Highlights from this issue

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Andrew Bush and Ian Pavord, *Editors*

Back to basics!

This unfortunate exhortation is usually the prelude to an outbreak of financial and sexual chicanery which would have caused comment even in the declining years of Imperial Rome (although not perhaps today in the same city). But this is the current exciting cystic fibrosis (CF) rallying cry. The treatment of CF has traditionally been fire fighting—treat the downstream consequences of cystic fibrosis transmembrane regulator (CFTR) dysfunction, like infection, inflammation and mucus hypersecretion. In the more than 20 years since the discovery of the CF gene, a series of focused studies have led to profound discoveries of the basic biology of CFTR and therefore to specific designer therapies to correct the basic defect, discovered by high-throughput screening of thousands of compounds. G551D CFTR reaches the apical cell membrane but functions abnormally. The ‘potentiator’ VX-770 has been shown to have dramatic effects in CF patients with this rare mutation (about 5% of the population), for example, *halving* sweat chloride (see *NEJM* 2011;365:1663–72). The most common mutation, ΔF_{508} , results in a protein which is largely destroyed in the endoplasmic reticulum. Clancy *et al* (Hot topic: see page 12) report on VX-809, a ‘corrector’ designed to allow the mutant protein to escape the endoplasmic reticulum and reach the cell surface. The medication was safe and there was a small, dose-dependent fall in sweat chloride, although an order of magnitude less than VX-770. Stuart Elborn reviews how translational science is changing the face of CF therapy in an accompanying editorial (see page 4). A note of caution—one of the lessons of the failure of denufosal, a CF medication for which there was an excellent theoretical basis for efficacy, is that we must not get too excited too soon about relatively small changes. However, CF is an area where treatments are being *found* in translation.

FEV₁ and the chest physician

Chest physicians are as attached to FEV₁ as diabetologists are to HbA_{1c}. However, as diabetologists have learnt with HbA_{1c}, we should be cautious about extrapolating changes in FEV₁ to long-term benefit as very different mechanisms could be responsible for the change. The FACET study (see *NEJM* 1997;337:1405–11) showed that the large improvement in FEV₁ seen after addition of formoterol to low-dose inhaled budesonide was associated with a small reduction in the risk of subsequent asthma attacks. The opposite was seen with a fourfold increased dose of budesonide. Two opinion pieces in this issue of *Thorax* highlight other issues with FEV₁. Dirkje Postma and colleagues (see page 88) argue convincingly that demonstration of irreversible airflow obstruction is hopelessly inadequate for disease diagnosis. We must insist on more than this. How much more informative is ‘this patient has symptoms as a result of fixed airflow obstruction associated with a 20 pack year smoking history and eosinophilic, potentially steroid responsive airway inflammation’ compared with ‘this patient has COPD’? Guy Marks (see page 85) argues that a low FEV₁ and FEV₁/FVC should be viewed as a risk factor along with other variables, and used to predict the likelihood of future clinically significant and potentially preventable events such as the onset of symptoms and the development of lung attacks. Both opinions raise the vexed question of definitions of abnormality, an argument that will never be resolved to the satisfaction of all. IP, for one, would be quite happy with a diagnosis of ‘irreversible airflow obstruction associated with ageing’. AB is in denial about ageing.

The early worm gets the bird

We have long known that it is a *bad thing* to be born very early, even if you

escape without the need for heroic intensive care, because there is increased morbidity and persistent airflow obstruction. However, the ‘late pretermers’ (born at 33–34 weeks’ gestation) have slipped under the radar. Kotecha and colleagues (Editors’ choice: see page 54) used the ALSPAC cohort to show that 33–34-week gestation babies had similar decrements in lung function at age 8–9 years as those born at 25–32 weeks, each group showing a further incremental decrease in those ventilated. By contrast, results in the 35–36-week gestation babies were the same as term controls. By age 17, there had been some catch-up in the late preterms, but spirometry was still abnormal. What will happen when these lungs start to age? Is this another high-risk group for premature airflow obstruction?

The late response to allergen and airway nerves

Here’s another observation on FEV₁. The same fall in FEV₁ seen after allergen challenge during the early and late response is associated with marked differences in symptoms (severe distress during early response, mild ‘chestiness’ during the late), response to β_2 agonists (good during the early response, poor during the late) and inflammation (marked eosinophilia after a late response, mast cell degranulation during the early). Clearly different mechanisms are involved. Raemdanck and colleagues (see page 19) make the interesting observation that the late response is blocked by general anaesthetic in sensitised rats. This probably occurred as a result of sensory nerve inhibition as other agents active against airway nerves, including tiotropium, had a similar inhibitory effect. Is this another example of a misleading animal model of asthma? We await clinical trials of tiotropium against allergen-induced asthma in humans with interest.