a consistent finding, it did it seem to impact their health status adversely.

Inevitably this well conducted trial will raise some further questions. The patients included here were less severe, as judged by their postbronchodilator lung function, than in other recent COPD studies (mean FEV_1 52% predicted here). They appeared to have a greater degree of reversibility than reported in other COPD trials, although the absolute lung function changes are difficult to calculate from the data given and are unlikely to be as great as the numbers based on a percentage change from baseline would suggest.[17] Over half of the patients were using inhaled corticosteroid during the trial and it would be interesting to know whether some of the clinical outcomes, such as the improvement in breathlessness or the exacerbation frequency, showed any interaction between this background treatment and the new drugs. Certainly, the exacerbation rate was lower than in other studies, perhaps reflecting the selection criteria or the use of concomitant medication. Similar problems have been seen when the effects of combination of treatments with monotherapy with long-acting β-agonists on these clinical outcomes have been compared in similar 1 year studies.[18] However, the data showing superiority of indicaterol to formoterol in terms of lung function are very convincing. Direct comparisons between indicaterol and long-acting antimuscarinic agents such as tiotropium will be awaited with interest and should resolve the long-standing question of whether drugs targeted to block or stimulate specific pathways moderating airway smooth muscle function do produce different responses in patients with COPD. Likewise it will be important to establish whether there are advantages in combining once-daily β-agonists with once-daily inhaled corticosteroids, which can also have clinical effects in COPD,[19] when compared with existing twice-daily regimes. For now we can be assured that long-acting inhaled β-agonists have arrived, are effective and offer the prospect of simpler treatment for our patients.

Competing interests I have advised and led clinical trials of bronchodilator therapy for several companies including GSK, Boehringer Ingelheim and AstraZeneca. I have advised Noartis, the study sponsors, on study design and serve on a data safety monitoring board for another trial they are running in COPD.

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Respiratory disease in 2010: looking to the past will prepare us for the future

David M Mannino

Correspondence to David M Mannino, Department of Preventive Medicine and Environmental Health, University of Kentucky College of Public Health, 121 Washington Avenue, Lexington, KY 40536, USA; dmannino@uky.edu

Hanging on the wall in my office are two obituaries, one of Dr Charles Fletcher who died in 1995[1] and the other of Dr Benjamin Burrows who died in 2002.[2] Their pictures look over the desk where I do a great deal of my work and provide inspiration and, through their collective body of work, guidance. I would like to think that the work that I do continues in a very small way the work that these giants in our field started. Dr Fletcher was responsible for, among other accomplishments, defining the natural history of chronic obstructive pulmonary disease in his landmark study of British men.[3-5] Dr Burrows founded the Tucson Epidemiological Study of Airway Obstructive Disease (TESAOD)[6] that has added greatly to our knowledge of respiratory disease. Drs Fletcher and Burrows trained and mentored many of our current leaders in respiratory health and coauthored several publications.[7][8] An ongoing legacy

of Dr Burrows is the TESAOD, which continues to provide valuable and important information relevant to today.

The publication by Guerra et al in this issue of Thorax (**see page 499**) provides an example of Dr Burrows' ongoing legacy and the convergence of his work with that of Dr Fletcher in trying to better understand the natural history of lung disease.[9] This analysis of the TESAOD data examined the baseline lung function, changes in lung function over the next 25 years of the study and the effects of lung function on mortality by year 34 of the study. The traditional view of the natural history of lung disease dating back to the time of Dr Fletcher has focused on lung function decline—the idea that, with each passing year, people lose some of their forced expiratory volume in 1 s and those who lose this more quickly develop chronic obstructive pulmonary disease (COPD).[3] [10] [11] This construct has provided the basis for the main paradigms by which we attempt to determine COPD progression and the effectiveness of treatment.[10] [12] [13] Ironically, though, the concept of 'lung function decline' is not terribly useful clinically. We know that an individual's lung function and reversibility testing can vary dramatically from day to day and even from test to test on the same day.[14] [15] Over the years I have made almost no clinical decisions in my patients with COPD on the basis of 'accelerated decline in lung function'. Rather, I have categorised patients' lung function, asked about their symptoms and exacerbations, and determined interventions based on the information gathered.

In the paper by Guerra et al, not one analysis attempts to determine lung function decline.[9] Rather, the authors classify subjects as obstructed or 'restricted' at baseline and follow-up visits and use these more clinically relevant categories to predict outcomes. This approach raises several issues, especially with regard to the 'restrictive spirometric' pattern. From the time of Hutchinson, clinicians have known that a low lung capacity resulted in a shorter life—this represents the origin of the term 'vital vapacity'.[16] In recent years the links between restrictive spirometric patterns and diabetes,[17] heart failure,[18] lung cancer,[19] asthma[20] and obesity[21] have been explored. In a large study from the Mayo Clinic[22] there is even evidence that this pattern can represent a subtype of COPD in some cases, with the thought process being that air trapping resulting in a smaller forced vital capacity may be one

of the initial manifestations of COPD. Of course, there are a host of other problems that can result in this pattern, ranging from muscle weakness to poor effort. Furthermore, the presence of a restrictive pattern, regardless of the aetiology, predicts worse outcomes such as deaths and hospitalisations.[23] This was confirmed in the analysis by Guerra et al of the TESAOD cohort.[9]

Guerra et al, however, took their analysis one step further by looking at longitudinal changes in lung function.[9] To accomplish this, rather than looking at lung function decline they examined what category the person was in at the time of the testing (obstructive or restrictive) and further classified them into one of six categories based on this pattern over time. The bottom line was that the presence of a restrictive pattern in just one of the evaluations predicted an increased risk in mortality that was similar in magnitude to that seen with 'recurrent obstruction' or COPD.[9]

The hallmark of the work of both Dr Fletcher and Dr Burrows was that they challenged the norms of their day and were willing to create new paradigms to advance medical knowledge and result in better interventions for our patients. Is it time for a new paradigm for chronic lower respiratory diseases (to include the various subtypes of asthma, COPD and restrictive lung diseases)? I believe it is! Moving away from Dr Fletcher's paradigm of 'lung function decline' to one that includes transitions between spirometric categories, radiographic data, cormorbid disease and, eventually, genomic, proteonomic and metabalomic information, is a change that I'm confident both Dr Fletcher and Dr Burrows would have happily embraced. Of course, this task will not be an easy one, but the tasks that Drs Fletcher and Burrows met head on and conquered in their day were, in many ways, more challenging than what we face today. Their biggest challenge was that they did not have the body of work of these giants in our field to rely on. As we prepare for the future, I encourage all researchers to study the work of these and other historic leaders in our field and, as they did, to keep an open mind, to challenge the status quo and to keep the ultimate goal of improving the lives of our patients central to our work.

Pharmaceuticals. He is also on the Board of Directors of the USCOPD Coalition and the COPD Foundation.

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Impact of the 2009 influenza pandemic

J Dunning, P J M Openshaw

A GENERALLY MILD DISEASE THAT SOMETIMES KILLED

One year on from the start of the 21st century's first influenza pandemic, it is a good time to take stock of how the outbreak evolved and what has been learned. Although we now know that many infections were mild or inapparent, it is important not to forget the severe disease that it sometimes caused, and may still cause, in future winters.

During April 2009, reports from Mexico provided a worrying picture of unusually severe influenza in large numbers of healthy people including healthcare workers.[1] The impact on hospitals was particularly marked with up to one in four specialist beds being occupied by patients with influenza, often needing highly specialised care and mechanical ventilation. Medical resources were exceeded by demand, and elective admissions and surgery halted; transmission to staff and to other patients was common, placing specialised nursing care, consumables, ventilators, drugs and containment facilities under great pressure.

Once cases began to appear in UK schools in May 2009, an intensive cooperative campaign of quarantine and antiviral prophylaxis was mounted by the Heath Protection Agency, the Department of Health and the NHS. Antiviral drugs have not been used in this way in previous pandemics; although it was unlikely that the spread of influenza could be halted, it was important to gather information about the pattern and severity of disease and to slow the spread, buying time for vaccine development and capacity building.

Imperial College London, London, UK

Correspondence to Professor P J M Openshaw, Imperial College London, St Mary's Campus, Respiratory Medicine, Norfolk Place, London W2 1PG, UK; p.openshaw@imperial.ac.uk

Despite the public health campaign, the numbers of cases increased in London and the West Midlands, putting considerable strain on primary care. By 2 July, case numbers were rising sharply in most parts of the UK and containment measures no longer seemed appropriate. Routine antiviral prophylaxis was discontinued and a telephone helpline was launched on 23 July.[2] Call centres took a history according to defined algorithms and authorised antiviral treatment for those with appropriate symptoms. Case numbers declined rapidly soon after schools broke up for the summer holidays in late July, with a second autumn wave occurring after children returned to school in September.

The impact of the outbreak on hospitals was considerable. Pandemic (H1N1) 2009 Influenza (pH1N1) spread predominantly among children and young adults, causing severe disease in some vulnerable adults (particularly patients with asthma, those with various chronic illnesses and pregnant women). In the first week of November there were approximately 850 patients hospitalised with confirmed pH1N1, 20% of whom required critical care. The worst recent daily estimate was at the height of the second wave (4 November) with 172 patients hospitalised in critical care and 848 patients hospitalised overall. Provisional data from a retrospective analysis of hospital admissions in the UK indicated that influenza-associated bed-days increased from 4163 in 2008 to 33 376 in 2009, about a sevenfold rise. In those aged 17–39 years of age the increase was from 169 to 6253 in the October to December period, an extraordinary 37-fold increase.[3] Fortunately, the number of confirmed UK deaths remains at 474, which is fewer than feared.[4]

The report by Fajardo-Dolci *et al* in this issue of *Thorax* describes the characteristics of the first 100 consecutive fatalities due to pH1N1 during Mexico's first wave of the pandemic (**see page 505**).[5] This is a particularly important study since it describes influenza-related deaths occurring close to the source of the pH1N1 outbreak, presumed to be in southern USA or Mexico. This study highlights several important features about pH1N1-related deaths that generally mirror those seen elsewhere across the globe.[6–8] Although the Mexican deaths were often in previously healthy people, metabolic syndrome, cardiovascular disease and chronic respiratory disease were identified as risk factors associated with high mortality. Obesity seems to be an important risk factor for hospital admission, but not necessarily for death.[9]

Although the relative contribution of individual at-risk groups appears to vary from country to country, the overall message so far appears to be that, when pH1N1 does kill, the majority who die are young to middle-aged adults with comorbidities, although 10–20% of those who died were previously healthy. pH1N1 tended to cause viral pneumonitis and acute lung injury, but antibiotic use was frequent in Mexico (as it was in many other countries). While sometimes complicated by bacterial pneumonia, confirmation of bacterial coinfection prior to death remains significantly lower than that described in the limited post-mortem series, although this may reflect how bacterial coinfection is both investigated and defined.[10–12]

It is also notable that almost 60% of cases described by Fajardo-Dolci *et al* received steroids, although it is not clear how many received high-dose corticosteroids, how many received steroids for adrenal support in sepsis and what proportion required continuation of pre-existing steroid treatment. The role of steroids in both the pathogenesis and potential treatment of viral pneumonitis remains unclear, but many authorities advise against routine use of high-dose steroids in viral pneumonitis based on experience with the management of SARS and H5N1 infection.[13]

Notably, Fajardo-Dolci *et al* reported that >80% of patients developed symptoms before a national influenza alert was issued. Local populations and healthcare providers may not therefore have been in

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