Chronic Obstructive Pulmonary Disease A View from the NHLBI

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The past decade has witnessed great progress in chronic obstructive pulmonary disease (COPD) research. New drugs have been developed and tested, indications for lung volume reduction surgery (LVRS) have been determined, and a growing base of scientific evidence now documents the efficacy of various therapies for symptoms and exacerbations. This advance in knowledge shatters the old conception of COPD as a hopelessly untreatable condition (1–4). It is clear that many patients with COPD can benefit from aggressive management, with a decrease in the frequency of hospitalizations and improvements in quality of life and survival. In addition, basic and clinical scientists have now identified cells, mechanisms, and molecules that appear to play key roles in disease pathogenesis. Additional novel treatments are on the horizon. The good news about COPD is getting out as many organizations are working effectively to increase awareness of the disease (5).

Despite advances in care, the COPD epidemic persists, causing more than 120,000 deaths per year in the United States alone. COPD's position as the fourth leading cause of death in the United States is ominous and the probability of the number of cases rising even further is disturbing. Population-based surveys show that as many as 24 million people in the United States have airflow limitation consistent with COPD and that half or more of these cases have not yet been diagnosed (6). Despite the availability of effective treatments for COPD, no existing therapy halts or reverses the progressive and accelerated decline in lung function that is characteristic of this condition. We are far from having a cure for COPD, and in fact, the most basic questions about this disease remain unanswered:

- Why do only a minority of smokers develop clinically significant COPD?
- Why is there great heterogeneity in the presentation of COPD?
- Which pathogenetic pathways are critical, and how can they be modulated therapeutically?
- Why does the disease continue to progress even after smoking cessation?
- How can the lung injury that characterizes COPD be reversed?

Better means of preventing and treating COPD are urgently needed, but it is not entirely clear what studies should be done.

The strategic decisions in COPD research—which investigative approaches to use, which hypotheses to test, which pathways to explore in detail, which basic findings to translate into human studies, and which therapeutic targets to test—are perhaps more difficult to make now than ever before. As opportunities for investigation in COPD have expanded, the pulmonary community's task of choosing the most effective directions and approaches for COPD research has become even more complex, and wise choices are critical to secure future success.

In this essay, we encourage the pulmonary medical community to think about needs, opportunities, and the most productive approaches for research in COPD. We summarize new research directions and findings, how the disease itself is evolving, what research activities are currently underway, and how the infrastructure and organization of the research enterprise in the United States is adapting to new biological and technological challenges and advances that offer unprecedented opportunities for COPD research. We close with a call to action that presses the pulmonary community to widen its horizons and build interdisciplinary teams to better confront the problems of COPD.

A VISION FOR BASIC RESEARCH

The pathogenetic view of COPD has expanded significantly from what was understood a decade ago. Moving beyond the original protease–antiprotease hypothesis, investigators now know that a COPD-like phenotype can be produced in animal models not only by manipulation of proteolytic pathways but also through targeting of the immune system or perturbation of apoptotic control in the pulmonary endothelium (7, 8). Distinctive immune features, such as nodules rich in both T and B cells, are found in the pulmonary lesions of patients with COPD, at least in later stages of disease (9). Altered T- and B-cell responses are also seen in the peripheral blood of patients with COPD, suggesting that immunodysregulation in COPD extends beyond the lung (10, 11). Such evidence supports the concept that multiple mechanisms converge to produce the final COPD phenotype and may also explain why the COPD population has such diverse clinical presentations and lung appearances by computed tomography imaging. In addition, the emerging view of COPD as a systemic, immunologically based disease offers an explanation for the multiple comorbidities seen in these patients.

With this better understanding of pathogenesis there have come many questions for future research and for the translation of basic findings into clinical application. What are the links between immune dysfunction and extracellular matrix remodeling or smoke-related proteolytic events? What roles do oxidative stress and associated protein modifications have in pathogenesis? Can all the diverse pathways implicated by animal models be verified and validated in patients with COPD? Is it possible to identify points of convergence? Is the immune infiltration seen in the airways of COPD-affected individuals a primary mechanism of disease development or the end result of tissue-localized

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reactions? Is there a pathogenic role for altered function of peripheral immune cells? Do these disparate findings explain the diversity of clinical phenotypes? Does the association of emphysema and lung cancer (12) reflect a common pathogenic mechanism? These questions are important because their answers may reveal novel therapeutic targets, support the wider application in COPD of drugs already in use for other diseases, and suggest strategies for lung regeneration using newly characterized precursor cells.

An important research opportunity in COPD is the identification of predisposing genetic factors. Strong rationale for this line of research is found in the resistance of some smokers to the development of COPD, the importance of genetically determined α_1 -antitrypsin deficiency in a minority of the patients, and the realization that a fraction of patients with COPD have never smoked (6). Clarification of COPD genetics will require studies of large, well-characterized cohorts of patients with COPD (13). One such cohort (COPDGene study) is currently being recruited with the concerted effort of pulmonary and patient communities. Ultimately, genetic data will need to be analyzed in conjunction with a detailed history of environmental exposures. As cigarette smoking declines, it will be increasingly important to study the role of occupational exposures in the causation of this disease (14).

A VISION FOR CLINICAL RESEARCH

Clinical characterization of patients with COPD and research on therapies have progressed enormously in the past 10 years. Although no pathognomonic sign or diagnostic blood test yet exists for COPD, less expensive and easier to use spirometers have facilitated its diagnosis, and sophisticated imaging techniques offer new possibilities for patient stratification and early recognition of disease. The heterogeneity of COPD has been clarified both by molecular characterization of pathobiological diversity and evidence that a multidimensional index (BODE [body mass index, airflow obstruction, dyspnea, and exercise capacity]) is better able to predict survival than FEV₁ alone (15).

Given the heterogeneity of COPD, most investigators do not anticipate the discovery of a single “magic bullet” intervention but rather expect that patients will need personalized treatments (1, 16). Many treatment alternatives are now available, but research is needed to optimize management strategies at the individual level. There are effective pharmacologic and counseling treatments for nicotine addiction, although there are continuing needs to increase the success of quitting and to better understand the molecular mechanisms of cigarette addiction (17). Long-acting β_2 -agonists, anticholinergics, phosphodiesterase inhibitors, and combinations of these with antiinflammatory agents have been shown to improve airflow obstruction (18), and even better outcomes may be possible using combination treatments. Further trials are needed to optimize these drug combinations (2). More extensive use of vaccine prophylaxis may reduce acute exacerbations and slow disease progression, but additional research is needed to prove vaccine efficacy and determine the best dosages and formulations. Treatments such as LVRS (19), pulmonary rehabilitation, and oxygen therapy have been shown to be effective in certain groups of patients with COPD (20, 21), but questions remain regarding the optimal approach to pulmonary rehabilitation and proper indications for oxygen therapy (22–24).

Of particular importance for future research is the fact that multiple concurrent pathologic conditions coexist in patients with COPD (25, 26). Although the advanced age of many patients with COPD no doubt contributes to the increased incidence of cardiovascular disease, lung cancer, diabetes, osteoporosis, and depression observed among these patients, age alone cannot fully

account for this observation. There appears to be a complex interplay between disease states, environmental exposure, and genetic predisposition (25). In fact, COPD may actually be a multiple organ syndrome with systemic manifestations directly involving the cardiovascular, musculoskeletal, endocrine, and neurologic systems (27, 28). Research is needed both on the pathogenetic mechanisms of comorbidity and on the practical question of how to coordinate the clinical management of COPD and associated extrapulmonary manifestations.

THE VISION FOR NHLBI-SPONSORED PROGRAMS: FROM THE PRESENT TO THE FUTURE

The NHLBI has a long-standing commitment to COPD, including prevention, treatments, and cure. We have supported major studies of COPD, such as the Lung Health Study, which showed that smoking cessation interventions improve survival, and the National Emphysema Treatment Trial, which demonstrated the value of LVRS in a selected group of patients. The COPD Clinical Research Network has recently been established and is now testing several drug treatments in those with moderate-to-severe disease and frequent exacerbations. The recently funded Specialized Centers of Clinically Oriented Research in COPD have brought together basic and clinical investigators to foster translational research in a continuum from pathobiology to therapy. The NHLBI has also established the Lung Tissue Research Consortium to promote tissue-based research on the pathogenic mechanisms of COPD. The recently started Long-term Oxygen Treatment Trial, a multicenter study in collaboration with the Centers for Medicare and Medicaid Services, will explore the efficacy of oxygen treatment in early stages of the disease. A new research program, called SPIROMICS, which will categorize patients with COPD on the basis of molecular fingerprinting and seek to identify and validate intermediate outcome measures that will expedite future clinical trials, is planned for initiation this year. These studies, together with the large number of investigator-initiated research projects that NHLBI supports, constitute a robust, thorough, and integrated program in COPD research.

To promote translation of research via dissemination, implementation, and diffusion of research findings, the NHLBI has recently launched the “COPD Learn More Breathe Better” campaign (<http://www.nhlbi.nih.gov/health/public/lung/copd/index.htm>) to promote COPD awareness, increase diagnostic rates, and combat the aura of stigma that still surrounds COPD. With the help of numerous stakeholders, the NHLBI is currently reaching out to both the public and to general practitioners to stress the new and diverse presentations of COPD, the importance of early diagnosis, the availability of treatments that improve longevity and quality of life, and the need for aggressive management of those with this disease.

WORKING TOGETHER FOR AN EXCITING FUTURE

Improved methods for patient care and the creation of new tools involving genetics, genomics, proteomics, metabolomics, and molecular imaging show promise for better risk determination and population stratification, identification of specific therapeutic targets, and personalized treatments. Efforts toward improving the methodology for clinical studies, such as the creation of translational networks and practice-based trials as well as the identification of specific intermediate outcomes, will improve patient management, enable proof-of-concept studies, maximize existing treatments, and accelerate testing of new therapeutics (29–31). Novel therapeutic approaches, such as local control of mucus production and inflammation, lung repair via stem cell

therapy, and individually targeted prevention and treatment of the disease, may soon be within reach. These represent important future directions in COPD research (32, 33). New efforts are necessary to explore the multiple comorbidities associated with COPD, not only for optimal patient management but also to better understand the basic biological mechanisms and pathways that cause many, apparently different, diseases to intersect, and to ultimately highlight potential targets for intervention.

COPD is a common and complex problem that requires a multifaceted approach. It is clear that such an effort needs, in addition to the NHLBI, the collective participation of many parties, including patients, family physicians, industry, and the pulmonary community. Together, we can make a real difference for the future of these patients through a sustained and coordinated effort by all stakeholders to address the wide range of issues involved with this devastating disease.

The vast array of basic and clinical research programs currently ongoing or in development offers the pulmonary community opportunities to participate in research, including possibilities for partnering with the pharmaceutical industry to pursue common goals. Pulmonary physicians can contribute to these efforts by educating patients and other family physicians about COPD, giving feedback on the program that is currently carried forward by the NHLBI, and supporting patients' participation in research.

COPD is a problem with an enormous public health burden that will require a matching effort and commitment from all stakeholders to achieve tangible progress in reducing morbidity, mortality, and health care utilization. The NHLBI and the pulmonary community need to push the frontiers of science to advance our knowledge, improve current treatments, and, ultimately, find cures to this devastating disease. The achievement of these goals will require a large and diverse workforce of committed physicians and scientists. The pulmonary medicine and biology communities must reach out to colleagues in other basic and applied disciplines to adopt, adapt, and apply relevant concepts and approaches to this field. The scientific opportunities and challenges in COPD are many and great. We must bring together the best and brightest minds with diverse backgrounds and talents in an interdisciplinary environment to solve the many unanswered questions about COPD.

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