Definitions, Causes, Course, and Prognosis of Chronic Obstructive Pulmonary Disease

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C *hronic obstructive pulmonary disease* (COPD) refers to a group of respiratory disorders, including chronic bronchitis, pulmonary emphysema, and asthmatic bronchitis, that commonly coexist to varying degrees. COPD causes clinically significant progressive obstruction to expiratory airflow. COPD is the fourth most common cause of death in the United States. In fact, 30 to 35 million Americans are believed to be afflicted, about half of whom are asymptomatic. The purpose of this article is to present simple and pragmatic definitions within the spectrum of COPD and to review briefly its risk factors, epidemiology, course, and prognosis.

DEFINITIONS*

COPD is characterized by chronic cough, expectoration, varying degrees of exertional dyspnea, and significant and progressive reduction in expiratory airflow. Most patients with COPD are smokers.[50] Airflow obstruction does not

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* The definition of COPD has varied over the years. Today it includes International Classification of Disease (ICD-9) codes for chronic bronchitis (491), emphysema (492), and other chronic airways obstruction (494-496). Isolated asthma, particularly reversible asthma (493), is not included. The definitions in this article are adapted from α-1-Antitrypsin Deficiency Registry Study Group: A registry of patients with severe deficiency of α-1-antitrypsin: Design and methods. Chest 106:1223–1232, 1994.

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show major reversibility in response to pharmacologic agents. Hyperinflation and a reduced diffusing capacity may be present. Inflammatory damage to both airways (bronchitis) and alveoli (emphysema) is found on postmortem examination.

Chronic Obstructive Bronchitis

Chronic obstructive bronchitis is defined as chronic cough and expectoration for at least 3 months a year for at least 2 years. Chronic obstructive bronchitis has diminished airflow that does not improve significantly after bronchodilator inhalation. Simple chronic bronchitis, or chronic cough and expectoration with normal airflow, is not included in this definition; simple chronic bronchitis without airflow obstruction has a good prognosis. Chronic obstructive bronchitis is distinguished from asthmatic bronchitis only by its lack of reversibility in response to pharmacologic agents. Patients with pure chronic obstructive bronchitis do not have physiologic or roentgenographic evidence of hyperinflation. Diffusion tests are normal.

Emphysema

Historically, emphysema was defined physiologically as reduced elastic recoil and pathologically as the disintegration of alveolar walls due to tissue breakdown. Clinically, emphysema patients exhibit varying degrees of dyspnea on exertion, cough, and irreversible airflow obstruction. These patients also demonstrate abnormalities at the air-blood interface that manifest in decreased carbon monoxide uptake (diffusion tests) and hyperinflation (judged clinically by physical examination, radiograph, and measurements of total lung capacity). Chronic bronchitis and emphysema often coexist because both are caused by cigarette smoking; most clinicians continue to use the term *COPD* for this reason.

Asthmatic Bronchitis

Patients with asthmatic bronchitis have pulmonary symptoms, including productive cough, varying wheeze, and exertional dyspnea, with airflow obstruction, but these symptoms and the obstruction reverse significantly in response to bronchoactive drugs such as bronchodilators and corticosteroids. In these patients, progressive airflow obstruction occurs over time and becomes less reversible in response to bronchodilators. Acute reversible and episodic asthma are not included in the asthmatic bronchitis designation.

Diagnosing asthmatic bronchitis in its early stages, when airflow abnormalities are just beginning to occur, may be profoundly important. In both asthmatic and chronic bronchitis, bronchial hyperreactivity probably results from airways inflammation caused by a variety of irritants. The regular use of bronchodilators or inhaled corticosteroids to try to reverse bronchial hyperreactivity and suppress inflammation in the early stages of disease may help forestall or prevent irreversible damage and fixed airways changes. This prompt treatment may make impairment, disability, and death from endstage COPD less likely.

In their later stages, chronic obstructive bronchitis and asthmatic bronchitis may become indistinguishable and intertwined with emphysema. Therefore, in advanced airflow obstruction it is better to use the umbrella designation of COPD to represent both irreversible damage to airways and alveoli.

CAUSES

In the simplest terms COPD can be considered a smoker's disease that tends to cluster in families and worsens with age. COPD is the end result of a number of host and environmental risk factors.

External and Environmental Risk Factors

Tobacco

The relationship between smoking and COPD has been established.[50] Evidence of the causation of COPD began to accumulate nearly 100 years ago.[30] A massive amount of evidence indicting tobacco smoke has been gathered in the past 40 years from both descriptive and major population studies.[', 8, 11, 13, 19, 20, 26, 31, 36] The probability that smoking cessation can dramatically reduce the rate of decline in pulmonary function also implicates smoking as a major factor in COPD (Fig. 1).

In a comprehensive study of four populations in and around Beijing in northern China and in and around Guangzhou in southern China, an increased risk of COPD was found in smoking versus nonsmoking men and women. The risk of COPD from smoking was much less than that in Western countries, however, suggesting that either the cumulative dose of smoking is too low to be a major causative factor or that racial susceptibility differences are present.[8] There is some evidence that women may be more susceptible to the harmful effects of tobacco smoke than men.[15]

Other Inhaled Agents

Occupational Dusts   Inhalation of occupational dusts can cause COPD. The clinical importance of coal dust exposure has been studied in British miners.[29] The investigators found that both smoking and coal dust exposure can cause pulmonary abnormalities. There was no evidence of synergism between smoking and dust exposure. Other contributing factors in COPD include air pollution, childhood respiratory infections, and nonspecific bronchial hyperreactivity. These factors have been discussed in complete detail (Table 1). Grain dust exposure also has been established as a risk factor in COPD, both in smokers and nonsmokers.[52] The mechanisms appear to be both immunologic and nonimmunologic; bronchial hyperresponsiveness is quite prevalent after grain dust exposure in susceptible individuals. Endotoxins, mites, and fungi also may be responsible for the affect on airflow obstruction and bronchospasm.[29]

Air Pollution   Air pollution has been casually linked with COPD, but its role has been considered minor compared with that of smoking. Bates[3] produced
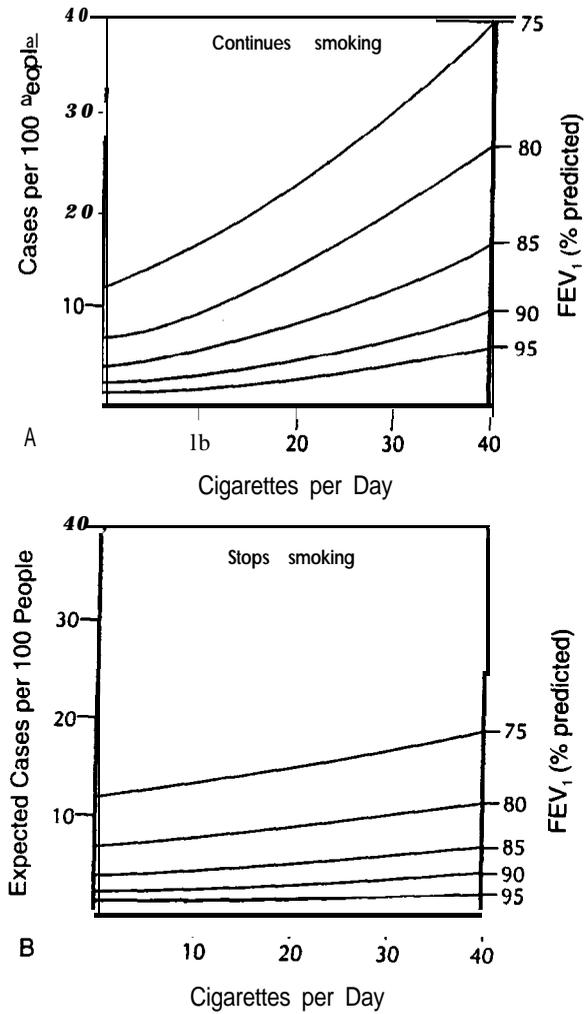
Figure 1 Probabilities of developing chronic obstructive pulmonary disease within ***10*** years for men ***45*** years of age. ***(Adapted from*** Burney P: The origins of obstructive airway disease. A role for diet?Am J Respir Crit Care Med 151:1292–1293, 1995; Official Journal of the American Thoracic Society, copyright American Lung Association, with permission.)

TABLE 1 Risk Factors for Chronic Obstructive Pulmonary Disease

Type	Known	Possible or Probable
Agent	Cigarette smoke Environmental or occupational dusts and gases	Air pollution Passive (involuntary) smoking Respiratory viruses Socioeconomic factors, living conditions Alcohol consumption
Host	α-1-Antitrypsin deficiency	Age Gender Familial or genetic factors Airway hyperresponsiveness

From Buist AS, Vollmer WM: Smoking and other risk factors. *In* Murray JF. Nadel JA (eds): Textbook of Respiratory Medicine, ed 2. Philadelphia, WB Saunders, 1995, pp 1259-1287.

some of the most convincing evidence in his study of veterans with equal smoking histories in four Canadian cities: chronic bronchitis was more prevalent in the three cities with significant air pollution than in the city relatively free of air pollution.[3] Another report related photochemical oxidants and multiple primary air pollutants such as sulfur dioxide particles and hydrocarbons to chronic respiratory symptoms and pulmonary function abnormalities in both smokers and nonsmokers.[40] Many more references to the association between air pollution and COPD have been made.[8]

Indoor Air Pollution Respiratory symptoms have been related to the use of several domestic cooking fuels, such as kerosene and other fuels in India[4] and wood burning for cooking and heating in Bogota, Colombia.[16] Indoor tobacco smoke pollution has been shown to have adverse effects on pulmonary function in children and adolescents.[48]

Socioeconomic Status

Low socioeconomic status had a deleterious effect in studies that controlled for smoking intensity, but its effect on pulmonary function was weak as compared with that of smoking.[22]

Childhood Respiratory Infections

A unique and comprehensive study on the epidemiology, course, and prognosis of COPD gave evidence that childhood respiratory infections were associated with relatively mild ventilatory impairment in young adults. Such patients demonstrated an accelerated rate of decline in lung function with advancing

years and cigarette use. It is possible to conclude from this study that damage to young developing airways sets the stage for more aggressive injury from tobacco smoke in later years.[14, 43]

Alcohol

Reports on the association between alcohol consumption and the prevalence of COPD vary. Heavy alcohol consumption was associated with respiratory symptoms and reduced lung function in a study by Lebowitz,[25] even when controlled for smoking; smoking, however, was judged to be a far more important risk factor. The effect of passive smoking also would have to be considered in any heavy drinker, smoker or not, who consumed his or her favorite beverage in heavily tobacco-polluted bars or restaurants. By contrast, no association between alcohol consumption and COPD was found in the study by Higgins et al.[21]

Diet

A carefully designed and administered questionnaire, along with biochemical tests, has shown decreased food intake and serum levels of the major antioxidant vitamins in smokers compared with nonsmokers.[5] Because oxidant injury is believed to be one of the mechanisms of alveolar and airway damage, antioxidant deficit could be a risk factor. If so, this could be an important factor in the development of COPD in areas of the world where malnutrition is prevalent.

Host Risk Factors

α-1-Antitrypsin Deficiency

Deficiency in a-l-antitrypsin is clearly defined as a risk factor in the small proportion of people with this hereditary deficit. Abnormalities in a-l-antitrypsin with multiple genotypes are almost limited to Caucasians. This deficiency state was first described in Scandinavia. The classic discovery of a marked reduction of the normal α-1 peak on simple paper electrophoresis, of which 90% is comprised of a-l-antitrypsin, ushered in a new era that began to focus on the basic biology and pathogenesis of emphysema.[24]

Later, many other investigators, most notably Janoff,[23] established the protease-antiprotease theory of disease as a result of tobacco smoke and the additional role of oxidants in inactivating the normally formed α-1-antitrypsin, and the complex number of codominant alleles involved in the hereditary deficiency state. The Pi ZZ, SZ, and Pi Null are the phenotypes most often linked with COPD. One problem with the elastase-antielastase concept is that not all patients with even the most risky genotypes and lower α-1-antitrypsin levels develop disease, even if they smoke.[44] Classically, α-1-antitrypsin deficiency is closely related to the early onset of emphysema and other forms of COPD, including asthmatic bronchitis, in a pattern that runs in families. Death may occur at an early age. Even nonsmokers with α-1-antitrypsin deficiency may develop the emphysema form of COPD, but usually late in life.

A registry of patients with severe a-1-antitrypsin deficiency has been established. This is a longitudinal study of the rate of decline in forced expiratory volume in 1 second (FEV,) in a wide spectrum of patients, both smokers and nonsmokers. Antiprotease therapy (Prolastin; Miles Inc., West Haven, CT) is being administered on an individual basis (the study is not randomized or controlled). Nonetheless, the long-term outcome of this large cohort will provide important insight concerning whether or not α-1-antitrypsin replacement alters the rate of decline in lung function, particularly if previous serial pulmonary function tests are available.'

Familial Clustering

Family clustering of COPD goes beyond the α-1-antitrypsin deficiency state. Socioeconomic status and smoking habits, however, are the major factors that cause clustering. One study found familial aggregation of pulmonary function abnormalities to be independent of smoking.[47] A search for additional COPD susceptibility genes is a highly complex matter, but it may become possible with modern molecular tools.*'

Bronchial Hyperreactivity

Nonspecific bronchial hyperreactivity has long been known to be associated with accelerated rates of decline in FEV_1, particularly in smokers. This decline is consistent with the original "Dutch hypothesis" of allergy and bronchial hyperreactivity as constitutional factors in the pathogenesis of COPD. A thorough review of this subject cites numerous references to support this association.[33]

COURSE AND PROGNOSIS

The course and prognosis in COPD varies with the clinical phenotype, stage of disease when first diagnosed, and responses to therapy. Patients who were heavier smokers with marked hyperinflation and a diffusion abnormality and with no features of atopy and little response to bronchodilators had the worst prognosis (Fig. 2). By contrast, patients with lower smoking intensity, the presence of some bronchodilator response, evidence of atopy, and without significant hyperinflation and no major abnormality at the air-blood interface (see Fig. 2) had a fairly good prognosis on long-term follow-up. These patients have the clinical features of asthmatic or chronic bronchitis.

Smoking cessation may dramatically alter the course and prognosis of COPD. In a follow-up of men who were able to stop smoking at approximately 45 years of age, the rate of decline in FEV, paralleled the age-related decline.[34] Even men who stopped smoking at 65 years of age with marked reduction in FEV, compared with 25 years of age had a survival benefit (Fig. 3).[34] Thus it is never too late to stop smoking, but it is much better to stop at an early age when lung function is relatively well-preserved.
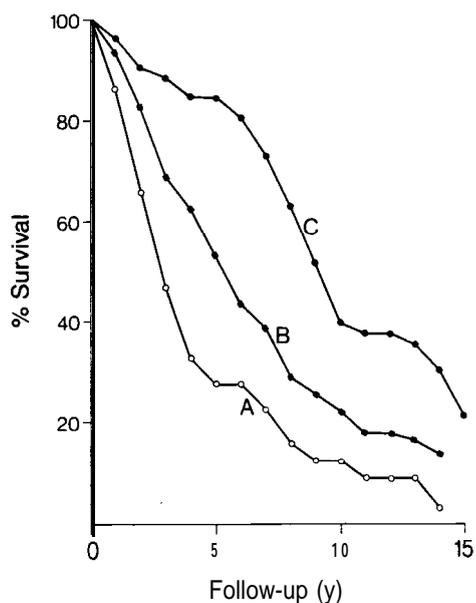
Figure 2 Survival curves of three phenotypically different types of chronic obstructive pulmonary disease. Group A includes patients with the heaviest smoking, hyperinflation. reduced diffusion, little response to bronchodilators, and no signs of atopy. Group C patients are ones with less intense smoking and included some nonsmokers, no hyperinflation, a near-normal diffusion test, and a significant but incomplete response to bronchodilators and signs of atopy. Group B patients have features of both Groups A and C. *(From* Burrows B, Bloom JM, Traver GA, et al: The course and prognosis of different forms of chronic airways obstruction in a sample from the general population. N Engl J Med 317:1309–1314, 1987; Copyright 1987, Massachusetts Medical Society, all rights reserved, with permission.)

This fact was borne out by the results of the Lung Health Study.[2] This study enrolled 5887 men and women in a prospective evaluation of the success and relative impact of smoking cessation on rate of change of FEV,. Figure 4 demonstrates that FEV, increased in those who successfully quit smoking for the entire 5-year follow-up, followed by only a minor decline.[2] At the end of 5 years, FEV, was only slightly lower than on admission to the study. Those who continued to smoke had a much greater rate of decline (see Fig. 4). Bronchial hyperreactivity was very prevalent in patients enrolled in the Lung Health Study.[49] Of the 5887 patients enrolled, 96 (0.4%) were challenged with methacholine. A positive response to 25 mg/mL methacholine was found in 85% of women and 59% of men. When 5 mg/mL was used, positive responses were 47% in women and 24% in men. The prevalence of bronchial hyperresponsiveness in women compared with men was not explored in this study.
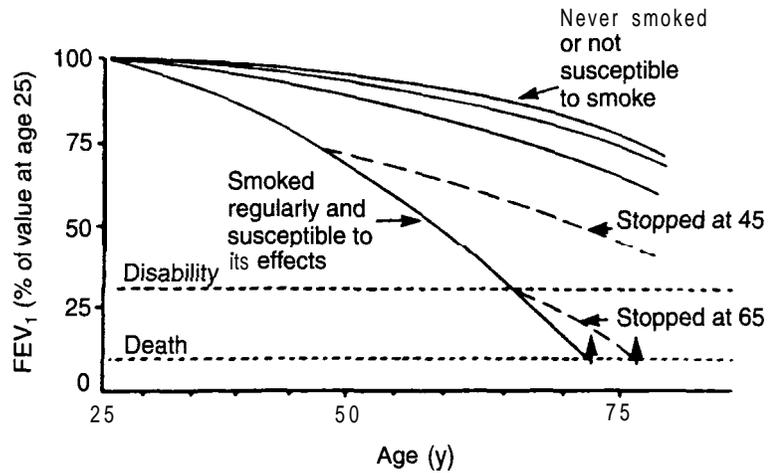
Figure *3* Results of stopping smoking at 45 years of age, when pulmonary function was approximately **70%** the value at **25** years of age. Notice that FEV, decline parallels increase in age. Most patients who stopped smoking at 65 years of age had a survival benefit, even though their FEV, was only 30% of that at **25** years of age. It is not known why some patients are not susceptible to damage from tobacco smoke. *(From* Peto R, Speizer FE, Cochrane AL, et al: The relevance in adults of airflow obstruction, but not of mucus hypersecretion to mortality from chronic lung disease. Am Rev Respir Dis **128:491−500,** 1983; with permission.)
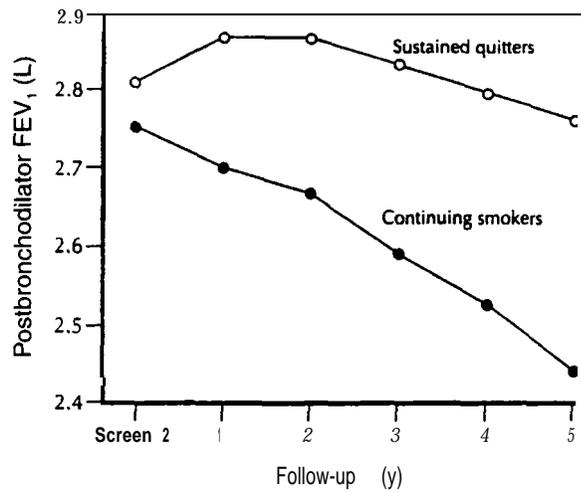

Figure 4 A slight improvement in FEV, was observed in sustained quitters through 5 years of follow-up. Continuing smokers had a much more rapid rate of decline in FEV,. *(From* Anthonisen NR, Connett JE, Kiley JP, et al: Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV,. The Lung Health Study. JAMA **272:1497−1505, 1994;** with permission.)

Ipratropium bromide was randomly given to one-third of patients in the Lung Health Study. It caused a statistically significant improvement in airflow throughout the 5-year study but had no effect on baseline pulmonary   function.[49] In another study, ipratropium bromide did demonstrate an increase in baseline lung function.[38] Whether or not the long-term use of any bronchoactive drug, such as an anticholinergic, β agonist, or inhaled corticosteroid, will alter the course and prognosis in the long term is not known and would require major controlled clinical trials. Currently two trials of inhaled corticosteroids are underway in the United States[28] and Europe.[51] One preliminary study showed a reduction in the rate of decline in FEV, in both COPD and asthma patients who used inhaled corticosteroids; the effect was much greater in asthma than in COPD.[17]

Screening for Chronic Obstructive Pulmonary Disease

In the United States, morbidity and mortality from COPD are more common in Caucasians compared with African Americans and in men compared with women (Fig. 5 presents the death rates for COPD by age, sex, and race in the United States in 1988.) The prevalence of COPD in developed countries is similar to that in the United States. Elsewhere in the world its prevalence not as well defined.

At least 16 million people in the United States have symptomatic COPD. Unfortunately most are not diagnosed until severe symptoms or severe physiologic impairments are present. The prevalence of asymptomatic COPD is not
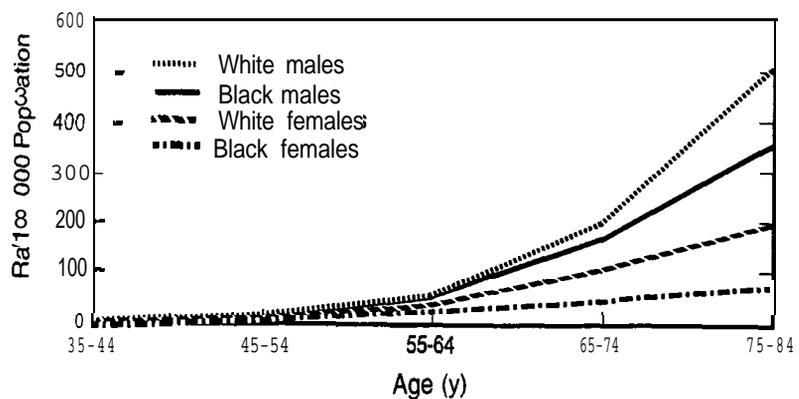

Figure 5 Death rates for chronic obstructive pulmonary disease by age, sex, and race in the United States in 1988. (From Vital Statistics of the United States, 1988, vol 2. Mortality, Part A. US Department of Health and Human Services publication PHS 90-110 PP490-492, 494-496. Hyattsville, MD, National Center for Health Statistics, 1990.)

known, but incipient disease may affect another 15 to 16 million Americans. Thus, in all, COPD probably affects 30 to 35 million people in the United States. Early stages of COPD usually are asymptomatic, and there are no reliable physical signs. Standard chest radiography is not helpful in identifying early stages of disease. Accordingly, it is incumbent on all primary care physicians to be alert to the possibility of COPD in all patients with productive cough, particularly in those who suffer exercise-related dyspnea and have a family history of the disease, and especially in those who are smokers. COPD must be identified early by simple spirometric measurements. When even minor reductions in the ratio of FEV, to forced vital capacity (below 0.70 or even 0.75) are present, there is a likelihood of further accelerated decline in absolute FEV, and thus a high likelihood of premature morbidity and mortality from COPD.[12] Patients experiencing such reductions should avoid all inhalation of irritant and toxic fumes, particles, and, most particularly, tobacco smoke. Smoking cessation also will help reduce the risk of death from lung and other cancers, as well as heart attack and stroke.

The National lung Health Education Program

The National Lung Health Education Program (NLHEP) is a new national health care initiative that aims to promote the early identification and intervention in COPD and related diseases.[35] The NLHEP is launching a major educational initiative for both primary care practitioners and the public, "Test Your Lungs/Know Your Numbers" is the call to arms of the NLHEP. It is hoped that the widespread availability of a new generation of simple, hand-held spirometers will revolutionize the approach to early diagnosis in all physicians' offices. Early identification is a key step to promoting smoking cessation, and use of vaccines and bronchoactive drugs can reduce the decline of lung function and prevent premature morbidity and mortality from COPD.

FUTURE DIRECTIONS

Once the public begins to take notice of the premature morbidity and mortality associated with COPD and primary care practitioners of all types learn to identify COPD in its early stages, a major revolution in the health care of smokers and others at risk of COPD will probably follow. Through the educational and publicity effects of the NLHEP, COPD should become a household word and FEV, and forced vital capacity should be as well known as blood pressure and cholesterol levels. Major efforts at smoking cessation must be made in all smokers who have any degree of airflow obstruction. It is well established via previous studies,[34] the Lung Health Study,' and other population studies[9] that smoking cessation will lessen the decline in FEV'. Thus smoking cessation becomes the key to the solution of COPD.

In the Lung Health Study, however, only 22% of patients randomized to receive special care, which included a major comprehensive effort in smoking cessation, actually quit for the full 5-year course of the study. With usual care, the quit rate was only 5%. Therefore, it is obvious that smoking cessation cannot be achieved in even one third of patients at risk of COPD. Other therapeutic approaches are needed.

Recent evidence indicates that diet may interact with the development of COPD.[6, 42, 45] When controlled for smoking, a diet high in N-3 polyunsaturated fatty acids[44] and in antioxidant vitamins C and E[6, 45] was associated with better pulmonary function. It is certain that an oxidant-antioxidant imbalance is key to the pathogenesis of COPD, even though the exact mechanisms of this imbalance remain to be explained.[37, 39] It is likely that genetic factors interact with environmental factors of tobacco smoke and other irritants to create this imbalance.[10, 39] In view of this new evidence, the physician should focus on smoking cessation and dietary pattern change, and prescribe antioxidant supplements when warranted.

In advanced stages of disease, nutritional depletion is common."' Attempts at correcting these deficiencies with nutritional supplementation have not been highly successful.[46] Use of synthetic androgens may play a role in combating the nutritional depletion in advanced stages of COPD.[41]

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