The Answer Is Fifteen Percent

What Is the Question?

Recently, while making bedside rounds in the ICU, I asked a medical student on my team to describe the incidence of a finding in a disease that the team was discussing. The student had difficulty answering the question, and the senior resident on our service quickly replied “ten percent.” He then turned to the flustered student and said “always answer ten percent or ninety percent; you’ll usually be right!” The “10 and 90” rule doesn’t always work, of course, but clinicians do like round numbers. One such number that fellows in my clinic become familiar with is that about fifteen percent of smokers (between ten and twenty percent, depending on the study) develop clinical signs and symptoms of COPD.

Why only a fraction of cigarette smokers develop clinical manifestations of COPD is an intriguing and important question. One obvious conclusion is that there is some factor or factors specific to the subpopulation of smokers who develop COPD that is different from other smokers. Efforts to identify these important risk factors have been a focus of research in COPD.

Either environmental or genetic factors may influence the development of COPD. Environmental factors that have been associated with the development of COPD include viral infections, especially during childhood, air pollution, and most commonly, smoking.

Genetic factors have attracted interest as they may help identify a subpopulation of smokers at risk for the development of COPD. Evidence that genetic factors are associated with the development of COPD comes from several sources.

Familial clustering of COPD has been observed, and twin studies have supported the concept of a genetic predisposition to COPD. Statistical models suggest that there are likely to be multiple genes that contribute to the genetic predisposition for COPD.

Several types of investigative tools may be used to study the relationships of genetic factors to the development of lung disease due to smoking. These include linkage analysis, whole genome screens, discovery of new genes by messenger RNA differential display, animal models, and study of candidate genes by association analysis. Linkage analysis involves the study of the relationships between the occurrence of COPD with that of known genetic markers in affected families. Linkage analysis is fraught with difficulties in COPD research because the genetic predisposition to COPD is likely to be polygenic. Additionally, COPD usually develops late in life so that several generations cannot be studied simultaneously by linkage analysis. Whole genome screening suffers from the drawback that it can only identify areas on chromosomes where there might be candidate genes, rather than identifying specific genes.

Messenger RNA differential display is a technique where the messenger RNA from cells of affected patients is compared with that from control subjects. Differences in messenger RNA expression between cells from affected patients and control subjects may be used in the future to find new genes that may be associated with COPD. Animal models for COPD have been studied, but none to date have been truly satisfactory for the study of human disease.

One promising avenue for genetic studies in COPD has been the study of candidate genes by association studies. Genes are selected for study based on knowledge of the pathophysiology of COPD. The occurrence of polymorphisms of these genes is studied with respect to disease occurrence and severity in unrelated individuals. One problem with this approach is that one may only study genes that are known. Another problem is that it can be difficult to control for ethnic origin. This latter point is important, as different ethnic groups may have different frequencies of alleles for a particular gene as well as different frequencies of the disease being studied. If an association is found between a gene and disease, the relationship may be due to linkage disequilibrium rather than a causal role.

Among the candidate genes that have been studied in COPD are genes that effect the production of proteases and antiproteases, genes that modulate the metabolism of toxic substances in cigarette smoke, genes in-
volved with mucociliary clearance, and genes that influence inflammatory mediators.6,7

One important candidate gene that received early and extensive attention is that for α1-antitrypsin.8 Studies concerning this antiprotease and its primary target enzyme, neutrophil elastase, ignited theories concerning the role of proteases and antiproteases in emphysema.9 Other antiproteases that have been studied include α1-antichymotrypsin, α1-macroglobulin, secretory leukocyte protease inhibitor, elafin, and tissue inhibitors of metalloproteases.6,7 Macro- 

phage-derived proteases such as the cathepsins and matrix metalloproteases have received some attention.6 Polymorphisms of enzymes that detoxify reactive substances in cigarette smoke could play important roles in the pathogenesis of emphysema. Metabolizing enzymes that have received study in COPD include microsomal epoxide hydrolase, glutathione S-transferases, and cytochrome P4501A1.6,7 Association studies6,7 of the cystic fibrosis transmembrane regulator gene with COPD have been con- 
ducted because of hypotheses that deranged mucociliary clearance in heterozygotes or in persons with variant alleles may contribute to the development of respiratory illness. These studies have not be- en conclusive. Because inflammatory processes are likely to be important in the pathogenesis of COPD, genetic polymorphisms that effect inflammatory mediators or the immune response may be of interest. Candidate genes that are involved with inflammatory processes and have been the subject of study include tumor necrosis factor-α, immunoglobulins, and vitamin D-binding protein (VDBP) [also known as Gc-globulin].6,7

VDBP was named for its role in binding circulating vitamin D, but it also has effects on inflammation. The gene for VDBP is located in humans on chromosome 4q11-q1310 and has three common alleles, identified as Gc1F, Gc1S, and Gc2.11 Com- 
plement factor C5a and its degradation product, C5a des Arg, are very potent leukocyte chemoattractants that have enhanced activity in the presence of serum. Kew and Webster12 identified VDBP as a serum factor that enhances the activity of C5a and C5a des Arg. In 1991, Metcalf and coworkers13 performed bronchoscopy with BAL on three groups of subjects: nonsmokers, asymptomatic smokers, and patients with COPD. Using an enzyme-linked immunosor- 
bent assay, they discovered that functionally active VDBP can be detected in BAL fluid and that levels are higher in COPD patients and asymptomatic smokers when compared with nonsmokers.13 This suggests that VDBP may play a role in the neutrophilic inflammation that occurs in the lungs of patients with COPD. In addition to playing a role in neutrophil chemotaxis, VDBP may act as a macro-

phage activating factor. Yamamoto and Homma14 demonstrated that the in vitro activation of mouse peritoneal macrophages required the presence of a serum factor; the precursor of this serum macro- 

phage-activating factor was shown to be VDBP.14

Because of the potential role for VDBP in the development of COPD, studies have been carried out seeking an association between the occurrence of COPD and the three common polymorphisms of the gene for VDBP. Three studies15-17 have suggested that the Gc2 allele is protective against the development of COPD, while one study18 has failed to confirm this result. Additionally, Horne and cowork- 
ers16 suggested that those individuals homozygous for Gc1F may be at increased risk for COPD. In this issue of CHEST (see page 63), Ito and coworkers have published an important contribution to this field. They compared the frequency of genotypes for VDBP in a group of patients with known COPD with a control group of “healthy smokers” from a special clinic devoted to disease prevention. Ito and coworkers demonstrate that there is a significantly increased proportion of individuals homozygous for the Gc1F allele in patients with COPD when compared with healthy smokers in their study. They also have found that COPD patients with the Gc1F allele have a larger decline over time in the FEV1 and more low attenuation areas on high-resolution CT than those COPD patients without this allele. These data sug- 

gest that VDBP polymorphisms have an important role in the development of COPD.

The design of this study is significant in several respects. First, it represents an important example of an association study examining a likely candidate gene in regards to the development of COPD. Second, because the study was conducted in Japan on native Japanese individuals, the study population is likely to be homogeneous in terms of allele and disease frequency, potentially making conclusions about associations more valid. The fact that the Gc1F allele occurs in a higher frequency in Japanese than in white populations, and that Gc1F has previ- 
cously been shown to be a risk factor for COPD development,16 could have important implications for the development of COPD in Japan. Finally, the study employed high-resolution CT scores of low attenuation areas as well as pulmonary function data in the assessment of severity of COPD, adding further strength to the conclusions of the study about relationships between COPD and polymorphisms of VDBP.

The results from Ito et al will need to be con- 

firmed and extended. Despite the suffering caused worldwide by COPD, research for COPD has been relatively underfunded compared with other diseas- 
es,19 and many important questions have been un-
answered. Ito and colleagues are to be congratulated for beginning to provide answers and insight regarding the selective occurrence of COPD in the smoking population.

COL Daniel R. Ouellette, MC, USA, FCCP
Ft. Sam Houston, TX

Dr. Ouellette is the Pulmonary Consultant to the US Army Surgeon General and the Associate Program Director for the Pulmonary and Critical Care Medicine Fellowship Program at the San Antonio Uniformed Services Health Education Consortium.

Dr. Ouellette is on active duty, US Army, is a member of the Speaker’s Bureau and Consultant, Ortho Biotech, and is on the Speaker’s Bureau, Pfizer. The opinions or assertions contained herein are the private views of the author and are not to be construed as reflecting the views of the Departments of the Army or Defense.

Reproduction of this article is prohibited without written permission of the Departments of the Army or Defense. The opinions or assertions contained herein are the private views of the author and are not to be construed as reflecting the views of the Departments of the Army or Defense.

To B or Not To B? It Still Is the Question

The relatively high sensitivity and specificity of open-lung biopsy (OLB) in chronic pulmonary diseases has made it a valuable diagnostic tool for those diseases. OLB is a surgical procedure requiring anesthesia and is associated with risks. Consequently, OLB is usually not considered a first-choice procedure in the diagnosis of most lung processes. OLB has been previously used in ARDS to identify the acute pathologic process (diffuse alveolar damage), and the ensuing fibroproliferative damage reported as ARDS progresses. In addition, OLB has been used when less invasive technology (eg, transbronchial biopsy) fails to provide a diagnosis for a rapidly deteriorating patient with ARDS. Most patients with ARDS are receiving mechanical ventilation and are critically ill at the time of OLB. This increases the risk of morbidity and mortality associated with the procedure and explains, in part, the infrequent reports of OLB during ARDS.

The earliest studies of OLB in patients with ARDS reported during the late 1970s and early 1980s were observations of small numbers of patients, and describe the acute pathologic and the late fibroproliferative changes. In spite of the institution of alternative therapies based on OLB findings (including high-dose corticosteroids), reported mortality remained high (57 to 78%).

Warner et al studied 80 patients who had OLB early in the course of acute respiratory failure. OLB functions as a chemoattractant in the lower respiratory tract. Am Rev Respir Dis 1991; 143:844–849


www.chestjournal.org CHEST / 125 / 1 / JANUARY, 2004 5

REFERENCES


To B or Not To B? It Still Is the Question

The relatively high sensitivity and specificity of open-lung biopsy (OLB) in chronic pulmonary diseases has made it a valuable diagnostic tool for those diseases. OLB is a surgical procedure requiring anesthesia and is associated with risks. Consequently, OLB is usually not considered a first-choice procedure in the diagnosis of most lung processes. OLB has been previously used in ARDS to identify the acute pathologic process (diffuse alveolar damage), and the ensuing fibroproliferative damage reported as ARDS progresses. In addition, OLB has been used when less invasive technology (eg, transbronchial biopsy) fails to provide a diagnosis for a rapidly deteriorating patient with ARDS. Most patients with ARDS are receiving mechanical ventilation and are critically ill at the time of OLB. This increases the risk of morbidity and mortality associated with the procedure and explains, in part, the infrequent reports of OLB during ARDS.

The earliest studies of OLB in patients with ARDS reported during the late 1970s and early 1980s were observations of small numbers of patients, and describe the acute pathologic and the late fibroproliferative changes. In spite of the institution of alternative therapies based on OLB findings (including high-dose corticosteroids), reported mortality remained high (57 to 78%).

Warner et al studied 80 patients who had OLB early in the course of acute respiratory failure. OLB