

## CORRESPONDENCE

## Muco-Obstructive Lung Diseases

**TO THE EDITOR:** The review article by Boucher (May 16 issue)<sup>1</sup> does not include a discussion of asthma as a muco-obstructive lung disease. In a subgroup of patients with asthma, clinically significant mucus plugging is detected on high-resolution computed tomographic imaging. This condition is characterized clinically by severe airflow obstruction and a lack of response to both bronchodilators and systemic glucocorticoids.<sup>2</sup> Mucus-derived obstruction is an important asthma phenotype because it may predict more persistent obstruction than that which is usually encountered and involve a treatment approach that is similar to that for other muco-obstructive diseases.

Furthermore, overall mucin concentrations have been found to be higher both in patients with stable asthma and in those with asthma exacerbations than in healthy persons, although the predominant mucin in patients with asthma is MUC5AC,<sup>3</sup> and goblet-cell hyperplasia has been associated with neutrophilic asthma, which shares many similarities with chronic obstructive pulmonary disease (COPD).<sup>4</sup> Finally, hypertonic saline, which is frequently used in patients with other muco-obstructive lung diseases, has been shown to increase ciliary clearance in patients with asthma and is an underused therapy in this population.<sup>5</sup>

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**TO THE EDITOR:** Boucher analyzes mechanistic routes that contribute to the pathogenesis of muco-obstructive lung diseases, including direct biophysical effects and downstream consequences of hypoxia-mediated modifications to the microbiota. The posited muco-inflammatory cycle resulting from cytokine release by hypoxic, activated macrophages is noted, but recent research findings indicate that a more multifaceted model of immune, inflammatory modulation in a high-mucin environment is warranted.<sup>1,2</sup>

Mucin hypersecretion not only causes release of proinflammatory cytokines but, in the vicious cycle of the inflamed lung, is also a consequence of inflammatory cytokine release. Overexpression of interleukin-8 in the lung causes dramatic upregulation of MUC5AC and MUC5B and changes to innate and adaptive immune programs that both combat infection and drive lung remodeling with damage to epithelial tight junctions.<sup>2</sup> Furthermore, local mucins modulate the function of dendritic cells, including the set point of proinflammatory or antiinflammatory mucosal immune recognition of microbiota species.<sup>3</sup> We think that this aspect of immune programming for lung host defense, including changes to antigen recognition of bacterial pathogens observed in patients with chronic lung diseases such as COPD and bronchiectasis, is important in understanding muco-obstructive diseases.<sup>1,2,4</sup>

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**THE AUTHOR REPLIES:** Most is correct that asthma can have characteristics of muco-obstruction. However, asthma was not included in my article because of missing information and differences in pathogenesis and phenotypes. First, unfortunately, data on mucus concentrations (particularly total mucin concentrations) in patients with asthma are lacking. Second, subgroups of patients with asthma who have mucus plugging typically have type 2 helper T (Th2) cell–high, MUC5AC-dominant phenotypes. In contrast, the muco-obstructive phenotype is dominated by MUC5B, which is regulated by type 17 helper T cells and interleukin-1.<sup>1</sup> Also, most patients with muco-obstructive diseases have persistent and high-density bacterial infection with staphylococcus, *Haemophilus influenzae*, and, ultimately, pseudomonas; these infections are not typically associated with asthma.

We do need a better name than “muco-obstructive lung diseases.” The initial goal with the use of that term was to better group diseases that are not adequately described by the term “chronic bronchitis.” The term “suppurative muco-obstructive disease” might be preferred if it is agreed that intense eosinophil-dominant inflammation is not suppurative. “MUC5B-dominant muco-obstructive disease” is an option, but data are not yet available to indicate whether this name distinguishes mild asthma, Th2-low asthma, or both from the diseases described in the article.

Finally, hypertonic saline may indeed be a useful therapy for asthma. If mucus in a patient with asthma proves to be hyperconcentrated,

and hyperreactivity of the airways is not problematic, as suggested by Alexis et al.,<sup>2</sup> clinical trials of hypertonic saline are warranted.

Boyton and Altmann are correct that muco-obstructive positive-feedback cycles involve not only the pathways described in my article but, indeed, many more pathways.<sup>1</sup> However, the intent of Figure 3 of the article was not to be inclusive but to highlight two key aspects of the pathogenesis of this complex disease. First, an imbalance between mucin secretion and fluid secretion is central to persistent muco-obstruction. Airway epithelia that respond to proinflammatory stimuli with mucin secretion but inadequate fluid secretion will have increased mucus concentrations and accumulation on airway surfaces. Accordingly, it may be useful in the future to assess the effects of inflammatory pathways in airway epithelia that have this phenotype.

Second, inflammation of the airways often occurs in hypoxic environments. Given the high partial pressure of oxygen in airway lumens, it may seem counterintuitive that inflammation and infection of airway mucus may be manifest in a hypoxic environment. However, because airway epithelia normally obtain oxygen from the lumen, the long diffusion distances imparted by mucus plaques render both plaques and airway epithelia hypoxic. Thus, future studies of inflammatory pathways might benefit from performance under hypoxic and normoxic conditions.

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Since publication of his article, the author reports no further potential conflict of interest.

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