EDITORIALS

Smoking, Not COPD, as the Disease

Leonardo M. Fabbri, M.D.

Smoking causes not only cancer but also cardiovascular diseases such as stroke, coronary heart disease, hypertension, thromboembolism, and peripheral artery disease, lung disease such as chronic obstructive pulmonary disease (COPD), and many other diseases, including (but not limited to) type 2 diabetes, rheumatoid arthritis, cataracts, and macular degeneration.[1] These diseases develop with age and contribute in different measure to the current epidemic of chronic noncommunicable diseases that are associated with smoking and aging.[1,2]

Even though the effects of smoking are broad and devastating, much smoking-related research traditionally focuses on the lung because the lung is considered to be the primary target organ of smoking.[3] Even though COPD is one of the major consequences of smoking, COPD usually does not exist by itself, because it is almost invariably associated with concomitant chronic respiratory and nonrespiratory diseases[3,4] that contribute to the clinical manifestations and severity of the smoking-induced systemic disease.

COPD, as defined by the Global Initiative for Chronic Obstructive Lung Disease, is diagnosed as persistent airflow limitation in smokers.[3] This definition has limitations for clinical practice, because it does not mention symptoms and applies only to smokers in whom airflow limitation has developed. In fact, the only COPD we know well is the one that is defined as airflow limitation in smokers, because most of the data available on the pathophysiology and management of COPD have been derived from smokers with airflow limitation that was defined according to spirometric assessment.[3]

Woodruff and colleagues report in this issue of the *Journal*[5] on a group of smokers with normal findings on spirometry who have chronic respiratory symptoms, exacerbations (identified as the use of antibiotic agents, systemic glucocorticoids, or both or an event of health care utilization such as an office visit, hospital admission, or emergency department visit for a respiratory flare-up), lower than normal exercise tolerance, and imaging evidence of bronchiolitis. Thus, they conclude that spirometry is not adequate to define the breadth of smoking-induced lung disease. These results confirm and extend the findings of another recent large study that showed that more than 50% of symptomatic smokers with normal findings on spirometry have considerable respiratory-related impairment and evidence of emphysema on imaging.[6] Most of these symptomatic smokers with normal findings on spirometry are often treated (without any evidence) with inhaled bronchodilators and glucocorticoids — that is, they are treated like patients with COPD, but they do not have COPD according to our current definition.

These two studies introduce an important paradigm shift in our approach to smoking-induced disease. Both studies show that patients who have chronic respiratory symptoms without airflow limitation have the same respiratory consequences as those who have mild-to-moderate airflow obstruction and get the official diagnostic label of COPD. This finding tells us that symptoms are at least as sensitive as airflow limitation in establishing a diagnosis of smoking-induced disease. The observation that bronchiolitis and emphysema that are detected by means of computed tomographic scanning may be present in some smokers without airflow limitation lends a firm biologic basis to these inferences and reminds us, once again, that COPD may be a disease of the "lung's quiet zone," as

defined by Mead almost 50 years ago — a place where there can be pathobiologic changes that are not detected by changes in the forced expiratory volume in 1 second (FEV_1).[7] These two studies have identified a complex clinical syndrome that is treated as COPD in practice even when airflow limitation is not present — a syndrome that very much resembles heart failure without impairment of ejection fraction.[8]

It would be useful if we had a way to detect abnormalities before they manifest clinically so that intervention can prevent full-blown disease. For more than 50 years, smoking-related research has focused on measurements of lung function, including spirometry, to detect early COPD.[9,10] Now we know that symptoms can be at least as sensitive, and certainly more useful, in identifying patients who need early intervention.[5,6,10] This finding clearly suggests that the FEV_1 is not sensitive in a large majority of smokers and may be just one of the tools needed to make an early diagnosis in a subgroup of smokers.

Using the COPD Assessment Test (CAT) questionnaire to investigate symptoms,[11] Woodruff et al. found that both respiratory symptoms (cough and sputum) and more systemic or less specific symptoms (dyspnea, wheezing, and limitation of activities and energy) are equally distributed among symptomatic smokers, regardless of whether there is impairment in the FEV_1. Even though the CAT is meant to be specific for COPD,[11] most of its domains are rather nonspecific and may reflect concomitant respiratory diseases (asthma and bronchiectasis) and nonrespiratory diseases (heart failure, ischemic heart disease, obesity, and depression) that contribute to the multifaceted chronic diseases induced by smoking. Interestingly, chronic bronchitis, which was once considered to be one of two characteristic components of COPD (the other was emphysema), is present in a minority of smokers, which suggests that systemic symptoms, such as chest tightness, breathlessness, and limited energy, may be more representative of the broad effects of smoking.

Both studies[5,6] appropriately focused on the presence of a history of smoking as the main entry criterion, but the focus of both studies was the lung as the target organ and COPD as the primary disease to be investigated. The results suggest that smoking itself should be considered the disease and should be approached in all its complexity.[1,12] Since our treatment database was derived only from people with airflow obstruction, we should probably limit recommendations to the diagnosis and treatment of the spirometrically confirmed COPD that is defined according to current guidelines.[3] These new studies[5,6] help us define this new cohort of patients with chronic respiratory symptoms without obstruction. It is now up to us to figure out how to treat them in order to help reduce symptoms and prevent exacerbations.[3,4,12]

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From Dipartimento di Medicina Metabolica, Nuovo Ospedale Civile Sant'Agostino Estense, Azienda Unitá Sanitaria Locale di Modena, Azienda Ospedaliero–Universitaria Policlinico di Modena, Università degli Studi di Modena e Reggio Emilia, Modena, Italy.

1. The health consequences of smoking — 50 years of progress: a report of the Surgeon General. Atlanta: Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.
2. Hunter DJ, Reddy KS. Noncommunicable diseases. N Engl J Med 2013;369:1336-43.
3. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2016) (http://www.goldcopd.org).
4. Vanfleteren LE, Spruit MA, Groenen M, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;187:728-35.
5. Woodruff PG, Barr RG, Bleecker E, et al. Clinical significance of symptoms in smokers with preserved pulmonary function. N Engl J Med 2016;374:1811-21.
6. Regan EA, Lynch DA, Curran-Everett D, et al. Clinical and radiologic disease in smokers with normal spirometry. JAMA Intern Med 2015;175:1539-49.
7. Mead J. The lung's "quiet zone." N Engl J Med 1970;282:1318-9.
8. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251-9.
9. Mannino DM, Make BJ. Is it time to move beyond the "O" in early COPD? Eur Respir J 2015;46:1535-7.
10. Rennard SI, Drummond MB. Early chronic obstructive pulmonary disease: definition, assessment, and prevention. Lancet 2015;385:1778-88.
11. Karloh M, Mayer AF, Maurici R, Pizzichini MM, Jones PW, Pizzichini E. The COPD Assessment Test: what do we know so far? A systematic review and meta-analysis about clinical outcomes prediction and classification of patients into GOLD stages. Chest 2016;149:413-25.
12. Celli BR, Decramer M, Wedzicha JA, et al. An official American Thoracic Society/European Respiratory Society statement: research questions in COPD. Eur Respir J 2015;24:159-72.

DOI: 10.1056/NEJMe1515508