WHAT'S AHEAD FOR COPD THERAPY?

An interview with William C. Bailey, MD

To provide primary care physicians, internists, and pulmonologists with insights and perspective on the most promising in-development therapies for COPD, we contacted William C. Bailey, MD, Director of the Lung Health Center and Professor of Medicine at the University of Alabama at Birmingham (UAB).

Dr. Bailey has been on the UAB faculty since 1973 and has been Professor of Medicine since 1979. He has practiced medicine, taught, performed research on the prevention of lung disease, and been involved in administrative endeavors for his entire career. Dr. Bailey has served on the Board of Directors of the American Thoracic Society and has also served on the Council of the National Heart, Lung, and Blood Institute. He has been a member of many editorial review boards of peer-reviewed journals, and has served as a frequent scientific reviewer of both scientific articles and peer-reviewed research. He has published over 200 scientific articles and has been the recipient of many grants and contracts from the National Institutes of Health and many other sources.

ASiM: Before we discuss specific new treatments in development, let's talk about how those treatments are developed. Specifically, are clinical researchers and the FDA [Food and Drug Administration] now more open to the idea of COPD [chronic obstructive pulmonary disease] endpoints other than FEV1 [forced expiratory volume in 1 second]? How important are outcomes such as quality of life?

Dr. Bailey: Clinicians are definitely more interested in endpoints such as quality of life and exercise tolerance. But the FDA still focuses mainly on the physiologic endpoint of pulmonary function. Changes in FEV1 are still the key part of the new drug application.

ASiM: Should the FDA be more interested in non-physiologic endpoints?

Dr. Bailey: Yes. Some studies have shown that certain treatments can improve exercise tolerance and quality of life, and perhaps even reduce hospitalizations, without causing significant change in the FEV1. So FEVs are clearly not the best measure of efficacy for some interventions. This means that more than pulmonary function is involved in the functional effectiveness of COPD treatments.

ASiM: What is the best way to measure quality of life in COPD?

Dr. Bailey: Several instruments are available. The St. George's questionnaire is currently the most popular. But clinicians must understand that none of the current instruments work well to evaluate outcomes in individual patients over weeks or months. Instead, these instruments are meant to gather aggregate outcomes in larger study populations. In actual practice, the traditional FEV1 and peak flow remain the proper tools for tracking treatment success. And in situations where the scientific literature does document improved quality of life, clinicians should ask the question about patient symptom improvement. In this setting, a simple tool like the 6-minute walk test can be used to document improvement.

ASiM: A recent report (Chest. 2002;121:1427) shows that the quality of life in smokers who do not have COPD was diminished by cough and phlegm. And the GOLD [Global Initiative for Chronic Obstructive Lung Disease] guidelines now list cough and phlegm as Stage 0 for COPD. Does this population of patients require treatment?

Dr. Bailey: The GOLD guidelines attempted to remind clinicians that some people with symptoms...
may not yet have pulmonary function impairment but are still at risk of significant disease. If these patients have risk factors such as smoking, then clinicians must modify these factors. So, it’s clear that pulmonary function can help grade COPD severity. The new guideline states that some patients may have no lung impairment but still have symptoms that should be followed up, especially if those patients have additional risk factors.

**ASiM:** Patients may respond differently to COPD treatment depending on their pathophysiology. Is there any progress in individualizing COPD therapy based on patient phenotype or suspected pathophysiology?

**Dr Bailey:** Tremendous progress has been made in predicting individual responses to treatments, especially with continuing development in pharmacogenetics, but there’s still a long way to go. With a few exceptions, it’s now trial and error with COPD therapy choices. There are a few subgroups of patients with COPD for whom therapy can be tailored. Patients with more severe disease tend to have frequent exacerbations, for example, and are better candidates for inhaled steroid therapy. Also, preliminary signs indicate that certain patients who take tiotropium, a long-acting anticholinergic, may have increased inspiratory capacity or decreased hyperinflation. So, some signs of drug-specific efficacy in subpopulations are becoming apparent.

**ASiM:** Are physicians underestimating the impact of exacerbation episodes in the quality of life of the patient?

**Dr Bailey:** Yes, many clinicians see diminished quality of life as part and parcel of the disease. But exacerbation rates vary from patient to patient. Among patients with COPD who have the same FEV1 and the same symptom level, 1 group seldom has exacerbations while another group has frequent exacerbations. The average patient has 2 or 3 per year, but a subgroup may have 4 or 5 exacerbations each year.

**ASiM:** How do exacerbations affect the progression of COPD pathology?

**Dr Bailey:** Most clinicians posit that exacerbations do speed progression of disease. For example existing data show that inhaled steroids can decrease the frequency of exacerbations, meaning that the anatomic remodeling of the lungs that might occur in COPD—such as the irreversible loss of the supporting structures, the development of emphysema, the fixed fibrosis of the airways—might be related to the type of inflammatory responses enriched by exacerbations. This efficacy of steroids also indicates that individuals who have more exacerbations may be similar to asthma patients, who have a more reversible disease and a tendency to get infections.

**ASiM:** What are the most promising new pharmacologic approaches to COPD?

**Dr Bailey:** The drug tiotropium, a long-acting anticholinergic, is already approved in Europe and other parts of the world. While tiotropium may be no more than a powerful bronchodilator, it does seem to work better than other agents in this class. And tiotropium can be given once a day, which is convenient for the patient. The drug’s long duration of effect may even allow near-continuous bronchodilation, which might reduce the release of the mediators that typically exacerbate inflammation. But before we discuss new drug classes, we should reiterate that learning how to better use drugs currently available in our patients is most important. I believe that clinicians may soon have the ability to be more specific about a patient’s likely response—as we already discussed with the targeted use of inhaled steroids in patients with exacerbations. For example, researchers have already discovered genes that may help in identifying patient responsiveness to leukotrienes or steroids, and many companies are pursuing this type of pharmacogenetic approach to COPD therapy.

**ASiM:** What are the specific pathophysiologic areas being evaluated by COPD genetic researchers?

**Dr Bailey:** There are many areas where candidate genes related to COPD are being evaluated: infection, inflammation, asthma, and even cystic fibrosis (CF). More than 900 distinct defects have been identified in the CF gene, each with varying effects on the severity of the CF clinical disease. Do some of those CF gene defects impact COPD, for example in those patients with COPD who also smoke? Clearly alpha-1-antitrypsin deficiency in the homozygous state can produce variations from asthma to emphysema. The heterozygous state is obviously less clinically destructive, but it may also be a risk factor for COPD. The risk may increase, for example, if this defect occurs concomitantly with a genetic tendency for another
destructive enzyme producing excess inflammation or increased oxidants. Sorting all of these potential gene combinations and gauging the connection to clinical risk will be difficult, but it's a worthy line of research.

**ASiM:** What is the mechanistic rationale for the PDE4 [phosphodiesterase 4] inhibitors?

**Dr Bailey:** Theophylline is the less-specific agent in this broad category of PDE inhibition. This agent is still used, of course, but there is a problem with toxicity and the cumbersome requirement of blood levels, which has reduced theophylline's value to many clinicians. With the more-specific agents, the bronchodilatory effect is evident as well as the possibility of some anti-inflammatory effect. Early research indicates the specific PDE4 inhibitors are helpful in patients with COPD and seem to reduce respiratory decline and produce bronchodilation. These compounds are promising, and continuing pharmacogenomic efforts may find there are individuals who are more likely to respond to these agents.

**ASiM:** What's the development status of other agents that target the inflammatory cascade in COPD?

**Dr Bailey:** Essentially all protein products of COPD-related genes are potential targets for new COPD therapies, and many of these genes do relate to inflammation. There are at least 2 antitumor necrosis factor agents in development for both asthma and COPD, as well as matrix metalloproteinase inhibitors. As the pharmacogenomic studies advance, additional potential drugs will be identified.

**ASiM:** If inflammation plays such a key role in COPD, why don't steroids work as well in COPD as they do in asthma?

**Dr Bailey:** I don't know. There is also a subgroup of asthmatics in which steroids don't work well, so more research is needed in that group as well. Some evidence indicates that certain substances inhibit steroid function in these patients. Patients with COPD, for example, may secrete inflammatory mediators that are steroid blockers or receptor blockers. Perhaps there is a molecule that can inhibit this process. There is already in vitro evidence showing steroid receptor binding can be improved by reducing these blocking substances.

**ASiM:** What's the development status of agents that might actually lead to repair of damaged tissue, improvement in FEV1, long-term maintenance of lung function, and prevention of progressive deterioration?

**Dr Bailey:** There are no agents that will be available soon, but there have been promising results with retinoids in animals. When rats with destroyed lungs were given retinoids, their lungs actually regenerated. This is exciting research, and the NIH [National Institutes of Health] has funded a clinical trial—of course, there are major physiologic and anatomic differences between the rat model and a human.

**ASiM:** What new surgical or device interventions can be expected in the next 5 to 10 years?

**Dr Bailey:** Lung volume reduction surgery is a surgical option currently being evaluated with NETT [National Emphysema Treatment Trial]. Results should be available later this year as to which COPD subgroups are appropriate for this surgery. The current trend is that patients with bullae and hyperinflation in the upper lobes of the lung are the best candidates for
lung volume reduction surgery, but NETT must define the parameters. In terms of home care, there are increasingly convenient oxygen devices that are smaller and contain liquid oxygen. Some devices can reduce the flow between breaths. A lighter oxygen device is easier for a patient to carry and allows a patient to exercise. But education requirements may be higher for these new devices, and the reimbursement rates may not be any higher, so home health companies may not have the incentives to introduce these devices to patients. In inpatient care, noninvasive ventilation has increased in both use and value in patients who have severe COPD. These methods reduce the need for intubation and may help keep patients from being placed on ventilatory assistance—which reduces some of the risk associated with a stay in the intensive care unit.

**ASiM:** You mentioned the NETT. What other large COPD multicenter clinical trials expect to publish results in the next few years?

**Dr Bailey:** The Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial is investigating whether tiotropium changes the natural history of COPD when given simultaneously with the patient's other medications for an extended period. UPLIFT is a 4-year longitudinal study funded by the manufacturer. Currently, smoking cessation is the only intervention other than oxygen in end-stage disease that clearly changes the natural history of COPD. Smoking cessation alters the decline of FEV₁, while oxygenation improves the patient's life span and decreases hospitalizations and exacerbations. At this point, there is no known intervention that fundamentally changes the clinical COPD situation. Some interventions may decrease symptoms and patient hospitalization but do not extend the patient's life span or change the rate of deterioration in pulmonary function.

**ASiM:** What are the most exciting developments on the horizon in COPD research?

**Dr Bailey:** There is much that can be accomplished with treatment now available for patients with COPD. The first priority is to ensure that more clinicians and more patients know about the existing therapy. Diagnosing all cases of COPD would be a first step but, in terms of research and new treatments, unraveling the genetics of COPD will lead to the greatest long-term gains. With more genetic information on COPD, clinicians will be able to target therapy. There are many genetic factors that predispose people to environmental influences. COPD is a multifactorial disease and if it can be determined why an individual patient is declining, then more specific treatment can be provided. This breakthrough is probably 10 years away, but I think it will happen.