Happy Birthday, Bronchiectasis: 200 Years of Targeting Mucus

The year 2019 marked a birthday of sorts for the field of bronchiectasis. The disease was first described 200 years ago, in 1819, by the French physician and inventor of the stethoscope, René-Théophile-Hyacinthe Laënnec, in his book "Traité de l'Auscultation Médiate," which was then translated over the next 2 years into the English version, "A Treatise on the Diseases of the Chest and on Mediate Auscultation" (1).

Age brings wisdom, but the move toward maturity in the field of bronchiectasis has been slow, held back by a perception that the disease is mild, unimportant, or too heterogeneous to tackle. Recent years have seen major advances in our understanding of bronchiectasis, with mounting evidence regarding the effectiveness of therapies such as macrolides and inhaled antibiotics, and increasing research into the underlying biology (2). The components of the classical vicious cycle are infection, inflammation, impaired mucociliary clearance, and structural lung damage. It is notable that for all of the progress we have made in the past 10 years, research and therapeutic development have been largely concentrated in the areas of infection and inflammation (3, 4).

A reading of Laënnec's original description of bronchiectasis reminds us that mucus is, in many ways, the central feature of bronchiectasis, or as he wrote, "the dilatation of the bronchi is only met with in cases of chronic mucous catarrh. This single fact, coupled with what we know respecting the long continuance of mucous sputa in the spot where they have been secreted, enables us to conceive the mode in which the disease is formed—a temporary dilatation produced by voluminous sputum, is rendered permanent by the constant and successive secretion" (1).

It is remarkable, therefore, how little research during the renaissance of bronchiectasis has focused on the role of mucus and mucociliary clearance. The study by Ramsey and colleagues (pp. 661–670) published in this issue of the *Journal* is thus a timely and important contribution (5).

Mucus is a protective coating that is secreted in healthy airways and is composed of water, salt, and proteins. The correct balance of these components is essential for the protective function of the mucus layer. Among the proteins, mucins are the major macromolecular component of the mucus gel in health. They are glycoproteins that are responsible for the protective and clearance properties of mucus (6). Several mucins have been described in the lower respiratory tract of healthy subjects, with MUC5AC and MUC5B being the most frequent (7). A dysregulation of mucin secretion has been described in chronic inflammatory airway diseases such as chronic obstructive pulmonary disease (COPD) (7) and cystic fibrosis (8).

Ramsey and colleagues now characterize in detail the role of mucins in bronchiectasis. In their study they used samples from the BLESS (Bronchiectasis and Low-Dose Erythromycin Study) cohort, which is a well-studied, randomized controlled trial cohort that was originally used to evaluate the efficacy and safety of erythromycin (3), and healthy control subjects. Using a comprehensive array of analytical techniques, the authors demonstrated that compared with samples from healthy subjects, sputum from patients with bronchiectasis had a higher percentage of solids, a higher DNA content, elevated total and individual mucin expression, and increased viscosity, elasticity, and mucus osmotic pressure. Together, these features suggest that, as in COPD and cystic fibrosis, mucus is hyperconcentrated in bronchiectasis.

MUC5B was the predominant mucin that was increased in the sputum, followed by MUC5AC and MUC2. This is in contrast to our pilot study of 50 patients, in which we found a correlation between mucin concentrations and disease severity, but no detectable levels of MUC5B (9). This discrepancy is likely explained by the use of different types of samples (ultracentrifuged supernatant vs. whole sputum) and the fact that we used ELISA to detect mucin, whereas Ramsey and colleagues used the gold-standard liquid chromatography/mass spectrometry method.

The comprehensive assessment of mucins by Ramsey and colleagues was then complemented by immunohistochemistry staining of bronchial biopsies and evaluation of gene expression. No differences were identified in the idiopathic pulmonary fibrosis–associated MUC5B promoter polymorphism between patients with bronchiectasis and control subjects.

The authors' ability to demonstrate a relationship between mucins and disease severity in this cohort was limited by their use of the BLESS study, which enrolled patients with two or more exacerbations per year to enrich for patients likely to benefit from macrolide therapy (3). Nevertheless, they did show that the extent of radiological bronchiectasis was related to the percentage of solids and osmotic pressure. Interestingly, there was no meaningful relationship between any mucus properties and FEV_1% predicted, adding to a body of literature showing that FEV_1 has limited value as a marker of bronchiectasis disease activity, being heavily influenced by smoking and coexisting airways disease (10). *Pseudomonas aeruginosa* infection is clearly associated with worse outcomes in bronchiectasis, but mucus parameters in this study were independent of the infecting pathogen. In contrast, all mucus parameters were highly correlated to markers of inflammation, including neutrophil elastase activity, IL-1β, and CXCL8, consistent with evidence that high bacterial

Originally Published in Press as DOI: 10.1164/rccm.201911-2261ED on December 20, 2019

loads of all pathogens, not just *P. aeruginosa*, drive neutrophilic inflammation (11). Neutrophilic inflammation *in vitro* promotes mucin expression as well as degradation of CFTR (cystic fibrosis transmembrane conductance regulator), thereby increasing mucin production and impairing mucin hydration (12, 13).

So, should we be treating mucin hyperconcentration? Ramsey and colleagues demonstrated that the use of hypertonic saline inhalation reduced mucus concentration by 25%, which suggests at least that mucin hyperconcentration can be therapeutically modified. Nevertheless, in keeping with the heterogeneity of bronchiectasis, there was great variability among the subjects with regard to mucus properties, suggesting (as ever) that a one-size-fits-all approach is unlikely to be successful. Dry-powder mannitol achieves mucus hydration and has been tested in large randomized trials in bronchiectasis with mixed results, and small studies of hypertonic versus isotonic saline have yielded similarly conflicting results (14). The work presented by Ramsey and colleagues may explain why individuals with the greatest symptoms and inflammation, and therefore the greatest mucus hyperconcentration, may be more likely to respond to mucoactive drugs, in keeping with the emerging "treatable traits" concept (15). Further research is required to understand the mechanisms of mucus hyperconcentration in bronchiectasis, including the potential role of genetic modifiers such as CFTR mutations and other channelopathies, and whether antiinflammatory and antiinfective treatments that reduce bacterial load and inflammation also alter mucus properties.

In summary, bronchiectasis was first described 200 years ago as a disease of mucus accumulation and inflammation leading to bronchial dilation (1). On this "birthday" of sorts, the most comprehensive study to date of mucus properties suggests the potential for new therapeutic development targeting mucus hyperconcentration. Therapeutic development in bronchiectasis has focused heavily in recent years on antiinfective and antiinflammatory targets, but there are signs this is changing, with large randomized trials now underway testing the effectiveness of mucoactive drugs such as hypertonic saline in bronchiectasis (ClinicalTrials.gov identifier: NCT04140214).

The final word belongs to Laënnec, who wrote in 1819, "This affection being only a consequence and a complication of the catarrh, it is evident that the only means we possess of restoring the bronchi to their natural size is by diminishing the secretion of the mucous membrane."

We agree with Laënnec and suggest that as we leave 2019 behind, it's time to target the mucus! ■

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

James D. Chalmers, M.B. Ch.B., Ph.D.
Division of Molecular and Clinical Medicine
University of Dundee
Dundee, United Kingdom

Oriol Sibila, M.D., Ph.D.
Servei de Pneumologia
Hospital Sant Pau
Barcelona, Spain

References

1. Laënnec R. A treatise on the diseases of the chest and on mediate auscultation. Paris: Samuel Wood and Sons; 1819. pp. 100–108.
2. Chalmers JD, Chotirmall SH. Bronchiectasis: new therapies and new perspectives. *Lancet Respir Med* 2018;6:715–726.
3. Serisier DJ, Martin ML, McGuckin MA, Lourie R, Chen AC, Brain B, *et al*. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. *JAMA* 2013;309:1260–1267.
4. Laska IF, Crichton ML, Shoemark A, Chalmers JD. The efficacy and safety of inhaled antibiotics for the treatment of bronchiectasis in adults: a systematic review and meta-analysis. *Lancet Respir Med* 2019;7:855–869.
5. Ramsey KA, Chen ACH, Radicioni G, Lourie R, Martin M, Broomfield A, *et al*. Airway mucus hyperconcentration in non–cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2020;201:661–670.
6. Boucher RC. Muco-obstructive lung diseases. *N Engl J Med* 2019;380: 1941–1953.
7. Kirkham S, Kolsum U, Rousseau K, Singh D, Vestbo J, Thornton DJ. MUC5B is the major mucin in the gel phase of sputum in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008;178: 1033–1039.
8. Henke MO, John G, Germann M, Lindemann H, Rubin BK. MUC5AC and MUC5B mucins increase in cystic fibrosis airway secretions during pulmonary exacerbation. *Am J Respir Crit Care Med* 2007;175: 816–821.
9. Sibila O, Suarez-Cuartin G, Rodrigo-Troyano A, Fardon TC, Finch S, Mateus EF, *et al*. Secreted mucins and airway bacterial colonization in non-CF bronchiectasis. *Respirology* 2015;20:1082–1088.
10. Polverino E, Dimakou K, Hurst J, Martinez-Garcia M-A, Miravitlles M, Paggiaro P, *et al*. The overlap between bronchiectasis and chronic airway diseases: state of the art and future directions. *Eur Respir J* 2018;52:1800328.
11. Sibila O, Laserna E, Shoemark A, Keir HR, Finch S, Rodrigo-Troyano A, *et al*. Airway bacterial load and inhaled antibiotic response in bronchiectasis. *Am J Respir Crit Care Med* 2019;200:33–41.
12. Fischer BM, Voynow JA. Neutrophil elastase induces MUC5AC gene expression in airway epithelium via a pathway involving reactive oxygen species. *Am J Respir Cell Mol Biol* 2002;26:447–452.
13. Cohen-Cymberknoh M, Kerem E, Ferkol T, Elizur A. Airway inflammation in cystic fibrosis: molecular mechanisms and clinical implications. *Thorax* 2013;68:1157–1162.
14. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, *et al*. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J* 2017;50: 1700629.
15. Boaventura R, Sibila O, Agusti A, Chalmers JD. Treatable traits in bronchiectasis. *Eur Respir J* 2018;52:1801269.