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Reply to Sohal

From the Authors:

We thank Dr. Sohal for his interest in our study. The airway epithelium is the lung's first line of defense against infectious and noninfectious environmental assaults. Once injury occurs, the airway epithelium must retain a robust capacity for self-repair so that normal structure and function can be maintained. Airway basal progenitor cells are one of the most important factors in normal repair because they can renew themselves, proliferate, and differentiate into all epithelial cell types that make up a normal airway. In other words, airway resilience depends heavily on a healthy basal progenitor population. Because the airway epithelium is not able to restore itself to normal structure and function in chronic obstructive pulmonary disease (COPD), we hypothesized that airway basal progenitor cells are dysfunctional. Consistent with this hypothesis, our study showed that basal progenitors in COPD are exhausted, and that loss of progenitors identifies a subset of subjects without COPD but with lung function that is intermediate between that of subjects with COPD and subjects without COPD but with high progenitor numbers. We concluded that progenitor exhaustion is involved in COPD pathogenesis (1).

Dr. Sohal suggested that epithelial-mesenchymal transition (EMT) could be a mechanism responsible for airway basal progenitor exhaustion. Classically, EMT is defined as a biological process in which polarized epithelial cells assume a

mesenchymal phenotype that includes an enhanced migratory capacity, invasiveness, resistance to apoptosis, and increased production of extracellular matrix components (2). Since its first recognition by Hay as a transient process involved in cancer metastasis (3, 4), EMT and its impact on pathological processes have become controversial. In contrast, the concept of epithelial plasticity, where epithelial cells transiently express mesenchymal markers during repair, has found a broader acceptance (5, 6). The presence of EMT-like changes in COPD epithelia has been reported by many groups, and in most cases such changes have been implicated as a process that is associated with aberrant repair (7–10). Induction of EMT was also observed *in vitro* when basal cells were treated with epithelial growth factor during air-liquid interface culture (11). Because this study was performed with unselected basal cells, the question of whether basal progenitors undergo such a change remains open. Both our study (1) and a recent study of basal progenitors in obliterative bronchiolitis (12) showed that functional and phenotypic subsets are present within the basal cell population in human airways. Basal progenitors are identified by their function because they are indistinguishable from nonprogenitor basal cells in terms of location and morphology. Thus, EMT-like changes may contribute to airway remodeling in COPD, but attributing EMT to basal progenitor exhaustion, while possible, is hypothetical and would require further research. Likewise, irrespective of any effect on EMT, inhaled corticosteroids will likely continue to have a limited role in established COPD (13) because they do not decrease the long-term decline in lung function or improve mortality in COPD (14). Similarly, a role for inhaled corticosteroids in lung cancer chemoprevention remains speculative (15). Whether inhaled corticosteroids will have a different effect on early, prediagnostic forms of COPD remains to be seen. ■

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Diagnostic Decision-Making in Hypersensitivity Pneumonitis: Toward a Consensus Statement

To the Editor:

I read with great interest the recently published perspectives on hypersensitivity pneumonitis (HP) by Salisbury and colleagues (1) and Vasakova and colleagues (2) summarizing the scientific knowledge accumulated on this topic over the past century. On the basis of this information, they both provide recommendations

for diagnosis, classification, and management, highlighting areas of uncertainty that require further investigation.

Currently, given the array of HP clinical phenotypes and the elusiveness of the inciting antigen in many cases, diagnostic certainty is often difficult to obtain. Even experienced physicians who practice in areas of high disease prevalence can be confounded when HP is in the differential (3). All too frequent and mystifying are scenarios with discordance between the chest imaging and pulmonary histology or, despite exhaustive investigation, an inciting antigen is never found or there is a lack of temporal agreement between the exposure and clinically apparent disease, or the disease progresses despite active therapy and apparent lack of exposure to the relevant antigen (4).

Over the last 3 decades, an extensive collection of HP reviews, classifications, and algorithms have been generated, but despite all of these, there is no clear consensus around diagnostic criteria when there is any deviation from the classic case. To date, all HP diagnostic and classification criteria integrate an exposure history with other clinical, chest imaging, immunological, and pathological data. As highlighted in the two perspectives, several years ago, two principles were established: 1) a presumptive diagnosis of HP can be made without identification of an exposure (5), and 2) most HP cases fit a two-cluster model, namely acute or chronic HP (6). However, given the clinical nuances of HP, this model is probably far too simplistic.

Although the perspectives by Salisbury and colleagues (1) and Vasakova and colleagues (2) are clearly complementary, they do not completely align on the issue of classifying the likelihood of disease. Improving understanding of HP, and thus moving the field, will require systematically designed investigation via a multicenter approach. That can occur only if there is agreement around diagnostic criteria and ultimately a framework for categorizing diagnostic certainty. Vital components that require integration include a definition for “adequate/exhaustive investigation” for the inciting antigen, how and by whom that investigation should happen, and what abatement/remediation efforts must entail. Moreover, “some birds are not meant to be caged,” and I advise extreme caution when using terms such as “cryptogenic,” given what we know about the pathobiology of HP and the critical importance of but sometimes-overlooked need for persistent search, identification, and abatement of the inciting antigen.

Support from a major society is critical to accomplishing these necessary first steps. In 2017, a multispecialty task force of international experts under the direction of the American College of Chest Physicians was assembled and has been actively engaged in the making of a multidisciplinary consensus statement to provide evidence-based recommendations for the diagnosis of HP. I applaud the American College of Chest Physicians for sponsoring ongoing efforts to develop the first-ever evidence-based international consensus guidelines on the diagnosis and classification of HP. Having these in place (and implemented) will promote between-study comparisons and integration of results across studies and facilitate essential multicenter research into the prevention, diagnosis, and management of this vexing problem. ■

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