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Closing the Loop on the Vicious Circle in Chronic Obstructive Pulmonary Disease

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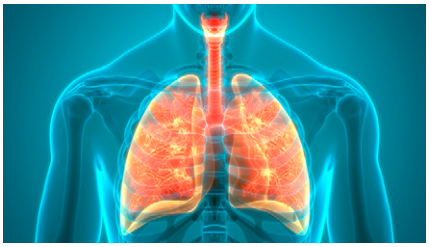

Yogi Berra said, "You can see a lot by just observing." When it comes to chronic human diseases that are difficult to replicate in animals and whose clinical courses span decades, for example, chronic obstructive pulmonary disease (COPD), well-planned and well-executed observational studies can yield important observations. Martínez-García and colleagues not only followed patients with COPD in their clinic but made standardized clinical and laboratory observations and then examined their accumulated data (1). This has already yielded seminal observations about the importance of bronchiectasis in patients with COPD (2). In this issue of *AnnalsATS* (pp. 1842–1847), the authors show that chronic bacterial infection (CBI), which was defined as three or more positive sputum cultures by the same potentially pathogenic microorganisms over 1 year, was associated with faster decline of lung function compared with individuals who did not have CBI (1). Furthermore, accelerated decline in forced expiratory volume in 1 second (FEV_1) was also seen among patients with at least one *Pseudomonas aeruginosa* (PA) isolation over the study period. In multivariable analysis, both the presence of CBI and at least one PA isolation during follow-up were independently associated with lung function decline.

A vicious cycle of inflammation and bacterial infection whereby each drives the other and causes airway damage was first described for bronchiectasis. Murphy and Sethi proposed in 1992 that a similar cycle could exist in COPD (Figure 1) (3). Since then, evidence supporting this hypothesis has been accumulating from various sources. Bronchoscopic sampling demonstrated that bacterial colonization in stable COPD was associated with neutrophilic airway inflammation (4). Increased daily symptoms and sputum interleukin-8 concentrations were found with bacterial presence in "stable" COPD (5). Pathological studies related progression of COPD to the development of airway germinal centers, and these could be replicated by repeatedly challenging a mouse airway with nontypeable *Haemophilus influenzae* (NTHI) (6, 7). The discovery of an abnormal abundant microbiome in the COPD lung that was dominated by Proteobacteria, a phylum that includes most of the well-known gram-negative respiratory pathogens, made it clear that the microbiome in the lung cannot be ignored (8). What was missing was the demonstration that this microbiome-driven inflammation was actually associated with lung damage, the standard measurement of which still remains FEV_1 decline. This study fills the gap and, despite its limitations, closes the vicious circle (1).

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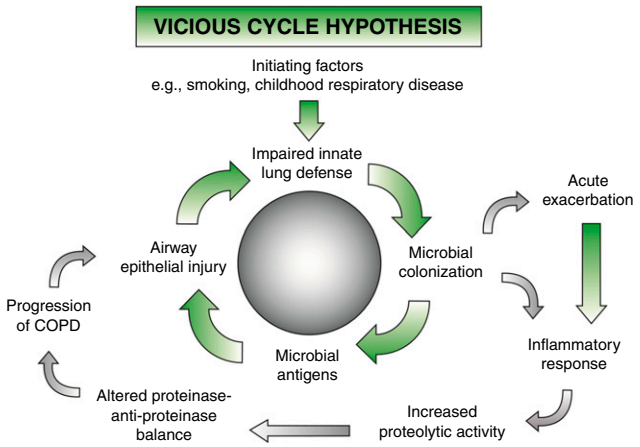

Figure 1. Vicious cycle hypothesis in COPD. COPD = chronic obstructive pulmonary disease.

With the emergence of readily applicable microbiome technologies, we have moved away from looking at individual pathogens. However, though the forest may be important, sentinel trees still stand out and cannot be ignored. In previous observations and in this study, these "trees" for COPD appear to be NTHI and PA (9). These pathogens appear very capable of establishing niches in unhealthy airways, as seen across a variety of lower airway diseases, including COPD, non–cystic fibrosis bronchiectasis, and cystic fibrosis. They induce inflammation in models of airway infection and cause acute infections in the respiratory tract. Martínez-García and colleagues (1) and previous work confirms the sentinel role of these pathogens in driving airway inflammation, which has the potential to cause airway damage and progression of lung disease, with NTHI appearing early and consistently and PA appearing later in some unlucky individuals.

Although PA has long been recognized as a potential pathogen in COPD, only recently have we begun to understand its role in clinical outcomes in this disease. An association between PA isolation and increased rates of exacerbation, hospitalization, and long-term mortality has been shown in many but not all studies (10–14). Faster FEV_1 decline with PA isolation as described in this study could be the pathophysiological link to worse clinical outcomes observed in other work.

Does inflammation related to CBI contribute to FEV_1 decline in all patients with COPD? Given the heterogeneity of COPD, that is unlikely. An infective COPD phenotype has emerged, with one or more of these features: chronic bronchitis, bronchiectasis on computed tomography, neutrophilic inflammation, low eosinophils, frequent exacerbations, and increased pneumonia predilection (especially with inhaled corticosteroid treatment). However, whether there are smaller but still significant contribution of microbiome-induced inflammation in the vast majority of individuals with COPD cannot be excluded. A closer examination of microbiome-driven inflammation in COPD across various phenotypes is needed.

Limitations of this study include a relatively small size and inconsistent sputum sampling. The observations are associations, mechanistic understanding is not provided, and causality must be inferred. Residual confounding by bronchiectasis, though it was included in the multivariable model, is still possible. Molecular detection of pathogens that are more sensitive, or microbiome techniques that are more comprehensive, was not applied. The definition of CBI is somewhat arbitrary. However, it is rather interesting how much significant and reproducible information has emerged in the past three decades from relatively small cohorts of patients with COPD in which careful systematic observations were conducted (2, 5, 15).

What are the clinical implications of this information? It does provide an impetus to identify individuals with COPD who exhibit the infective phenotype. But then what? How do we deal with the vicious circle? Antibiotics on a long-term or a regular intermittent basis, either orally or by inhalation, can suppress CBI and improve clinical outcomes, as has been shown in cystic fibrosis. More data are needed, especially for inhaled antibiotics in individuals with COPD, before this approach can be recommended. Should early eradication of PA in individuals with COPD be attempted, as is the practice in cystic fibrosis? How about dealing with inflammation and thus interrupting the cycle? This requires antiinflammatory agents that are not immunosuppressive and do not alter the microbiome in a negative manner. Unfortunately, corticosteroids, oral or inhaled, currently the most used antiinflammatory treatment in COPD, do exactly that. However, there is hope on the horizon with the new antiinflammatory drugs being developed for COPD, such as inhaled phosphodiesterase inhibitors and alarmin pathway blockers. It would be interesting to see what effects they have on the microbiome and whether interrupting inflammation is adequate to reduce microbial colonization and thus the impact of the vicious cycle. As our appreciation of the importance of the microbiome in COPD pathogenesis grows, it creates another avenue to address the progression of COPD. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Clearing Some of the Haze around E-cigarette or Vaping Product Use-Associated Lung Injury (EVALI)

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E-cigarette or vaping product use-associated lung injury (EVALI) is a severe pulmonary illness associated with the use of e-cigarettes or vaping products that was officially identified and named in 2019. From 2019–2020, The U.S. Centers for Disease Control and Prevention (CDC) reported 2,807 patients hospitalized with EVALI in the United States, and 68 died from their illness (1). Despite the thousands of individuals affected and the severity of the illness, follow-up with these individuals was relatively sparce, and we know little about the long-term consequences of EVALI. Only one retrospective study of similar size has been reported thus far on the 1-year outcomes of EVALI (2). In this issue of *AnnalsATS*, Blagev and colleagues (pp. 1892–1899) report the first prospective cohort study examining 1-year outcomes in patients with EVALI, which includes quantitative survey analysis of respiratory symptomology and mental health questionnaires (3). With such limited data reported thus far, the study by Blagev and colleagues is essential for our understanding of the long-term outcomes of EVALI.

It is especially important that we continue to elucidate the long-term consequences of EVALI as cases are still being reported and the numbers of those affected are still growing (2). Although EVALI has been primarily associated with individuals who vaped tetrahydrocannabinol-containing e-cigarettes that included the additive vitamin E acetate (VEA) (1), approximately 20% of patients reported using only nicotine e-cigarettes (4). Further, there have been sporadic cases of respiratory disease associated with e-cigarette use for years prior to the naming of EVALI and inclusion of VEA in e-cigarettes (5, 6). These cases highlight that EVALI remains an ongoing risk to e-cigarette users in the population and is a potential source for long-term illness.

In this study, Blagev and colleagues sought to determine the long-term respiratory, cognitive, mood disorder, and vaping behavior outcomes in patients suffering from an initial episode of EVALI. This study has many strengths, including patients who were prospectively enrolled from two health systems (University of Utah