Vascularity in asthmatic airways: relation to inhaled steroid dose

J C Hogg

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. 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, and Freedman provided an excellent review of its functional significance in 1972. 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. A series of studies followed that further explored this problem using both quantitative histology and computer based models of the airways. Wiggs et al 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 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 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 vasculature in asthma 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/mm² of lamina propria induced by steroids correlated with the percentage change in forced expiratory volume in one second (FEV₁) 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.

J C HOGG

UBC Pulmonary Research Laboratory, St Paul's Hospital, 1981 Burrard Street, Vancouver, BC V6Z 1Y6, Canada

1 Huber HL, Koessler KK. The pathology of bronchial asthma. Arch Intern Med 1922;38:689–760.
7 Takasawa T, Thurbeck WM. Muscle and mucous gland size in the major bronchi of patients with chronic bronchitis, asthma and asthmatic bronchi.
18 Carroll NG, Cooke C, James AL. Bronchial blood vessel dimensions in asthma. Am J Respir Crit Care Med 1997;155:689–95.
Sex differences and sleep apnoea

R J Schwab

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 suggested 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. However, more recent and rigorous epidemiological studies have shown 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. One reason for the higher prevalence in men may be that women are less likely to report symptoms associated with sleep apnoea. However, several studies 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 lumenal 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 genioglossus muscle activity compared with age matched men. 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. 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. Studies in normal subjects using acoustic reflection have shown that the upper airway is larger in men than in women. However, when the pharyngeal cross sectional area was normalised for body surface area there were no significant differences between men and women. Body surface area, however, may not be the appropriate control. A more recent study 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). Computed tomography (CT) and magnetic resonance imaging (MRI) provide a better anatomical representation of the upper airway than acoustic reflection. Schaw and colleagues 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 5 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. The data from all these studies 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. 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. 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 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). 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. The data presented by Whittle and colleagues lend partial support to such a hypothesis.
Obesity is known to predispose to obstructive sleep apnoea so it has been hypothesised 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. Increased adipose tissue surrounding the upper airway has been demonstrated in obese and non-obese patients with sleep apnoea. Upper airway MRI studies 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. Men tend to have predominantly upper body fat whereas women have lower body fat distribution. 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. Such information may be useful in screening these and other morphometric characteristics of men and women. In addition, it is known that fat distribution is different in men and women.21 22 Men tend to have predominantly upper body fat whereas women have lower body fat distribution.21 22 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 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 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 or upper airway calibre, were not specifically examined. Schwab and coworkers 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. 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. 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. 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, race, and genetics. 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.

RICHARD J SCHWAB
Center for Sleep and Respiratory Neurobiology, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania 19104–4283, USA

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

Martin J Tobin, Edward Hines Jr

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.1 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.2 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.2,3 In the 1960s and 1970s technological advances pioneered for aerospace research were directly incorporated into intensive care monitoring.4 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.5

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.6 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”.7 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.8 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.9 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

---

*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.
EUROSCOP, ISOLDE, and the Copenhagen City Lung Study

P Sherwood Burge

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 FEV1/VC ratio of < 70%, irrespective of their FEV1. They have the least diseased group with a mean FEV1 of 85% predicted and include many subjects whose FEV1 was within the normal range; indeed, only 39% had an FEV1 of < 80% predicted. The subjects in the ISOLDE study were mostly recruited from respiratory clinics and have the most severe COPD with a mean FEV1 of 50% predicted. The EUROSCOP group is intermediate in severity with a mean FEV1 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 criteria relating to smoking; 76% were current smokers.

The principal outcome measure for all three studies was longitudinal decline in FEV1. 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 FEV1, with any certainty within this time, as the short term reproducibility of FEV1 measurements is around five times the normal annual decline in FEV1. A reduction in FEV1 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, as an outcome difficult in the more diseased group. All three studies used the mixed effects model to estimate the FEV, 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 both showed reductions in the FEV, slope which were not statistically significant when analysed in the whole study group.

The mixed effects model in each study produced estimates for FEV, 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, 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, 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, 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,. The run in period was only eight weeks, during which those withdrawn from inhaled corticosteroids declined faster than those who were steroid naive. A tentative estimate of decline can be made from the steroid naive subjects who were randomised to placebo. Their observed FEV, 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, 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.1

Showing small changes in FEV, 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, 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, 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, was greater in those with lower starting values of FEV,. 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,. 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.

P SHERWOOD BURGE

Birmingham Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS, UK

Pulmonary and critical care medicine: a peculiarly American hybrid?

MARTIN J TOBIN and EDWARD HINES, JR

Thorax 1999 54: 286-287
doi: 10.1136/thx.54.4.286

Updated information and services can be found at:
http://thorax.bmj.com/content/54/4/286

These include:

References
This article cites 9 articles, 0 of which you can access for free at:
http://thorax.bmj.com/content/54/4/286#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Errata
An erratum has been published regarding this article. Please see next page or:
/content/54/6/564.full.pdf

Topic Collections
Articles on similar topics can be found in the following collections

- Adult intensive care (179)
- Drugs: infectious diseases (968)
- Epidemiologic studies (1829)
- Neuromuscular disease (86)
- Tropical medicine (infectious diseases) (26)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/
Pulmonary embolism

We must express serious concerns about the internal validity and conclusions of the recent paper by Egermayer et al. in which the authors suggest that normal results of D-dimer, arterial blood gas tensions, and respiratory rate measurements can be used to rule out pulmonary embolism. With respect to blood gases, two earlier well designed studies reported that the PaO\textsubscript{2} and PaCO\textsubscript{2}, alone or in combination, did not exclude pulmonary embolism.\(^1\) If a low PaCO\textsubscript{2} is taken as a reasonable surrogate for tachypnoea, these studies directly contradict Egermayer’s findings. We attribute this discrepancy to a serious flaw in study design.

In any valid evaluation of the accuracy of a diagnostic test, comparison must be made with an appropriate reference standard.\(^2\) Being able to conclude that any test can exclude pulmonary embolism, as the authors have done, mandates that the selected reference standard accurately and objectively rules out pulmonary embolism in all patients who truly do not have it and confirms the diagnosis of pulmonary embolism in all those who truly do. What was the reference standard? The authors apply strict criteria for establishing an objective diagnosis of pulmonary embolism but make no attempt to rule it out with any degree of objectivity. It is clear that their composite reference standard does not divide patients into those with and without pulmonary embolism, but into those who meet the authors’ criteria for “objective pulmonary embolism” and everything else. In only 2\(^1\text{st}\) of the 507 patients with suspected pulmonary embolism (154 with normal lung scans, 36 with high probability scans, and 24 with pulmonary angiograms) was a diagnosis made; in the remaining 98% of cases pulmonary embolism was neither proven nor excluded. Furthermore, among the 27 patients who died within 10 days of evaluation, only five had a necropsy examination. The authors argue that a diagnosis of death and, specifically, the possibility of fatal pulmonary embolism in the remaining 22 is unknown.

Among the 317 patients with non-diagnostic scans there were 135 indeterminate scan results and 182 low probability scans. In the PIOPED study\(^3\) pulmonary embolism was present in 29% and 12% of such patients, respectively. If we assume that the percentages here are similar, 61 of these patients would be expected to have pulmonary embolism. Yet from the results and conclusions published it is apparent that this entire group was designated as having had pulmonary embolism excluded!\(^4\)

The results as presented are highly misleading and cannot justify the conclusions. It is impossible to determine whether a test excludes pulmonary embolism when the reference standard to which it is being compared does not itself exclude pulmonary embolism. Unfortunately, by neglecting this fundamental aspect of study design the authors have invalidated their findings. All that has been shown is that patients with normal D-dimer levels, blood gas tensions, or respiratory rates are unlikely to have the combination of a high probability lung scan together with a high clinical suspicion of pulmonary embolism. Patients with “negative” test results still have a significant probability of pulmonary embolism and it is a dangerous mistake to think otherwise.

This simple but useful observation is also contrary to the conclusion of Egermayer et al.\(^5\) that normal results of the PaO\textsubscript{2} and PaCO\textsubscript{2} may be confusing tachypnoea with hyperventilation, which implies a high minute volume.

We have not drawn any conclusions about the usefulness of normocarbia or of the arterial–alveolar gradient for excluding pulmonary embolism. As far as we are aware, our study is the first to evaluate prospectively the hypothesis that a normal respiratory rate excludes pulmonary embolism. We have found that this simple but useful observation is also often overlooked by doctors who wrongly assume that normal pulmonary angiography or a lung scan will provide a definitive diagnosis in all cases.\(^6\)

It is suggested that a reference standard with 100% sensitivity and specificity is required to evaluate diagnostic tests properly. Such a standard does not exist in the area of venous thromboembolism. Pulmonary angiography for pulmonary embolism falls far short of this standard due to technical limitations and interobserver disagreement in nearly 40% of cases involving smaller emboli.\(^7\)

We were interested in assessing the usefulness of various observations for predicting the absence of “objectively diagnosed” pulmonary embolism (according to our predetermining criteria).\(^8\) The most appropriate calculation for this purpose is the proportion of correct exclusions—that is, the predictive value—which is defined as true positives/true positives + false positives. This calculation does not require the accurate identification of true negatives. We were already aware from previous studies that the D-dimer test was likely to have a very poor specificity for diagnosing pulmonary embolism and did not consider it worthwhile to demonstrate this further.

Drs Stanbrook and Geererts are concerned about the possibility of unrecognised pulmonary embolism among the 22 patients who died and did not have a necropsy. We would like to point out that inadequate investigation of many of the patients with intermediate probability ventilation perfusion lung scans undoubtedly led to cases of pulmonary embolism remaining undiagnosed. However, it would be unrealistic to assume that more aggressive investigations would detect most cases of major pulmonary embolism since these are often asymptomatic.\(^9\) Nevertheless, subsequent analysis of outcomes over two years in untreated patients with pulmonary embolism showed an excellent prognosis even without treatment.\(^10\) They overlook the more obvious problem of false positive diagnoses of pulmonary embolism in two of the five patients who did have a necropsy. Anticoagulant treatment was the direct cause of death in one of these. A previous study conducted at a different New Zealand hospital showed a similar false positive rate.\(^11\) The diagnosis of pulmonary embolism of nearly 50% among patients who underwent a necropsy examination following a perfusion lung scan in addition to objectively diagnosed pulmonary embolism in our study, there were a further 68 patients who received a diagnosis of pulmonary embolism without adequate supporting evidence or, in many cases, despite evidence to the contrary such as a normal lung scan or normal pulmonary angiogram. Of this group of 68 patients 19 (28%) had a negative D-dimer test, the result of which was not known to the physicians responsible for the care of the patient. It is possible that greater utilisation of tests which help to exclude pulmonary embolism could reduce the dangers of misdiagnosis and inappropriate treatment. 

The need for venous thromboembolism is the concept that many clinicians find difficult. The impulse is to continue searching until some evidence of thrombosis is found to justify the use of anticoagulant therapy. It is, of course, impossible to prove that a patient does not have venous thromboembolism. The best that can be aimed for is to reach a point where it is considered no longer profitable to continue the search. There is rarely only one possible methodology to achieve this pur-
pose: one must first carefully define what one is looking for and then prospectively search a large series of cases to see whether the entity exists. We identified 93 consecutive patients with a negative SimpliRED test and Pao2 of >80 mm Hg and did not find any with objectively diagnosed pulmonary embolism. We concluded that this combination of findings excluded objectively diagnosed pulmonary embolism with a very high level of confidence.

Whether or not it is “dangerous” to withhold anticoagulant therapy in patients with negative test results remains to be determined. Further prospective studies with analysis of clinical outcomes are being planned to investigate this question.1

PAUL EGMAYER
GIAN TOWN
Department of Medicine, Christchurch School of Medicine, Christchurch Hospital, P.O. Box 4345, Christchurch, New Zealand

7 Egmayer P. Follow up of death or recurrence is not a reliable way of assessing the accuracy of diagnostic tests for thromboembolic disease. Chest 1997;111:1410–13.

Chronic cough

McGarvey et al have described the causes of cough and the predictive values of appropriate diagnostic tests in a group of patients presenting to a specialist clinician.2 They have used a histamine challenge test to support the diagnosis of asthma and to justify a trial of inhaled corticosteroid therapy. We agree with the authors’ conclusion that a negative histamine challenge effectively rules out asthma as the cause of chronic cough, but disagree that this obviates the need for a trial of inhaled corticosteroids. Eosinophilic bronchitis presents with a chronic cough and sputum eosinophilia, but without the variable airflow obstruction or airway hyperresponsiveness seen in asthma.1 In common with asthma and in contrast to patients with cough without sputum eosinophilia, the cough improves with inhaled corticosteroid therapy. Eosinophilic bronchitis can only be diagnosed if airflow obstruction is assessed.

We have prospectively looked for evidence of eosinophilic bronchitis in new patients referred to over a two year period with isolated chronic cough.2 Patients were investigated using a standard protocol similar to that suggested by McGarvey et al with the addition of induced sputum. Eosinophilic bronchitis was diagnosed if patients had no symptoms suggesting variable airflow obstruction, normal spirometric values, normal PEF variability, a methacholine provocation concentration causing a 20% fall in FEV1 (PC20) of >8 mg/ml, and a sputum eosinophilia (>3% non-squamous cells). In our patients with chronic cough were identified out of a total of 856 new referrals (10.6%). The primary cause was eosinophilic bronchitis in 12 (13.2%). All improved after treatment with inhaled budesonide 400 µg twice daily and in eight who had a follow up sputum analysis the eosinophil count decreased significantly from 16.8% to 1.6%.

The important practical implication of our findings is that a significant proportion of patients with corticosteroid responsive cough have normal airway responsiveness and no other features of asthma. We suggest that a trial of inhaled corticosteroid therapy, preferably after an assessment of airway inflammation, should be part of the diagnostic algorithm of chronic cough, whether there is hyperresponsiveness or not.

C E BRIGHTLING
T D PAVORD
Department of Respiratory Medicine, Glenfield Hospital NHS Trust, Gillybro Road, Leicester LE3 9QF, UK


AUTHORS’ REPLY We welcome the comments of Drs Brightling and Pavord. The assessment of airway inflammation using induced sputum is not currently a routine part of our diagnostic algorithm. The data presented by Pavord et al suggest that our group of patients should have included approximately six patients with eosinophilic bronchitis. Since all our patients with a negative histamine challenge responded to treatment either for postnasal drip syndrome (PNDS) or gastrooedosapheal reflux (GOR), or failed to respond to any treatment including inhaled steroids, we feel it unlikely that patients with steroid responsive cough were missed.

We do, however, recognise the concept of airway inflammation in non-asthmatic coughers and currently have an article in press in which we report that eosinophil numbers are significantly increased in bronchoalveolar lavage fluid from patients with GOR compared with controls. This was not the case for patients with PNDS or idiopathic cough. All the patients with GOR had resolution of cough with acid suppression therapy. Although bronchoalveolar lavage fluid findings may not be directly comparable to induced sputum findings, we suggest that not all patients with chronic cough and a predominant eosinophil component to their airway inflammation require a trial of inhaled steroids.

We agree that assessment of airway inflammation should be considered when evaluating patients with chronic cough and induced sputum may prove to be the best technique. However, it does require certain expertise which may not be readily available in all units encountering patients with chronic cough.

Furthermore, airway inflammation is a dynamic process and sampling at one time point only may not reflect relevant airway events. In addition, there may be difficulties in interpreting the cellular profile in induced sputum as evidenced by analysis of samples obtained from mild asthmatics during exacerbations.3


We read with great interest the article by McGarvey et al concerning the evaluation of patients with non-productive cough. Nowadays “chronic cough” is a well established, uniformly defined entity both in the English and German literature.4 Its relation to gastrooedosapheal reflux disease (GERD) is generally acknowledged. The reader may be interested in a very early description of this entity by Thomas Mann in his novel “Buddenbrooks” published in 1901 (Nobel Prize 1929), Volume 1, Part 6, chapter X, translated by H T Lowe-Porter in 1996 (Minerva paperback edition, Mandarin Paperbacks, London): “Never”, she (Tony Buddenbrook) said. And she gave a long audible outward breath and cleared her throat, also at length and deliberately. It was like she had of late become almost a habit with her, and had probably to do with her digestive trouble (in German “Magenleiden” = gastric suffering).

By his persistent interest in medical issues, particularly tuberculosis, and his famous expertise in observing individuals, the novelist may have become the first to describe “chronic cough” due to GERD.

JÜRGEN MEIER-SYDOW
Prädyschale der Nr.11, 61352 Bad Homburg, Germany

PETER KARDOS
Krankenhaus Melsungen, Scheffelstraße 2-16, 60318 Frankfurt, Main, Germany


Childhood empyema

We read with interest the letter by Playfor et al relating to childhood empyema in Nottingham. Many centres in the UK have noted an increase in this condition over the past three years and, indeed, it has been the subject of discussions at recent meetings of the British Paediatric Respiratory Society (BPRS). Urokinase has been used spasmodically in childhood empyema in the UK over...
the past three years and one of us (AHT) has used it successfully in 28 consecutive patients.

A decision was taken at the BPRS to instigate a national study to compare the effectiveness of intrapleural urokinase with normal saline. The study received MREC approval and has now been underway for approximately 12 months. Another 40 patients are needed for the trial to be completed. If any centres would like to take part would they please contact Anne Thomson, Department of Paediatrics, The John Radcliffe Hospital, Oxford.

We hope that this study will answer the questions raised by Playfor et al and thank everyone who has so far participated in the study.

A H THOMSON
Principal Co-ordinator, Childhood Empyema Study, Oxford, UK

W LENNIEY
Academic Department of Paediatrics, City General Hospital, Stoke-on-Trent, Staffs ST4 6GG, UK

Duchenne muscular dystrophy

In their recently published paper Simonds et al importantly emphasised the desirability of using non-invasive intermittent positive pressure ventilation (IPPV) rather than tracheostomy for optimising quality of life in patients with hypercapnic Duchenne muscular dystrophy, and suggested that the use of nocturnal nasal IPPV can help to prolong survival. They also noted that five of the 23 patients treated in this manner died from respiratory failure two years after beginning nocturnal nasal IPPV, and that most subsequent “admissions were for treatment of chest infections”. In reality, nocturnal nasal IPPV is only likely to prolong the lives of those patients who would otherwise develop hypercapnic coma as they get weaker and weaker. This is uncommon in Duchenne muscular dystrophy. In fact, 90% of episodes of respiratory failure and death in these patients occur during treatment of intercurrent chest colds and result from the inability to cough out secretions. 1 During these episodes non-invasive IPPV often needs to be provided 24 hours a day for ventilation and for air stacking maximal breaths to assist coughing. Also, with the use of non-invasive respiratory aids such as the combination of manually assisted coughing and mechanical insufflation-exsufflation, episodes of respiratory failure and death due to respiratory failure can be virtually eliminated in patients with Duchenne muscular dystrophy. This paper, like others before it, 1 misses the point that just providing nocturnal nasal IPPV is insufficient compared with supporting both the inspiratory and expiratory muscles (non-invasively) during intercurrent chest colds.

YUKA ISHIKAWA
Department of Pediatrics, National Yokumo Hospital, Miyazawacho 126, Yokumo, Yamashita-gun, Hokkaido 049-3116, Japan

JOHN R BACH
Department of Physical Medicine and Rehabilitation, University of Medicine & Dentistry of New Jersey, Newark, New Jersey 07103-2406, USA


AUTHOR’S REPLY There is no question that support of the inspiratory and expiratory muscles is helpful in patients with Duchenne muscular dystrophy and this is stressed in the discussion in our paper. Contrary to Ishikawa and Bach’s series, over 50% of our patients presented with symptomatic diurnal hypercapnic respiratory failure without evidence of an acute chest infection. The suggestion that nocturnal nasal intermittent positive pressure ventilation (NIPPV) “misses the point” or is “insignificant” in this group is ludicrous, and a more balanced approach is required. All our patients with Duchenne muscular dystrophy are taught to carry out regular physiotherapy with assisted coughing while receiving NIPPV, as described in the methods section of the paper. NIPPV combined with physiotherapy is therefore used to support the inspiratory and expiratory muscles. There is no firm evidence as yet that any one method of assisting cough is superior. Of the five patients who died, two had elected to receive palliative care only and so were not avoidable deaths, as is implied.

Notwithstanding the above arguments, the Emerson cough insufflator-exsufflator is not currently available for purchase by hospitals in the UK/Europe as it does not have the CE mark (personal communication, J H Emerson Co). Alternatives therefore need to be explored. Although the methods described by Ishikawa and Bach clearly may be effective, it is notable that they do not give their one year and five year survival data either in the publications cited or elsewhere.

A K SIMONDS
Sleep and Ventilation Unit, Respiratory Support Service, Royal Brompton and Harefield NHS Trust, London SW3 6NR, UK

Medical students’ knowledge of tobacco

The review on educating medical students about tobacco by Robyn Richmond published in the January issue of Thorax was very timely and informative. 1 However, the information that no medical school in Italy has a syllabus which specifically teaches about tobacco related issues is out of date. 2 At the University of Siena medical school we currently offer a specific course on “Tobacco smoke: health effects and the role of health operators”. Of course, now in its second edition, takes the form of a three day, 12 hour series of interactive sessions with participation by experts in epidemiology, pathogenesis, toxicology, psychology, and ethical aspects of tobacco smoke and smoking cessation. Students are also involved in the design, collection, and analysis of small smoking related projects such as a survey on tobacoo smoking inside the hospital. The course is open to students from all of the six months of the medical school and it provides 5 educational credits (over a total of 1000 credits required for graduation).

The awareness of tobacco related health issues by the medical profession is increasing, and reviews such as those published recently in Thorax are very helpful in advancing this process.

PIERSANTE SESTINI
Institute of Respiratory Diseases, Viale Bracchi, 5-53100 Siena, Italy

UK Lung Volume Reduction Trial

The BUPA Charitable Foundation has agreed to fund a national multicentre randomised controlled trial of lung volume reduction surgery in the UK. One hundred and twenty suitable patients with severe emphysema will be recruited over a period of 1–2 years and assigned to either surgery and pulmonary rehabilitation or to pulmonary rehabilitation alone. Further details may be obtained from Professor D Lomas or Mr F Wells at Papworth Hospital, Ms Deidre Watson at Norfolk & Norwich Hospital, Mr W Fountain at Harefield Hospital, Mr J Dussek at Guy’s Hospital, Dr M Morgan or Mr D Waller at Glenfield Hospital, Mr W Walker at the Edinburgh Royal Infirmary, or Mr P Rajesh at the Birmingham Heartlands Hospital.

NOTICE

Pulmonary and critical care medicine

In the editorial entitled “Pulmonary and critical care medicine: a peculiarly American hybrid” by Martin J Tobin which appeared on pp 286–7 of the April issue of Thorax the name Edward Hines Jr which was part of the address mistakenly appeared as an author. The publishers apologise for this error.