

LETTERS TO THE EDITOR

Pulmonary embolism

We must express serious concerns about the internal validity and conclusions of the recent paper by Egermayer *et al*¹ 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 P_{aO_2} and P_{aCO_2} , alone or in combination, did not exclude pulmonary embolism.^{2,3} If a low P_{aCO_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.⁴ 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 in this case? 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 everyone else. In only 214 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 58% of patients pulmonary embolism was neither proven nor excluded. Furthermore, among the 27 patients who died within 10 days of evaluation, only five had a necropsic examination. The cause 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 study⁵ 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!

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.

MATTHEW B STANBROOK
WILLIAM GEERTS
Sunnybrook Health Science Centre,
University of Toronto,
Toronto,
Ontario,
Canada M4N 3M5

- 1 Egermayer P, Town GI, Turner JG, *et al*. Usefulness of D-dimer, blood gas, and respiratory rate measurements for excluding pulmonary embolism. *Thorax* 1998;53:830-4.
- 2 Stein PD, Goldhaber SZ, Henry JW, *et al*. Arterial blood gas analysis in the assessment of suspected acute pulmonary embolism. *Chest* 1996;109:78-81.
- 3 Jones JS, Neff TL, Carlson SA. Use of the alveolar-arterial oxygen gradient in the assessment of acute pulmonary embolism. *Am J Emerg Med* 1998;16:333-7.
- 4 Jaeschke P, Guyatt G, Sackett DL for the Evidence-Based Medicine Working Group. Users' guides to the medical literature: III. How to use an article about a diagnostic test: A. Are the results of the study valid? *JAMA* 1994;271:389-91.
- 5 PIOPED. Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). *JAMA* 1990;263:2753-9.

AUTHORS' REPLY Thank you for the opportunity to respond to the concerns raised by Stanbrook and Geerts regarding our recent study.¹ Two retrospective studies have been cited to justify the conclusion that a P_{aO_2} of >80 mm Hg (10.6 kPa) does not exclude pulmonary embolism.^{2,3} Neither was "well designed" from the point of view of answering the questions we were addressing since neither gave any information concerning the proportion of patients referred for pulmonary angiography who actually had their blood gas tensions measured. In our institution this figure would be approximately 50% (excluding those who were enrolled in our prospective trial). We did not conclude that normoxaemia excludes pulmonary embolism since in our study four of 34 patients (12%) with objectively diagnosed pulmonary embolism had a P_{aO_2} of >80 mm Hg. Allowing for the different methodology, this is similar to the findings of the two studies quoted earlier. It would indeed be surprising if subsegmental pulmonary embolisms caused significant hypoxaemia. What we do conclude from our study and from previous studies is that the finding of normoxaemia significantly reduces the likelihood of clinically important pulmonary embolism.

Contrary to what is stated, hypocarbia is not a reasonable surrogate for tachypnoea since in our study over 30% of patients with a respiratory rate of ≥ 20 breaths/min had an arterial P_{aCO_2} of >35 mm Hg (authors' unpublished data). Stanbrook and Geerts may be confusing tachypnoea with hyperventilation, which implies a high minute volume. We have not drawn any conclusions about the usefulness of normocarbica 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 pulmonary angiography or a

lung scan will provide a definitive diagnosis in all cases.⁴

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. For example, 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.⁵

We were interested in assessing the usefulness of various observations for predicting the absence of "objectively diagnosed" pulmonary embolism (according to our predetermined criteria).¹ The most important 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 Geerts are concerned about the possibility of unrecognised pulmonary embolism among the 22 patients who died and did not have a necropsy. They also rightly 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.⁶ Nevertheless, subsequent analysis of outcomes over two years in untreated patients with pulmonary embolism showed an excellent prognosis even without treatment.⁷ 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 for diagnosis of pulmonary embolism of nearly 50% among patients who underwent a necropsic examination following a perfusion lung scan.⁸ In addition to the 40 cases of 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.

Excluding venous thromboembolism is a 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 really 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 P_{aO_2} 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.⁸

PAUL EGERMAYER
G IAN TOWN

Department of Medicine,
Christchurch School of Medicine,
Christchurch Hospital,
P O Box 4345,
Christchurch,
New Zealand

- 1 Egermayer P, Town GI, Turner JG, *et al*. Usefulness of D-dimer, blood gas and respiratory rate measurements for excluding pulmonary embolism. *Thorax* 1998;53:830-4.
- 2 Stein PD, Goldhaber SZ, Henry JW, *et al*. Arterial blood gas analysis in the assessment of suspected acute pulmonary embolism. *Chest* 1996;109:78-81.
- 3 Jones JS, Neff TL, Carlson SA. Use of the alveolar-arterial oxygen gradient in the assessment of acute pulmonary embolism. *Am J Emerg Med* 1998;16:333-7.
- 4 Egermayer P. Perfusion scintigraphy in the diagnosis of pulmonary embolism. *NZ Med J* 1980;92:462-4.
- 5 Greenspan RH. Pulmonary angiography and the diagnosis of pulmonary embolism. *Prog Cardiovasc Dis* 1994;37:93-106.
- 6 Egermayer P, Town GI. The clinical significance of pulmonary embolism: uncertainties and implications for treatment—a debate. *J Intern Med* 1997;241:5-10.
- 7 Egermayer P, Town GI. The mortality of untreated pulmonary embolism in patients with intermediate probability lung scans (letter). *Chest* 1999 (in press).
- 8 Egermayer P. Follow up for 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 clinic.¹ 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.² 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 airway inflammation is assessed.

We have prospectively looked for evidence of eosinophilic bronchitis in new patients referred over a two year period with isolated chronic cough.³ 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 FEV_1 (PC_{20}) of >8 mg/ml, and a sputum eosinophilia ($>3\%$ non-squamous cells). Ninety one patients with chronic cough were identified out of a total of 856 new referrals (10.6%). The primary diagnosis was eosinophilic bronchitis in 12 (13.2%). All improved after treatment with inhaled budesonide 400 μ g 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
I D PAVORD

Department of Respiratory Medicine,
Glenfield Hospital NHS Trust,
Groby Road, Leicester
LE3 9QB UK

- 1 McGarvey LPA, Heaney LG, Lawson JT, *et al*. Evaluation and outcome of patients with chronic non-productive cough using a comprehensive diagnostic protocol. *Thorax* 1998;53:738-43.
- 2 Gibson PG, Dolovich J, Denburg J, *et al*. Chronic cough: eosinophilic bronchitis without asthma. *Lancet* 1989;ii:1346-8.
- 3 Brightling CE, Ward R, Goh KL, *et al*. Eosinophilic bronchitis is an important cause of cough. *Thorax* 1998;53:A39.

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 gastro-oesophageal reflux (GOR), or failed to respond to any treatment including inhaled steroids (idiopathic coughers), 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 press¹ 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.²

L P A MCGARVEY
L G HEANEY
M ENNIS
J MACMAHON
Department of Respiratory Medicine,
Belfast City Hospital,
Lisburn Road,
Belfast BT9 7AB,
UK

- 1 McGarvey LPA, Forsythe P, Heaney LG, *et al*. Bronchoalveolar lavage findings in patients with chronic non productive cough. *Eur Respir J* 1999 (in press).
- 2 Turner MO, Hussack P, Sears MR, *et al*. Exacerbations of asthma without sputum eosinophilia. *Thorax* 1995;50:1057-61.

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.² Its relation to gastro-oesophageal 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 a dry cough which 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
Friedrichsdorfer Strasse 11,
61352 Bad Homburg,
Germany

PETER KARDOS
Krankenhaus Maingau,
Scheffelstrasse 2-16,
60318 Frankfurt,
Main,
Germany

- 1 McGarvey LPA, Heaney LG, Lawson JT, *et al*. Evaluation and outcome of patients with chronic non-productive cough using a comprehensive diagnostic protocol. *Thorax* 1998;53:738-43.
- 2 Kardos P, Gebhardt T. Chronisch persistierender Husten (CPH) in der Praxis: Diagnostik und Therapie bei 329 Patienten in 2 Jahren. *Pneumologie* 1996;50:437-41.

Childhood empyema

We read with interest the letter by Playfor *et al*¹ 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 LENNEY

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

- 1 Playfor SD, Stewart RJ, Smith CM, *et al*. Childhood empyema. *Thorax* 1999;54:92.

Duchenne muscular dystrophy

In their recently published paper Simonds *et al*¹ 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 colds² and result from the inability to cough out secretions.³ 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 expiratory 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,^{4,5} misses the point that just providing nocturnal nasal IPPV is insignificant compared with supporting both the inspiratory and expiratory muscles (non-invasively) during intercurrent chest colds.

YUKA ISHIKAWA

Department of Pediatrics, National Yakumo Hospital,
Miyazono-cho 128, Yakumo, Yamakoshi-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

- 1 Simonds AK, Muntoni F, Heather S, *et al*. Impact of nasal ventilation on survival in hypercapnic Duchenne muscular dystrophy. *Thorax* 1998;53:949-52.
- 2 Bach JR, Rajaraman R, Ballanger F, *et al*. Neuromuscular ventilatory insufficiency: the effect of home mechanical ventilator use vs. oxygen therapy on pneumonia and hospitalization rates. *Am J Phys Med Rehabil* 1998;77:8-19.
- 3 Bach JR, Ishikawa Y, Kim H. Prevention of pulmonary morbidity for patients with Duchenne muscular dystrophy. *Chest* 1997;112:1024-8.
- 4 Raphael JC, Chevret S, Chastang C, *et al*. Randomised trial of preventive nasal ventilation in Duchenne muscular dystrophy. *Lancet* 1994;343:1600-4.
- 5 Vianello A, Bevilacqua M, Salvador V, *et al*. Long-term nasal intermittent positive pressure ventilation in advanced Duchenne's muscular dystrophy. *Chest* 1994;105:445-8.

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 6NP, 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". The 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, completion, and analysis of small smoking related projects such as a survey on tobacco smoking inside the hospital. The course is open to students from all of the six years of the medical school and it provides 15 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 Bracci, 3-53100 Siena,
Italy

- 1 Richmond R. Teaching medical students about tobacco. *Thorax* 1999;54:70-8.
- 2 Quaranta A, Bilancia R. Fighting against smoking in Italy: insufficient rules, scarce control and indifferent attitude of the medical school and physicians. *Lotta contro la tubercolosi e le malattie polmonari sociali* 1994;64:38-42.

NOTICE

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.

CORRECTION

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.