Mechanisms of COPD*

Clinical Relevance of Research Presentations at the Thomas Petty Aspen Lung Conference 1999

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It is a privilege to have been asked to summarize my views of the clinical relevance of this conference. It is always a wonderful honor to be asked to participate in the Thomas Petty Aspen Lung Conference, which I attended for the first time in 1968. This is a conference that I've always thoroughly enjoyed. I have invariably gone away from it inspired and motivated to look differently at some aspects of lung research and clinical medicine. It is exciting to see so many basic and clinical investigators gathered to discuss COPD and emphysema, particularly now when for the first time in many years there are new therapeutic modalities on the horizon.

If a busy clinician were to attend this conference, he would ask each presenter the following question: What can I take to my patients and use tomorrow, next month, or next year? Let me state at the outset that little of the material presented at this conference will have an immediate impact on the clinical practice of pulmonary and critical care medicine, but the future things look promising. Clearly, one cannot summarize all or even most of the material from the conference, so I will mention what most appealed to me. Please don't take this to imply that what is not mentioned is less important, but rather that I will speak to what I understand the best.

Dr. Milic-Emili started the conference by reminding us that there is not a good correlation between the dyspnea experienced by our patients with COPD and standard pulmonary function tests. He pointed out that hyperinflation correlates better with dyspnea in some provocative tests such as histamine, and encouraged us to reexamine the tests we use to assess the results of any intervention. His evocative presentation raised an important issue that must be faced by any clinical trial, i.e., what to measure and what measures validate an intervention. His views were particularly germane, since clinical investigators in the area of lung volume reduction surgery are questioning whether the FEV₁ should be used as the major outcome parameter. Hopefully, we will examine other and perhaps better ways to characterize the clinical and physiologic aspects of COPD.

There was a great deal of data presented on the animal models for emphysema. Dr. Shapiro gave an excellent summary of this area of research. My conclusions from the presentations were that the early simplistic model using papain and simple proteases to induce emphysema was too simple. Current animal models have become more complex and involve many more cellular and subcellular systems than I could comprehend. Details of this work will be addressed elsewhere. What is exciting for the clinicians is that this new interest in animal models and techniques to detect early emphysema will eventually come into the clinical arena and allow testing of new drug interventions in a more rapid fashion. One of the methods discussed was the quantitative analysis of the CT of the chest for humans, which has been recently reported by Dr. Harvey Coxson and collaborators, could be adapted to the animal model. Use of this technique would be an excellent way to track the progression or regression of emphysema in a noninvasive way. One might ask, why talk about animal models in a clinical summary? Well, the excitement and skepticism were rampant throughout the conference on the subject of retinoic acid as a possible therapy for COPD. It has been reported by Masaro et al to cause growth of new alveoli in an animal model of emphysema. Clearly, if this effect is reproducible in human studies, it will revolutionize our treatment of emphysema. A human clinical trial is scheduled to start shortly.

Dr. Jeffery reviewed the inflammation seen in obstructive airway disease and stressed that while asthma and COPD both involve the large and small airways, only COPD includes involvement of the lung parenchyma. Many speakers reminded us that smoking produces inflammatory changes in lung (and perhaps a systemic inflammatory reaction), but only 15 to 20% of heavy cigarette smokers develop severe respiratory impairment with airflow obstruction. It seemed to me that many of the speakers implied, without actually stating it, that the latter group of smokers represented those who developed significant emphysema. Dr. Hogg presented a summary of the excellent work done at St. Paul's Hospital in Vancouver and offered a unique hypothesis for why the latter group of patients develops severe respiratory insufficiency. He presented evidence that latent adenovirus infection in the distal airways and lung may produce an enhanced inflammatory response to cigarette smoke. This amplified inflammatory response is present even long after the active infection has resolved. It therefore could lead to an amplification of inflammation and hence a more vigorous release of enzymes that disrupt the pulmonary parenchyma to produce emphysema. He also reviewed data on the quantitative analysis of the CT of the chest, which has been validated using quantitative histology. Since I have been a collaborator in the development of this technique, my view may not be totally unbiased, but I believe it shows great promise. It offers a way of improving patient selection for therapeutic interventions, as well as a means of following the effectiveness of therapy.

Dr. Nadel suggested that in the near future there might be a new way to address mucus hypersecretion in our patients and suggested new pharmacologic interventions are not far away. Dr. Casaburi reviewed the extensive literature on exercise in COPD and reminded us that, while rehabilitation does not appear to change mortality, it does improve the quality of life of our patients. Dr. Wouters offered a very preliminary hypothesis that malnutrition might be part of a systemic inflammatory reac-

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(CHEST 2000; 117:294S–295S)
tion and summarized the data from his laboratory. From these last two presentations, one could conclude that the role of nutritional support, exercise, and anabolic agents needs to be evaluated in larger controlled clinical trials.

The role of corticosteroids, which remains the only widely used anti-inflammatory drug used in the therapy of COPD, was reviewed in detail. The conclusions were fairly straightforward, namely that systemic corticosteroids appear to have a modest effect on decreasing the length of exacerbations in hospitalized patients, but clearly do not improve long-term outcome. Hence, long-term steroid use was not supported. Inhaled corticosteroids have recently been tested in several large multicenter studies that have shown a modest decrease in the number and duration of exacerbations, but do not prevent the decline in airway function.

The take-home message for clinicians is that, while there is no immediate new effective wonder drug available to us, the future looks brighter and more exciting since more research is being done than ever before. It is our hope that these new interventions will be successful and available to our patients in the future.

Protease Injury in the Development of COPD*

Thomas A. Neff Lecture

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*CHEST 2000; 117:295S–298S

Proteases are a class of hydrolytic enzymes mediating irreversible disruption of protein amide bonds. Based on the key amino acids used by proteases to attack the targeted bond, these enzymes are commonly classified into four distinct groups: serine, metallo, aspartate, and cysteine.1 Proteolysis mediated by these enzymes is vital to many aspects of normal cell function, including regulation of the interface between cells and the extracellular matrices in which they reside. And yet, unchecked extracellular proteolytic activity is linked to excessive destruction of extracellular matrices and untoward clinical events such as bleeding, joint destruction, and osteoporosis.2–4 Since the discovery that deficiency of a serine protease inhibitor, α1-antitrypsin (AAT), is a cause of panlobular lung destruction, the pathogenesis of emphysema has been strongly linked to the excessive action of proteolytic enzymes.5 This discovery prompted the widespread belief that COPD, and smokers’ emphysema in particular, is due to excessive activity of the major serine protease inhibited by AAT, neutrophil elastase. However, numerous attempts in the ensuing 35 years to prove this hypothesis has instead left considerable doubt as to the role of neutrophil elastase and possibly proteases in general in the development of smokers’ emphysema. This discussion will attempt to provide a current perspective on the role of proteases in the pathogenesis of COPD.

PROTEASES POTENTIALLY INVOLVED IN THE PATHOPHYSIOLOGY OF COPD

Is excessive extracellular proteolysis actually involved in the pathogenesis of emphysema? The reason for asking this question is that morphologic abnormalities developing during the course of emphysema show progressive loss of alveolar tissue with little evidence of necrosis. Loss of tissue without necrosis is typical of an apoptotic process, a process not envisioned by the early framers of the protease/protease inhibitor imbalance hypothesis. However, the fact that patients with AAT deficiency are susceptible to emphysema and mice with metalloprotease deficiency are protected sustains the notion that proteases play a critical role in the pathophysiology of COPD.6 It should be noted in this regard that a major signal for cellular apoptosis is loss of extracellular matrix contact.7 Most cells are ready to commit to programmed cell death (apoptosis) when faced with an unsolvable loss of matrix attachment. Indeed, cellular survival may depend on signals from the integrin family of adhesion receptors continuously sensing the extracellular milieu.8 Thus it is likely that the development of emphysema involves apoptosis of cells of the alveolar wall following focal proteolytic damage to their underlying matrix (or the cells themselves). To what extent excessive proteolysis actually promotes emphysema changes by initiating an apoptotic program within the lung remains to be defined.

The major difficulty with the idea that a relative deficiency of AAT, and by inference excessive neutrophil elastase activity, underlies the majority of emphysema is that most patients are not demonstrably deficient in AAT.9,10 This does not mean that excessive and likely highly focal neutrophil elastase activity in lungs is unimportant to collagen and elastin degradation leading to COPD. Rather, this observation suggests that enzymes in addition to neutrophil elastase may be important and in some cases critical. Experiments in animals indicate that elastases are the most potent enzymes in causing emphysematous changes in the lung.5 The known mammalian elastases are listed in Table 1. These enzymes include members of the serine, cysteine, and metalloprotease families, indicating many enzymes in addition to neutrophil elastase have the potential to damage the delicate elastin network of lungs. This point is illustrated by recent studies of mice with targeted deficiency of the enzyme macrophage metalloelastase (MME).8 Such mice are protected from emphysematous changes induced in C57/J129 mice by daily cigarette smoke exposure for 4 to 6 months. Indeed MME−/− mice show defective alveolar macro-