windpipe.
<b>Bronchodilator</b>	A drug that relaxes the smooth muscles and opens the constricted airway.
<b>Capillaries</b>	The smallest blood vessels in the body through which most of the oxygen, carbon dioxide, and nutrient exchanges take place.

<b>Cor pulmonale</b>	Heart disease due to lung problems.
<b>Corticosteroids</b>	A group of hormones produced by adrenal glands.
<b>Continuous positive airway pressure (CPAP)</b>	A mechanical ventilation technique used to deliver continuous positive airway pressure.
<b>Cyanosis</b>	Bluish color of the skin associated with insufficient oxygen.
<b>Dyspnea</b>	Shortness of breath; difficult or labored breathing.
<b>Elastin</b>	An elastic substance in the lungs (and some other body organs) that support their structural framework.
<b>Elastase inhibitors or Antielastases</b>	Substances in the blood transported to the lungs and other organs which prevent the digestive action of elastases.
<b>Elastin degrading enzymes (elastases)</b>	Substances in the blood transported to the lungs and other organs which digest or breakdown elastin.
<b>Gas exchange</b>	A primary function of the lungs involving transfer of oxygen from inhaled air into blood and of carbon dioxide from blood into lungs.
<b>Hypoventilation</b>	A state in which there is an insufficient amount of air entering and leaving the lungs to bring oxygen into tissues and eliminate carbon dioxide.

<b>Hypoxemia</b>	Deficient oxygenation of the blood.
<b>Hypoxia</b>	A state in which there is oxygen deficiency.
<b>Intermittent positive pressure breathing (IPPB) machine</b>	A device that assists intermittent positive pressure inhalation of therapeutic aerosols without hand coordination required in the use of hand nebulizers or metered dose inhalers.
<b>Laser</b>	In the context of a therapeutic tool, it is a device that produces a high-intensity light that can generate extreme heat instantaneously when it hits a target.
<b>Lavage</b>	To wash a body organ.
<b>Neonatal</b>	Period up to the first 4 weeks after birth.
<b>Pneumonia</b>	Inflammation of the lungs.
<b>Postural bronchial drainage</b>	Draining of liquids from the lungs by placing the patient in postures (e.g., head below chest) which facilitate liquid flow.
<b>Vaccination</b>	Administration of weakened or killed bacteria or virus to stimulate immunity and protection against further exposure to that agent.
<b>Ventilation</b>	The process of exchange of air between the lungs and the atmosphere leading to exchange of gases in the blood.

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