Are COPD and Lung Cancer Two Manifestations of the Same Disease?*

COPD and lung cancer loom as two of our greatest challenges in pulmonary medicine. Both are smoking-related diseases that cluster in families and worsen with age. COPD and lung cancer are often related to smoking and/or various occupational exposures, but this remarkable association remains yet to be better studied and explained.

The pathogenesis of COPD is currently being understood through intense studies originating from many laboratories. Mechanisms in the pathogenesis of lung cancer are also being aggressively approached concurrently. Are these really two diseases or two manifestations of the same disease with genetic predisposition, smoking, and environmental exposures as common denominators? This commentary explores the pathogenesis of COPD and lung cancer and considers common factors in the association between these two rising killers.

Considering their relationship, we might consider both COPD and lung cancer as genetically determined diseases that create a predisposition for personal and environmental insults that result in clinical expressions of both diseases. Smoking and occupational toxins, as well as community air pollution, may impose a series of accumulated and damaging mutations that ultimately inflame and destroy airways alveoli and also induce dysplastic and ultimately neoplastic changes in the lungs of patients with COPD and lung cancer. The exact mechanisms by which lung inflammation occurs and dysplastic changes are induced continue to be explored, and new theories are evolving.

In contrast to alveolar inflammation in the spectrum of interstitial lung diseases, alveolar damage in emphysema is apparently not a result of alveolitis. No fibrosis occurs in uncomplicated emphysema. Studies from Kasahara et al indicate that loss of alveolar walls is a consequence of loss of capillaries from reduced vascular endothelial growth factor (VEGF). The pulmonary capillary bed is comprised of the alveolar nutrient vessels. As capillaries drop out through accelerated apoptosis, so do alveolar walls. Thus, while the airway lesions are inflammatory in nature, the alveolar lesions might best be conceptualized as ischemic.

In moderate stages of COPD, VEGF may be involved in adverse pulmonary vascular responses resulting in pulmonary hypertension. However, in advanced emphysema, VEGF was found to be reduced in tissues obtained at resection for lung cancer or for lung volume reduction surgery.

Beyond the study of genetic background factors and environmental provocations and their resultant lesions, it is important to consider COPD as a systemic disease. Specific questions to be answered are why do individuals with only mild-to-moderate COPD have impaired exercise tolerance and inability to achieve a targeted heart rate, as well as failure to achieve targeted oxygen uptake? Could this exercise impairment already be due to emerging pul-
monary hypertension and right ventricular afterload in mild-to-moderate COPD. Mild-to-moderate COPD is usually not associated with hypoxemia, so perhaps other mechanisms are involved.

Since oxygen uptake indicates the sum of metabolic activities at the tissue level, these observations suggest impaired oxygen utilization. Perhaps poor oxygen utilization may be caused by inflammatory cytokines involved in COPD, and perhaps lung cancer that somehow are toxic to mitochondria and their ability to create energy through the metabolism of foodstuffs made possible by oxygen. The body wasting with weight loss and skeletal muscle atrophy are further manifestations of the systemic nature of COPD, but the mechanisms are unknown. Muscle wasting is common in symptomatic stages of lung cancer.

Centrilobular emphysema is primarily an upper-lobe destructive process. Why does lung cancer locate in the apices in smoking-related centrilobular emphysema? One hypothesis is that it may be due to the relative hypoxia of the apices. It is known that there are hypoxia-related genes that may promote angiogenesis. Evidence suggests that angiogenic dysplasia is a prelude to invasive carcinoma. Is VEGF the cause of angiogenic dysplasia that appears to be a precancerous lesion?

Today we need expanded research in both COPD and lung cancer, but we also need applied clinical research programs to improve patients now. The National Lung Health Education Program (NLHEP), as well as the Global Initiative in Chronic Obstructive Lung Disease (GOLD), promote the early identification and intervention in COPD and related disorders. The NLHEP has stimulated the production of simply new practical office spirometers, which have been validated in field testing. The NLHEP recommends that all smokers, both current and former ≥ 45 years old, should have simple spirometric testing. The GOLD classifies even with a normal absolute FEV1 percentage of 80%. The NLHEP recommends using the forced expiratory volume in 6 s as a surrogate for FVC.

What about steroids in COPD and in lung cancer? Controlled clinical trials do not show a reduction in the decline of FEV1. Other studies suggest a reduction in fall of FEV1 and even the possibility of reduced mortality is associated with the use of inhaled corticosteroids in COPD. Could budesonide also be effective in the chemoprevention of lung cancer? Can steroids and Cox-2 inhibitors be used in the chemoprevention of lung cancer?

Can industry produce a well-tolerated bronchodilator that can retard the rate of decline of FEV1 in COPD? Ipratropium was effective in the Lung Health Study throughout 5 years of observation, but it did not slow the rate of decline of FEV1. Perhaps the newly introduced anticholinergic, tiotropium, may be more effective in both physiologic improvement and control of symptoms, and in slowing of FEV1, decline over time. The slowing of lung function decline could also be a favorable factor in lung cancer prevention.

In summary, huge challenges in COPD and lung cancer exists for basic scientists applied scientists and clinicians. These can only be solved by well-organized and orchestrated collaborative efforts.

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Denver, CO

*Based on the Keynote Speech, Lovelace Respiratory Research Institute, Annual Scientific Meeting, Santa Fe, NM, October 10, 2003.

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Treatment for Secondary Pulmonary Hypertension

No therapy for idiopathic pulmonary fibrosis (IPF) has been proven to improve mortality or quality of life. However, like many diseases for which we now have cures, disease pathogenesis needed to be understood first before we could develop effective medications. Most of us have thought for a long time that pulmonary hypertension (PH) is a very bad marker of IPF severity. In this issue of CHEST (see page 2393), Nadrous et al report on the outcome of a large cohort of patients at the Mayo Clinic showing that PH has a significant correlation with mortality due to IPF. While not surprising, there is certainly a more positive spin to these data that needs to be explored.

The primary IPF symptom is dyspnea. Despite the fact that FVC remains the most robust correlate of IPF prognosis,2,3 the cause of exercise intolerance is not the associated limitation of exercise tidal volume. Instead, exercise intolerance is related more to cardiovascular limitations, including the oxygen desaturation associated with poor ventilation and perfusion matching.4 Maybe, if we cannot change ventilation, we should explore methods to change perfusion.

The pathogenesis of PH in IPF has not been comprehensively studied. Historically, the feeling has been that lung fibrosis also envelopes some of the vasculature. Therefore, the treatment of secondary PH is to reverse lung fibrosis. At this level of understanding, the refractoriness of secondary PH to vasodilators is no surprise.

In patients with IPF, areas of honeycomb lung at the lung bases that involve the pulmonary vasculature will transition pulmonary artery blood flow toward the lung apex, an area of the lung that is more rarely involved with fibrosis. As >50% of the vasculature is obliterated, pulmonary artery pressure will rise. The first possible detection of elevated pulmonary artery pressure will occur when exercise increases cardiac output through an increased pulmonary vascular resistance. Only later will resting echocardiography detect disease. Using this model, the height of systolic pulmonary artery pressure should mirror the extent of lung fibrosis.

However, in the case series by Nadrous et al, the correlation between FVC and pulmonary artery pressures as detected by echocardiography did not even reach statistical significance. The correlation with the diffusing capacity of the lung for carbon dioxide was present but not robust. If this is true, then we must redefine our understanding of PH in IPF patients. Some of this discordance may relate to cigarette smoking and falsely preserved FVC due to IPF. While not surprising, there is certainly a more positive spin to these data that needs to be explored.

We will continue to debate the issue of whether echocardiography is sufficiently accurate for the diagnosis of pulmonary arterial hypertension. In secondary PH, the debate is just as robust. In the Mayo Clinic series, the subgroup in which PH could not be estimated because of the lack of tricuspid regurgitation did not have the longest survival time. Therefore, should we advance to clinical trials, right