

# Mucoactive Agents for Airway Mucus Hypersecretory Diseases

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## Introduction

## Sputum

## Profile of Airway Inflammation and Mucus Hypersecretory Phenotype in Asthma, COPD, and CF

## Which Aspect of Airway Mucus Hypersecretion to Target?

## Theoretical Requirements for Effective Therapy of Airway Mucus Hypersecretion

## Current Recommendations for Clinical Use of Mucolytic Drugs

## Mucoactive Drugs

### N-Acetylcysteine: How Does it Work? Does it Work?

### Dornase Alfa

### Hypertonic Saline

### Surfactant

## Analysis

## Summary

**Airway mucus hypersecretion is a feature of a number of severe respiratory diseases, including asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF). However, each disease has a different airway inflammatory response, with consequent, and presumably linked, mucus hypersecretory phenotype. Thus, it is possible that optimal treatment of the mucus hypersecretory element of each disease should be disease-specific. Nevertheless, mucoactive drugs are a longstanding and popular therapeutic option, and numerous compounds (eg, N-acetylcysteine, erdosteine, and ambroxol) are available for clinical use worldwide. However, rational recommendation of these drugs in guidelines for management of asthma, COPD, or CF has been hampered by lack of information from well-designed clinical trials. In addition, the mechanism of action of most of these drugs is unknown. Consequently, although it is possible to categorize them according to putative mechanisms of action, as expectorants (aid and/or induce cough), mucolytics (thin mucus), mucokinetics (facilitate cough transportability), and mucoregulators (suppress mechanisms underlying chronic mucus hypersecretion, such as glucocorticosteroids), it is likely that any beneficial effects are due to activities other than, or in addition to, effects on mucus. It is also noteworthy that the mucus factors that favor mucociliary transport (eg, thin mucus gel layer, "ideal" sol depth, and elasticity greater than viscosity) are opposite to those that favor cough effectiveness (thick mucus layer, excessive sol height, and viscosity greater than elasticity), which indicates that differ-**

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**ent mucoactive drugs would be required for treatment of mucus obstruction in proximal versus distal airways, or in patients with an impaired cough reflex. With the exception of mucoregulatory agents, whose primary action is unlikely to be directed against mucus, well-designed clinical trials are required to unequivocally determine the effectiveness, or otherwise, of expectorant, mucolytic, and mucokinetic agents in airway diseases in which mucus hypersecretion is a pathophysiological and clinical issue. It is noteworthy that, of the more complex molecules in development, it is simple inhaled hypertonic saline that is currently receiving the greatest attention as a mucus therapy, primarily in CF. Key words: mucus, hypersecretion, asthma, chronic obstructive pulmonary disease, COPD, cystic fibrosis, mucolytic, mucokinetic, expectorant, mucoactive, N-acetylcysteine, erdosteine, ambroxol. [Respir Care 2007;52(9):1176–1193. © 2007 Daedalus Enterprises]**

## Introduction

Patients with asthma, chronic obstructive pulmonary disease (COPD), or cystic fibrosis (CF) invariably exhibit characteristics of airway mucus hypersecretion, namely sputum production,<sup>1,2</sup> excessive mucus in the airway lumen<sup>3</sup> (Figs. 1 and 2), goblet cell hyperplasia,<sup>3–6</sup> and submucosal gland hypertrophy.<sup>3,5</sup> The pathophysiological sequelae of mucus hypersecretion are airway obstruction, airflow limitation, ventilation-perfusion mismatch, and impairment of gas exchange. In addition, compromised mucociliary function, with reduced mucus clearance, can encourage bacterial colonization, leading to repeated chest infections and exacerbations, particularly in COPD and CF. In COPD, a city-wide epidemiological study in Copenhagen showed that a number of clinical variables, including deterioration in lung function, risk of hospitalization, and risk of death, were greater in patients with COPD who had chronic mucus hypersecretion, compared with patients with either no sputum production or with only a small amount of intermittent sputum production<sup>7</sup> (Fig. 3). In addition, patients who had chronic airway mucus hypersecretion and were also susceptible to chest infections had greater mortality and morbidity, compared with patients with mucus hypersecretion but without infections (see Fig. 3). In contrast, the contribution of mucus to pathophysiology and clinical symptoms in asthma or CF is less well defined. In asthma, excess mucus may not only obstruct the airway lumen, but also contribute to the development of airway hyperresponsiveness.<sup>8</sup> The latter possibilities led to the suggestion that chronic mucus hypersecretion reflects lack of asthma control, leading in turn to accelerated loss of lung function and increased mortality.<sup>7</sup> In CF, mucus accumulation is associated with airway obstruction and with bacterial colonization of the airways, leading to cycles of infection and exacerbations.<sup>9</sup>

The association of airway mucus hypersecretion with asthma, COPD, and CF does not necessarily imply causation. The excess mucus may merely be a result of the inflammatory processes that cause the disease. Consequently, treating the mucus problem will not inevitably

treat the disease, especially if the changes that have led to increased mucus production are irreversible. Nevertheless, as discussed above, mucus hypersecretion does contribute to clinical symptoms in certain groups of patients with asthma, COPD, or CF. This suggests that it is important to develop drugs that address the airway mucus problem in these patients. There are 2 points that need considering when developing drugs aimed at reducing airway hypersecretion:

- The nature of the underlying disease process in asthma, COPD, and CF, and how this relates to the mucus hypersecretory phenotype in each condition
- The aspect(s) of mucus hypersecretion that should be targeted

This paper considers the validity of using compounds with potential beneficial effects on airway mucus as treatments in asthma, COPD, and CF. To set these drugs in context, the paper begins with discussion of sputum, airway mucus, and mucins, followed by an outline of the characteristics of mucus hypersecretion in asthma, COPD, and CF, and emphasizes differences between the 3 conditions, and the theoretical requirements for drugs aimed at effectively inhibiting airway mucus hypersecretion.

## Sputum

Coughing or “hawking” to bring up “phlegm” is a sign of respiratory disease.<sup>2,10</sup> It indicates airway mucus hypersecretion, coupled with impaired mucus clearance and mucus retention, and is an aspect of many lung infections, asthma, COPD, bronchiectasis, and CF. The expectorated excessive secretions are referred to as sputum. The characteristics of mucus change with infection and inflammation. Inflammation leads to mucus hypersecretion, ciliary dysfunction, and changes in the composition and biophysical properties of airway secretions.<sup>11</sup> Inflammatory cells, particularly neutrophils, which are recruited to the airway to combat infection, disappear from the airway, either through programmed cell death (apoptosis) or by necrosis.

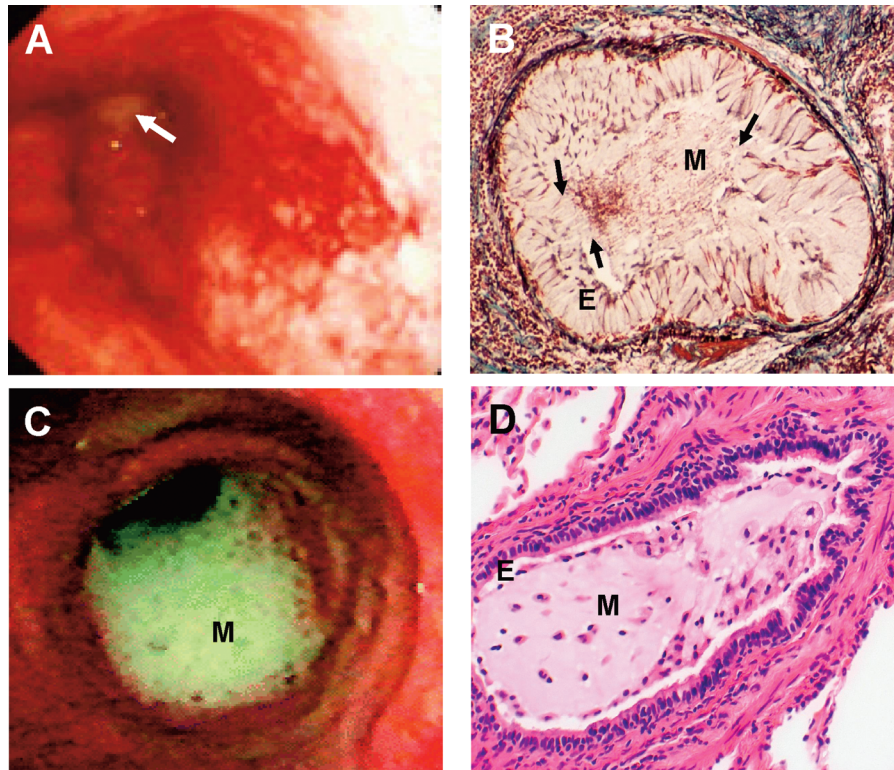


Fig. 1. Airway luminal mucus in respiratory diseases. A: Mucus (M) secretions (arrow) in an intrapulmonary bronchus in a patient with asthma. B: Airway mucus "tethering" in asthma. Transverse section through a bronchiole of a patient with asthma, showing incomplete release, or "continuity," of secreted mucin from airway epithelial goblet cells (arrows). Similar appearances of mucus tethering are not observed in chronic obstructive pulmonary disease (COPD). E = epithelium. C: Mucopurulent secretions in an intrapulmonary bronchus in a patient with COPD. D: Mucus (M) occluding a bronchiole in a patient with cystic fibrosis (CF). E = epithelium.

Necrotic neutrophils release pro-inflammatory mediators that damage the epithelium and recruit more inflammatory cells. They also release deoxyribonucleic acid (DNA)<sup>12</sup> and filamentous actin (F-actin) from the cytoskeleton. DNA and F-actin copolymerize to form a second rigid network within airway secretions<sup>13,14</sup> (Fig. 4). Neutrophil-derived myeloperoxidase imparts a characteristic green color to inflamed airway secretions, which are termed mucopurulent. Excessive infection turns the secretions dark yellow, green, or brown, and these are termed purulent.

#### Profile of Airway Inflammation and Mucus Hypersecretory Phenotype in Asthma, COPD, and CF

Asthma, COPD, and CF, although all are inflammatory conditions of the airways, are different diseases with different pathophysiological and clinical characteristics.<sup>15</sup> These differences and similarities extend to the mucus hypersecretory phenotype (Fig. 5). In order to develop appropriate models of airway mucus hypersecretion and design drugs to address the mucus problems in these diseases, it is necessary to understand the similarities and

differences in the features of mucus obstruction in different hypersecretory conditions.

First, although the underlying pulmonary inflammation of asthma, COPD, and CF shares many common features, there are specific characteristics unique to each condition.<sup>15-17</sup> Asthma is usually an allergic disease that affects the airways, rather than the lung parenchyma, and in general is characterized by Th2 (CD4<sup>+</sup>) lymphocyte orchestration of pulmonary eosinophilia. In contrast, in severe asthma, or when patients are on chronic corticoid treatment, neutrophilia often predominates. The reticular layer beneath the basement membrane is markedly thickened, and the airway epithelium is fragile, which are features not usually associated with COPD or CF. Neutrophils are generally sparse in stable disease, but may play a role in severe disease.

In contrast to asthma, COPD and CF are predominantly neutrophilic disorders orchestrated largely by macrophages and epithelial cells. In addition, and in contrast to asthma, CD8<sup>+</sup> T lymphocytes predominate, and pulmonary eosinophilia is generally associated with exacerbations. COPD is associated primarily with cigarette smoking, whereas CF is associated with abnormalities in the CF transmem-

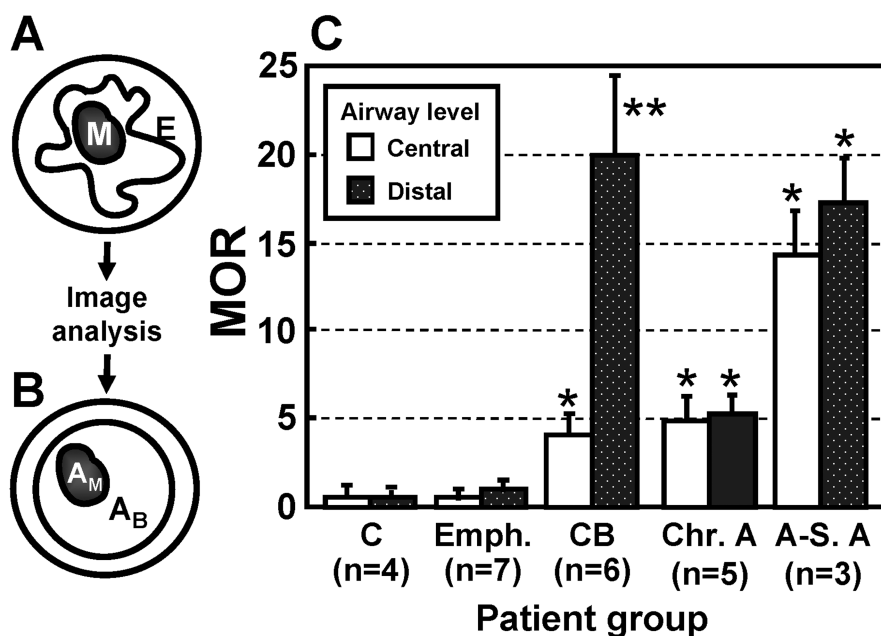


Fig. 2. Relative amounts of airway luminal mucus in different airway diseases. A. Lungs from patients dying of causes other than lung disease (controls, C), or from emphysema (Emph), chronic bronchitis (CB), chronic asthma (Chr. A) or acute-severe asthma (A-S. A) were cut into histological sections, which were stained for mucin (M). The stained sections were viewed by light microscopy and intrapulmonary airways assessed for amount of luminal mucus. E = bronchial epithelium. B. Airways of interest were subjected to computer-based image analysis. The irregular perimeter of the bronchial epithelium was digitally-converted to a circle, from which the area of mucus ( $A_M$ ) was expressed as a ratio of the area of the bronchus ( $A_B$ ), to give a mucus-occupying ratio, MOR ( $A_M/A_B$ ), as shown in panel C. \* $p < 0.01$ , \*\* $p < 0.01$  compared with controls. (Redrawn from data in References 3 and 4.)

brane-conductance regulator.<sup>9,18</sup> COPD comprises 3 conditions, namely, chronic bronchitis (mucus hypersecretion), bronchiolitis (also known as small airways disease), and emphysema (alveolar destruction) (Fig. 6). The latter 2 pathophysiologies are not associated with asthma or, in general, with CF. The contribution to clinical symptoms of bronchitis, bronchiolitis, and emphysema in any one patient is uncertain, and, therefore, the contribution of mucus obstruction to airflow limitation is unclear (Fig. 6). Asthma, COPD, and CF have a characteristic “portfolio” of inflammatory mediators and enzymes, many of which differ between the conditions.<sup>19,20</sup> At a simplified level, histamine, interleukin-4, and eotaxin are associated with asthma, whereas interleukin-8, neutrophil elastase, and matrix metalloproteinases are associated with COPD and CF. Thus, there are specific differences in airway inflammation and remodeling between asthma on the one hand, and, to a certain extent, COPD and CF together on the other hand. These differences may in turn exert different influences on the development of airway mucus obstruction in the 3 conditions (see Fig. 5).

Airway mucus in asthma is more viscous than in COPD or CF. In asthma the airways tend to develop and become blocked by gelatinous “mucus” plugs.<sup>8</sup> Interestingly, CF sputum is less viscous than either normal secretions or sputum from patients with asthma or COPD, possibly due

to less mucin in CF sputum.<sup>21,22</sup> Whether mucus in asthma has an intrinsic biochemical abnormality is unclear. In general terms, sputum from patients with asthma is more viscous than that from patients with chronic bronchitis or bronchiectasis.<sup>23–25</sup> Mucus plugs in asthma differ from airway mucus gels in chronic bronchitis or CF, in that they are stabilized by noncovalent interactions between extremely large mucins assembled from conventional-size subunits.<sup>26</sup> This suggests an intrinsic abnormality in the mucus due to a defect in assembly of the mucin molecules, and could account for the increased viscosity of the mucus plugs in asthma. Plug formation may also be due, at least in part, to increased airway plasma exudation in asthma, compared with COPD or CF.<sup>27</sup> In addition, and in direct contrast to COPD, exocytosed mucins in asthma are not released fully from the goblet cells, leading to “tethering” of luminal mucins to the airway epithelium.<sup>28</sup> This tethering may also contribute to plug formation. One explanation of mucus tethering is that neutrophil proteases (the predominant inflammatory cell in COPD<sup>29</sup>) cleave goblet-cell-attached mucins. In asthma, the inflammatory cell profile, predominantly airway eosinophilia,<sup>30</sup> does not generate the appropriate proteases to facilitate mucin release.

Different mucin gene (MUC) products, or at least different proportions of these mucins, appear to be present in respiratory tract secretions in COPD, asthma, and CF.

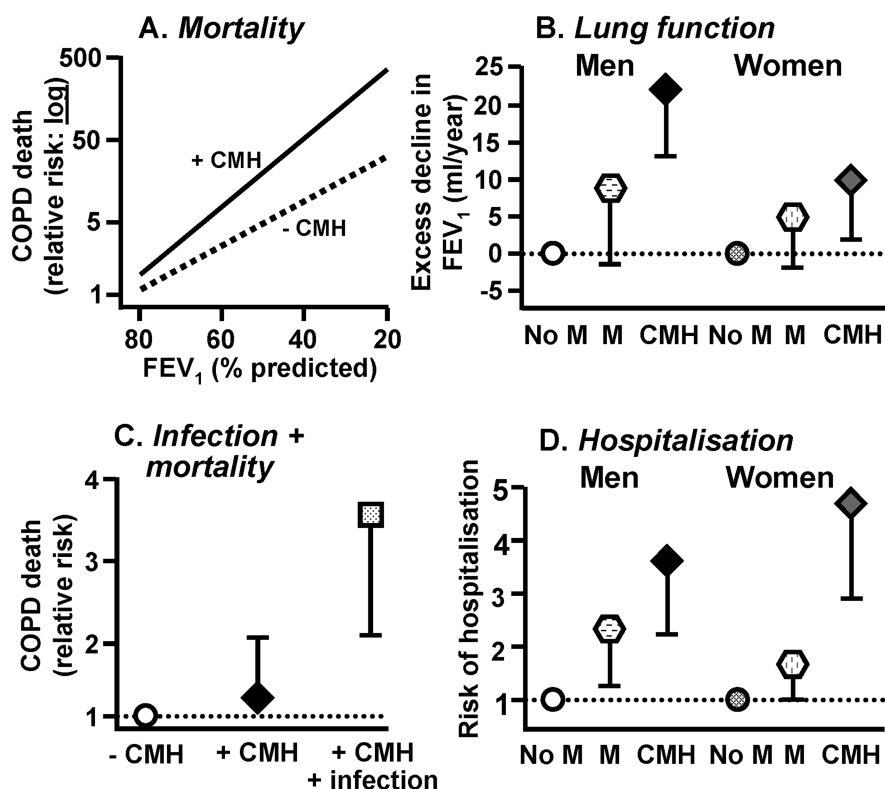


Fig. 3. Clinical impact of airway mucus hypersecretion in chronic obstructive pulmonary disease (COPD). The Copenhagen Heart Study showed that patients with chronic mucus hypersecretion (CMH), as defined by long-term phlegm production, had an increased risk of death (A), and accelerated decline in lung function (B), a further decline in lung function when linked with pulmonary infection (C), and an increased risk of hospitalization (D), when compared with subjects without mucus production (No M) or patients with any mucus production (M) but without CMH. (From data in Reference 7.)

MUC5AC and MUC5B are the major mucin species in airway secretions from patients with COPD, asthma, or CF.<sup>31–35</sup> In general, there is significantly more of the low-charge glycoform of MUC5B in respiratory disease than in normal control secretions.<sup>35</sup> An interesting difference is that there is a proportional increase in the low-charge glycoform of MUC5B mucin over the MUC5AC mucin in airway secretions from patients with COPD, compared with secretions from patients with asthma.<sup>31</sup> These data require confirmation in more samples.

The importance of the difference in MUC5B glycoforms between asthma and COPD is unclear, but it may relate to differences in propensity for bacterial colonization of the lungs. It is noteworthy that COPD patients are prone to pulmonary infections,<sup>9,29</sup> and have proportionally fewer serous cells, in contrast to patients with asthma, who are not so notably prone to chest infection. Possibly one of the most important differences between asthma, COPD, and CF is that in CF there are markedly fewer MUC5AC and MUC5B mucins in airway secretions, compared with normal control subjects.<sup>22</sup> This is in contrast to asthma and COPD, in which these mucins are above normal (see above). The reduction in MUC5AC and

MUC5B mucins is not thought to be due to sputum abnormalities,<sup>36</sup> but may reflect disease severity or be due to a primary defect in mucin secretion in CF. For example, for the latter suggestion, CF bronchi secrete less mucin than do non-CF control tissue in response to a variety of stimuli.<sup>37,38</sup>

In contrast to healthy individuals, goblet cells in airways from patients with COPD contain not only MUC5AC but also MUC5B<sup>33,39</sup> and MUC2.<sup>40,41</sup> This distribution is different than that in the airways of patients with asthma or CF, where MUC5AC and MUC5B show a similar histological pattern to normal controls.<sup>42,43</sup> It is noteworthy that, although MUC2 is located in goblet cells in irritated airways, and MUC2 messenger ribonucleic acid (mRNA) is found in the airways of smokers,<sup>44</sup> MUC2 mucin is either not found in airway secretions from normal subjects or patients with chronic bronchitis,<sup>32</sup> or is found only in very small amounts in asthma, COPD, or CF.<sup>35,45</sup> The importance of the above combined observations is unclear but suggests that there are differences in goblet cell phenotype between asthma, COPD, and CF.

Another notable difference between asthma and COPD is in the bronchial submucosal glands.<sup>46</sup> In asthma, al-

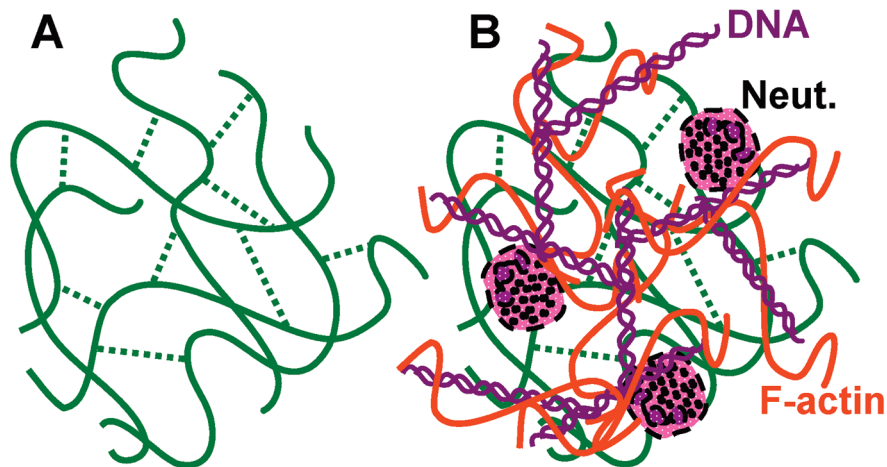


Fig. 4. Mucin, deoxyribonucleic acid (DNA), and actin interactions in mucus. A: Secreted mucins are thread-like and form a tangled network on the airway surface, with individual threads linked together by low-energy, noncovalent bonds (dotted lines), including ionic bonds, hydrogen bonds, and van der Waals forces. B: In respiratory conditions in which neutrophilic inflammation is a pathophysiological feature (CF more than in chronic obstructive pulmonary disease or severe asthma, and much more than in stable asthma), necrotizing neutrophils (Neut) release DNA, which increases the viscosity of the mucus. Cell-derived filamentous (F) actin also increase the viscosity of the mucus. The DNA and F-actin co-polymerize to form thick bundles,<sup>14</sup> although the mucin network is distinct.

though hypertrophied, the glands are morphologically normal and there is an even distribution of mucous and serous cells. In contrast, in chronic bronchitis, gland hypertrophy is characterized by a markedly increased number of mucous cells, relative to serous cells, particularly in severe bronchitis. The reduction in number of gland serous cells may have clinical importance. The serous cells are a rich source of antibacterial enzymes such as lysozyme and lactoferrin.<sup>47</sup> Thus, the airway mucus layer in patients with COPD may have less antibacterial potential than in patients with asthma. This reduction, coupled with the change in MUC5B glycoforms in COPD (see above), could further explain, at least in part, the much higher incidence of bacterial chest infections in COPD, compared with asthma.

#### Which Aspect of Airway Mucus Hypersecretion to Target?

From the above it may be seen that there are theoretical and actual differences in the nature of airway mucus obstruction between COPD, asthma, and CF. How these relate to pathophysiology and clinical symptoms in the 3 conditions is, for the most part, unclear. However, these dissimilarities indicate that different treatments are required for effective control of airway mucus obstruction in different respiratory diseases. Despite these differences, use of drugs that “thin” mucus (termed mucolytic drugs) is the traditional pharmacotherapeutic approach to alleviating the symptoms of airways mucus hypersecretion (coughing, “phlegm” production, and airway obstruction). However, airway hypersecretion in asthma, COPD, and CF is a mul-

tifactorial process that involves increases in the amount of mucus-producing tissues, changes in phenotype of these tissues, changes in mucus viscosity, possible changes in expression of the protein products of MUC genes, and changes in the interaction of mucus with other components of the airway liquid (eg, serum proteins such as albumin). Although these changes are considered to be involved in the pathophysiology of airway hypersecretion, the relative contribution of each change to disease development and clinical symptoms is unresolved. Consequently, it is unclear which pathophysiological aspect(s) should be targeted by mucoactive drugs for optimal benefit. It is easily conceivable that merely thinning mucus is not effective without additional effects on other aspects of hypersecretion, such as reducing the amount of mucus-secreting tissue.

#### Theoretical Requirements for Effective Therapy of Airway Mucus Hypersecretion

The discussion above on the characteristics of mucus hypersecretion in asthma, COPD, and CF, as well as that on the differences in hypersecretory phenotype between the 3 conditions (see Fig. 5), demonstrates that effective long-term therapy of airway mucus hypersecretion in these 3 conditions is likely to entail more than just “thinning” of mucus, and could be different for each condition. There are 2 objectives in treatment of mucus hypersecretion, namely, short-term relief of symptoms and long-term benefit (Table 1). The first of these involves facilitating mucus clearance, and entails changing the viscoelasticity of mu-

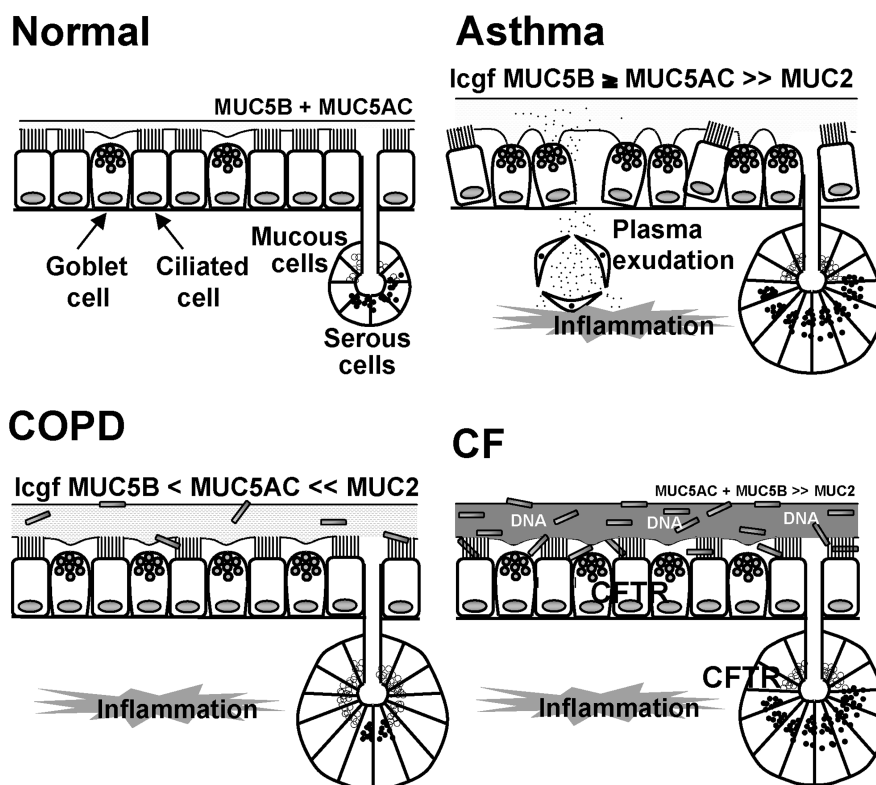


Fig. 5. Putative differences in the airway mucus hypersecretory phenotype between asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF). Compared with normal, in asthma, there is airway inflammation (predominantly eosinophils and Th2 lymphocytes), an increased amount of luminal mucus with an increased content of MUC5AC and MUC5B mucins (large font), with the possibility of an increased ratio of the low charge glycoform (lcgf) of MUC5B to MUC5AC, the “appearance” of small amounts of MUC2 in the secretions, epithelial “fragility” with loss of ciliated cells, marked goblet cell hyperplasia, submucosal gland hypertrophy (although, in contrast to COPD or CF [see below], without a marked increase in mucous cell to serous cell ratio), “tethering” of mucus to goblet cells, and plasma exudation. In COPD, there is airway inflammation (predominantly macrophages and neutrophils), increased luminal mucus, increased amounts of MUC5AC and MUC5B mucins (large font), an increased ratio of lcgf MUC5B to MUC5AC above that in asthma, small amounts of MUC2, goblet cell hyperplasia, submucosal gland hypertrophy (with an increased proportion of mucous to serous cells), and a susceptibility to infection (rod shapes in mucus). In CF, the defect in the cystic fibrosis transmembrane-conductance regulator (CFTR) is associated with airway inflammation (predominantly macrophages and neutrophils), increased luminal mucus (with increased amounts of DNA), decreased amounts of MUC5AC and MUC5B (small font) compared with normal, small amounts of MUC2, goblet cell hyperplasia, submucosal gland hypertrophy, and a marked susceptibility to infection. Many of these differences require further investigation in greater numbers of subjects.

cus (the change in viscosity and/or elasticity will depend upon whether mucociliary clearance or cough is “preferred”: see below), increasing ciliary function, and, possibly, encouraging cough. Theoretically, cough clearance is optimized when there is high viscosity and low tenacity. Tenacity is the product of adhesivity and cohesivity (“stickiness” and “stringiness”). Decreasing viscosity may not markedly change mucus clearance. Of greater importance is the degree of adhesion of the mucus to the epithelium: decreased adhesion is linked to increased clearance. In addition, in asthmatic patients, facilitating the release of the tethered goblet cell mucin should improve airflow. Long-term benefit involves reversal of the hypersecretory phenotype and entails reducing the number of goblet cells and the size of the submucosal glands. In addition, in asthma it may be useful to inhibit plasma exudation. In

COPD, correction of the increased submucosal gland mucous cell to serous cell ratio and the increased MUC5B to MUC5AC ratio may be of benefit. It is unlikely that the activity of current compounds intended to treat airway mucus hypersecretion, or even those in development, on the above variables is clearly defined.

Enhancing mucus clearance, with perceived reductions in airway obstruction and airflow limitation, is a primary objective for short-term relief of symptoms in airway mucus hypersecretory diseases. This concept is supported by the observation that less chronic cough or sputum production is a predictor of decline in lung function in patients with asthma.<sup>48</sup> The implication is that failure to clear airway mucus, for whatever reason, is associated with increasing airway obstruction. Consequently, aiding clearance would seem a viable therapeutic option, by enhancing

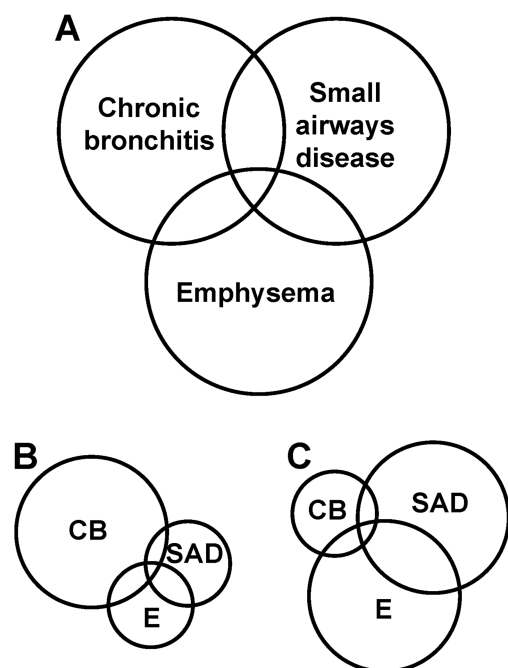


Fig. 6. Components of chronic obstructive pulmonary disease (COPD). A: COPD comprises 3 interlinked conditions, namely, chronic bronchitis (CB, airway mucus hypersecretion), small airways disease (SAD, chronic bronchiolitis), and emphysema (E, alveolar destruction). The relative contribution to airway obstruction of each component in any one patient is often unclear. B: Patient in whom mucus hypersecretion predominates (may be identifiable by excessive sputum production). C: Patient in whom mucus hypersecretion contributes proportionally less to airflow limitation than SAD and E.

the effectiveness of mucociliary clearance and cough. However, mucociliary clearance and cough exist as a “yin-yang” pairing, in that the mucus variables that favor effective mucociliary clearance are directly opposite to those that favor effective cough<sup>49</sup> (Table 2). For example, a thin mucus layer and an “ideal” depth of the sol, or periciliary, layer favor mucociliary clearance. The ideal sol depth is purported to be just less than the height of the cilia, to allow effective coupling between ciliary tips and the surface mucus gel layer. In contrast, a thick mucus layer and a sol depth that raises the gel phase away from the cilia favor cough clearance. Mucus is a non-Newtonian fluid in that it has both viscous (liquid) and elastic (solid) properties.<sup>50</sup> Viscosity represents energy loss, whereas elasticity represents energy storage. Consequently, the effectiveness of mucociliary clearance has a direct relationship with elasticity, whereby kinetic energy from beating cilia is transmitted to the mucus, and an indirect relationship with viscosity (limiting energy loss). Conversely, cough effectiveness has an indirect relationship with elasticity (to limit elastic recoil of cough-sheared mucus), and a direct relationship with viscosity.<sup>51</sup> In addition, low adhesivity of mucus favors cough due to ease of lifting of the mucus

layer from the airway surface, by allowing “wave” formation in the gel (Fig. 7). High adhesivity hinders wave formation and, to a certain extent, favors mucociliary clearance over cough. In addition, mucus depth alters the influence of viscosity, elasticity, and adhesivity on the effectiveness of cough clearance (see Fig. 7). In general terms, it is easier to clear relatively large amounts of viscous mucus with cough, than small amounts of elastic mucus; this is akin to being able to empty a full ketchup bottle with a single shake than one with only a smear of ketchup around the inside (Fig. 8).

From the above it may be reasoned that if the mucus obstruction in any one patient could best be cleared by cough (eg, mucus accumulation in more proximal airways), then drugs that enhance cough would be preferred. Conversely, if mucus obstruction is in more distal airways, or if a patient has a weak cough reflex, then drugs that favor mucociliary clearance would be preferred. The challenges are first, in identifying which patients would benefit from which treatment option, then second, in choice of drug to best exploit that option.

#### Current Recommendations for Clinical Use of Mucolytic Drugs

The overt clinical symptoms of cough and expectoration, coupled with the concomitant perceived importance of mucus in pathophysiology of many severe lung conditions, including asthma and COPD, have led to worldwide development of drugs thought to affect respiratory mucus. At present, over 50 compounds have potentially beneficial actions on some aspect of mucus or its secretion (Table 3). In reality, less than a third of these are listed in national formularies worldwide.<sup>52</sup>

Despite the abundance of mucoactive drugs available, few are recommended for use in respiratory hypersecretory disease. For example, although the United Kingdom’s National Institute for Clinical Excellence recommends mucolytic therapy in clinical management of COPD, most guidelines for management of COPD do not advocate such treatment. Neither the British Thoracic Society<sup>53</sup> nor the European Respiratory Society<sup>54</sup> currently recommend mucolytic drugs in treatment. In Canada, mucolytics are listed as one of a number of treatments “under investigation” and are not specifically recommended in disease management.<sup>55</sup> The American Thoracic Society suggests that “mucokinetic” agents be considered in “step 3” as an adjunct to bronchodilators where there is a mild to moderate increase in symptoms, and also in severe exacerbations if sputum is “very viscous.”<sup>56</sup> In its asthma management guidelines the British Thoracic Society does not mention mucolytic treatment,<sup>57</sup> whereas the American Thoracic Society makes no recommendations for use of mucolytics or expectorants.<sup>58</sup>



## MUCOACTIVE AGENTS FOR AIRWAY MUCUS HYPERSECRETORY DISEASES

Table 1. Theoretical Requirements for Pharmacotherapy of Airway Mucus Pathophysiology in Asthma, COPD, and CF

Overall Effect	Component Effects*
Facilitate mucus clearance (short-term relief of symptoms)	Reduce viscosity (increase elasticity?) Reduce DNA/filamentous actin content of mucus (CF > COPD) Increase ciliary function Induce cough Facilitate release of "tethered" goblet cell mucin (asthma) Inhibit mucin secretion
Reverse hypersecretory phenotype (long-term benefit)	Treat airway/pulmonary inflammation Reduce goblet cell number Reduce submucosal gland size Inhibit plasma exudation (asthma) Correct increased ratio of gland mucous cells to serous cells (COPD) Reverse increased ratio of low-charge glycoform MUC5B to MUC5AC (COPD)

\*The relative importance of the individual component effects to airway mucus pathophysiology is unclear. Consequently, it may be unnecessary to meet all theoretical requirements, with inhibition of only certain aspects having important clinical benefit.

COPD = chronic obstructive pulmonary disease

CF = cystic fibrosis

DNA = deoxyribonucleic acid

MUC = mucin gene product

Table 2. Differential Effects of Airway Mucus Properties on Mucociliary Clearance and Cough

Favors Mucociliary Clearance	Favors Cough
Thin mucus layer	Thick mucus layer
"Ideal" sol depth	Excess sol (height above cilia)
Direct relationship with elasticity	Indirect relationship with elasticity
Indirect relationship with viscosity (ie, elasticity > viscosity for energy transfer)	Direct relationship with viscosity (ie, viscosity > elasticity)

### Mucoactive Drugs

From the above it may be seen that although mucus hypersecretion is associated with morbidity and mortality in asthma, COPD, and CF, there is controversy concerning the therapeutic value of drugs that affect mucus properties. Nevertheless, there are numerous compounds in development aimed at alleviating airways mucus hypersecretion. For the most part, the mechanism of action of these compounds is either unknown or incompletely characterized.

Useful attempts have been made to precisely categorize compounds that affect mucus.<sup>59,60</sup> However, a more simple classification system is followed herein (Table 4). Compounds are classified as expectorants, mucolytics, mucokinetics, or mucoregulators according to the following characteristics, based loosely on putative mechanism(s) of action.<sup>61</sup>

Expectorants (see Tables 3 and 4) probably increase secretion of mucins and/or increase mucus hydration to a point where a sufficient volume of mucus is produced to enable it to be coughed up. These drugs may also be irritants and initiate cough to dislodge mucus.

Mucolytics "lyse," or reduce the viscosity of, mucus. Respiratory mucins, in common with other mucins, contain disulphide bonds that contribute to the long, thread-like structure of mature mucins and aid gel formation.<sup>40,62</sup> The term mucolytic refers to compounds with sulfhydryl groups that are able to dissociate disulphide bonds and potentially reduce mucus viscosity. The "classical" mucolytic compounds have either "exposed," or "free," sulfhydryl groups (for example N-acetylcysteine) that directly break disulphide bonds, or have "blocked" sulfhydryl groups that are exposed upon metabolism in the body (for example carbocysteine) (Fig. 9). Other compounds, such as proteolytic enzymes and recombinant human deoxyribonuclease (also known as dornase alfa or rhDNase) (see Table 3), also break up mucus, but do so via mechanisms other than dissociating disulphide bonds in mucin molecules, and, as such, are not strictly mucolytic.

Mucokinetic agents increase mucus "kinesis," effectively increasing the transportability of mucus by cough. These agents include  $\beta_2$ -adrenoceptor agonist bronchodilators (eg, albuterol) and surfactant.  $\beta_2$  agonists probably increase mucus clearance by increasing airflow and ciliary beat, with consequent effects on mucus movement, as well as increasing  $\text{Cl}^-$  and, hence, water secretion, and also mucin secretion (albeit that the latter effect is small), which may increase mucus volume and thereby aid cough clearance (see above). Surfactant aids cough clearance by reducing the adherence of mucus to the epithelium. Drugs such as ambroxol (see Fig. 9) may increase cough effectiveness by stimulating surfactant secretion.

Mucoregulators are drugs that do not directly have any great influence on airway mucus, but they may reduce the

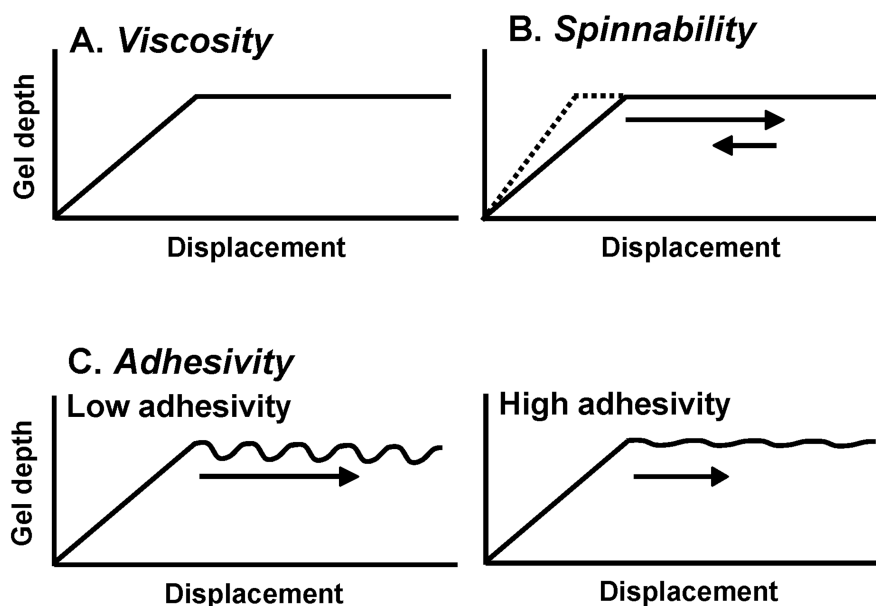


Fig. 7. Interaction between mucus gel depth and mucus biophysical variables on effectiveness of cough clearance. A: Data from a simulated cough machine demonstrates that cough-type clearance relates primarily to mucus gel viscosity. B: For a given viscosity, clearance is also impaired by spinnability (the capacity of the mucus to form threads, and an index of large deformation elasticity). Viscous deformation (due to cough) is reduced by elastic recoil in the mucus. C: At constant viscosity and spinnability, clearance is further impaired by an increase in the adhesivity of the mucus (indicated by reduced capacity of cough airflow to raise the gel into “waves,” which facilitates lifting of the mucus from the epithelium). (From data in Reference 51.)



Fig. 8. Mucus volume and cough effectiveness: the ketchup bottle analogy. A: It is easier to empty a full ketchup bottle (left) with a vigorous palm-slap on the bottom than one containing only a small amount of ketchup (right). (Photograph courtesy of Kate Rogers, author’s daughter.) B: Large sputum sample coughed out in one episode by a patient with bronchorrhea.

process of chronic mucus hypersecretion, either by their anti-inflammatory activity (including glucocorticosteroids and macrolide antibiotics) or by inhibiting a particular aspect of mucus physiology (eg, anti-cholinergic drugs that inhibit cholinergic nerve-induced mucus secretion, in addition to their anticholinergic bronchodilator activity).

The above terms are useful in categorizing mucoactive drugs in terms of their putative mechanisms of action.

However, it should be noted that many mucoactive drugs have activities additional to their perceived activity on mucus (eg, antioxidant activity). N-acetylcysteine is a mucoactive drug with putative mucolytic and antioxidant activity. It is considered below as an illustration of the origin of the doubts raised concerning the therapeutic potential in general of mucoactive drug therapy in mucus hypersecretion airway diseases. It highlights the confusion raised by

## MUCOACTIVE AGENTS FOR AIRWAY MUCUS HYPERSECRETORY DISEASES

Table 3. Mucoactive Agents

Mucolytics
Cysteine
N-Acetylcysteine
Nacystelyn
Ethylcysteine
Nesosteine
Dithiothreitol
MESNA (2-mercaptoethanesulphonate sodium)
Thiopronine
Urea
Tasuldine
Carbocysteine*
Carbocysteine-Lys*
Erdosteine*
Fudosteine*
Letosteine*
Stepronin*
Usherdex-4 (a low-molecular-weight form of dextran)
Expectorants/Mucokinetics
Ambroxol
Ambroxol-theophylline-7-acetate
Bromhexine
Guaiacol and derivatives
Guafenesin
Guaimosal
Hypertonic solutions (saline)
Inorganic iodides
Organic iodides
Ipecacuanha
Sobrerol
Sodium citrate
Squill
Volatile inhalants and balsams
$\beta_2$ -Adrenoceptor agonists
Surfactant
YM-40461 (surfactant secretagogue)
Peptide Mucolytics (Enzymes)
Bromelain
$\alpha$ -Chymotrypsin
Recombinant human deoxyribonoclease I (aka, dornase-alfa and rhDNase)
Fericase
Ficin
Gelsolin
Helicidin
Leucine amino peptidase
Neuraminidase
Onopronase
Papain
Serratopeptidase
Streptodornase
Streptokinase
Thymosin beta 4
Trypsin

\*Metabolized endogenously to form compounds with free sulphhydryl groups

Table 4. Mucoactive Agents Putative Mechanisms of Action

Mucoactive Agent	Putative Mechanism of Action
Expectorant	Increases volume and/or hydration of secretions. May also induce cough (eg, guaifenesin, hypertonic saline)
Mucolytic	Reduces viscosity of mucus Non-peptide ("classical") mucolytics cleave disulphide bonds ("free" or "blocked" sulphhydryl groups). Low-molecular-weight saccharide mucolytics interfere with non-covalent interactions in mucus, and may osmotically pull water into airway lumen. Peptide mucolytics degrade deoxyribonucleic acid (DNA) or actin
Mucokinetic	Increases "kinesis" of mucus and facilitates cough "transportability" of mucus $\beta_2$ -adrenoceptor agonists increase airflow, ciliary beat, $\text{Cl}^-$ /water secretion, and mucin secretion (small effect). Surfactant reduces mucus adherence to epithelium.
Mucoregulator	Reduces process of chronic mucus hypersecretion (eg, glucocorticosteroids, anticholinergics, macrolide antibiotics)

uncertainties about mechanism of action and imprecision in clinical trial design. In contrast, dornase alfa has a well-defined mechanism of action (ie, degrades DNA) and is considered below to contrast with N-acetylcysteine. In addition, hypertonic saline and aerosolized surfactant are also mentioned below as examples of interventions that are currently under consideration as agents with potentially beneficial effects on airway mucus.

### N-Acetylcysteine: How Does it Work? Does it Work?

N-acetylcysteine is the mucolytic compound most-listed in pharmacopoeias worldwide,<sup>52</sup> and has been used for many years in the treatment of patients with a variety of respiratory conditions.<sup>63</sup> N-acetylcysteine is mentioned in the COPD guidelines of both the European Respiratory Society<sup>54</sup> and the American Thoracic Society.<sup>56</sup> However, although it is considered a mucolytic drug, this activity is not well documented,<sup>64</sup> and after oral dosing it is not found in airway secretions.<sup>65</sup> N-acetylcysteine is also considered to have antioxidant properties, because it contains free thiol groups. A related compound, N-isobutyrylcysteine, has higher levels of free thiols than N-acetylcysteine. However, unlike N-acetylcysteine,<sup>66,67</sup> N-isobutyrylcysteine had no effect on exacerbation rate in COPD,<sup>68</sup> which questions the validity of the free thiol hypothesis for N-acetylcysteine activity.

The pharmacokinetics of N-acetylcysteine depend upon its route of administration. Aerosolized inhaled N-acetyl-

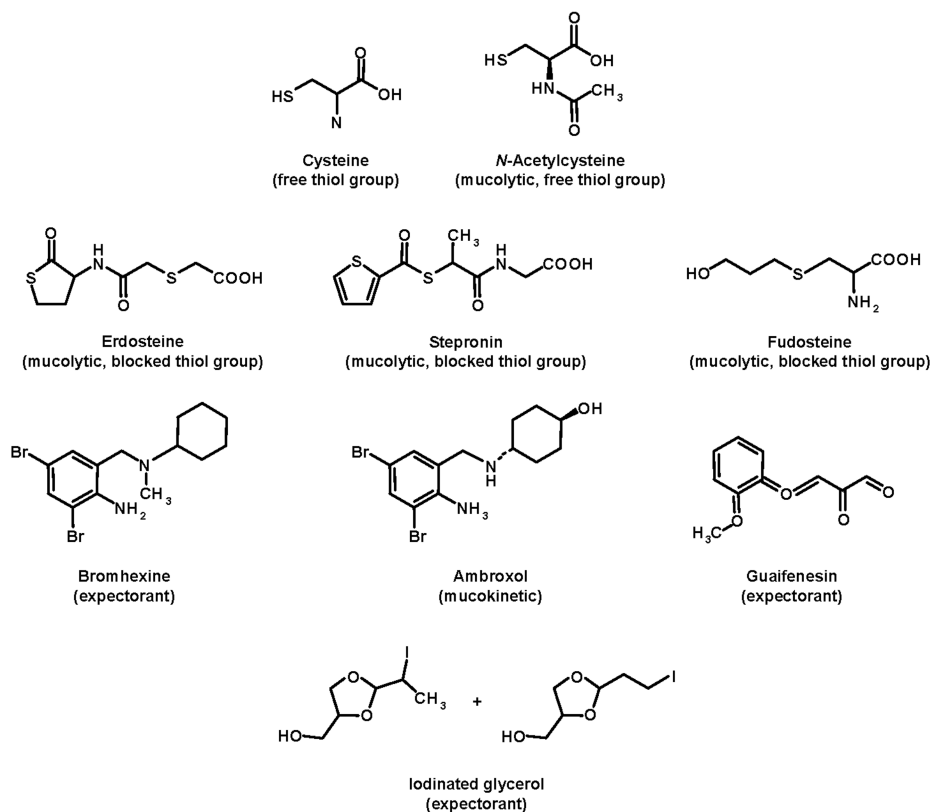


Fig. 9. Structures of some mucolytic, mucokinetic, and expectorant drugs (see text for details).

cysteine dissociates mucin disulphide bonds to reduce viscosity. In contrast, oral N-acetylcysteine has low bioavailability,<sup>69</sup> and is de-acetylated to cysteine, whose thiol group possesses reducing and antioxidant properties.<sup>70</sup> N-acetylcysteine is not detected in plasma or bronchoalveolar lavage fluid following oral dosing for up to 14 days,<sup>65,71</sup> although increases in plasma cysteine concentrations were reported.<sup>65</sup> Cysteine is a substrate in the biosynthesis of glutathione, an important intracellular and extracellular antioxidant.<sup>72</sup> Hence, increased plasma cysteine should be followed by a concomitant increase in plasma glutathione concentrations. Accordingly, oral N-acetylcysteine (600 mg daily) increased levels of glutathione in both plasma<sup>65,71</sup> and lung.<sup>65</sup> However, in patients with COPD, plasma concentrations of glutathione are unchanged following this dose of N-acetylcysteine, although increases are seen with a higher dose of 600 mg 3 times daily.<sup>73</sup> N-acetylcysteine (200 mg orally 3 times daily for 8 weeks) reduces superoxide radical generation by alveolar macrophages from healthy smokers.<sup>63</sup>

N-acetylcysteine treatment is also associated with a reduction in airway bacterial load,<sup>74</sup> possibly because it reduces the ability of bacteria to adhere to epithelial cells.<sup>75</sup> In an animal model of chronic bronchitis, oral N-acetylcysteine inhibited cigarette-smoke-induced goblet cell hyperplasia,<sup>76</sup> and the associated mucus hypersecretion,<sup>77</sup> and

speeded resolution of the goblet cell hyperplasia after cessation of smoke exposure.<sup>78</sup>

Thus, from the above, it may be seen that any beneficial clinical effects of N-acetylcysteine are not necessarily due to mucolytic activity, antioxidant activity, or to direct beneficial effects on mucus.

Data from clinical trials of N-acetylcysteine are equally ambiguous. A trial of inhaled N-acetylcysteine in chronic bronchitis found no effect on feelings of well-being, dyspnea, cough, mucus production and expectoration, or lung function after treatment for 16 weeks.<sup>79</sup> The trial did not assess effects on exacerbation rate, because of the low number reported during the trial. Adverse effects included nausea and stomatitis, whereas hyperresponsive asthmatics can develop bronchospasm. Oral dosing is associated with dyspepsia, nausea, and diarrhea. Oral N-acetylcysteine has been reported to cause changes in sputum composition in patients with chronic bronchitis and excessive sputum production.<sup>80</sup> Patients treated with N-acetylcysteine had increased sputum volume, decreased sputum thickness, and improvements in scores for dyspnea and ease of expectoration. The study also reported improvements in peak expiratory flow and forced expiratory volume in the first second (FEV<sub>1</sub>) in patients treated with N-acetylcysteine, compared with a placebo group. However, the latter result should be treated with caution because of differ-

ences in lung function between the 2 groups at baseline. A large placebo-controlled trial in patients with chronic bronchitis found that oral N-acetylcysteine treatment (200 mg twice daily) led to changes in sputum composition; the patients reported lower scores for sputum volume, degree of purulence, thickness of sputum, difficulty in expectoration, and severity of cough.<sup>81</sup> These changes in sputum properties were accompanied by a significant reduction in exacerbations.<sup>81,82</sup> In contrast, a further large placebo-controlled trial that used a higher dose of oral N-acetylcysteine (200 mg 3 times daily) did not find a significant difference in exacerbation rate between the treated and placebo groups, although there was a trend of fewer exacerbations in the N-acetylcysteine-treated group ( $p = 0.08$ ).<sup>83</sup> The latter study differed from the former 2 studies<sup>81,82</sup> in that the patients had not only chronic bronchitis but also severe airways obstruction. Oral N-acetylcysteine (300 mg twice daily as slow-release tablets) has also been shown to reduce days taken off work due to illness in patients with chronic bronchitis.<sup>84</sup> There was a significant difference in the number of sick leave days between the N-acetylcysteine and placebo groups, following 4 months of treatment. However, after 6 months, although there were still fewer sick leave days in the N-acetylcysteine group (260 d vs 739 d with placebo), that difference failed to reach statistical significance ( $p = 0.09$ ). In contrast, a placebo-controlled trial of 600 mg twice-daily sustained-release N-acetylcysteine reported improvements in “general well-being” in patients with chronic bronchitis.<sup>85</sup> This result should be interpreted with caution, because there was an imbalance between the groups’ “well-being” scores at the start of the trial, and the study found no statistically significant differences between treatments in subjective symptom scores, lung function, or number or severity of exacerbations.

### Dornase Alfa

DNA is released in large amounts from necrotic neutrophils into the airway mucus. Highly polymerized DNA increases mucus viscosity in purulent lung secretions (see above). Thus, reducing the concentration of highly polymerized DNA in airway secretions should reduce mucus viscosity. Consequently, dornase alfa has been developed for treatment of mucus hypersecretion, in particular in CF.<sup>86</sup> Dornase alfa reduces the viscosity of purulent sputum in CF patients.<sup>87</sup> In a number of clinical trials, daily inhalation of dornase alfa in conjunction with standard therapies is well tolerated, usually improves the rheological properties of CF sputum, usually with associated improvement in cough clearability of secretions, and reliably improves lung function.<sup>88–91</sup> Similarly, small case study reports indicate that dornase alfa could be used in clinical management of lobar atelectasis due to retained secretions.<sup>92–95</sup> In contrast, in patients with bronchiectasis not

caused by CF, dornase alfa did not alter sputum transportability, lung function, dyspnea, or quality of life,<sup>96</sup> and may in fact be potentially harmful.<sup>97</sup>

In COPD, dornase alfa also reduces the viscosity and favorably alters the surface properties in vitro of purulent sputum from patients with chronic bronchitis.<sup>98</sup> However, phase II and III clinical trials of the effects of dornase alfa in COPD are, to date, still only reported in abstract form, with limited data on patient characteristics, disease severity, and concomitant treatment.<sup>99–101</sup> The results of the latter studies are equivocal. Consequently, dornase alfa is not recommended in clinical management of patients with COPD.<sup>102,103</sup>

### Hypertonic Saline

Inhaled hypertonic saline is currently routinely used as an expectorant in experimental studies of biomarkers in induced sputum.<sup>104</sup> When used as a mucolytic agent, it most probably works by reducing the entanglements in the airway mucus gel.<sup>105,106</sup> It may also osmotically draw liquid through the airway epithelium to dilute the inhaled saline, and thereby increase the water content of the airway mucus.<sup>107</sup> The hydrated airway mucus may, therefore, be more easily removed by mucociliary clearance, or, if sufficiently increased in volume, by cough (see above and Fig. 8). Hypertonic saline may also separate DNA from mucin in infected mucus, thereby reducing the viscosity of the mucus.<sup>108</sup>

Interest in the potential clinical benefit of hypertonic saline in airway diseases associated with mucus hypersecretion dates back to the 1970s, when it was found that, compared with normal saline, hypertonic saline increased the weight of sputum produced and doubled the rate of mucociliary clearance in patients with chronic bronchitis.<sup>109</sup> Despite this, current guidelines on clinical management of COPD do not recommend interventions that purport to increase airway mucus clearance.<sup>29</sup> Consequently, it is as treatment for the mucus clearance problems in CF that hypertonic saline is receiving the greatest current interest.

Airway surface dehydration has been proposed as the initiating event in CF lung disease.<sup>110,111</sup> The proposal predicts that airway surface dehydration produces the mucus adhesion, inflammation, and bacterial colonization characteristic of CF. Thus, as indicated above, inhaled hypertonic saline should osmotically draw water onto airway surfaces, thereby improving mucus clearance and pulmonary function, and reducing exacerbations in CF patients. Consequently, a number of clinical studies have explored the hypothesis that rehydrating dehydrated CF airways with inhaled hypertonic saline would be therapeutically beneficial. Initial short-term (single administration or up to 2 weeks administration) studies in variable num-

bers (10–52) of patients showed that inhaled hypertonic (7%) saline was well tolerated and increased clearance of inhaled radioaerosol, lung function, and effectiveness of chest physiotherapy.<sup>112–114</sup> Two more recent longer-term studies (28 days or 48 weeks of administration), again in variable numbers (24 or 164) of patients, confirmed that inhaled hypertonic saline was well tolerated and improved mucus clearance and lung function, and also reduced exacerbations.<sup>115,116</sup>

### Surfactant

A thin layer of surfactant is thought to separate the periciliary and gel layers of airway mucus.<sup>117</sup> Theoretically, surfactant decreases the adhesion of mucus to the airway epithelium and, thereby, aids cough-clearance of mucus. Experimental studies concur, by demonstrating that phosphatidylglycerol distearoyl, the longest chain saturated fatty acid component of surfactant, significantly improves experimentally modeled cough clearance.<sup>118</sup> Interestingly, smokers and patients with either chronic bronchitis or CF have reduced amounts of bronchial surfactant,<sup>119</sup> and also have abnormal sputum phospholipid composition,<sup>120,121</sup> which would tend to increase tenacity and thereby decrease the efficiency of mucus clearance. Consequently, decreasing mucus adhesivity with surfactant enhances the effectiveness of cough.<sup>122</sup> Thus, in patients with stable chronic bronchitis, aerosolized surfactant (607.5 mg dipalmitoyl phosphatidyl choline/d for 14 d) increased *in vitro* sputum transportability, improved FEV<sub>1</sub> and forced vital capacity by more than 10%, and decreased trapped thoracic gas (ratio of residual volume to total lung capacity) by more than 6%.<sup>123</sup> The beneficial effect persisted for at least a week after the end of treatment.

### Analysis

From the standpoint of treatment options for asthma or COPD, neither the European Respiratory Society,<sup>54</sup> the British Thoracic Society,<sup>53,57</sup> the American Thoracic Society,<sup>56,58</sup> nor the Canadian Thoracic Society<sup>55</sup> specifically recommends mucolytics in clinical management. Despite this, numerous mucolytic and mucoactive drugs are available worldwide, and N-acetylcysteine, bromhexine, and carbocysteine are listed extensively in international drug formularies.<sup>52</sup> This paper and a recent review<sup>124</sup> indicate that the discrepancy between drug listing and recommended treatment is related to the ambiguity in data from clinical trials of mucoactive drugs. For example, N-acetylcysteine has an impressive therapeutic profile in preclinical experimental studies, whereas in the 8 clinical studies reported here, N-acetylcysteine was beneficial, to a greater or lesser extent, in six, and of no benefit in two. In common with many clinical studies with other mucoactive drugs, not all

of the studies that found benefit from N-acetylcysteine measured an objective end point or were well controlled. This point was highlighted in a recent meta-analysis of the efficacy of N-acetylcysteine in COPD.<sup>66</sup> Of 29 reported trials, 20 were excluded from the analysis because they did not meet the inclusion criteria of being double-blind, placebo-controlled, and having data sufficient to calculate an outcome variable that permits direct comparison of studies (effect size) for both the N-acetylcysteine and placebo groups. A similar exclusion rate was found in a meta-analysis of clinical trials of mucolytics in COPD.<sup>125</sup> From 72 papers, the authors excluded 57 because they were either (1) not double-blind and placebo-controlled with treatment for at least 8 weeks, and/or (2) did not provide information on primary outcome, and/or (3) did not give error measures for outcomes. Thus, better clinical studies are required. Guidelines for clinical trials of mucolytics highlight the need for studies to be double-blind, placebo-controlled, and randomized, with well-defined primary end points, including the effects of drugs over short or long periods.<sup>126,127</sup>

It would also be useful to have data on rate of hospital admissions in response to mucolytic treatment. Hospital admission contributes greatly to the cost of treating severe COPD. A systematic review analyzed randomized, double-blind, placebo-controlled studies of oral mucolytics for exacerbations of COPD.<sup>67</sup> Of 27 trials identified, 4 were excluded because of a lack of information on primary end point. The conclusion drawn by those authors, based on the results of the remaining 23 trials, was that treatment for at least 2 months with oral mucolytic drugs (primarily N-acetylcysteine, ambroxol, bromhexine, carbocysteine, iodinated glycerol, methylcysteine, or sobrerol) was associated with a 29% reduction in exacerbation rate, compared with the control group. Days of illness also fell, but there was no effect on lung function.

Another rigorous meta-analysis of trials of oral N-acetylcysteine in COPD also found a reduction in exacerbations.<sup>66</sup> Treatment with N-acetylcysteine for 3–6 months was associated with a 23% reduction in exacerbation rate, compared with placebo.

For both of the above meta-analyses it should be noted that investigation of exacerbations tends to overestimate the annual rate because more exacerbations occur during the winter, when most studies are performed.

The conclusion from the present article and the meta-analyses<sup>67,125</sup> is that maintenance treatment with mucoactive drugs is not associated with significant improvements in lung function in patients with asthma or COPD. Until data from more rigorously conducted trials become available, it is difficult to recommend the use of mucolytic or mucoregulatory drugs in these patient populations. Nevertheless, in COPD, treatment with certain mucolytic (and antioxidant) drugs is associated with a reduction in exac-

eruations and days of illness.<sup>66,67</sup> However, the cost-effectiveness of treatment of this patient group for at least 3–6 months a year is debatable.<sup>128</sup> It is likely that patients with more severe COPD, or those who are repeatedly admitted to hospital with exacerbations of COPD, would benefit most from treatment with mucolytics, and that the treatment would be cost-effective.

### Summary

It is unlikely that expectorants, mucolytics, and mucokinetic agents will play anything other than a relatively minor role in symptom relief, reduction in exacerbations, or disease modification in asthma, COPD, or CF, although study of their effects may provide interesting insights into pathophysiology. In CF, the fundamental issue of the defect in CF transmembrane-conductance regulator will not be addressed by mucolytic therapy. In the case of COPD, the major risk factor of cigarette smoking is established, and smoking cessation is the only intervention shown to slow the decline in lung function. Many COPD patients are asymptomatic until late in their condition, by which time they may have lost the greater proportion of their lung function. Introduction of mucolytic therapy at such a late stage is unlikely to significantly affect the decline in lung function. Similarly, in asthma, inhaled corticosteroids and  $\beta_2$  agonists are highly effective in improving symptoms and reducing risk of death.

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## Discussion

**Rubin:** Actually, a bit of clarification first—those pooled study and most of the studies that were done with acetylcysteine [NAC] have looked at the oral form. I believe that aerosol acetylcysteine is very rapidly inactivated at the airway. And there are questions as to whether it may be effective at all when given as an aerosol. Is that not correct?

**Rogers:** That’s absolutely correct. The thing with N-acetylcysteine is that it’s been around for a long time, but it’s very difficult to demonstrate that it works in human airways in vivo. For example, when given orally, it’s very difficult to find N-acetylcysteine within mucus in the airways. And even when given by aerosol, again it seems to be inactivated and/or it doesn’t get into the mucus. But there are new molecules, for example nalcystelyn,<sup>1</sup> which has a variety of biochemical parameters that make it superior to N-acetylcysteine. So it looks as if there are developments in the mucolytic field, based on existing drugs, but moving them onto the next phase to make them more effective.

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**Rubin:** A follow-up question. When you talked about the potential use of mucolytics in cystic fibrosis [CF], there were you referring strictly to dornase alfa? Are there any data at all that show that acetylcysteine does anything of any value in CF?

**Rogers:** To find a good clinical study that anyone in here would recognize as a good clinical study for the effect of N-acetylcysteine in CF is not easy. Nevertheless, there have been some reports that it works. However, as it stands at the moment, Dornase alfa is really the mucolytic that stands up to scrutiny in terms of being effective in CF. And, possibly, gelsolin, if there is a lot of actin present in the mucus. In summary, I think the jury is still out with N-acetylcysteine in general, including its effectiveness in CF.

**MacIntyre:** I’m reminded of the old television ad: “It’s not nice to fool with Mother Nature!” And it’s a theme

I brought up earlier. It makes me nervous, not only with the mucus story, but with so many things we do in medicine. We always seem to be operating at the very end of the pathway, at the manifestations of disease. In contrast, I keep thinking we’re spending time taking care of the *manifestations* of respiratory failure. A lot of this pharmacology is monkeying around with reflexes that were put there for a purpose. It’s frustrating that we can’t seem to get closer to the actual *triggers* of the disease, as opposed to trying to manipulate these things at the end of the pathway. I guess it’s not really a question—it’s more of a comment.

I was really struck by the conflicting goals of cough and mucociliary clearance; that’s a real problem, because if you’re pushing on one, you may really hamper the other, and that may end up doing more harm than good. Obviously, none of these products that we’re discussing are going to be able to be recommended until they actually go through real clinical trials and show a real clinical outcome.

**Rogers:** I think that’s right. Good clinical studies are required. But you will still need to ascertain what as

pects of the mucus problem need addressing—for example, acute, protective hypersecretion versus chronic, nonprotective hypersecretion. With the latter, you start to get clinical symptoms of mucus hypersecretion, followed by the associated pathologies you see in the clinic.

And it is uncertain what parameters of the mucus problem these interventions address. At one level—and what that may be is uncertain—mucus is clearly protective. But then it switches over to being not at all protective; in fact, it becomes pathophysiological. But where you tip over from it being secretion to hypersecretion, physiological to pathophysiological, is essentially unclear at the moment. Unlike bronchospasm, where patients know if their airways are tightening up. It is easy to recommend a straight reversal of that process, but less obvious with mucus.

**MacIntyre:** That's a good point.

**Rogers:** I think that it is difficult to identify exactly what is best to do to the mucus in any given clinical situation: do you want to make it a bit more viscous, or a bit more elastic, or both—or neither—or maybe just less of it?

**Pierson:\*** I have a question about your ketchup bottles. You showed the nice full bottle on the left, with the comment that having all that ketchup in there, you could get it out easily, and a nearly empty ketchup bottle on the right, with perhaps 5% of the ketchup left, which drives us all crazy getting that last bit out. Obviously, those 2 ketchup bottles are exactly the same. One's got ketchup in it, and the other mostly doesn't.

My question is: Does the presence of a lot of ketchup (ie, a lot of mucus

in the airways) somehow facilitate emptying of all the mucus, or is there *always* that 5% of residual ketchup? In other words, is having just a rim of mucus in the airways a particular problem, or does that just represent the last bit that's always there after the bulk of the mucus has been expectorated?

**Rogers:** I think the issue is that in, for example, COPD, where there may be a relatively thin film of mucus over the airway epithelium that's beyond physiological but isn't overtly pathophysiological, then it's going to be hard to tell. However, in asthma a different scenario is possible because of the interaction between mucus and bronchoconstriction.

Airway narrowing can be defined according to Poiseuille's law. Poiseuille was essentially a French plumber who was interested in the flow of water down pipes, but the same relationship can be applied to the flow of air in the bronchi. His law states that the resistance to flow is inversely proportional to the radius of the tube, water pipe, or airway, raised to the 4th power (ie,  $1/r^4$ ). It's the raising to the 4th power that is the critical aspect of the relationship, and means that airway resistance is an exponential function of airway patency.

If you have a thin film of mucus around the inside of an airway, it might do very little to airflow under normal circumstances. However, combine bronchoconstriction with the film of mucus around the inside of the tube, and because the mucus occupies relatively more space in the narrowed lumen, the increase in airway resistance rises exponentially. So, the impact on airflow of a thin film of mucus compared with a thick layer of mucus will depend on the patient within whom that mucus resides, and then you can make a judgment as to likely pathology.

**Pierson:** But back to the ketchup bottle—if I take a brand new full bottle of ketchup, can I squirt it *all* out?

**Rogers:** Yes.

**Pierson:** Right then and there. Now I have an *empty* ketchup bottle. In other words, is there a circumstance where a lot of mucus has been secreted, and because it's all there together, I can get it *all* out, or is there inevitably a rim left? And all you're seeing when there's lots of mucus is the fact that, yes, lots more comes out.

**Rogers:** That's incredibly interesting. I don't know. I don't think those sorts of experiments have been done—how much is left when you can get a great big gob of stuff to come out. Patients can feel very much better after hawking up a large amount of mucus.

**Wojtczak:†** I'm wondering what happens to these mucus-secreting cells when one blocks exocytosis and the extrusion of mucus. Do they eventually just explode? And do you get ketchup all over the place?

**Rogers:** That is the issue! We've investigated this very aspect.<sup>1</sup> Unstimulated secretory cells contain stainable mucus. They lose the mucus after stimulation. At the IC<sub>50</sub> of our inhibitory construct, the cells contain mucus because secretion has been inhibited. If you give the top dose of the construct, there is intracellular accumulation of mucus, with more mucus in those cells than there is in the control cells. And you would think, as you suggest and I thought, that they might eventually explode.

However, we looked at mucin (MUC5AC) gene expression because we wondered whether the cells might try to turn off mucus production to compensate for the retained secretions. I was surprised to see that, in fact, as mucus secretion is inhibited, with a progressive increase in intracellular mucus, there is a concomitant progres-

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sive inhibition of MUC5AC gene expression. So, it looks as if there's a negative feedback mechanism between mucin synthesis and secretion. I was very surprised by that.

But, of course it's absolutely ridiculous that I should be surprised, because any cell producing packaged granules—for example, a mast cell or a neutrophil—must have a physiological turnoff mechanism. Because, even under normal circumstances, cells will need to register when to stop synthesizing intracellular stored product. Presumably, this mechanism holds true in pathophysiological circumstances. In the short-term studies that we've been doing in vitro, the accumulation of intracellular mucin is associated with the turning off of the mucin gene and, presumably, mucin synthesis.

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**Wojtczak:** If I could ask you a second question. Those of us who take care of CF patients are rapidly adopting hypertonic saline as an aid for airway clearance, and I think it's still not clear in my mind, and maybe in the literature, as to whether it's just a cough stimulant, or whether it's a hydrator. I would be interested in your comments on that.

**Rogers:** It's certainly a cough stimulant. And the reasons why it's a cough stimulant are debated. One of the theories is that there are nerves within the airway epithelium, and the nerves seem to penetrate between the epithelial cells. The theory is that giving hypertonic saline takes water out of the epithelium and, therefore, dehydrates it. That dehydration causes the cells to shrink and, thereby, deform, and that triggers the nerve endings, leading to reflex cough. So, that's how it could work, but it's essentially unproven.

In terms of what the hypertonic saline might do to the mucus, because

positive ions (ie, in Na<sup>+</sup>) are being introduced into the mucus, this could nullify some of the ionic attraction between the mucus molecules, and so they will tend to move apart more. So there could be thinning of the mucus. The end result could be a thinning of the mucus plus a cough response, and they're acting synergistically to get rid of mucus from the airway.

**Rubin:** I'd also like to remind you that hypertonic challenges with mannitol or hypertonic saline are extremely potent secretagogues. And so you can be increasing the amount of mucus that's being generated and sent out into the airways. A secretagogue can potentially improve the ability to expectorate.

**Rogers:** So there are various things going on.

**Howard:\*** We just completed an over-400-subject COPD study using erdosteine in a couple of different doses. I can't give you all the details on that, but I think it's the biggest study that's ever been done with a mucolytic in COPD patients. And we'll probably have a report on that in maybe 4-6 months. We found some things; no doubt about that, definitely a drug effect there. But the biggest thing that we learned is how *tremendously* hard it is to quantify how much mucus production a patient has coming into the study. Did you affect that during the study? And if you did, did it have any positive bearing on the health of the subject? I would say that in all honesty, it proved to be much, much, much, much more difficult than we anticipated. The subject is ripe for further investigation, but I would guess I would count myself among the bruised and cut, trying to look at the effect of a mucolytic on COPD.

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**Tecklin:†** Just a comment really, almost amusing, if you will, regarding the studies on inhaled N-acetylcysteine. Most of them were done 45 years ago, or even longer ago than that, when it wasn't as critically important to have double-blind randomized controlled trials. I think when we look back at those studies today, using today's criteria, the studies don't bear much weight and really don't say much. But there must have been something going for folks with CF to have used that drug for 20-30 years, anecdotally or otherwise. So I wonder if it might not be a time to maybe try the N-acetylcysteine or its derivatives, again in a fairly good trial in CF. Just a comment.

**Rubin:** There has been a preliminary trial of high-dose oral NAC in CF that did show benefit.<sup>1</sup> However, to my knowledge all of the studies that have been at all well-controlled with inhaled NAC in CF have not shown benefit, and in fact, there's been a hint that it may be detrimental. But they are going forward with further studies of higher-dose NAC as an antioxidant in CF, given as an oral agent. I think that's what you were alluding to.

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**Rogers:** Just to make the point, I think that CF is a tough nut to crack because, as well as the airway inflammation, there's the defined genetic defect in the CFTR [CF transmembrane conductance regulator], and whatever you do is only going to be palliative compared to correcting the CFTR defect. You are never going to actually treat the disease. It's just that your

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window of opportunity is so much reduced in CF compared with asthma or COPD, because the CFTR defect has such a fundamental clinical impact over and above treating mucus in isolation.

**Myers:** Duncan, you had mentioned earlier if we could increase that surfactant layer in the airways, that additional surfactant may actually enhance mucociliary clearance. Obviously, the problem in the past has been the delivery vehicle to get surfactant into the airways. A recently completed Phase 2 trial<sup>1,2</sup> looked at aerosolized lucinactant in premature nonintubated infants. And it actually was pretty safe and efficacious. So could you describe in more detail what, potentially, the benefits to *increase* that surfactant layer in the airway could be? Because it may be a reality very shortly. And which patients would benefit?

1. Finer N, Merritt T, Bernstein G, et al. A multicenter pilot study of Aerosurf delivered via nasal continuous positive airway pressure (nCPAP) to prevent respiratory distress syndrome in preterm neonates (abstract). *Pediatr Res* 2006;59:4840.
2. Mazela J, Merritt TA, Finer NN. Aerosolized surfactants. *Curr Opin Pediatr* 2007; 19(2):155-162.

**Rogers:** Bruce would know more about this than I. But I'll just make a few preliminary comments. Morgenroth and Bolz<sup>1</sup> visualized a surfactant layer that separates the upper, gel phase of the mucus from the lower, sol phase. Why it is there, I don't think is necessarily clear, but it could be that it facilitates sliding of the gel phase during mucociliary clearance. The idea behind increasing surfactant volume is that it may facilitate mucus clearance.

However, what you actually want to do in any one patient takes us back to my previous paradigm of what you want to achieve. Do you want to favor mucociliary clearance, or do you want to encourage cough? Increasing the surfactant layer is not necessarily go-

ing to enhance mucociliary clearance because you are going to disassociate the gel from the tips of the cilia. However, if treatment is intended for patients in whom cough is beneficial, raising the surfactant layer would tend to disassociate the gel phase, which could then be shifted by cough.

1. Morgenroth K, Bolz J. Morphological features of the interaction between mucus and surfactant on the bronchial mucosa. *Respiration* 1985;47(3):225-231.

**Rubin:** Two things. First, there have been studies suggesting that it prevents those cilia from getting entangled in the mucus.<sup>1</sup> It allows them to pull through. But there is surfactant dysfunction that's been well described in asthma, cystic fibrosis, and in COPD. Probably due to endogenous production of secretory phospholipase A2, as well as to albumin and other things that lead to breakdown of that and a marked increase in surface tension, or interfacial tension of airway secretions. And there have been studies of aerosolized surfactant in both COPD and cystic fibrosis that have shown benefit in lung function.<sup>2</sup> So, your comment is well taken. With improved ways of delivering surfactant, it's terribly difficult to nebulize, because it tends to foam, and the like. This may become a reality.

1. Anzueto A, Rubin BK. Mucokinetic agents and surfactants. In: Rubin BK, van der Schans CP, editors. *Therapy for mucus clearance disorders*. New York: Marcel Dekker; 2004: 307-326.
2. Anzueto A, Jubran A, Ohar JA, Piquette CA, Rennard SI, Colice G, et al. Effects of aerosolized surfactant in patients with stable chronic bronchitis. A prospective randomized controlled trial. *JAMA* 1997;278(17): 1426-1431.

**Wojtczak:** Duncan, I was curious as to whether you think that you can achieve mucolysis with mechanical measures such as vibration, whether you're using an external vibratory device and/or an internal airway vibratory device. And does that break the covalent bonds?

**Rogers:** I think we will be having specific presentations on this topic later in the meeting. However, in brief, these devices may indirectly work in a similar way to drug interventions. For example, vibrations will probably break some of the ionic bonds, hydrogen bonds, and van der Waal's forces holding the mucus molecules together, leading to thinning of the mucus. However, these bonds will re-form because they're not hard and fast. Thus, mechanical devices may not affect those sorts of bonds long-term, but may affect other types of bonding, and break up the mucus in that way.

**Hornick:** Duncan, there are some reports of using dornase alfa in bronchoalveolar lavage fluid for severe mucus obstruction in asthma.<sup>1,2</sup> I don't remember specifically if they were neutrophilic infiltration in those patients or whether it is eosinophilic, but is there any actual benefit in that type of situation? And if so, is it from the dornase alfa, or simply because of the lavage fluid that's used?

1. Durward A, Forte V, Shemie SD. Resolution of mucus plugging and atelectasis after intratracheal rhDNase therapy in a mechanically ventilated child with refractory status asthmaticus. *Crit Care Med* 2000;28(2):560-562.
2. Grealley P. Human recombinant DNase for mucus plugging in status asthmaticus. *Lancet* 1995;346(8987):1423-1424.

**Rogers:** This is put in, is it?

**Hornick:** Put in. Yes. With a bronchoscope. Right?

**Rogers:** I don't really know about that. What has been looked at is the effect of dornase alfa in patients with CF, where it seems to work, presumably by breaking up DNA, and in patients with COPD. As it stands at the moment, clinical studies in patients with COPD do not demonstrate a beneficial effect for dornase alfa. The reasons for that are not clear, but perhaps there is just not enough DNA present for any degradation of it to have an impact on overall mucus biophysical

properties. In terms of asthma, I don't think dornase alfa has been investigated, because you've got to have DNA present in the mucus, because the drug works by degrading DNA, and DNA is not a feature of asthmatic airway mucus.

**Homnick:** These are just case reports. And I'm not sure there was any real rationale for using it.

**Rogers:** In CF, there is a lot of airway pus, meaning lots of neutrophils, which presumably are dying and releasing a lot of DNA—you can measure the quantity of DNA in cystic fibrosis sputum, and it's very high. There is also neutrophilic infiltration in the airways in COPD, but dornase alfa doesn't seem to work very well, maybe because there are insufficient neutrophils or they are less chronically present compared with CF.

In asthma, where neutrophilic infiltration is not a feature of stable disease, there would be no rationale for dornase alfa to work. However, in exacerbations of asthma, there is invariably marked neutrophilic infiltration, so severe asthma is slightly akin to COPD and CF. Thus, there could be potential benefit of dornase alfa in patients with severe asthma.

**Restrepo:** I just wanted to have a better understanding about the importance of bulk movement of mucus for mucociliary clearance. This is in regard to how important it would be to hydrate that high mucin mucus. So how much importance would you have when you have bulk movement of mucus for patients who have adequate viscosity versus low viscosity of the mucus?

**Rogers:** I'm not sure I'm with you.

**Restrepo:** I guess I'm talking about, let's say CF patients, with low mucin secretions versus the hyperviscosity or

high mucin concentration in asthmatics. How much of the bulk movement, and again, going to the ketchup . . .

**Rogers:** All right. It's the cough aspect.

**Restrepo:** So, if that is actually important in impacting mucociliary clearance, again, bulk movement and actually having the property of elasticity, due to the mucin, what would be the effect of just simply hydrating the mucus that is actually low in mucin?

**Rogers:** The hydration issue is very interesting. There is dehydration in patients who are intubated, but that is probably related to the intubation. Otherwise, it would appear that, in general, mucus isn't necessarily overly dehydrated in most respiratory disease conditions, even in CF. It is all relative and not a special issue. Nevertheless, if you could hydrate the mucus to cause it to expand—as an interventional procedure, to make it more easily cleared, presumably by cough—then that might be a good idea. However, it is very difficult to hydrate mucus once it has been secreted.

Of interest is an epidemiological study<sup>1</sup> that looked at a whole range of predictors of decline in lung function in asthma and COPD, including cough and mucus. The intriguing observation from the point of view of this meeting was that in asthma less chronic cough and sputum production was associated with an accelerated decline in lung function. This indicates either that cough and sputum production was not relevant in those patients, and they had some other pathophysiology, or that an inability to cough and bring up mucus, for whatever reason—for example, poor cough reflex or mucus blocking the airways—was actually contributing to their decline in lung function. The conclusion from that analysis is that coughing up sputum is actually a good idea, because at least

you are getting rid of the excess mucus.

1. Hesselink AE, van der Windt DAWM, Pennix BWJH, Wijnhoven HAH, Twisk JWR, Bouter LM, van Eijk JTM. What predicts change in pulmonary function and quality of life in asthma or COPD? *J Asthma* 2006; 43(7):513-519.

**Rubin:** If I could just comment. It's extraordinarily difficult to hydrate secretions sitting in an airway. Bill Abraham and Adam Wanner in Miami did a study several years ago giving a lot of additional I.V. fluid to asthmatic sheep.<sup>1</sup> This is a pretty good model for human asthma, with their airway structure and size. In providing additional hydration, they got their animals much sicker, because most of the fluid extravasated into the interstitium, and did nothing to the airway.

There have been other studies<sup>2</sup> where patients with COPD would drink *huge* amounts of water—absolutely no benefit. They were up all night peeing. And if you've ever tried to hydrate secretions when you've had a cold, if you've ever hawked up luggies, for example in a bowl of water, you'll see it tends to remain fairly cohesive. It doesn't very rapidly hydrate. So once it's there, and once it's in the airway, it appears to be difficult to hydrate the mucus itself. Even the inhalation of dry powder mannitol or inhaled hyperosmolar saline is thought, perhaps, to hydrate the periciliary fluid, rather than the secretion itself—which would not be a bad thing if you were trying to cough out these things coherently.

1. Marchette LC, Marchette BE, Abraham WM, Wanner A. The effect of systemic hydration on normal and impaired mucociliary function. *Pediatr Pulmonol* 1985;1(2):107-111.
2. Shim C, King M, Williams MH. Lack of effect of hydration on sputum production in chronic bronchitis. *Chest* 1987;92(4):679-682.