the role of platelets and of platelet-derived chemokines during respiratory infections is currently an understudied area.

The novel findings of Han and colleagues provide intriguing early insights into the possible roles of CXCL4 in RSV bronchiolitis and open new and tantalizing avenues of research. Additionally, the initial gain-of-function experiments identified a further 48 host factors that exhibited suppression of RSV replication. Powerful techniques such as those deployed by Han and colleagues are set to reveal the role of other host factors and to provide additional insights to the biology of viral infections and potential therapeutic strategies. ■

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

Dexter J. Wiseman, M.D.
Ryan S. Thwaites, Ph.D.
Peter J. M. Openshaw, M.D., Ph.D., F.R.C.P., F.Med.Sci.
National Heart and Lung Institute
Imperial College London
London, United Kingdom

ORCID IDs: 0000-0003-3052-2793 (R.S.T.); 0000-0002-7220-2555 (P.J.M.O.).

References

1. Coultas JA, Smyth R, Openshaw PJ. Respiratory syncytial virus (RSV): a scourge from infancy to old age. *Thorax* 2019;74:986–993.
2. Wilkinson TM, Donaldson GC, Johnston SL, Openshaw PJ, Wedzicha JA. Respiratory syncytial virus, airway inflammation, and FEV1 decline in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;173:871–876.
3. Mazur NI, Higgins D, Nunes MC, Melero JA, Langedijk AC, Horsley N, *et al*.; Respiratory Syncytial Virus Network (ReSViNET) Foundation. The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates. *Lancet Infect Dis* 2018;18: e295–e311. [Published erratum appears in *Lancet Infect Dis* 18:941.]
4. Amand C, Tong S, Kieffer A, Kyaw MH. Healthcare resource use and economic burden attributable to respiratory syncytial virus in the United States: a claims database analysis. *BMC Health Serv Res* 2018;18:294.
5. Han Z, Rao J, Xie Z, Wang C, Xu B, Qian S, *et al*. Chemokine (C-X-C motif) ligand 4 is a restrictor of respiratory syncytial virus infection and an indicator of clinical severity. *Am J Respir Crit Care Med* 2020;202: 717–729.
6. Auerbach DJ, Lin Y, Miao H, Cimbro R, Difiore MJ, Gianolini ME, *et al*. Identification of the platelet-derived chemokine CXCL4/PF-4 as a broad-spectrum HIV-1 inhibitor. *Proc Natl Acad Sci USA* 2012;109:9569–9574.
7. Guo L, Feng K, Wang YC, Mei JJ, Ning RT, Zheng HW, *et al*. Critical role of CXCL4 in the lung pathogenesis of influenza (H1N1) respiratory infection. *Mucosal Immunol* 2017;10:1529–1541.
8. Battles MB, McLellan JS. Respiratory syncytial virus entry and how to block it. *Nat Rev Microbiol* 2019;17:233–245.
9. Ngwuta JO, Chen M, Modjarrad K, Joyce MG, Kanekiyo M, Kumar A, *et al*. Prefusion F-specific antibodies determine the magnitude of RSV neutralizing activity in human sera. *Sci Transl Med* 2015;7: 309ra162.
10. Marcandalli J, Fiala B, Ols S, Perotti M, de van der Schueren W, Snijder J, *et al*. Induction of potent neutralizing antibody responses by a designed protein nanoparticle vaccine for respiratory syncytial virus. *Cell* 2019;176:1420–1431, e17.
11. Donalisio M, Rusnati M, Cagno V, Civra A, Bugatti A, Giuliani A, *et al*. Inhibition of human respiratory syncytial virus infectivity by a dendrimeric heparan sulfate-binding peptide. *Antimicrob Agents Chemother* 2012;56:5278–5288.
12. Lefrançais E, Ortiz-Muñoz G, Caudrillier A, Mallavia B, Liu F, Sayah DM, *et al*. The lung is a site of platelet biogenesis and a reservoir for haematopoietic progenitors. *Nature* 2017;544: 105–109.
13. Fox JM, Kausar F, Day A, Osborne M, Hussain K, Mueller A, *et al*. CXCL4/Platelet Factor 4 is an agonist of CCR1 and drives human monocyte migration. *Sci Rep* 2018;8:9466.
14. Thwaites RS, Coates M, Ito K, Ghazaly M, Feather C, Abdulla F, *et al*. Reduced nasal viral load and IFN responses in infants with respiratory syncytial virus bronchiolitis and respiratory failure. *Am J Respir Crit Care Med* 2018;198:1074–1084.

Defining Airflow Obstruction: More Data, Further Clarity

Journals do not normally write editorials about letters. Of course, some letters merit attention being drawn to them. When Watson and Crick wrote a letter to *Nature* in 1953 proposing a new structure for deoxyribose nucleic acid (1), they changed the world and, ultimately, clinical practice. Their letter was really a scientific paper rather than normal correspondence, but research letters can make important contributions to our understanding, which is why this Journal accepts them. A good example of this process is the letter in this issue of the *Journal* by Neder and colleagues (pp. 760–762), which contributes to the continuing debate about how to interpret the FEV_1/FVC ratio when diagnosing chronic obstructive pulmonary disease (COPD) (2). Before considering their findings, it is worthwhile remembering how this debate began and why it is more important than simple semantics.

Since the 1950s, when the FEV_1/FVC ratio was first described, respiratory physiologists have empirically used a value of 0.7 to define airflow obstruction, as it related well to other more invasive physiological measurements of airflow limitation in patients. This convention was followed when the Global Initiative in Chronic Obstructive Lung Disease incorporated spirometry into their definition of COPD and has remained so since (3).There was a general awareness that the ratio declined with age in apparently healthy people, a point highlighted in a study of older Norwegians (4), which was one of the first to point out the implications of this change for the diagnosis of COPD. Subsequently, the Global Lung Function Initiative developed values for the lower limit of normal (LLN) of the ratio, which meant that many older people with ratios below 0.7 would be considered healthy, and, if

Originally Published in Press as DOI: 10.1164/rccm.202005-1551ED on May 13, 2020

symptomatic, their problems would be attributed to other conditions. This distinction is at the heart of this debate about definitions. Proponents of the LLN approach believe that abnormal values are those that fall outside the range seen among healthy people, whereas advocates of the fixed ratio believe that delayed lung emptying is abnormal regardless of the age at which it occurs. Here, the example of hypertension is instructive. When I graduated, a systolic blood pressure of 160 mm Hg in a man of 70 was considered "normal aging," but treatment intervention studies have shown that clinical outcomes can be improved by bringing systolic pressure down to a more "physiological" range. Hence, definitions have consequences.

Many studies have tried to address this conundrum. Population data have shown that the outcomes for patients with a reduced fixed ratio that was within the LLN (discordant values) were little different from those with a fixed value above 0.7 (5). *Post hoc* analysis of large populations recruited to a clinical trial because they had symptoms and a fixed ratio below 0.7 found that patients discordant for the diagnosis of COPD using LLN criteria were somewhat more likely to report cardiovascular comorbidity but were as likely as other participants to die during follow up (6). More recently, a study of over 24,000 people found that hospitalization and death were more common in discordant patients than in those with a ratio above the LLN and 0.7, and it identified 0.7 as the fixed value with the best discrimination of outcomes (7).

The data reported by Neder and colleagues add to that approach. Like Bhatt and colleagues (7), they sampled a general population and studied 715 tobacco-exposed people: 323 with normal values by LLN and fixed definitions, 134 with discordant values, and 258 in whom both metrics were abnormal. As expected, the discordant individuals were older, were more likely to be male, and reported more cardiovascular comorbidity than the healthy concordant group. This investigation focused on the differences in lung mechanics and exercise performance between these groups. Table 1 of their paper shows a gradation in the degree of absolute abnormality of FEV_1/FVC across the three groups, which is paralleled by increases in residual volume and falls in D_{LCO}. Interestingly, the degree of ventilatory inefficiency and peak work rate were reduced to a similar degree in the discordant and concordant obstructed groups, whereas more patients in each group were limited by breathlessness rather than leg fatigue compared with concordant unobstructed subjects. This helps explain why the discordant obstructed group reported a higher Medical Research Council grade than the unobstructed concordant subjects.

Inevitably, the reader craves more information. It would have been helpful to have quantitative computed tomography data in the discordant patients and more data about the functional impact of the cardiovascular comorbidities. Likewise, data on the exercise performance of those not reporting cardiac problems in each group would have been of interest. Given that these investigators have led the way in our understanding of dynamic hyperinflation in COPD even in those with mild airflow obstruction, data about this variable would be of considerable interest. The letter format makes it impractical to explore the data in such detail, but future investigators should purse these avenues to better characterize what is likely to be a heterogeneous subgroup of people.

The work described in this letter compliments that of large longer studies (7), and together, they suggest that an abnormal fixed ratio does identify people at risk for both physiological and clinical problems. However, the specificity of any of these indices in those on the borderline between health and disease remains uncertain. This has led to a series of investigators analyzing data from COPDGene to propose a new definition of COPD by incorporating computed tomography variables that are abnormal before either the LLN or fixed ratio change (8). How easily this approach translates to the clinical arena remains to be seen (9). As Neder and colleagues suggest, a more holistic approach looking at both physiological and clinical abnormalities when attributing a diagnostic label to people with borderline spirometric abnormality is required. In the future, studies directed to this not inconsiderable subgroup of people are needed to determine whether other interventions, especially pharmacological ones, are of value. ■

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

Peter M. A. Calverley, M.B. Ch.B.*
University Hospital Aintree
Liverpool, United Kingdom

ORCID ID: 0000-0003-4676-9993 (P.M.A.C.).

*P.M.A.C. is Associate Editor of *AJRCCM*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

References

1. Watson JD, Crick FH. Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. *Nature* 1953;171:737–738.
2. Neder JA, Milne KM, Berton DC, de-Torres JP, O'Donnell DE; CRRN; CanCOLD Collaborative Research Group. Exercise tolerance according to the definition of airflow obstruction in smokers [letter]. *Am J Respir Crit Care Med* 2020;202:760–762.
3. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. *Am J Respir Crit Care Med* 2017;195: 557–582.
4. Hardie JA, Buist AS, Vollmer WM, Ellingsen I, Bakke PS, Mørkve O. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. *Eur Respir J* 2002;20:1117–1122.
5. Vaz Fragoso CA, Concato J, McAvay G, Van Ness PH, Rochester CL, Yaggi HK, *et al*. The ratio of FEV1 to FVC as a basis for establishing chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010;181:446–451.
6. Calverley PMA, Mueller A, Fowler A, Metzdorf N, Wise RA. The effect of defining chronic obstructive pulmonary disease by the lower limit of normal of FEV_1/FVC ratio in tiotropium safety and performance in respimat participants. *Ann Am Thorac Soc* 2018;15:200–208.
7. Bhatt SP, Balte PP, Schwartz JE, Cassano PA, Couper D, Jacobs DR Jr, *et al*. Discriminative accuracy of FEV1:FVC thresholds for COPD-related hospitalization and mortality. *JAMA* 2019;321:2438–2447.
8. Lowe KE, Regan EA, Anzueto A, Austin E, Austin JHM, Beaty TH, *et al*. COPDGene® 2019: redefining the diagnosis of chronic obstructive pulmonary disease. *Chronic Obstr Pulm Dis (Miami)* 2019;6: 384–399.
9. Barnes PJ, Vestbo J, Calverley PM. The pressing need to redefine "COPD". *Chronic Obstr Pulm Dis (Miami)* 2019;6:380–383.