Natural Histories of Chronic Obstructive Pulmonary Disease

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Concepts relating to the natural history of chronic obstructive pulmonary disease (COPD) arise most importantly from the classic study of Fletcher and colleagues (*The Natural History of Chronic Bronchitis and Emphysema*, Oxford University Press, New York, 1976). This study, which evaluated working English men over 8 years, was used to construct a proposed life-long natural history. Although this is a classic study that has greatly advanced understanding of COPD, it has a number of limitations. Its duration is relatively short compared with the duration of COPD, so it is more cross-sectional than longitudinal. It was unable to distinguish among varied "natural histories." It assessed primarily the FEV_1, and the natural history of other features of COPD is largely undescribed. With advances in understanding the clinical features of COPD and with the development of evaluating new tools to assess patients with COPD, longitudinal studies evaluating COPD in novel ways and for longer durations are needed.

Keywords: lung function; severity; symptoms; biomarkers

The progressive nature of chronic obstructive pulmonary disease (COPD) is believed to be sufficiently fundamental that it is included in the definition adopted in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (1). COPD, however, progresses slowly and variably and is often diagnosed relatively late in its course. Moreover, COPD is heterogeneous. Studies of the natural history of COPD, therefore, are difficult, both because of the size of the study needed and the duration required to obtain truly longitudinal data. Such studies are crucially needed, because interventions designed to alter the natural history of COPD hold the promise of altering the generally poor long-term prognosis of this condition.

The classic monograph of Fletcher and colleagues, *The Natural History of Chronic Bronchitis and Emphysema*, published in 1976, remains the landmark reference for the natural history of COPD (2). This monograph presented conclusions based on an 8-year prospective study of working men in London. It was motivated, in large part, to test the hypothesis that mucus hypersecretion is related to progressive loss of lung function, the so-called British hypothesis. Conclusions relating to life-long natural history of COPD, which resulted in the much reproduced diagram, frequently termed the "Fletcher-Peto curve" (Figure 1A) (3), were not based on life-long longitudinal data, but were compiled from the set of 8-year data. This is nearly a cross-sectional dataset compared with the expected human lifespan. Nevertheless, the concepts proposed in this analysis remain the most common summary of COPD natural history and continue to form the basis for understanding the progression of this disorder.

The major outcome variable on which Fletcher and colleagues focused was expiratory airflow limitation defined as FEV_1 measured by spirometry (2). This was entirely reasonable because the major underlying question being evaluated in their study was the relationship between mucus hypersecretion and airflow limitation. Fletcher and colleagues were certainly aware of other relevant outcome measures. They present evidence and make a strong conclusion that "chest infections," what would currently be termed "exacerbations," are strongly related to mucus hypersecretion, for example (2, 4). Nevertheless, the focus on the FEV_1 together with the compelling visual impact of the Fletcher-Peto curve has resulted in the FEV_1 becoming the *condicio sine qua non* for COPD progression.

As pointed out by Fletcher and colleagues, in normal non-smoking individuals, lung function declines with age through adulthood (2, 3). This rate of decline accelerates with increasing age. Aging is associated with structural changes in the alveolar wall including increase in the size and number of alveolar pores (5, 6), which may enlarge sufficiently to form fenestrae together with effacement of alveolar walls, and increase in alveolar size (7, 8). Whether these are related, however, remains unknown. At present, neither the pathogenesis of senile emphysema nor the anatomic basis for loss of expiratory airflow with "normal aging" is established.

Among individuals who smoke, expiratory airflow is lost at an increased rate (2, 3). On average, this is approximately twice that associated with normal aging (Figures 1A–1C). However, there is considerable variation in the rate at which lung function is lost, a fact also recognized by Fletcher and colleagues. Modest degrees of physiologic compromise are often undiagnosed, perhaps because patients can avoid symptoms of dyspnea by gradually restricting activity and thus by avoiding the tachypnea-induced hyperinflation that is believed to be the most common mechanism for dyspnea (9). As a result, individuals are typically diagnosed with COPD when sufficient physiologic compromise results in undeniable symptoms. Often this occurs only after more than half of the initial lung function is lost, resulting in relatively late diagnosis. Fletcher and colleagues suggested, from their data, that approximately 13% of smokers would be diagnosed with COPD (*see* p. 83 of Reference 1). This has been rounded off and misquoted, stating that 15% of smokers will get COPD. In fact, the percentage of smokers who develop COPD, using current definitions, is more likely around 50% (10).

Fletcher and colleagues did not comment about accelerated loss of airflow among nonsmokers. Although less common than in smokers, a percentage of nonsmokers also develop COPD, a finding that has been observed consistently (Figure 2) (10, 11). The prevalence of nonsmokers with COPD will depend on the prevalence of smoking in a population. In the United States, 20% of those who have low lung function and 20% of those who die of COPD are nonsmokers (12, 13). This represents approximately 25,000 deaths annually in the United States, and is therefore a significant public health problem. Nevertheless, and perhaps as a consequence of nonsmokers who develop COPD being omitted from the Fletcher-Peto curve, few studies have been performed
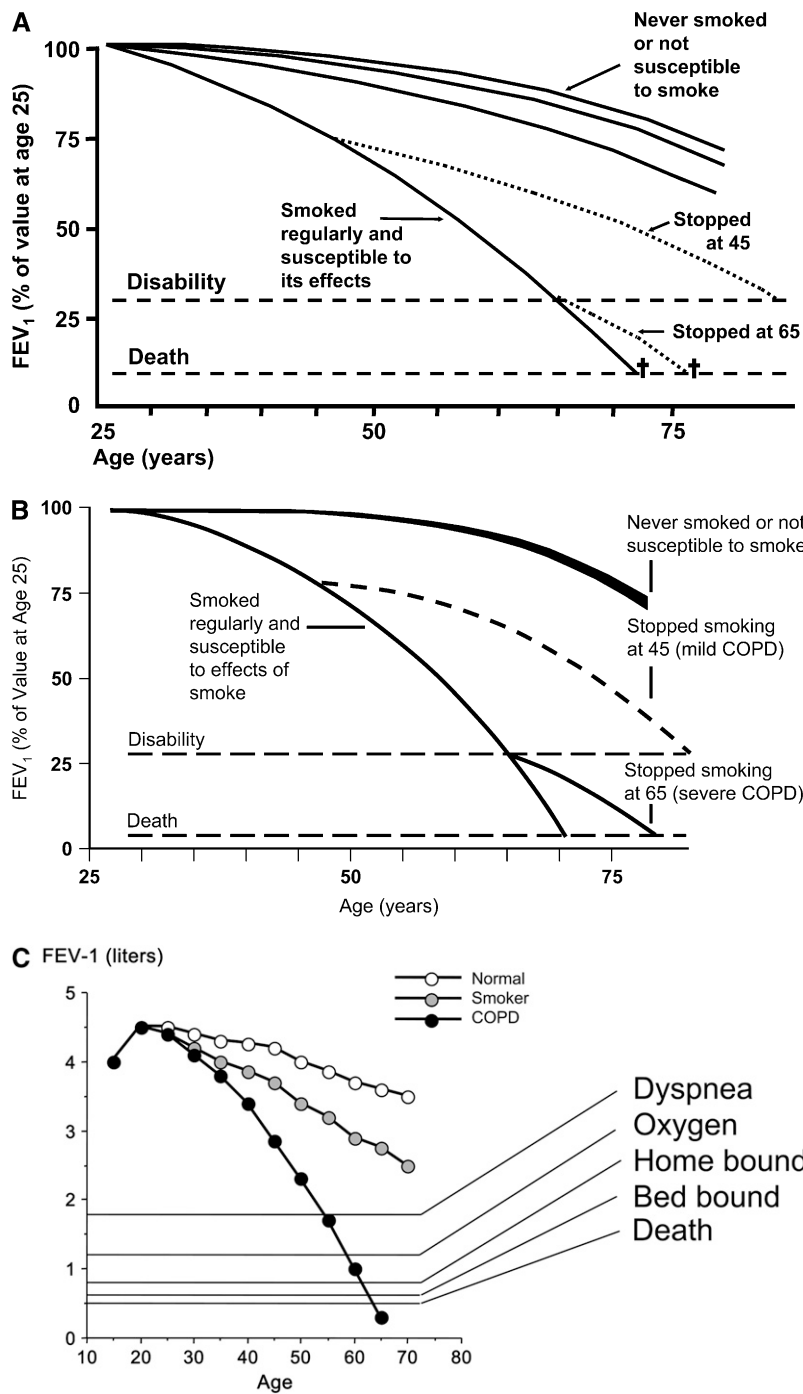
Figure 1. Natural history of chronic obstructive pulmonary disease (COPD). (*A*) Fletcher and Peto suggested a "natural history" for the airflow limitation in patients with COPD based on their 8-year study of working English men (3). Their exclusion of nonsmokers who develop COPD may have led to this group being relatively understudied. Reprinted by permission from Reference 3. (*B*) One of many derivative versions of the Fletcher-Peto curve, presented in the GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines slide set, which has been rendered in black and white by the authors. Reprinted by permission from Reference 1. (*C*) A version prepared by the author using data from Reference 2. As airflow worsens, symptoms increase, but there is tremendous variability among individual patients in this regard. (*D*) Variable "natural histories" that can lead to severe COPD as described by Burrows (34). Although these may represent distinct pathophysiologic processes, by the time diagnosis is made, they may be impossible to distinguish using FEV_1 since their natural histories will overlap. Reprinted by permission from Reference 34.

in this group, and little is known regarding their natural history and clinical course. In fact, this underlines one of the unspoken rules in epidemiology: the only risk factors that can be identified are those that are assessed. It is generally stated that 85–90% of COPD is caused by smoking in the Western world. This is likely wrong and Marsh and coworkers have suggested that only half of cases of COPD are caused by smoking (14).

FEV_1, which was the single physiologic parameter used by Fletcher and colleagues to track the natural history of COPD, may be altered by several anatomic lesions (15). These include alveolar wall destruction, the defining feature of emphysema, which leads to both loss of lung elastic recoil and loss of anatomic tethering of small airways. Both can lead to collapse of distal airways, particularly with forced exhalation, resulting in

decreased expiratory airflow. In addition, airway disease can also compromise airflow. Peribronchiolar fibrosis can develop, particularly in the small airways. Like all fibrotic lesions, these airways are contracted, and the resulting airway narrowing compromises airflow. In addition, airway secretions are associated with increased airflow limitation (16). Interestingly, Fletcher and colleagues noted the association of mucus hypersecretion with progressive airflow limitation. However, when they adjusted their data for cigarette smoking, the statistical significance for the effect of mucus hypersecretion on loss of FEV_1 was lost (*see* chapter 5 of Reference 1). This led them to reject the British hypothesis. More recent data, however, confirm that mucus hypersecretion is associated not only with exacerbations but that mucus hypersecretion and exacerbations
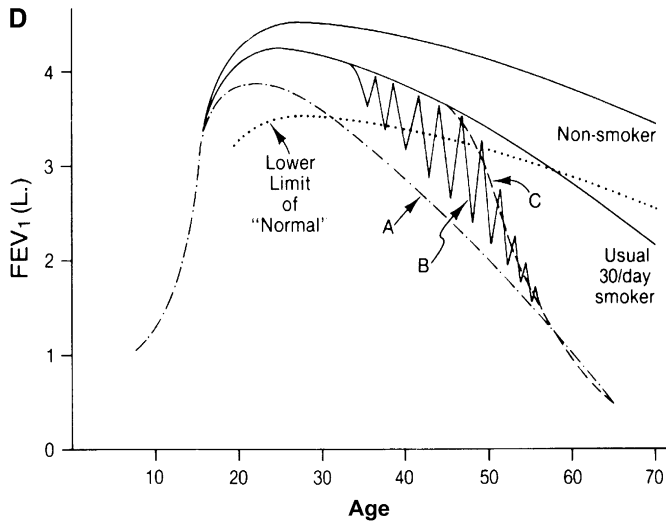
Figure 1. (*Continued*).

most important anatomic correlate of airflow limitation was the disease in small airways (22, 23). In contrast, autopsy studies have suggested that emphysema is the more important lesion (24, 25). Although this could be due to differences in patient sampling, both results could be correct if airway disease was the major determinant of airflow limitation in younger individuals with relatively milder disease, whereas emphysema was the major determinant in older individuals with more severe disease who are at risk for death from their COPD.

Both airway disease and emphysema are strongly related to cigarette smoking. However, it is likely that these two anatomic lesions differ in the details of their pathophysiology (26). Consistent with this, it is also clear that there are genetic factors that account for the varying susceptibility of smokers to develop COPD (27, 28). However, it appears that different genetic determinants may impact airway disease and emphysema (29). This is consistent with differences in pathophysiology between airway disease and emphysema. Moreover, it is consistent not only with variable susceptibility to these two conditions but also with variable time courses for their progression.

Smoking cessation can clearly alter the natural history of COPD. The prospective Lung Health Study clearly demonstrated a reduction in the rate at which lung function was lost with successful smoking cessation among patients with relatively mild disease (30). However, it is unclear whether this was due to an effect on emphysema, airway disease, or both. Moreover, it is unknown if similar benefits would accrue in individuals with severe disease. In addition, cessation, at least in established COPD, does not appear to reverse the increased inflammation over the time frames studied (31, 32) and quitters with normal lung function are still at higher risk of COPD than never-smokers (33). Thus, whereas smoking cessation can alter COPD natural history, there are many questions about the natural history of COPD after cessation that remain unanswered.
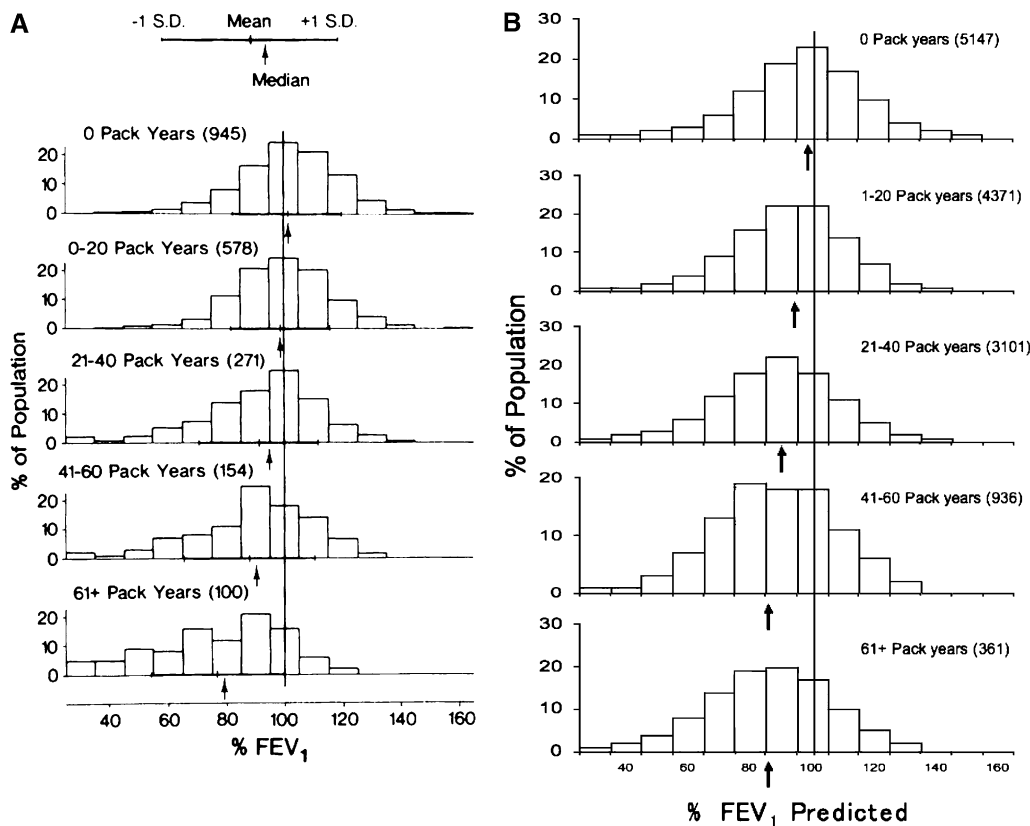
are also related to progressive loss of airflow (17, 18). It is likely that mucus hypersecretion is also related to clinical features of COPD other than FEV_1 decline (19–21).

Although it is clear that there is progressive loss of expiratory airflow in patients with COPD, it is not clear that airway disease and emphysema have the same natural history. The two lesions are often present in the same individual, but their relative importance can vary greatly. In addition, emphysema and airway disease could progress at different rates at various times in the life of a given individual. In this context, studies using specimens obtained at surgery have suggested that the

Figure 2. Distribution of FEV_1 values in relationship to smoking history. Note that there is a reduction in FEV_1 with increasing smoking history. For each smoking history, however, there is considerable heterogeneity in FEV_1 response. Even among nonsmokers, there is a subset with severe lung function impairment. Note the striking similarity of the data presented by (*A*) Burrows (11) and that of the (*B*) Copenhagen City Study several decades later (10) Reprinted by permission from Reference 10. The time course for the progression of individuals with varying smoking histories is unknown and likely follows many "natural histories."

The cross-sectional nature of the data used by Fletcher and colleagues to suggest a natural history has another major limitation. Specifically, it is unclear if patients with COPD all track along a similar course or if there are a number of alternatives. This was discussed by Benjamin Burrows, who pointed out that several "natural histories" are possible (Figure 1D) (34). For example, some may lose lung function at an accelerated rate throughout life. Others may have relatively normal lung function until some event in midlife results in an accelerated course. Yet others may have periods of exacerbation and remission with each successive episode that result in progressive loss of function. These three distinct natural histories would be extremely difficult to distinguish when COPD is most commonly diagnosed—that is, in a patient's mid-60s when, on average, FEV_1 is approximately 45% of predicted. By this time, the course of lung function decline for the various natural histories will largely overlap. Support for part of Burrows' concept is provided by the observation of the relationship between exacerbations and lung function decline (17, 18).

To further complicate things, Burrows also pointed out that it is possible for individuals to be endowed with variable levels of lung function, a theme well illustrated by Kerstjens and colleagues (35). In this context, lung volumes increase with growth from infancy into adulthood, and airflows increase as well. In general, maximally attained lung function is achieved in young adulthood after a growth spurt in adolescence. A number of early life events can affect maximally attained lung function (36, 37). Maximally attained lung function, moreover, appears to be an independent risk factor for the subsequent development of COPD (38). Consistent with this, Barker and colleagues suggested that low birth weight was associated with increased risk for low lung function in the elderly and that this risk factor was independent of smoking status (39), although these results have not been uniformly replicated (40). Although the factors that determine maximally obtained lung function remain incompletely defined, these observations suggest that the natural history of COPD begins well before smoking starts. The physiologic and pathologic processes involved and their natural histories remain undefined.

For historical reasons noted above, expiratory airflow limitation has been the primary measure used to track the natural history of COPD. It has also been used to grade COPD severity. However, because COPD progresses with age, severity and progression are not equivalent. Specifically, a young and old individual with the same severity stage of COPD will likely be progressing on different natural history trajectories (Figure 3). Frequently, individuals of a similar severity stage are grouped together for therapeutic or mechanistic studies. However, using severity stage to "phenotype" patients with COPD without considering age is likely to confound groups with different natural histories.

The fact that clinical features other than airflow limitation are relevant to COPD natural history, however, has been well understood for many decades. As noted above, Fletcher and colleagues commented about the relationship between mucus hypersecretion and exacerbations (see chapter 7 of Reference 1). More recently, efforts have been taken to develop tools that could measure features of COPD independent of FEV_1. Among these is health status (41), sometimes termed "quality of life." These measures, which are based on patient responses to standardized questions, have been validated and found to be tractable clinical measures (41). Importantly, they appear to measure something distinct from the FEV_1. The St. George's Respiratory Questionnaire (SGRQ), for example, is correlated, but very weakly, with the FEV_1 (42). The weak relationship suggests that other factors drive health status and implies that these other factors will have
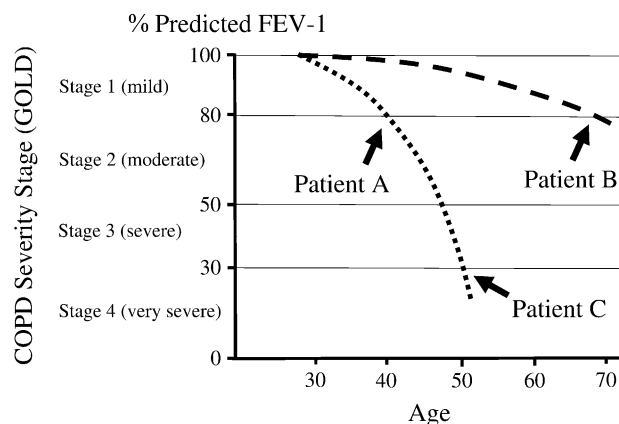

Figure 3. Severity stage and natural history of chronic obstructive pulmonary disease (COPD). Two theoretical natural histories are shown. Grouping by severity would pool a 40-year-old (patient A) with a rapidly progressive natural history (*dotted line*) and a 70-year-old (patient B) with a slowly progressive natural history (*dashed line*). Conversely, to group individuals of many ages with the rapidly progressive natural history (*dotted line*), individuals with differing severities (patients A and C) would need to be grouped. GOLD = Global Initiative for Chronic Obstructive Lung Disease.

a natural history. The SGRQ, in this context, is more strongly related to exercise capacity, although this parameter is also, to some extent, independent (43).

The number of distinct variables required to define the COPD population remains undefined. Evaluating clinical databases with techniques such as principle components analysis, however, supports the concept that multiple parameters are required. Celli and colleagues reviewed a dataset from two clinical trials and concluded that at least six variables—FEV_1, cough, health status, airflow reversibility, body mass index, and dyspnea—yielded independent information (44). Using a smaller dataset, Wegner and colleagues concluded that FEV_1, dyspnea, and lung volumes yielded independent information (45). Similarly, Ries and associates derived four factors, which they believed reflected exercise/gas exchange, disease severity, lung volumes, and airflow (46). Wu and colleagues, reviewing a health claims dataset, suggested that 12 parameters were independent (47). Although the number of factors required to describe the COPD patient population remains undefined, each distinct factor may have a different natural history. Moreover, as with FEV_1, each could also have multiple pathogenetic mechanisms and a heterogeneous time course. Defining the Fletcher-Peto curves for these variables, such as health status, is a major unmet clinical need. That such analyses can contribute to understanding the clinical condition, however, is well supported by existing data.

Clinical studies with therapeutic interventions have clearly demonstrated divergent natural histories for different COPD outcomes. Rehabilitation, for example, has been well demonstrated to have no effect on airflow limitation (48, 49). Despite this, rehabilitation has dramatic effects on health status. The impact of rehabilitation on airflow and health status is thus clearly distinct. Similarly, oxygen therapy clearly impacts COPD natural history because it improves survival in hypoxic patients with COPD (50, 51), but it has no apparent effect on airflow limitation. Interestingly, over the last several decades, COPD survival for hypoxic patients with COPD has further improved (52). Although there are many reasons for changes in prognosis over time, comparison with historical data suggests that some factors are altering COPD natural history.

Patients with COPD are affected not only by pulmonary problems but also by problems in other organ systems (53–57). Cardiovascular disease is the most common cause of death for patients with COPD (13), and the risk of a cardiac event is strongly related to the severity of the COPD (58). Importantly, the cardiac risk is present even with minor degrees of airflow limitation and appears to be independent of smoking (58, 59). Similarly, patients with COPD appear to be at increased risk for a variety of conditions, including osteoporosis, muscle weakness, anemia, depression, and thrombotic disease. Whether these conditions should be regarded as comorbidities or as nonpulmonary manifestations of COPD remains unsettled. However, the natural history of these nonpulmonary clinical problems in the patient with COPD and whether they differ in important ways from the natural history in the patient with COPD remains largely unstudied.

Because COPD progresses slowly, and because the disease is mechanistically and clinically heterogeneous, there is considerable interest in defining biomarkers that can be used to subcategorize the COPD population and to gauge disease severity and progression. A large number of biomarkers have been evaluated, to some degree, in these contexts. None have yet been validated as effective clinical tools (60–63). As the study of these makers advances, however, it will be important to define their "natural histories" in the context of COPD, both as they relate to "stable" disease and to acute exacerbations.

There are, therefore, many crucial unaddressed questions relating to COPD natural history. First, the outcome measures that are both necessary and sufficient to track COPD natural history remain to be defined. Second, methods to evaluate these parameters must be applied in sufficiently large studies. Cross-sectional studies will provide some insight. However, as pointed out by Burrows, these studies will suffer from the same limitations as the initial study of Fletcher and colleagues. The heterogeneity of COPD natural history can only be determined by longitudinal studies. This is a particular problem for studies of stable disease that progresses over decades. Among the practical problems that these studies present is that investigators are unlikely to be attracted to such studies: It is a poor career choice to do lifetime studies of one's own species. Longitudinal studies of shorter duration are likely to provide insight into the natural history of acute exacerbations and may help define endpoints that can be used to assess interventions with the potential for altering the course of COPD. Full understanding of COPD natural history, however, will require investigators who are ready to initiate studies that others will bring to completion.

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