associated with HIV infection. In work from our lab, we have seen a significant increase in the total virome burden in the lungs of asymptomatic HIV-infected individuals compared with healthy control subjects, with various herpes virus species being a major driver of this difference (unpublished results, H. Twigg III and colleagues), and we are in the process of linking the lung virome to local inflammation and evidence of lung disease.

Not all of the news is bad. In the article by Collini and colleagues, there is a strong positive association between the BAL CD4:CD8 ratio and the ability of alveolar macrophages to undergo apoptosis after pneumococcus exposure. This suggests that pulmonary immune reconstitution can return alveolar macrophage function toward normal. Furthermore, individuals with the greatest concentrations of gp120 in BAL had the lowest peripheral blood CD4 counts. In this regard, it is notable that the mean nadir peripheral blood CD4 count in the subjects on ART was 216 cells/mm³. This in fact is a potential limitation of the study by Collini and colleagues, as CD4 levels this low are not commonly encountered these days, when early treatment with ART is the standard for HIV-infected subjects (13). Thus, the subjects in the study by Collini and colleagues demonstrated a more profound immune defect at the time of HIV diagnosis, which is known to impact an individual's ability to recover normal immune function even in the presence of good viral control (14).

The longer we live, the more likely we are to acquire viruses, many of which are capable of establishing a latent or persistent infection. Any immunodeficiency can accelerate this process. Most clinicians are already cognizant that many viruses, once acquired, are almost impossible to eradicate, including herpes viruses and papilloma viruses. For now, until the NIH HIV Cure initiative reaches its goals, so is HIV. The inability to detect viruses in blood or tissues at any one time is not synonymous with cure. Successful approaches to curing viral infections will involve not only controlling active replication but also eradicating viral stores, wherever they may lie. Only in this way can we finally get rid of potentially pathologic viruses and their proteins, and hopefully along the way abrogate the chronic inflammation that leads to disease in both HIV-infected and aging populations. ■

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

Homer L. Twigg III, M.D.

Division of Pulmonary, Critical Care, Sleep, and Occupational Medicine
Indiana University Medical Center
Indianapolis, Indiana

ORCID ID: 0000-0002-0689-5867 (H.L.T.).

References

1. Grubb JR, Moorman AC, Baker RK, Masur H. The changing spectrum of pulmonary disease in patients with HIV infection on antiretroviral therapy. *AIDS* 2006;20:1095–1107.
2. van Sighem AI, Gras LA, Reiss P, Brinkman K, de Wolf F; ATHENA National Observational Cohort Study. Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. *AIDS* 2010;24:1527–1535.
3. Collini PJ, Bewley MA, Mohasin M, Marriott HM, Miller RF, Geretti A-M, et al. HIV gp120 in lungs of antiretroviral therapy-treated individuals impairs alveolar macrophage responses to pneumococci. *Am J Respir Crit Care Med* 2018;197:1604–1615.
4. Twigg III HL, Weiden M, Valentine F, Schnitzlein-Bick CT, Bassett R, Zheng L, et al.; AIDS Clinical Trials Group Protocol 723 Team. Effect of highly active antiretroviral therapy on viral burden in the lungs of HIV-infected subjects. *J Infect Dis* 2008;197:109–116.
5. Appay V, Sauce D. Immune activation and inflammation in HIV-1 infection: causes and consequences. *J Pathol* 2008;214:231–241.
6. Palella FJ Jr, Phair JP. Cardiovascular disease in HIV infection. *Curr Opin HIV AIDS* 2011;6:266–271.
7. Aberg JA. Aging, inflammation, and HIV infection. *Top Antivir Med* 2012;20:101–105.
8. Deeks SG, Verdin E, McCune JM. Immunosenescence and HIV. *Curr Opin Immunol* 2012;24:501–506.
9. Kahan SM, Wherry EJ, Zajac AJ. T cell exhaustion during persistent viral infections. *Virology* 2015;479–480:180–193.
10. Cadwell K. The virome in host health and disease. *Immunity* 2015;42:805–813.
11. Rezaee-Zavareh MS, Tohidi M, Sabouri A, Ramezani-Binabaj M, Sadeghi-Ghahrodi M, Einollahi B. Infectious and coronary artery disease. *ARYA Atheroscler* 2016;12:41–49.
12. Virgin HW, Wherry EJ, Ahmed R. Redefining chronic viral infection. *Cell* 2009;138:30–50.
13. Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, Sharma S, et al.; INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015;373:795–807.
14. McKinnon LR, Kimani M, Wachihi C, Nagelkerke NJ, Muriuki FK, Kariri A, et al. Effect of baseline HIV disease parameters on CD4+ T cell recovery after antiretroviral therapy initiation in Kenyan women. *PLoS One* 2010;5:e11434.

Copyright © 2018 by the American Thoracic Society

Generic Respiratory Symptoms and Branded Lung Diseases Same Difference?

From time immemorial, the learned have known that most things in the universe exist along a continuum. Lesser mortals and clinicians must contend with deviations from the normal arc, and consensus thresholds for normality and the diagnosis of disease.

Supported by NIH grant K23HL133438.

Originally Published in Press as DOI: 10.1164/rccm.201801-0191ED on February 8, 2018

In this issue of the *Journal*, Kalhan and colleagues (pp. 1616–1624) blur the boundaries of normal health and lung disease (1). There is a growing awareness that lung function later in life is substantially influenced by early life exposures, starting almost from the time of conception (2). Airway branching is complete in late pregnancy, and the branching pattern can significantly influence the likelihood of lung disease later in life (3). Airway caliber and function are influenced by early life exposures, and *in utero* exposures to environmental pollution, cigarette smoke, toxins, and stress have

been well documented to result in airway hyperresponsiveness, immunological impairments, and structural changes in the airways. Recent studies suggest that alveolar growth continues well into adulthood, and lung function appears to peak in most individuals at approximately 25 years of age. A combination of the peak achieved and the decline from this peak determines the overall deviation from the arc of optimal lung health.

Multiple cohort studies have documented several early-life risk factors with substantial effect sizes for lung function impairment and chronic obstructive pulmonary disease. These include *in utero* exposure to maternal smoking (3.4-fold for one pack of cigarettes a day) (4), parental asthma (2.5-fold), and childhood asthma (6- to 32-fold) (5, 6). Once peak lung function (optimal or suboptimal) is attained, established risk factors for a decline in lung function over and above the age-associated decline are few, and include cigarette smoking and environmental pollution. What drives the subclinical loss of lung function in some individuals in the absence of overt exposures is of great interest for investigators seeking to develop preventive strategies aimed at preserving lung health. Kalhan and colleagues hypothesized that persistent respiratory symptoms early in life, even in the setting of normal lung function, are associated with an accelerated decline in lung function (1). To test this hypothesis, they analyzed data from the CARDIA (Coronary Artery Risk Development in Young Adults) study, in which participants aged 18–30 years at enrollment underwent spirometry testing at baseline and every 5 years, and respiratory symptoms were ascertained annually for approximately 30 years. Computed tomography (CT) was performed at Year 25. They defined persistent respiratory symptoms by their presence at both baseline and Year 2. They found that the persistent presence of any respiratory symptom was associated with an additional 2.7 ml/year decline in FEV₁ and a 2.2 ml/year decline in FVC, as well as 1.6-fold greater odds of developing airflow obstruction, and 1.4-fold higher odds of showing restrictive spirometry at Year 30. They also reported a differential risk, in that cough-related symptoms were associated with greater risk of airflow obstruction and CT emphysema, and that dyspnea was associated with

spirometry suggestive of restriction. Although the greater decline in lung function in symptomatic individuals compared with those without symptoms has previously been documented (7, 8), the current study reports novel findings of accelerated lung function decline that are different for FEV₁ and FVC in cough- and dyspnea-predominant phenotypes, respectively. In contrast to multiple other studies, this study also assessed changes in airflow obstruction by estimating the decline in FEV₁/FVC.

Kalhan and colleagues raise important questions as to the significance of respiratory symptoms in the absence of a known chronic disease. Presumably, these symptoms did not represent major respiratory illnesses (e.g., pneumonia) that could result in significant structural damage. What, then, could be the mechanisms for the accelerated decline in the absence of overt persistent exposure? Episodes of bronchitis or mild parenchymal infections can result in structural damage with consequent mechanical effects (9). Airway inflammation can result in bronchiectasis or more subtle mucus clearance and hypersecretion issues (10). Mild respiratory infections can result in alterations in the lung microbiome, and the reduced complexity of the microbiome can result in persistent inflammation (11). Could atopy explain some of these persistent symptoms, given that atopy is associated with an accelerated decline in lung function (12)? Forty percent of the participants had respiratory symptoms at baseline and at Year 30. Misclassification bias, resulting in some cases of asthma being missed, might explain some of the findings. In individual patients, however, it is equally likely that mild respiratory infections result in a decrease in lung function that does not return to baseline, and these individuals then suffer an age-related decline. Exacerbation-like events in the setting of “normal” lung function are associated with an accelerated rate of lung function decline (13). Exacerbations of established disease are associated with a drop in lung function that does not return to baseline in a substantial proportion of patients even 3 months after an exacerbation, and in some patients, it is possible that it may not return to baseline at all (14). Further, exacerbations with

Figure 1. Two-continuum schema for lung health and lung disease. Individuals can be on different points along the spectrum of lung disease and lung health; the two are not on a single continuum. At any level of lung health that is not optimal, individuals do not function at optimal capacity and may have symptoms or signs of lung disease even if they do not fit a predefined label.

prolonged recovery are associated with a faster lung function decline (14). It is also possible that these persistent symptoms are a manifestation of the same early-life exposures that are risk factors for adult-onset chronic lung disease (15).

Several limitations of the study preclude definitive answers. For example, it is not known how chronic these persistent symptoms were, as they were ascertained at two time points with no information on symptom burden in the interim. In addition, the primary outcome of FEV₁ changes was treated as an annualized change between Years 5 and 30. This raises concerns as to whether the participants actually experienced an accelerated decline or simply a stepwise drop in lung function with acute respiratory events followed by a period of age-related decline. The authors tested generalized estimating equation models to account for repeated measures and showed that at a population level, persistent symptoms were associated with decline beyond that anticipated for aging, but the spirometry intervals were at least 5 years apart. The absolute decline in FEV₁, although statistically significant, is of unclear clinical significance. Over 25 years, an excess decline of 2.7 ml/year translates into an absolute decrease of 68 ml. The authors address this partially by demonstrating a greater risk for obstructive and restrictive spirometry, as well as parenchymal disease on CT, but the magnitude of decline is not commensurate with the occurrence of disease. Smoking status was ascertained at baseline, but the cumulative pack-years of smoking burden were not accounted for in the assessment of the odds of incident disease. Indeed, a substantial proportion of the subjects who reported symptoms at baseline were active smokers. Approximately 29% of the participants were lost to follow-up at Year 30, and those lost to follow-up had greater respiratory symptoms at baseline.

Despite these limitations, this study is a strong reminder that health is more than the mere absence of disease, and that we should not ignore persistent symptoms in early life even in the presence of “normal” lung function. Unfortunately, clinicians typically pay scant attention to early life exposures (16). As previously noted by Keyes, health and illness are not opposite ends of the same continuum, and measures of health correlate modestly with measures of disease (17). The absence of disease does not always equate to healthy lungs, and a deviation from normal does not always equate to lung disease. Perhaps health and disease exist on parallel continuums. Figure 1 shows a two-continuum model of lung health and lung disease. At times, we may be ill-served by thresholds and labels, and should change our perspective to evaluating patients on a continuum to enable better lung health practices. This is akin to the continuum of coronary atherosclerosis that has not been labeled as a significant coronary artery disease but is still important and modifiable. Preserving lung health involves a combination of a number of existing interventions, such as avoiding certain environmental exposures and cigarette smoke, early and adequate treatment of atopy and asthma, and vaccination against seasonal influenza, as well as the development of novel interventions. It is easy to ascertain respiratory symptoms in clinical practice, and such symptoms should be considered risk factors for the loss of lung health and for future lung disease. ■

Surya P. Bhatt, M.D.

Division of Pulmonary, Allergy and Critical Care Medicine
UAB Lung Imaging Core
and
UAB Lung Health Center
University of Alabama at Birmingham
Birmingham, Alabama

ORCID ID: 0000-0002-8418-4497 (S.P.B.).

References

1. Kalhan R, Dransfield MT, Colangelo LA, Cuttica MJ, Jacobs DR Jr, Thyagarajan B, et al. Respiratory symptoms in young adults and future lung disease: the CARDIA Lung Study. *Am J Respir Crit Care Med* 2018;197:1616–1624.
2. Bush A. Lung development and aging. *Ann Am Thorac Soc* 2016;13:S438–S446.
3. Smith BM, Traboulsi H, Austin JHM, Manichaikul A, Hoffman EA, Bleecker ER, et al.; MESA Lung and SPIROMICS Investigators. Human airway branch variation and chronic obstructive pulmonary disease. *Proc Natl Acad Sci USA* 2018;115:E974–E981.
4. Upton MN, Smith GD, McConnachie A, Hart CL, Watt GC. Maternal and personal cigarette smoking synergize to increase airflow limitation in adults. *Am J Respir Crit Care Med* 2004;169:479–487.
5. Tagiyeva N, Devereux G, Fielding S, Turner S, Douglas G. Outcomes of childhood asthma and wheezy bronchitis: a 50-year cohort study. *Am J Respir Crit Care Med* 2016;193:23–30.
6. Tai A, Tran H, Roberts M, Clarke N, Wilson J, Robertson CF. The association between childhood asthma and adult chronic obstructive pulmonary disease. *Thorax* 2014;69:805–810.
7. Lindberg A, Larsson LG, Rönmark E, Jonsson AC, Larsson K, Lundbäck B. Decline in FEV₁ in relation to incident chronic obstructive pulmonary disease in a cohort with respiratory symptoms. *COPD* 2007;4:5–13.
8. de Marco R, Accordini S, Cerveri I, Corsico A, Antó JM, Künzli N, et al. Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. *Am J Respir Crit Care Med* 2007;175:32–39.
9. Bhatt SP, Bodduluri S, Hoffman EA, Newell JD Jr, Sieren JC, Dransfield MT, et al.; COPDGene Investigators. Computed tomography measure of lung at risk and lung function decline in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2017;196:569–576.
10. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. The presence of chronic mucus hypersecretion across adult life in relation to chronic obstructive pulmonary disease development. *Am J Respir Crit Care Med* 2016;193:662–672.
11. Mammen MJ, Sethi S. COPD and the microbiome. *Respirology* 2016;21:590–599.
12. Tracey M, Villar A, Dow L, Coggon D, Lampe FC, Holgate ST. The influence of increased bronchial responsiveness, atopy, and serum IgE on decline in FEV₁: a longitudinal study in the elderly. *Am J Respir Crit Care Med* 1995;151:656–662.
13. Dransfield MT, Kunisaki KM, Strand MJ, Anzueto A, Bhatt SP, Bowler RP, et al.; COPDGene Investigators. Acute exacerbations and lung function loss in smokers with and without chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2017;195:324–330.
14. Donaldson GC, Law M, Kowlessar B, Singh R, Brill SE, Allinson JP, et al. Impact of prolonged exacerbation recovery in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2015;192:943–950.
15. Svanes C, Omenaas E, Jarvis D, Chinn S, Gulsvik A, Burney P. Parental smoking in childhood and adult obstructive lung disease: results from the European Community Respiratory Health Survey. *Thorax* 2004;59:295–302.
16. Bolton CE, Bush A, Hurst JR, Kotecha S, McGarvey L, Stocks J, et al. Are early life factors considered when managing respiratory disease? A British Thoracic Society survey of current practice. *Thorax* 2012;67:1110.
17. Keyes CL. The mental health continuum: from languishing to flourishing in life. *J Health Soc Behav* 2002;43:207–222.

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

Copyright © 2018 by the American Thoracic Society