

# Definition, Epidemiology, Course, and Prognosis of COPD

Thomas L. Petty, MD

Professor of Medicine  
Division of Pulmonary Sciences and Critical Care Medicine  
Department of Internal Medicine  
University of Colorado School of Medicine  
Denver, Colorado

*Chronic obstructive pulmonary disease (COPD) is now recognized as our nation's most rapidly growing health problem. It ranks as the 4th most common killer and is the only disease in the top 10 whose rank is rising. In 2000, more women than men (59,936 vs 59,118) died of COPD (1). The National Heart, Lung, and Blood Institute has calculated that in 2001, COPD was a \$34.4 billion burden on society (both direct and indirect costs) (2). Two new initiatives, the National Lung Health Education Program (NLHEP) (3,4) and the Global Initiative for Chronic Obstructive Lung Disease (5), promote the early diagnosis and intervention of COPD. Both initiatives offer guidelines for the care of patients with all stages of COPD. The NLHEP recommends spirometry in all current or former smokers age  $\geq 45$  years and anyone with symptoms of chronic cough, excessive dyspnea on exertion, or wheezing (6). "Test your lungs, know your numbers" is the motto of the NLHEP. Most patients with COPD are first seen by their primary care practitioner well before symptoms or signs of moderate-to-advanced stages of the disease are present. Thus, the primary care practitioner, working on the front line, is in the position to make a difference in the treatment and outcome of this devastating disorder.*

## DEFINITION

Chronic obstructive pulmonary disease (COPD) is a disease spectrum characterized by progressive airflow obstruction that is not fully reversible in response to bronchodilators. COPD should be considered in any patient with chronic cough, excessive mucus production, wheezing, and dyspnea on exertion, particularly in persons who smoke tobacco and other products. COPD does not include other diseases where airflow obstruction is present, such as cystic fibrosis, other forms of bronchiectasis, acute and chronic bronchiolitis, and the fibrotic diseases that may affect small airways function, for example, asbestosis and silicosis.

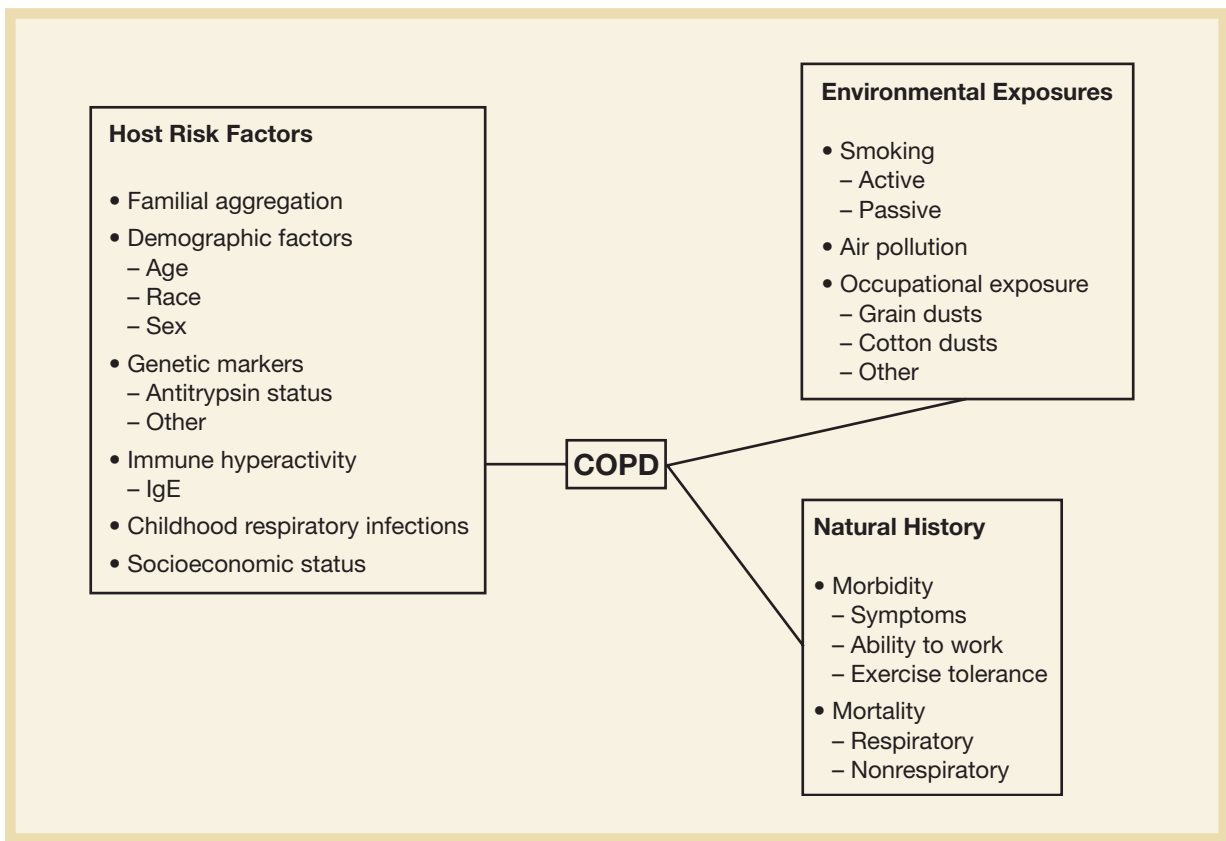
COPD is thought of as a smoker's disease that clusters in families and worsens with age. Although true, this statement is a gross oversimplification. Population studies have shown that  $\leq 15\%$  of patients with COPD are nonsmokers (7).

## KEY POINT

**COPD is a disease spectrum characterized by progressive airflow obstruction that is not fully reversible in response to bronchodilators. Most COPD patients have elements of airway inflammation such as bronchitis, bronchiolitis, and emphysema.**

## EPIDEMIOLOGY

The relation between host risk factors and environmental exposures (**Figure 1**) is well recognized. Genetic risk factors go beyond the  $\alpha_1$ -antitrypsin deficiency state, which is responsible for  $\sim 3\%$  of patients with COPD. COPD also occurs in families with normal  $\alpha_1$ -antitrypsin phenotypes. Immune



**Figure 1.** The relation between host risk factors and environmental exposures.

hyperreactivity, childhood respiratory infections, and low socioeconomic status are other risk factors.

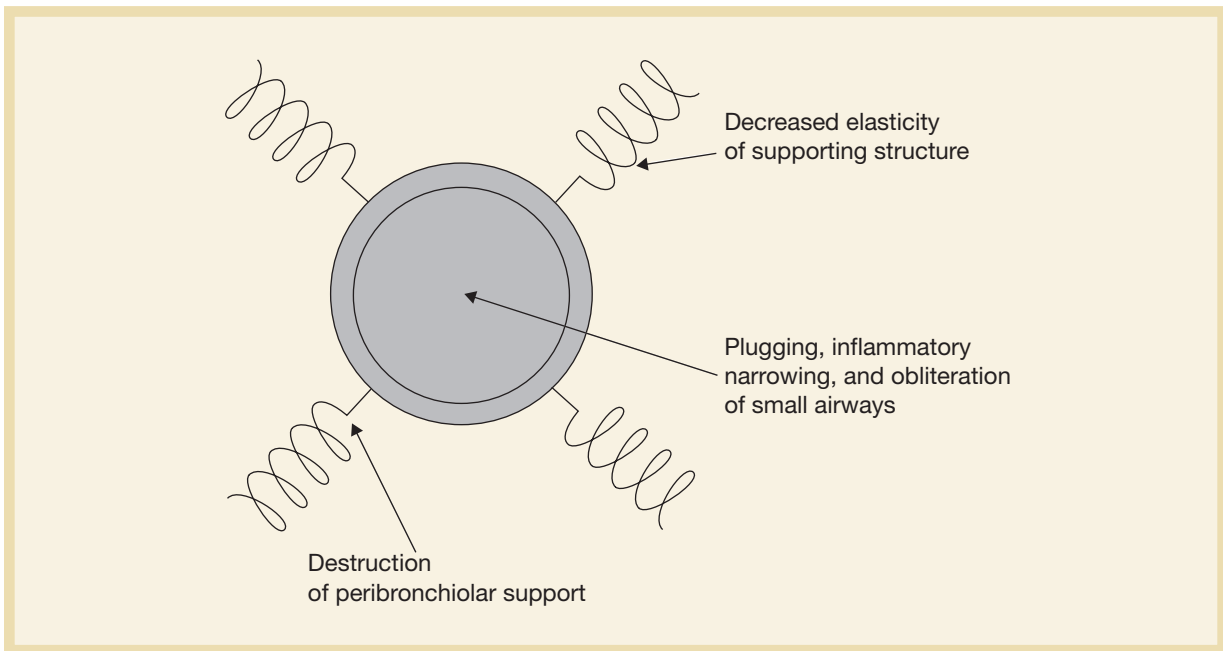
By far, the most powerful environmental exposure is tobacco smoke, with air pollution and occupational pollutants also playing roles. Both host risk factors and environmental exposures conspire to create relentless inflammatory damage of the small conducting airways as well as the large airways and, often simultaneously, attack the alveolar attachments of the small airways. The mechanisms of airflow obstruction include both a loss of elastic recoil and airway narrowing (**Figure 2**).

Extensive studies in whole, freshly excised human lungs available at autopsy have shown that the majority of patients with COPD have elements of airway inflammation (bronchitis and bronchiolitis) and emphysema. Sometimes smooth-muscle hyperplasia and hypertrophy are present, which are characteristic of asthmatic bronchitis (8,9). The overwhelming majority of these specimens showed various stages of emphysema. Emphysema with related hyperinflation due to air trapping is the

most disabling feature of COPD and must be considered an integral part of COPD. Thus, COPD/emphysema is a conceptual continuum that results in progressive degrees of physiologic impairment, premature morbidity, and mortality.

### CONCOMITANT DISEASES

Patients with COPD often have concomitant diseases, particularly as they age. Both anxiety and depression permeate the course of patients with all stages of COPD. However, coronary artery disease with arrhythmias is probably no more common in COPD than in patients with normal airflow. A strong association between COPD and lung cancer has been known for many years (10). Whether COPD/emphysema and lung cancer are different diseases or different manifestations of the same disease is currently being debated. Even with mild degrees of airflow obstruction, lung cancer is ~6 times more common than when airflow is normal, taking into account smoking and family histories and occupational risks (10).



**Figure 2.** Mechanisms of airflow obstruction.

Venous thromboembolism is believed to be more common in patients with COPD than in the general population (11). The reason for this association might be increased platelet adhesiveness due to smoking, hypoxemia, states of erythrocytosis, advanced age, inactivity, or other mechanisms.

### COPD as a Systemic Disease

Today, most experts in the field recognize COPD as more than a pulmonary disease (12). An affective component of anxiety and depression, cardiovascular and musculoskeletal abnormalities, metabolic and nutritional disturbances with hypermetabolism, and often weight loss in later stages of disease are common.

### COURSE AND PROGNOSIS OF COPD

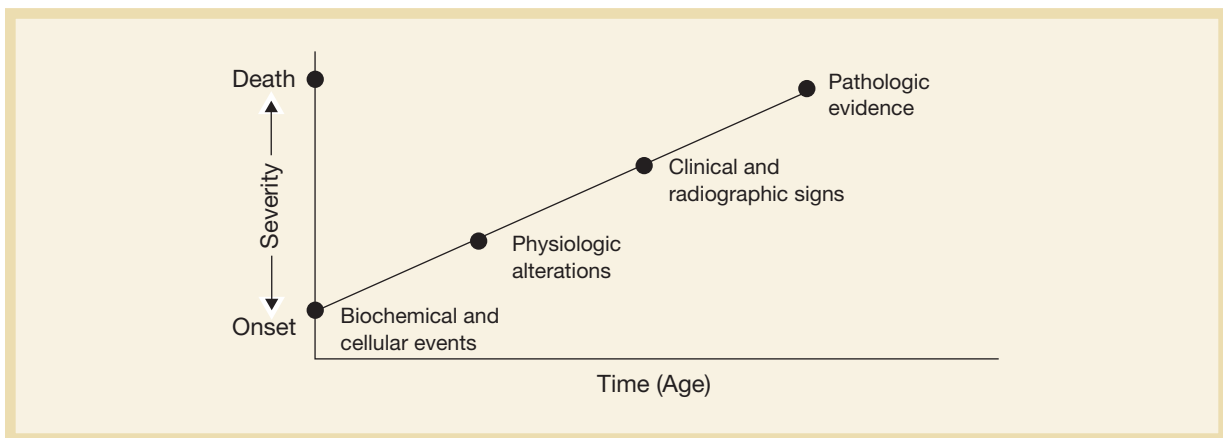
The course and prognosis of COPD (**Figure 3**) depend on the rate of decline in airflow as judged by the forced expiratory volume in one second ( $FEV_1$ ) (4,5,13).  $FEV_1$  is affected by small airways function, large airways function, elastic recoil, and interdependence between alveoli and airways as well as the expiratory effort. Thus, the  $FEV_1$  is a simple expression of a complex process. One in 5 smokers develops COPD. Decline in  $FEV_1$  is related to age

#### KEY POINT

**Tobacco smoke is the most common cause of COPD. Other pollutants and hereditary predisposition are also key factors.**

at onset of smoking, smoking intensity, and the familial susceptibility factor. The biochemical and cellular events that cause damage to small airways and alveoli cause physiologic alterations even in early stages of COPD (14). The Global Initiative for Chronic Obstructive Lung Disease, or GOLD as it is known, defines mild COPD as an  $FEV_1/FVC$  (forced vital capacity) of  $<70\%$  even if the  $FEV_1$  is  $>80\%$  of predicted volume with or without the chronic symptoms of cough, sputum production, and exertional dyspnea (5). Moderate COPD is defined as a ratio and  $FEV_1$  of  $<80\%$  of predicted volume (**Table**).

Most patients with COPD remain asymptomatic or have stable symptoms that are denied by the patient, such as a morning cigarette cough for 20 to 30 years before  $>50\%$  of the normal  $FEV_1$  is lost (**Table**). Thus, a clinician cannot rely on clini-



**Figure 3.** Natural history of COPD.

cal symptoms and signs or even radiographic abnormalities to define the presence of mild-to-moderate COPD. Spirometric measurements of expiratory airflow are required for the diagnosis of COPD and monitoring of response to therapy. Spirometry measures airflow over time or flow over volume, a function of pressure, to determine airflow and airway resistance. Therefore, loss of elastic recoil from emphysema and airway narrowing from bronchospasm, chronic inflammation, and mucus retention lead to expiratory airflow obstruction. Both the  $FEV_1$  and FVC or the surrogate forced expiratory volume in 6 seconds ( $FEV_6$ ) (15) are necessary in defining the presence of COPD and monitoring response to therapy. Spirometry will also separate the restrictive diseases from the obstructive diseases. In the spectrum of restrictive lung diseases, the FVC is  $<80\%$  of predicted capacity and the  $FEV_1/FVC$  is  $>80\%$ .

Other tests of small-airways dysfunction are purported to be more sensitive but are not. Tests such as the forced expiratory flow rate between 25% and 75% of the FVC and other flow points on the expiratory flow volume curve should be eliminated because these tests have no special meaning and often are misleading. The clinician should rely on simple 2-parameter spirometry in assessing lung mechanics.

### RESPONSE TO BRONCHODILATORS

A growing number of bronchoactive drugs are now available to improve airflow in symptomatic patients (16). Although COPD has been defined as

KEY POINT

Spirometry, which records any airflow obstruction, is the only means for diagnosing COPD and monitoring response to therapy.

being irreversible and, by general agreement, present when response to inhaled bronchodilators (both beta agonists and anticholinergics) is  $<12\%$  in  $FEV_1$  or an improvement in  $FEV_1$  is  $<200$  cc, this is an oversimplification (17). COPD is commonly reversible in response to bronchodilators, particularly in patients who can stop smoking. It has also been well established that the initial response to bronchodilators in office testing bears little or no relation to later responses (18). Thus, COPD may be substantially reversible, similar to the partial reversibility in airflow in some chronic asthmatics. This fact defines the grey area between COPD and asthma. Both disease states may occur in the same patient; consequently, the differential diagnosis between COPD and asthma may be difficult in smokers. Very few asthmatic patients smoke.

Newer therapies are emerging that may cause sustained improvement in airflow obstruction, such as tiotropium\* (19). Other drugs such as phospho-

\*Not FDA approved. Application in process.

TABLE.

## CLASSIFICATION OF COPD BY SEVERITY

Stage	Characteristics
0: At risk	<ul style="list-style-type: none"> <li>● normal spirometry</li> <li>● chronic symptoms (cough, sputum production)</li> </ul>
I: Mild COPD	<ul style="list-style-type: none"> <li>● <math>FEV_1/FVC &lt; 70\%</math></li> <li>● <math>FEV_1 \geq 80\%</math> predicted volume</li> <li>● with or without chronic symptoms (cough, sputum production)</li> </ul>
II: Moderate COPD	<ul style="list-style-type: none"> <li>● <math>FEV_1/FVC &lt; 70\%</math></li> <li>● <math>30\% \leq FEV_1 &lt; 80\%</math> predicted volume <ul style="list-style-type: none"> <li>– IIA: <math>50\% \leq FEV_1 &lt; 80\%</math> predicted volume</li> <li>– IIB: <math>30\% \leq FEV_1 &lt; 50\%</math> predicted volume</li> </ul> </li> <li>● with or without chronic symptoms (cough, sputum production, dyspnea)</li> </ul>
III: Severe COPD	<ul style="list-style-type: none"> <li>● <math>FEV_1/FVC &lt; 70\%</math></li> <li>● <math>FEV_1 &lt; 30\%</math> predicted or <math>FEV_1 &lt; 50\%</math> predicted plus respiratory failure or clinical signs of right heart failure</li> </ul>

$FEV_1$  = forced expiratory volume in one second; FVC = forced vital capacity; respiratory failure = arterial partial pressure of oxygen ( $P_{aO_2}$ ) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of  $CO_2$  ( $P_{aCO_2}$ ) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level. Reprinted with permission from Pauwels RA, Buist AS, Calverly PM, et al. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2001;163:1256–1276.

## KEY POINT

**COPD may be substantially reversed in response to bronchodilators, especially in patients who stop smoking.**

diotenase-4 inhibitors, currently under phase II and III investigational stages, also may soon be available to aid practitioners in the management of their patients (13). Cessation of smoking, of course, is the most fundamental treatment for COPD (20), but one must recognize that patients with this disorder are heavily addicted to nicotine. Several nicotine products and bupropion are helpful in mitigating the depression, anxiety, and somatic preoccupation that are so common in patients with all stages of COPD.

## SUMMARY

COPD is a common disease due largely to smoking but also to other air pollution and hereditary predispositions that are not yet well defined. COPD can

be diagnosed only by spirometry, which is also essential for tracking response to therapy and for predicting the prognosis of COPD. All primary care physicians, including family practitioners, should have and use spirometers in their daily practice, and this is the major goal of the National Lung Health Education Program. Because primary care practitioners see most COPD patients well before symptoms or advanced stages of the disease are present, they are on the front line for detecting and treating this devastating and growing health problem.

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## Dialogue Box

### ADVISORY BOARD

**What measurement of pulmonary function testing is most reliable for the early detection of COPD?**

#### PETTY

The FEV<sub>1</sub>/FVC ratio. This is the measurement used by the GOLD criteria, with a ratio <70% defining a patient with mild COPD. Although not particularly specific, this parameter is more sensitive than criteria requiring a reduction in absolute FEV<sub>1</sub>. My work, as well as the work of Ben Burrow, has shown that when COPD begins, the FVC goes up before the FEV<sub>1</sub> comes down.

### ADVISORY BOARD

**At one time, weren't midrange flow measurements, such as the forced expiratory flow rate between 25% and 75% of the FVC (FEF<sub>25%-75%</sub>), believed to be of value for detecting small airway obstruction?**

#### PETTY

Yes they were, but that's been shown to be a fallacy. Those lung function parameters do not measure small airway disease any better than the FEV<sub>1</sub>/FVC ratio.

### ADVISORY BOARD

**Are you saying then that a 50 pack-year smok-**



## Dialogue Box

**er who has an  $FEV_1/FVC > 70\%$  is normal no matter how low the  $FEF_{25\%-75\%}$  may be?**

### PETTY

I don't know if that smoker is normal or not, but I can tell you that measurements of  $FEF_{25\%-75\%}$  can be quite variable. In addition to not being more sensitive for detecting mild COPD, this parameter can actually be misleading because if the FVC goes up and the  $FEV_1$  also goes up even a little bit, the  $FEF_{25\%-75\%}$  can actually go down if the expiratory time is slightly prolonged since it measures the flow rate in midportion of the curve. This and other midexpiratory flow measurements have no real value diagnostically—they are not indicative of small airway disease—and there is now a movement to get rid of these measurements altogether.

### ADVISORY BOARD

**Is there a circumstance where a patient with emphysema can have a normal diffusion capacity?**

### PETTY

Yes, there are a few people with emphysema who lose elastic recoil before they lose alveolar wall. The loss of elastic recoil and loss of alveolar walls are 2 parallel processes, but they're not cause and effect. Thus, you can have a patient with emphysema who despite having a low  $FEV_1$  and an increased total lung capacity with marked hyperinflation, still has a normal diffusion capacity because although the elastic fibers are damaged in the alveolar walls, the walls have not yet dropped out.

### ADVISORY BOARD

**Since both the numerator and denominator would be expected to decline with age, how does interpretation of the  $FEV_1/FVC$  vary with age?**

### PETTY

There are predicted values for the ratio, but very few people use it because there are only slight changes over time. Specifically, the ratio decreases from 75% at age 20 years down to ~69% at age 80 years. Thus, you see only a 6% change in a lifetime. For all intents and purposes, an  $FEV_1/FVC$  ratio  $<70\%$  should be regarded as abnormal.

### ADVISORY BOARD

**Please elaborate on the concept that COPD and lung cancer may be viewed as a continuum.**

### PETTY

That's kind of a wild idea of mine. It becomes plausible when one considers that if you have COPD, particularly emphysema, you have ~6 times the likelihood of lung cancer than if your airflow is normal after controlling for other known risk factors, such as smoking history, family history, and occupational history. Moreover, in patients with emphysema who develop lung cancer, the lung cancer is almost always where the emphysema is and that's in the upper half of the lung.

### ADVISORY BOARD

**Any thoughts regarding a possible mechanism?**

### PETTY

It has been theorized that emphysema is an ischemic lesion due to accelerated apoptosis of lung capillaries, which in turn causes the alveolar walls to drop out. I think there may be a steal of apoptotic mechanisms by the emphysema cells, which leaves behind rogue clones that can't go through programmed death. These rogue clones of cells in turn ultimately mutate and lead to the development of lung cancer. This situation might be viewed as analogous to the high risk of breast cancer seen in patients with cystic mastitis and the



## Dialogue Box

high risk of colon cancer in patients with inflammatory bowel disease.

### ADVISORY BOARD

**Is there a fundamental difference in the inflammatory mechanisms seen in the COPD emphysema patient versus the asthma patient?**

#### PETTY

Yes, there are clearly different inflammatory mechanisms involved. On a basic level, one can think of asthma as an eosinophilic bronchitis and COPD as a neutrophilic bronchitis. It's important to appreciate, however, that this represents a gross oversimplification since the cytokine mechanisms involved in these 2 disorders differ greatly. Although they're both inflammatory diseases, the pathogenic mechanisms are quite different, and I think this best explains why asthma patients routinely respond to corticosteroid treatment and COPD patients do not.

### ADVISORY BOARD

**One of the reasons cited for the earlier use of steroids in patients with asthma is to prevent the remodeling of airways. Is remodeling in inadequately treated asthma patients an important cause of COPD?**

#### PETTY

Yes, I think it is. There are a growing number of papers, mostly from Europe, that indicate asthma with airway remodeling does evolve into COPD. This is why I included the term "asthmatic bronchitis" as part of the COPD spectrum, which also includes chronic bronchitis and emphysema. Although it can be argued that asthmatic bronchitis and chronic bronchitis are the same disease, at this point I prefer to regard them as 2 distinct entities. These labels notwithstanding, what's really

important is the functional change in response to therapy, ie, whether there is reversal of obstruction with bronchodilator therapy.

### ADVISORY BOARD

**Do you think that all COPD patients who continue to be symptomatic despite bronchodilator therapy, regardless of the demonstration of reversibility of airway obstruction on lung function testing, warrant a trial of inhaled corticosteroids?**

#### PETTY

I'd go even further than that. I think everybody with COPD ought to have a trial of systemic steroids at least once to see whether there's occult reversibility. It is overly simplistic to think that a single test of bronchodilator response on pulmonary function testing (PFT) is an adequate test of underlying airway responsiveness. In fact, about 10% of people labeled to have COPD without airway reversibility on PFT are subsequently found to have major reversibility on corticosteroids. Now maybe they represent hidden asthmatics, but it really doesn't matter. The trick is to find the lowest dose of steroid that will maintain the benefit.

### ADVISORY BOARD

**Please comment further on the concept of COPD being a systemic disease?**

#### PETTY

When one considers the background of people with all stages of COPD and their families, one finds a high level of anxiety, depression, and somatic preoccupation. The COPD patient not infrequently deals with these issues by using tobacco because tobacco mitigates anxiety and depression and often helps alleviate somatic pre-



## Dialogue Box

occupation. It is ironic that the thing that's killing them is also the thing that makes their life more tolerable. That's often why a COPD patient can't stop smoking—the smoker needs to smoke to keep feeling well. Beyond these psychosocial issues, COPD patients also have muscle wasting and impaired cardiovascular responses. Even patients with mild COPD without hypoxemia, say an FEV<sub>1</sub> of 2.5 liters (65% of predicted), are often unable to achieve a targeted heart rate on treadmill testing because they can't increase their maximum oxygen consumption like normal people. COPD isn't just a lung disease, it's also a mental disease, heart disease, and skeletal muscle disease. And that to me makes it very, very intriguing.

### ADVISORY BOARD

**Outside of smoking cessation, do any of the other currently available intervention options appear to be disease modifying?**

### PETTY

No. There are drugs under study such as the phosphodiesterase-4 inhibitors, of which there are 2 in phase III trials, that appear to be disease modifiers, but their utility still remains to be proved. In addition, a new, very long-acting anticholinergic, tiotropium, which will be known as Spiriva\*, may be disease modifying since it appears to bump up baseline lung function and keep it up. We think there are disease modifiers out there, but so far in controlled clinical trials smoking cessation in early disease and oxygen in late disease are the only proven therapies.

### ADVISORY BOARD

**How long after the discontinuation of smoking**

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\*Not FDA approved. Application in process.

**is benefit seen in the COPD patient?**

### PETTY

With regard to the development of coronary artery disease, it's within the first year. With regard to COPD, if you stop smoking, although you may not regain your lung function, the age-related decline of pulmonary function is reduced. Thus, you can prevent or forestall premature morbidity and mortality. With respect to the development of lung cancer, the risk never goes away completely even after 20 years. There's still an elevated risk.

### ADVISORY BOARD

**How do you manage the cachexia seen in end-stage COPD?**

### PETTY

Inexorable cachexia is just another reflection of COPD being a systemic disease. Patients with advanced emphysema invariably have a BMI <18 because of a number of factors, including a high resting energy expenditure, high levels of circulating catecholamines, and elevated levels of tumor necrosis factor alpha. We're learning it can be reversed with feeding and anabolic hormones. COPD patients gain fat weight if given megestrol acetate and protein weight if treated with oxandrolone or testosterone propionate. Weight loss, if it can't be reversed, is a bad prognostic indicator.

### ADVISORY BOARD

**Since smoking cessation is the only disease-modifying intervention available for patients and since most primary care physicians routinely strive to get their smoking patients to stop, why the need for screening for early disease with office spirometry?**



## Dialogue Box

### **PETTY**

Although smoking cessation may be on the agenda of the physician, both the patient and the physician will likely approach it with greater enthusiasm if it can be shown that there is something objectively wrong. In addition, spirometric abnormalities correlate with all-cause mortality and that's the single most valuable thing a family practitioner can do

for the database in terms of future prognosis. Spirometric abnormalities not only tell you about obstructive diseases and restrictive diseases, but also identify patients at high risk for the development of lung cancer, heart attack, and stroke. In my opinion, an office spirometer is a more important piece of equipment to have in a doctor's office than an electrocardiograph.