anaesthesiology programmes accredited for critical care fellowship training, 33% did not have a single fellow over a two year period.[9] Almost 40% of these programmes receive only one or two applications each year, whereas a typical combined pulmonary and critical care medicine fellowship programme receives more than 100 applications every year. Board certification in critical care medicine has been obtained by seven times fewer anaesthesiologists than internal medicine specialists (854 and 6054, respectively; Karen Mullian, personal communication).

Directors of Pulmonary Divisions and Fellowship Training Programs in the United States recognise that their survival and growth is vitally linked with critical care medicine. In recognition of this fact, most divisions appended "critical care" to their name throughout the 1980s. In response to this change in focus, the American Thoracic Society (ATS) revised its mission statement explicitly to embrace critical care medicine. Of the 12 Assemblies within the ATS, the Critical Care Assembly has the largest membership. Since 1993 the society's scientific programme committee has ensured at least two critical care symposia each day of the annual international conference. The following year the society's journal changed its name to the *American Journal of Respiratory and Critical Care Medicine*. In an official statement in 1995 the ATS Board of Directors[10] pointed out that, for optimal delivery of health care, the pulmonary and critical care physician "will provide principal care for all patients in (medical) ICUs".

Pulmonary medicine has re-invented itself repeatedly. Physicians with a special interest in tuberculosis were one of the first to break away from the parent specialty of internal medicine and become subspecialists in 1941.[11] With the development of effective antimicrobial therapy, sanatoria closed and the tuberculosis physician acquired a new body of knowledge and developed skills in pulmonary function testing, bronchoscopy, and, later, polysomnography. This transition occurred not only in the United States but also in Europe. As the new millennium approaches, pulmonary medicine is now well advanced in the latest phase of its chimerical evolution. Newly qualified pulmonologists in the United States regard the practice of pure pulmonary medicine as an anachronism of a bygone era in the way that those of us who graduated from training programmes in the 1980s viewed the subspecialist in tuberculosis. Until this latest phase, the subspecialty of pulmonary medicine has evolved along similar lines on both sides of the Atlantic, and it will be interesting to see whether the combination of pulmonary and critical care medicine will be replicated in Europe or remain a peculiarly American hybrid.

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EUROSCOP, ISOLDE and the Copenhagen City Lung Study

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In some countries inhaled corticosteroids are widely prescribed for patients with chronic obstructive pulmonary disease (COPD), despite the lack of good studies to support their use. In the last 12 months these three important large, parallel group, placebo controlled studies have reported at scientific meetings but, at the time of going to press with this article, they have not been published. This review will give an individual view of what has been presented, and provide a basis for the assessment of the trials when they are published.

All three studies used similar definitions of COPD and excluded patients with a clinical diagnosis of asthma or significant bronchodilator responsiveness. The Copenhagen study also excluded those with a prednisolone response, which was found in only 5% of their otherwise unselected population. The Copenhagen study started with a random population survey which identified all those with an FEV_1/VC ratio of <70%, irrespective of their FEV_1. They have the least diseased group with a mean FEV_1 of 85% predicted and include many subjects whose FEV_1 was within the normal range; indeed, only 39% had an FEV_1 of <80% predicted. The subjects in the ISOLDE study were mostly recruited from respiratory clinics and have the most severe COPD with a mean FEV_1 of 50% predicted. The EUROSCOP group is intermediate in severity with a mean FEV_1 of 77% predicted.

The EUROSCOP subjects were all current smokers, having failed to quit in a three month period during the run in. The ISOLDE subjects had all been smokers, but only 48% were smoking at trial entry. The Copenhagen study did not have any entry criteria relating to smoking; 76% were current smokers.

The principal outcome measure for all three studies was longitudinal decline in FEV_1. It was thought that the pathology of COPD was largely irreversible, and that untreated patients with COPD deteriorate more quickly than normal, leading to premature disability and death. All three studies set out to include data over three years for each subject. It is not possible to establish individual rates of decline of FEV_1 with any certainty within this time, as the short term reproducibility of FEV_1 measurements is around five times the normal annual decline in FEV_1. A reduction in FEV_1 slope can be difficult to show, as demonstrated by the Lung Health Study of smoking cessation in which subjects were followed up for five years and yet significant effects were only found with subgroup analysis.[1] Although

some have suggested that more than five years are required for such studies, the problem is that, even with a three year follow up, 46% of the ISOLDE subjects withdrew before the end of the study period, making longer studies with FEV_1 as an outcome difficult in the more diseased group. All three studies used the mixed effects model to estimate the FEV_1 slope with time. This is the best method available at present, but weights the estimates in favour of those reaching the end of the study, who are likely to be the least affected. The model is therefore conservative and will tend to underestimate any effect. The model was not applied as planned in the EUROSCOP and ISOLDE studies as there was a small increase in FEV_1 in the first 3–6 months, precluding a linear model using the initial data points.

No study showed an unequivocal difference in the FEV_1 slope between treatment groups. The Copenhagen study showed no evidence of any difference at all between groups, whilst the EUROSCOP and ISOLDE studies both showed reductions in the FEV_1 slope which were not statistically significant when analysed in the whole study group.

The mixed effects model in each study produced estimates for FEV_1 decline that were not more than twice the predicted values for normal subjects. Those in the EUROSCOP and ISOLDE studies would not have reached their pre-trial FEV_1 if they had, at some time in their lives, had measurements close to 100%. It is therefore important to know the rate of decline in FEV_1 before trial entry. The Copenhagen study has the best data, the majority of subjects having measurements taken 13 years previously. The estimates from the mixed effects model and the 13 year observations were similar. Subjects in the EUROSCOP study had a six month run in period and the FEV_1 decline in this six months was much larger than that estimated from the mixed effects model during the trial. Few, if any, subjects had been taken off inhaled corticosteroids before entry to the trial. The ISOLDE study has the greatest difficulty in estimating pre-trial decline in FEV_1. The run in period was only eight weeks, during which those withdrawn from inhaled corticosteroids declined faster than those who were steroid naïve. A tentative estimate of decline can be made from the steroid naïve subjects who were randomised to placebo. Their observed FEV_1 decline in the 5.5 months from recruitment was more than twice that estimated from the mixed effects model during the trial.

Exacerbations of COPD are related to the severity of the disease and to increasing age. They were only common in the ISOLDE group and were significantly reduced by active treatment. The Copenhagen study showed that current sputum production increased the risk of an exacerbation requiring hospital admission fivefold,[2] and the ISOLDE study showed that exacerbations were increased in the eight weeks after stopping inhaled corticosteroids in the 55% taking them prior to the run in period. Exacerbations are a clinically relevant outcome with substantial costs. One other shorter study has confirmed the reduction of exacerbations with inhaled fluticasone propionate.[3]

Showing small changes in FEV_1 slope (or failing to show such changes) is difficult to interpret in clinical terms. Health effects measures (quality of life) are important in aiding interpretation and as an outcome in their own right. The ISOLDE study used the St George's respiratory questionnaire and showed reduced rates of decline in the scores in each domain. The effects were linear with time, the difference between active and placebo groups increasing with time. The Copenhagen study used a less sensitive measure which showed no impairment in most of their subjects and was therefore not a useful outcome measure. The EUROSCOP study did not incorporate a health effects questionnaire.

Overall, the Copenhagen study showed no benefit from inhaled budesonide 800 μg daily (with 1.2 mg for the first six months) on any outcome measure. The EUROSCOP study showed non-significant benefit in terms of FEV_1 decline with budesonide 800 μg daily, whilst the ISOLDE study showed benefit in terms of quality of life, along with non-significant improvement in FEV_1 decline, with fluticasone propionate 1 mg daily. These differences could be due to the differences in severity of the disease, inhaled corticosteroids working best for those with the most severe disease, or it could be a dose related effect, the ISOLDE study using a significantly higher relative dose than the other studies. A meta-analysis of three previous small studies of inhaled corticosteroids in COPD suggests that beclomethasone dipropionate in a dose of 800 μg was significantly less effective than budesonide in a dose of 1.6 mg or beclomethasone dipropionate at 1.5 mg/day (this estimate was based on very small numbers), and also showed that the decline in FEV_1 was greater in those with lower starting values of FEV_1.[4] It is therefore probable that the two budesonide studies were suboptimally dosed. Lack of compliance with the study inhalers is an unlikely reason for the differences since compliance was measured in each study and exceeded 80%.

Safety of relatively high doses of inhaled corticosteroids is an important issue and was best studied in the EUROSCOP trial where a significant small increase in skin bruising was seen with active treatment. No study showed an increase in fractures. Bone density was measured in a subset of subjects in the EUROSCOP trial and those on budesonide had less bone loss than those on placebo. There was also a small increase in dysphonia and oral candidiasis with active treatments.

COPD has mixed pathology, including emphysema, small airways disease, and changes in mucous glands and goblet cells. It is likely that different pathologies respond differently to inhaled corticosteroids. The studies are likely to be analysed with such subgroups; none has yet been presented. There is a large and conflicting literature on predictive factors for short term steroid response and, as yet, no known relationship between the short term effects and longitudinal decline in FEV_1. The EUROSCOP study can investigate this by relating the improvement in the first six months of treatment with subsequent decline; the ISOLDE study included an open steroid trial after randomisation and before active or placebo treatments. Help with the usefulness of short term steroid trials (or lack of it) should be available soon.

COPD is emerging from the backwaters of respiratory medicine. These three trials, when published, will provide good evidence for the place of inhaled corticosteroids in disease management and will suggest that they are unlikely to be the ideal drugs for this disease. One positive aspect of this is that it now leads us to look for alternative treatments for COPD. The three studies have produced important guidance on how such treatments could be evaluated.

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