

caveat is that it may be better, at least theoretically, to seek a surrogate for lung disease, rather than a surrogate for a surrogate (FEV<sub>1</sub>).

The study by Mayer-Hamblett and colleagues in this issue (pp. 822–828) exemplifies this quest (5). Using a large cohort of patients, collected from four separate studies, the study shows that inflammatory markers in sputum correlate with FEV<sub>1</sub>, when studied cross-sectionally. Specifically, neutrophil count and neutrophil elastase account for the majority of the correlation, in keeping with the domination of this cell type in the endobronchial inflammation seen in CF. Such findings are encouraging, and are complementary to those reported in smaller studies that suggested similar links between inflammatory markers and FEV<sub>1</sub> (6). Clearly, however, the link may not be causal. A further issue is correlating sputum sampling at a single time point in the evolution of lung disease with FEV<sub>1</sub>, which reflects the lifetime history of the problem. This issue can, at least in part, be ameliorated by longitudinal measurements.

Additional potential surrogates to follow in CF have been suggested by other groups. In general, such surrogates fall into the categories of inflammation, infection, imaging, and lung physiology. However, in our view, there are two as yet unmet and crucial challenges to the field. First, do any of these young pretenders provide a more sensitive marker of lung disease for a novel therapy aimed at the basic defect? Second, how does the optimal one(s) correlate with assays of CFTR molecular function?

The U.K. CF Gene Therapy Consortium (7) has grappled with these two challenges over a number of years. However, we have been unable to produce a shortcut to a laborious, expensive, and time-consuming program. To address the first question of identifying highly sensitive assays, we have designed a large, multidose, double-blind, placebo-controlled trial administering gene therapy over a 1-year period, assuming that this may be the minimal period over which changes in chronic lung pathophysiology have a reasonable chance to become apparent. Before treatment, a larger group of some 200 patients with CF, including children, will be longitudinally assessed over a 12- to 18-month period; approximately 100 of these subjects will then move forward into the gene therapy trial. We have assembled a large group of CFTR “clinical function” assays that will be assessed at multiple time points through both stages of this program.

To address the second question, we will look for correlations between these clinical function parameters and a basket of assays related to CFTR “molecular function,” including bioelectric measurements, consequent changes in airway surface liquid height, and bacterial adherence. Many groups have shown alterations in some of these markers using either small molecule or gene-based therapies (8, 9), and some of them are likely to be more sensitive than clinical assays given the high degree of variability in clinical status demonstrated by patients. However,

it is unclear whether the magnitude of such changes will in any way predict alterations in assays of CFTR clinical function. Our trial will, therefore, incorporate bronchoscopic assessment of CFTR molecular function from the lower airways, and may allow us to gain a handle on how, and if, CFTR molecular function relates to more relevant clinical assays. If a relationship is established, smaller, easier, and cheaper trials using sensitive molecular function endpoints may be able to provide signposts to the clinical relevance of a potential new therapy.

Both the Cystic Fibrosis Trust, through the U.K. CF Gene Therapy Consortium, and the Cystic Fibrosis Foundation, through the Therapeutic Development Network, have put into place ways in which assay development can be catalyzed. Patient databases are increasingly being unified, and one of these, Port CF, has recently been accepted by a large proportion of those in the CF field. This may, in time, allow a more universal combination of data on novel assays, likely of benefit to patients and researchers. There is still a considerable amount of hard work needed over the next few years, but CF biomarkers are progressing well.

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## Hold the Front Page Smoking Bans Good for (Most) Workers' Health

The start of 2007 saw yet more smoking bans come into effect as Belgium, Lithuania, and France took the plunge in Europe, and Washington, DC, joined them in the United States. Unfortunately, the bans in France and Belgium do not yet cover all hospitality venues. Customers and staff will continue to be ex-

posed to secondhand smoke in Belgian cafes and bars until further notice. Hospitality workers and patrons in France will have to wait until January 2008 before they will be able to enjoy the benefits of smoke-free workplaces already in force elsewhere across the country.

In many jurisdictions, bars and restaurants continue to be the crucible on which attempts to obtain comprehensive smoke-free workplace laws falter despite the fact that hospitality workers are exposed to some of the highest levels of occupational secondhand smoke (1).

This distinction between hospitality venues and other workplaces is nonsensical from a public health and legal perspective. We know from the implementation of smoke-free laws around the world that the most successful laws are those that protect all workers and make no distinction between different workplaces. Irish Health Minister Michael Martin was convinced of this in 2003, and lawmakers in various U.S. states and countries around the world since have been as well. Yet clearly, there is still a job to be done to persuade other lawmakers of this fact.

The article by Goodman and colleagues (2) in this issue of the *Journal* (pp. 840–845) adds to the evidence from other studies that what smoke-free advocates have said all along is true: comprehensive smoking bans in bars dramatically reduce the levels of fine-particulate matter, chemicals, and gases in the air and improve bar workers' health (3, 4).

There is an important caveat to the findings of Goodman and colleagues. Although the health of the nonsmoking and ex-smoker barmen improved significantly, the respiratory health of the smokers in the study continued to decline, with the exception of the findings on irritant sensitivity. Given the known health effects of secondhand smoke exposure and the reported reduction in mean exposure from 40.5 hours preban to 0.42 hours postban, this is a disappointing finding, especially since the reported exposure outside of the workplace also decreased by 42%.

It is also important to note that, because the study relied on volunteers, the subjects were all men. Given the lack of sex-specific studies on women and occupational disease (5), and evidence that secondhand smoke exposure levels are often underestimated in nonsmoking women, this was unfortunate, although unavoidable.

The significant improvement in the health of the nonsmoking bar workers is very welcome, but the findings of the study underline the fact that we still need to do much more to help smokers quit and enable them to share in the benefits of smoke-free policies. Since 1998 and 2004, there has been an 8% reduction in Irish smoking prevalence. This has been attributed to the introduction of a comprehensive set of tobacco control policies, including advertising bans, tax increases, better warning labels, and the smoking ban (6). The latter has been credited with a reduction in prevalence of 1.45%, and Irish smoking rates now stand at 25% (7). However, there are signs that smoking rates are edging up again after a failure by the Irish government to maintain tobacco tax increases after the introduction of the smoking ban (8). These figures underline the fact that no one measure, however successful, can on its own drive down smoking prevalence.

Although unexplored by this study, the findings on median exhaled CO are also pertinent. Some research, such as the Montana study, has shown dramatic short-term reductions in rates of myocardial infarction following smoking bans (9, 10), but these findings have been questioned because of important methodologic limitations (11). The median exhaled CO findings in Goodman and colleagues' study do not resolve this debate but they do provide further evidence that smoking bans reduce exposure to a key determinant of myocardial infarctions. The role of and speed at which smoking bans can reduce cardiovascular disease rates is a key public health question that is still to be completely resolved. The evaluation of the Scottish smoke-free law, which took effect in March 2006, will include a study to test the Montana findings with a prospective design aimed at

overcoming some of the methodologic shortcomings of that study (12).

The study findings on the reduction of secondhand smoke exposure outside work also add to a growing body of evidence of this point. They are important from a research and advocacy perspective in refuting arguments from opponents of clean indoor air laws that workplace bans will displace smoking into the home (13). Previous research on the adverse impact of secondhand smoke on children's lung health illustrates the importance of ensuring that such displacement activity does not result from smoking bans (14). Although they do not deal specifically with domestic exposure, Goodman and colleagues' findings reinforce the evidence from other evaluations of the Irish smoke-free law, which did analyze this point (15).

More research on the impact of smoke-free policy is now being conducted. The Scottish evaluation is one of the most comprehensive studies into the impact of such laws ever undertaken. The CHETS (Changes in Child Exposure to ETS [environmental tobacco smoke]) study will measure changes in children's exposure to ETS and assess whether displacement has taken place in the homes of smokers. A study on bar workers' respiratory health Bar workers' Health and ETS Exposure [BHETSE] is also being undertaken to see if the findings in Goodman and colleagues' article are replicated in Scotland. This evaluation will also conduct new research to assess the impact of the law in urban and semirural settings, paying particular attention to any impact on health inequalities.

The impact of the Irish ban has been enormous in Europe, and it has been estimated that if all European Union countries were to adopt a similar law, between 5 and 10 million premature deaths from smoking could be prevented. The present study is further welcome proof that smoke-free laws protect the health of workers and of the enormous public health gains that stand to be made from the introduction of comprehensive clean indoor air laws.

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