

## Editorials

## Vascularity in asthmatic airways: relation to inhaled steroid dose

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The physiological consequences of altered airways structure on the function of asthmatic airways has been of interest to clinicians and physiologists since the classic study of Huber and Koessler in 1922.<sup>1</sup> These authors provided the first measurements of airway wall thickness in relation to their size and reported that the airway wall of patients who died of asthma was thicker than that of controls. Many have subsequently commented on this finding,<sup>2-7</sup> and Freedman provided an excellent review of its functional significance in 1972.<sup>8</sup> A systematic analysis of the effect of wall thickening on airway function by Moreno and colleagues showed that a thickening of the inner aspect of the airway wall that had little or no effect on baseline airways resistance was capable of amplifying the effect of smooth muscle shortening on airway calibre to account for the airways hyperresponsiveness of asthmatic subjects.<sup>9</sup> A series of studies followed that further explored this problem using both quantitative histology and computer based models of the airways.<sup>10-15</sup> Wiggs *et al*<sup>15</sup> used a computer model to argue that the greatest effect of the combination of smooth muscle shortening and wall thickening on the reduction of airway calibre is in the peripheral airways because these structures are encircled by airway smooth muscle. Yanai *et al*<sup>16</sup> subsequently investigated the site of increased resistance in human airways using direct measurements of pressure and flow to establish that the peripheral airways were the major site of lower airway obstruction in asthma.

In this issue of *Thorax* Orsida and colleagues<sup>17</sup> provide information on the nature of the vascular changes in bronchial biopsy specimens, arguing that the observations made in the bronchi reflect those in the smaller airways. They compare biopsy tissue from a control group with that from two groups of asthmatic patients—one treated and the other not treated with inhaled steroids—and show an increase in the number of vessels and total area of submucosa occupied by vessels in the biopsy specimens from patients with asthma. They also found that inhaled steroids reduced the area of the submucosa occupied by vessels in the asthmatic patients without influencing the number of vessels observed.

This study extends the available data on airway vascularity in asthma<sup>18-21</sup> and is consistent with the concept that the inflammatory response that underlies asthma increases the submucosal vascular compartment, possibly by inducing the growth of new vessels. The authors argue that these vascular changes alter airways function because they found that the change in number of vessels/mm<sup>2</sup> of lamina propria induced by steroids correlated with the percentage change in forced expiratory volume in one second (FEV<sub>1</sub>) after bronchodilator and the airways response to inhaled

methacholine. They suggest that a positive effect of inhaled steroids may be in reducing the size of this vascular compartment, but recognise that this finding will need to be confirmed by future longitudinal and interventional studies before being fully accepted. However, the possibility that the inflammatory process responsible for asthma results in vascular congestion with proliferation of new vessels and that these changes influence airway function is an interesting one that deserves to be fully investigated.

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## Sex differences and sleep apnoea

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Although obstructive sleep apnoea is a highly prevalent disorder with major public health ramifications for both men and women, very little is known about sex differences in the pathogenesis of this disorder. Initial studies<sup>1–3</sup> indicated that sleep apnoea was much more common in men than in women. It was originally thought that the male to female ratio for obstructive sleep apnoea was approximately 8:1.<sup>1–3</sup> However, more recent and rigorous epidemiological studies<sup>2,4</sup> have shown that the male to female ratio for sleep apnoea is in the range of 2:1. Young and colleagues<sup>4</sup> reported that the prevalence of obstructive sleep apnoea associated with excessive daytime sleepiness in the 30–60 year old population is 4% in men and 2% in women. Gislason and coworkers<sup>2</sup> estimated that the lower limit of the prevalence of sleep apnoea in middle aged Icelandic women was 2.5%. These studies indicate that sleep apnoea is common in women. Moreover, studies have shown that the clinical presentation of sleep apnoea is similar in men and women, although the prevalence is higher in men.<sup>5</sup> One reason for the higher prevalence in men may be that women are less likely to report symptoms associated with sleep apnoea.<sup>6</sup> However, several studies<sup>7–10</sup> have demonstrated sex differences in the structure and physiological behaviour of the upper airway. Such data imply that sex differences in the prevalence of sleep apnoea are not solely related to the under-reporting of symptoms but rather are related to pathological differences in the presentation of this condition in men and women.

What are the possible mechanisms underlying the differences in the pathogenesis of obstructive sleep apnoea in women and men? Two important determinants of upper airway luminal calibre are the activity of the upper airway dilator muscles, which tend to increase airway dimensions, and the anatomy of the oropharynx. Upper airway size presumably reflects a balance between these two factors, and women differ from men in both of them. Studies have found that during wakefulness women have augmented genioglossal muscle activity compared with age matched men.<sup>7</sup> Theoretically, increased activity of the genioglossus muscle would result in greater upper airway stability. Moreover, female hormones (possibly progesterone) have been shown to have an impact on genioglossus muscle activity.<sup>8</sup> If this augmented genioglossus muscle activity persists during sleep, the upper airway of women may be less likely to collapse or narrow than that of men. Thus, one possible explanation for the reduced prevalence of sleep apnoea in women is that upper airway dilator muscle activity is increased, making upper airway closure less likely to occur during sleep.

In addition to changes in upper airway motor tone, the configuration and anatomical structure of the upper airway appear to be different in men and women. Differences in upper airway shape between men and women could theoretically increase the risk for sleep apnoea by making the airway more likely to collapse during sleep.<sup>11</sup> Studies in normal subjects using acoustic reflection have shown that the upper airway is larger in men than in women.<sup>9,10</sup> However, when the pharyngeal cross sectional area was normalised for body surface area there were no significant differences between men and women.<sup>10</sup> Body surface area, however, may not be the appropriate control. A more recent study<sup>12</sup> using acoustic reflection did not find sex

related differences in the average cross sectional airway between supine men and women. Unfortunately, acoustic reflection is not an ideal upper airway imaging modality since the mouth is opened during imaging (once the mouth is opened the soft palate elevates from the tongue altering pharyngeal anatomy).<sup>13</sup> Computed tomography (CT) and magnetic resonance imaging (MRI) provide a better anatomical representation of the upper airway than acoustic reflection.<sup>13</sup> Schwab and colleagues<sup>14</sup> performed dynamic computed tomography (electron beam) to evaluate respiratory related changes in the upper airway during wakefulness. No significant differences in upper airway calibre during respiration were noted between normal men and women but the sample size was too small (10 men and five women) to draw definitive conclusions. Studies of pharyngeal resistance have not shown any differences between men and women, which suggests that upper airway calibre is similar in the two sexes.<sup>7</sup> The data from all these studies<sup>7,9,10,12,14</sup> are conflicting as to whether or not there are truly sex related differences in upper airway calibre.

In order to answer this fundamental question more definitively, Whittle and colleagues have used MRI to examine upper airway and soft tissue differences in normal men and women and their results are reported in this issue of *Thorax*.<sup>15</sup> Magnetic resonance scanning is an ideal modality to examine sex related differences in upper airway anatomy since it provides excellent airway and soft tissue resolution (including adipose tissue), accurately determines cross sectional area and volume, and provides the capability of imaging in the axial, sagittal and coronal planes.<sup>13</sup> They examined normal men and women matched for age and body mass index but found no sex related differences in the minimum cross sectional area. The mean cross sectional area was similar in men and women in the palatal region but was significantly greater in men in the subpalatal region. These data indicate that upper airway calibre may be similar in men and women, at least in certain anatomical regions. However, upper airway volume or regional volumes (retropalatal and retroglossal) may be a more definitive measurement than upper airway area but these were not determined in this investigation. Further studies are still needed to determine whether volumetric differences in upper airway calibre exist between men and women.

In addition to upper airway calibre, Whittle *et al*<sup>15</sup> studied sex related differences in upper airway soft tissue structures in normal men and women. It is critical to examine upper airway soft tissue and bony structures since these structures are the determinants of upper airway calibre (examination of the doughnut rather than the hole in the doughnut). The primary determinants of upper airway calibre are thought to arise from three domains: upper airway adipose tissue, craniofacial morphology, and size of the surrounding soft tissue structures (tongue, soft palate, lateral pharyngeal walls).<sup>13</sup> Women are known to have a smaller neck size than men so it would be reasonable to hypothesise that craniofacial structure, upper airway fat deposition, and size of the critical soft tissue structures should be smaller in women than in men.<sup>12</sup> The data presented by Whittle and colleagues<sup>15</sup> lend partial support to such a hypothesis.

Obesity is known to predispose to obstructive sleep apnoea<sup>16</sup> so it has been hypothesised<sup>17, 18</sup> that increased upper airway adipose tissue, specifically deposited in the lateral parapharyngeal fat pads, results in airway narrowing. Indeed, upper airway imaging studies have found that the size of the lateral parapharyngeal fat pads is increased in obese patients with apnoea.<sup>17, 18</sup> Increased adipose tissue surrounding the upper airway has been demonstrated in obese and non-obese patients with sleep apnoea.<sup>19</sup> Upper airway MRI studies<sup>18, 20</sup> have confirmed that the total volume of fat in the lateral parapharyngeal fat pads is greater in patients with sleep apnoea than in normal subjects. In addition, it is known that fat distribution is different in men and women.<sup>21, 22</sup> Men tend to have predominantly upper body fat whereas women have lower body fat distribution.<sup>21, 22</sup> It would therefore be reasonable to hypothesise that upper airway fat deposition and, specifically, lateral parapharyngeal fat pad size is greater in men than in women. However, the data reported by Whittle and colleagues<sup>15</sup> do not support this hypothesis. No significant differences between normal men and women were found in the volume of upper airway fat, and the deposition of upper airway fat was greater in men than in women only in the anterior segments inside the mandible in the palatal region.

The major finding from the investigation by Whittle *et al*<sup>15</sup> was that total neck soft tissue volume was significantly greater in men than in women. Since they found fat volumes to be similar in men and women, the increased tissue volume in men was related to enlargement of upper airway soft tissue structures. They found that the mean cross sectional area of the tongue and soft palate was larger in men than in women. Unfortunately, the lateral pharyngeal walls, a key mediator of upper airway calibre, were not specifically examined. Schwab and coworkers<sup>20</sup> have shown that the thickness of the lateral pharyngeal muscular walls is an important anatomical factor in airway narrowing in subjects with sleep apnoea. These lateral walls, if measured, may have been part of the increased tissue found in the upper airway of men by Whittle and colleagues.<sup>15</sup> Volumetric imaging of the tongue, soft palate, and lateral walls should now be performed to determine definitively whether sex related differences exist in the upper airway soft tissue structures and to establish which of these structures is the most important. It is not known why the upper airway soft tissue structures are larger in men than in women, but it is possible that obesity (increased fat and fat free tissue), genetic, or hormonal factors underlie this process.<sup>13, 20</sup>

Craniofacial morphology may also be important in examining sex differences in upper airway size and structure. Studies have shown certain craniofacial morphometric features of women with mild sleep apnoea, including a narrow hard palate, overjet, triangular chin, and class II malocclusion.<sup>3</sup> Further studies are needed to evaluate these and other morphometric characteristics of men and women. Such information may be useful in screening populations for sleep disordered breathing.

Why is the upper airway different in men and women? I do not believe we entirely understand the answer to this

question although upper airway soft tissue structures (tongue, soft palate, possibly lateral pharyngeal walls) appear to be larger in men than in women. However, sex is likely to be only one of several important factors which mediate upper airway calibre and increase the risk for sleep apnoea. Other important factors are thought to include age,<sup>12</sup> race,<sup>23</sup> and genetics.<sup>13</sup> These factors may interact and be intimately affected by regional obesity. It will be critical in the future to understand the various risk factors for sleep apnoea so that suitable screening techniques can be used. Volumetric imaging studies may provide the tools to examine these risk factors. Sex will undoubtedly be an important factor in such an equation.

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# Pulmonary and critical care medicine: a peculiarly American hybrid?\*

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The evolution of pulmonary medicine over the last 15 years has differed in the United States from that in other countries. Today, most fellow applicants to a pulmonary training programme seek combined training in pulmonary medicine and critical care medicine. Programmes that offer fellowship training in pulmonary medicine alone, without critical care training, are decreasing in number. Of the 2019 fellows trained in pulmonary medicine in the United States over the last five years, 79% obtained their training in a three year combined pulmonary and critical care medicine programme; this number increases to 88% if programmes in New York are excluded.<sup>1</sup> Applicants to fellowship programmes that offer training in critical care medicine alone have concurrently decreased. As such, the majority of newly certified pulmonary physicians in the United States also obtain certification in critical care medicine, and vice versa. This experience is very different from that of pulmonary medicine in Europe, and even from that in Canada.

Critical care medicine is one of the most recent disciplines in medicine. The crucible for its development was the polio epidemic in Copenhagen in 1952. An anaesthesiologist, Bjorn Ibsen, found that the combination of careful airway management and positive pressure ventilation—skills previously confined to the operating theatre—resulted in a dramatic reduction in mortality of patients presenting with respiratory paralysis.<sup>2</sup> With the focus on airway care and ventilator management, it is not surprising that anaesthesiologists led the way in the introduction of intensive care units (ICUs) and the development of the new discipline of critical care medicine.<sup>3,4</sup> In the 1960s and 1970s technological advances pioneered for aerospace research were directly incorporated into intensive care monitoring.<sup>5</sup> These technological advances, especially in cardiopulmonary monitoring and treatment, combined with the considerable growth in knowledge of the pathophysiology of critical illness, attracted internal medicine physicians into the ICU.<sup>5</sup>

In the late 1970s efforts were initiated to formalise the training and certification process in critical care medicine. The American Board of Medical Specialties (ABMS)† convened a meeting of the four interested primary specialty boards—anaesthesiology, internal medicine, pediatrics, and surgery—to consider certification in critical care medicine.<sup>6</sup> A joint committee, formed in 1980, held discussions on certification in critical care medicine defined as “a multidisciplinary endeavour that crosses traditional departmental and specialty lines”.<sup>3</sup> Disagreements arose on eligibility criteria and the ability to develop a common certification examination for candidates with such diverse medical backgrounds. The dissolution of this committee in 1983 was regarded by some commentators as evidence that American medicine did not accept critical

care medicine as a discipline that crossed primary specialty lines.<sup>7</sup> In 1985 the American Board of Medical Specialties approved the development by individual primary specialty boards of their own individual certification processes. The first examination for internal medicine specialists was held in 1987 and has since been offered on a biannual basis.

Not only did the primary medical boards fail to reach consensus on critical care medicine, disagreement also arose among internal medicine specialists as to the place of this new discipline.<sup>8</sup> Some consider it a separate distinct subspecialty, while others regard it as a form of special competence held by certain physicians already certified in one of the pre-existing nine subspecialties of internal medicine such as pulmonary medicine or cardiology. To cater for both philosophies, trainees can choose one of three pathways: training in a subspecialty (for example, two years fellowship training in pulmonary medicine or any other subspecialty) plus one additional year in a certified critical care medicine programme; a three year fellowship in a combined pulmonary and critical care medicine programme; or two years of training in a stand alone critical care medicine fellowship programme. Before commencing fellowship training, applicants must have first completed a residency in a certified internal medicine training programme (minimum of three years) and be eligible to sit the board examination in internal medicine.

A combined fellowship in pulmonary and critical care medicine is now the most popular approach for training and certification. To date, 6054 internal medicine specialists have obtained board certification in critical care medicine, and only 7% of these listed a straight two year critical care fellowship as their training pathway. Moreover, of the 746 internists who have taken the re-certification examinations in critical care, 78% also possess board certification in pulmonary medicine (Karen Mullian, ABIM, personal communication). One reason that a combined pulmonary and critical care medicine fellowship has become the most popular pathway is the fear of “burn out” among physicians who practise critical care medicine on a full time basis. As physicians grow older, those with qualifications in both pulmonary medicine and critical care medicine have the option of increasing the pulmonary component of their practice and spending less time in the ICU. In the recent survey by the Committee on Manpower for Pulmonary and Critical Care Societies (COMPACCS), pulmonary and critical care physicians reported that pulmonary medicine accounted for most of their clinical time and about one third of their time was spent in the ICU (Randy Young MD, personal communication).

In contrast to the early domination of critical care medicine by anaesthesiologists, their involvement is now small in the United States. To be eligible to take the critical care examination sponsored by the American Board of Anaesthesiology, candidates must have completed a one year fellowship in critical care medicine (this contrasts with the two year minimum of fellowship training required to take the examination offered by the American Board of Internal Medicine). Like internal medicine trainees, they must have first completed a three year residency in anaesthesiology and be eligible to sit the primary board certification examination. In a recent survey of 36

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†The American Board of Medical Specialties (ABMS) is the overall “holding company” of all medical specialty boards, of which there is a total of 23. The American Board of Internal Medicine (ABIM) was established in 1936 and there are now a total of nine subspecialty boards, such as in pulmonary disease.

anaesthesiology programmes accredited for critical care fellowship training, 33% did not have a single fellow over a two year period.<sup>9</sup> 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<sup>10</sup> 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.<sup>11</sup> 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<sub>1</sub>/VC ratio of <70%, irrespective of their FEV<sub>1</sub>. They have the least diseased group with a mean FEV<sub>1</sub> of 85% predicted and include many subjects whose FEV<sub>1</sub> was within the normal range; indeed, only 39% had an FEV<sub>1</sub> 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<sub>1</sub> of 50% predicted. The EUROSCOP group is intermediate in severity with a mean FEV<sub>1</sub> 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<sub>1</sub>. 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<sub>1</sub> with any certainty within this time, as the short term reproducibility of FEV<sub>1</sub> measurements is around five times the normal annual decline in FEV<sub>1</sub>. A reduction in FEV<sub>1</sub> 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.<sup>1</sup> 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<sub>1</sub> as an outcome difficult in the more diseased group. All three studies used the mixed effects model to estimate the FEV<sub>1</sub> 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<sub>1</sub> in the first 3–6 months, precluding a linear model using the initial data points.

No study showed an unequivocal difference in the FEV<sub>1</sub> 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<sub>1</sub> slope which were not statistically significant when analysed in the whole study group.

The mixed effects model in each study produced estimates for FEV<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub>. 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<sub>1</sub> 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,<sup>2</sup> 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.<sup>3</sup>

Showing small changes in FEV<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> was greater in those with lower starting values of FEV<sub>1</sub>.<sup>4</sup> 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<sub>1</sub>. 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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