are fundamentally different diseases: Asthma is viewed as largely an allergic phenomenon, whereas COPD results from smoking-related inflammation and damage. Determination of the validity of the Dutch hypothesis versus the British hypothesis awaits identification of all of the genetic predisposing factors for asthma and/or COPD, as well as the interactions between these postulated genetic factors and environmental risk factors.

Longitudinal studies that compared airway responsiveness at the beginning of the study to subsequent decline in pulmonary function have demonstrated that increased airway responsiveness is clearly a significant predictor of subsequent decline in pulmonary function. Thus, airway hyperresponsiveness is a risk factor for COPD.

RESPIRATORY INFECTIONS

The impact of adult respiratory infections on decline in pulmonary function is controversial, but significant long-term reductions in pulmonary function are not typically seen following an episode of bronchitis or pneumonia. The impact of the effects of childhood respiratory illnesses on the subsequent development of COPD has been difficult to assess due to a lack of adequate longitudinal data. Thus, although respiratory infections are important causes of exacerbations of COPD, the association of both adult and childhood respiratory infections with the development and progression of COPD remains to be proven.

OCCUPATIONAL EXPOSURES

Increased respiratory symptoms and airflow obstruction have been suggested to result from exposure to dust and fumes at work. Several specific occupational exposures, including coal mining, gold mining, and cotton textile dust, have been suggested as risk factors for chronic airflow obstruction. Although nonsmokers in these occupations can develop some reductions in FEV_1, the importance of dust exposure as a risk factor for COPD, independent of cigarette smoking, is not certain for most of these exposures. However, among coal miners, coal mine dust exposure was a significant risk factor for emphysema in both smokers and nonsmokers. In most cases, the magnitude of these occupational exposures on COPD risk is likely substantially less important than the effect of cigarette smoking.

AMBIENT AIR POLLUTION

Some investigators have reported increased respiratory symptoms in those living in urban compared to rural areas, which may relate to increased pollution in the urban settings. However, the relationship of air pollution to chronic airflow obstruction remains unproved. Prolonged exposure to smoke produced by biomass combustion—a common mode of cooking in some countries—also appears to be a significant risk factor for COPD among women in those countries. However, in most populations, ambient air pollution is a much less important risk factor for COPD than cigarette smoking.

PASSIVE, OR SECOND-HAND, SMOKING EXPOSURE

Exposure of children to maternal smoking results in significantly reduced lung growth. In utero, tobacco smoke exposure also contributes to significant reductions in postnatal pulmonary function. Although passive smoke exposure has been associated with reductions in pulmonary function, the importance of this risk factor in the development of the severe pulmonary function reductions in COPD remains uncertain.

GENETIC CONSIDERATIONS

Although cigarette smoking is the major environmental risk factor for the development of COPD, the development of airflow obstruction in smokers is highly variable. Severe α_1AT deficiency is a proven genetic risk factor for COPD; there is increasing evidence that other genetic determinants also exist.

α_1 Antitrypsin Deficiency Many variants of the protease inhibitor (PI or SERPINA1) locus that encodes α_1AT have been described. The common M allele is associated with normal α_1AT levels. The S allele, associated with slightly reduced α_1AT levels, and the Z allele, associated with markedly reduced α_1AT levels, also occur with frequencies of >1% in most white populations. Rare individuals inherit null alleles, which lead to the absence of any α_1AT production through a heterogeneous collection of mutations. Individuals with two Z alleles or one Z and one null allele are referred to as Pi^Z, which is the most common form of severe α_1AT deficiency.

Although only approximately 1% of COPD patients are found to have severe α_1AT deficiency as a contributing cause of COPD, these patients demonstrate that genetic factors can have a profound influence on the susceptibility for developing COPD. Pi^Z individuals often develop early-onset COPD, but the ascertainment bias in the published series of Pi^Z individuals—which have usually included many Pi^Z subjects who were tested for α_1AT deficiency because they had COPD—means that the fraction of Pi^Z individuals who will develop COPD and the age-of-onset distribution for the development of COPD in Pi^Z subjects remain unknown. Approximately 1 in 3000 individuals in the United States inherits severe α_1AT deficiency, but only a small minority of these individuals has been identified. The clinical laboratory test used most frequently to screen for α_1AT deficiency is measurement of the immunologic level of α_1AT in serum (see "Laboratory Findings").

A significant percentage of the variability in pulmonary function among Pi^Z individuals is explained by cigarette smoking; cigarette smokers with severe α_1AT deficiency are more likely to develop COPD at early ages. However, the development of COPD in Pi^Z subjects, even among current or ex-smokers, is not absolute. Among Pi^Z nonsmokers, impressive variability has been noted in the development of airflow obstruction. Asthma and male gender also appear to increase the risk of COPD in Pi^Z subjects. Other genetic and/or environmental factors likely contribute to this variability.

Specific treatment in the form of α_1AT augmentation therapy is available for severe α_1AT deficiency as a weekly IV infusion (see "Treatment," below).

The risk of lung disease in heterozygous Pi^{MZ} individuals, who have intermediate serum levels of α_1AT (~60% of Pi^{MM} levels), is controversial. Several recent large studies have suggested that Pi^{MZ} subjects are at slightly increased risk for the development of airflow obstruction, but it remains unclear if all Pi^{MZ} subjects are at slightly increased risk for COPD or if a subset of Pi^{MZ} subjects are at substantially increased risk for COPD due to other genetic or environmental factors.

Other Genetic Risk Factors Studies of pulmonary function measurements performed in general population samples have suggested that genetic factors other than PI type influence variation in pulmonary function. Familial aggregation of airflow obstruction within families of COPD patients has also been demonstrated.

Association studies have compared the distribution of variants in candidate genes hypothesized to be involved in the development of COPD in COPD patients and control subjects. However, the results have been quite inconsistent, often due to underpowered studies. However, a well-powered association study comprising 8300 patients and 7 separate cohorts found that a minor allele single nucleotide polymorphism (SNP) of *MMP12* (rs2276109) associated with decreased MMP12 expression has a positive effect on lung function in children with asthma and in adult smokers. Recent genome-wide association studies have identified several COPD susceptibility loci, including a region near the hedgehog interacting protein (*HHIP*) gene on chromosome 4, a cluster of genes on chromosome 15 (including components of the nicotinic acetylcholine receptor), and a region within a gene of unknown function (*FAM13A*). A regulatory SNP upstream from the *HHIP* gene has been identified as one potential functional variant; the specific genetic determinants in the other genomic regions have yet to be definitively identified.

NATURAL HISTORY

The effects of cigarette smoking on pulmonary function appear to depend on the intensity of smoking exposure, the timing of smoking exposure during growth, and the baseline lung function of the individual; other environmental factors may have similar effects. Most individuals follow a steady trajectory of increasing pulmonary function with