

PostScript

LETTERS TO THE EDITOR

Surgery in early NSCLC and co-morbidity

We would like to congratulate Janssen-Heijnen *et al*¹ on their well performed study and on their significant contribution to resolving the problem of treatment in patients with non-small cell lung cancer (NSCLC) and co-morbidity. However, we could not find a description of the surgical approach used and would like to ask the authors to provide details of the surgical procedures adopted and the accompanying survival rates. We think,² in agreement with other authors³ that, for patients with early stage NSCLC and co-morbidity, a less invasive surgical approach should be used. This view is supported by studies in elderly patients or in patients with co-morbidity showing that a less invasive approach does not influence survival rates. Only the recurrence rate seems to be increased by a less invasive surgical approach such as segmentectomy or pulmonary wedge resection.³⁻⁵

Several factors determine whether conservative or invasive resection should be used for NSCLC. We think that a less invasive approach should be chosen as the first therapeutic step, even for early stage NSCLC, and that elderly patients should be treated less aggressively than younger patients.

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Authors' reply

We agree with Sortini and colleagues that the type of surgical procedure may influence survival. Several studies have shown that less invasive resections might be a good

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alternative for the elderly and those with co-morbidity because postoperative mortality and complications are rather high in these patients.¹⁻⁵ We did not present survival rates for the different surgical approaches because the numbers of patients in the subgroups were rather small, especially for the less invasive resections like sleeve resection, segmentectomy, and wedge resection. However, at the request of Sortini and colleagues, we here present the results for the different surgical approaches.

Figure 1 shows the proportional distribution of surgical approaches in resected patients with stage I and II NSCLC according to age and number of co-morbid conditions. Elderly patients received a pneumonectomy less often, while the proportion of lobectomies and less invasive resections increased with age. In age groups <60 years and 70-79 years patients with co-morbidity received

pneumonectomy less often and a lobectomy/less invasive resections more often than those without co-morbidity. In patients older than 80 years the number of patients was too small to draw any conclusions.

In the multivariate survival analysis of resected stage I and II NSCLC patients, those treated with bilobectomy (HR = 0.70, p = 0.08) or lobectomy (HR = 0.70, p = 0.003) had a significantly better survival than those treated with pneumonectomy, adjusted for age, sex, tumour size, histological subtype, and co-morbidity. Survival in patients treated with less invasive resections was not significantly different. The absence of a difference might be explained by the small number of patients in this subgroup (n = 47).

We want to emphasise that this is an observational population based study and not a randomised controlled trial. Among the elderly, probably only the fittest patients were selected for surgery. Although we adjusted for the above mentioned patient related and tumour related factors in the multivariate survival analysis, other selection factors for surgery such as performance status, ASA score, forced expiratory volume in 1 second, and patient's choice might have confounded the results.

Since the recurrence rate has been shown to be higher in patients who underwent less invasive surgery (such as wedge resection), lobectomy or pneumonectomy remain the surgical approaches of first choice in patients who are fit enough to undergo invasive surgery.⁴ Since it is still not clear what assessment is necessary in order to assess whether an older patient is fit enough for

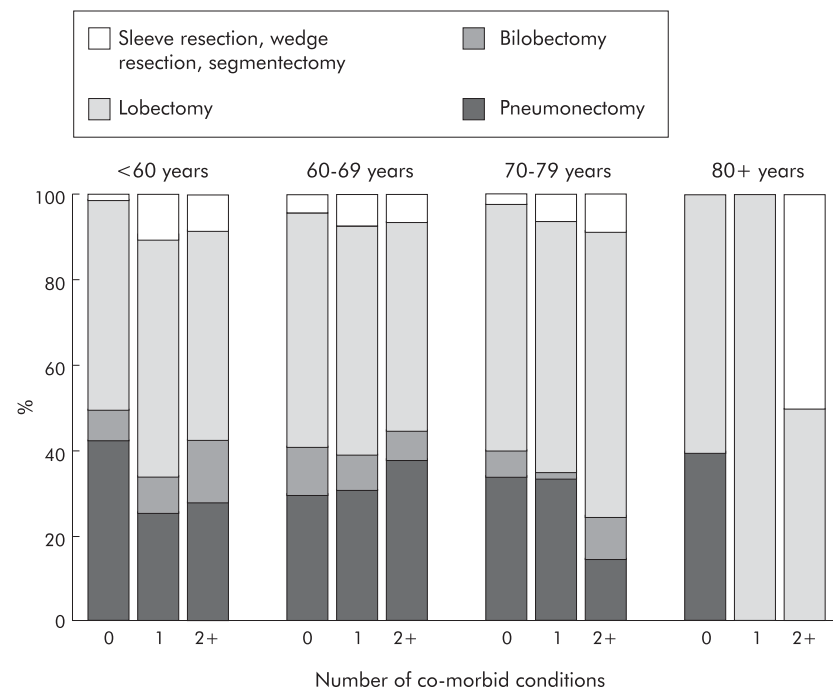


Figure 1 Surgical approach for surgically resected localised NSCLC according to age and co-morbidity.

invasive surgery, future studies should focus on this topic.

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Recruitment of ethnic minorities to asthma studies

The research letter by Sheikh and co-authors¹ addresses an important area but, regrettably, does not hit the nail on the head. Information on ethnicity of study participants is often missing in asthma studies, as the authors clearly show. However, presenting this information—for example, in the table of baseline characteristics when reporting a clinical trial—is only a first step. Much more important is the inclusion of this characteristic in the analysis of effect modification or subgroup analysis. Only then will we know whether ethnicity really matters when applying a certain intervention.

I would welcome a further report from the authors giving details about the actual incorporation of ethnicity in data analysis.

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Authors' reply

We are grateful to Dr van der Wouden for raising the important point of ensuring that ethnicity data are used when analysing trial results. Of the 23/70 studies (32.8%) reporting information on ethnicity in the trial report, all confined mention of ethnicity only to baseline characteristics of included participants. Thus, none of these 23 studies factored ethnicity into the analysis of results. A possible explanation for this rather disappointing observation is that the number of subjects recruited from minority ethnic

groups tended to be small, thereby precluding any meaningful ethnic-specific subgroup analysis. Unfortunately, this is a problem not solely confined to asthma studies; for example, less than 30% of clinical trials on epilepsy which reported ethnicity used the information in the analysis.¹

In designing clinical trials, pragmatic and cost considerations often force investigators to focus on the main objectives of the study, forcing considerations concerning subgroup analyses onto the back burner during trial planning. Most clinical trials therefore lack sufficient power for subgroup analyses;² however, this appears to be a problem that is particularly common in relation to subgroup analysis by ethnicity.³

Our motivation for undertaking this study was to highlight the disparity in recruitment between ethnic minorities and the majority into trials in a disease where ethnic considerations may be relevant. Asthma is one such area, but there are also others.⁴ van der Wouden is entirely correct in asserting that improving recruitment of minority ethnic groups is only half the battle; at least equally important—if not more so—is ensuring that information on ethnicity is meaningfully and competently used when analysing data and presenting results.⁵ Both issues should now be prioritised by the respiratory research community.

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EBC pH and chronic cough

We read with interest the recent article by Niimi *et al* reporting low levels of exhaled breath condensate (EBC) pH in patients with chronic cough.¹ We and others have described low EBC pH in association with airway inflammation in allergic asthma, cystic fibrosis, and chronic obstructive pulmonary disease.^{2–4} In these studies there is a relatively close association between inflammation and low pH which is shown by the further fall in pH during exacerbations.² However, in

non-asthmatic chronic cough, while there is a low grade inflammation present in some subjects, this is much less than would be required to invoke inflammation as the major cause of airway acidification.

It is unclear from the description of the assessment protocol how patients were allotted their individual diagnostic categories. A positive methacholine challenge test is not infrequently found in patients with reflux⁵ and, even in classical asthma, reflux is a common phenomenon.⁶ We would suggest that there has been a significant under-diagnosis of reflux disease in this cohort because of the lack of a structured history, the non-uniform application of investigations, and the failure to perform full oesophageal assessment, particularly manometry. We have shown that, when oesophageal manometry is not performed, a significant number of patients with reflux cough will be missed.⁷ Proton pump inhibitors at conventional doses only temporarily increase the pH of gastric reflux and do not prevent reflux *per se* and, unsurprisingly, only improve symptoms in a proportion of patients with reflux cough. A failure of cough to improve with proton pump inhibitors does not therefore adequately rule out reflux cough.

The simplest explanation for the low airway pH observed by Niimi *et al* is that a large proportion of the subjects had laryngopharyngeal reflux. This would also explain the otherwise surprising finding of a similar EBC pH across the authors' diagnostic categories.

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Effect of oxygen on recovery from maximal exercise in COPD

I read with great interest the article by Stevenson and Calverley and related editorial.^{1 2} An important and unexplained finding was the fact that instrumented patients using a mouthpiece and noseclip took significantly longer to recover from breathlessness after exercise than those who wore only a face-mask (non-instrumented), irrespective of oxygen or air delivery. The mean (SE)

difference was 3.94 (1.77) minutes in a total exercise recovery period of 11.38 (1.49) minutes for fully instrumented patients. Various theories to explain this exceptional difference have been offered both by the authors and reviewer. These have mainly centred on the theme of inhibition of ventilation from the persistence of primitive diving reflexes.³ However, the precise mode of ventilation of these patients in the recovery phase via the mouth or nose needs consideration.

We have recently reported that normal subjects have both quantitative and qualitative differences in ventilation and ventilatory patterns when adopting nasal compared with oral routes for ventilation.⁴⁻⁵ Minute ventilation and its components (tidal volume and breathing frequency) were reduced by a mean of 33% and followed a shift of thoracoabdominal respiration to favour "diaphragmatic" breathing during nasal ventilation and "upper thoracic cage" during mouth breathing. The clinical implications of this have been explored by using a specifically designed questionnaire to discover breathing preferences (mouth/nose) in patients with chronic respiratory diseases including COPD. The findings revealed a high prevalence of symptoms of dysfunctional ventilation and, for the first time, strongly linked them to a preference for mouth breathing.^{6,7}

Evidence now suggests that proprioceptive input from a number of sources (including pulmonary and chest wall) forms the final common pathway for the perception of breathlessness.⁸ Thus, it seems that mouth breathing per se may predispose to the perception of breathlessness by dynamically changing chest wall mechanics by a resultant increase in ventilation and subtle shift in thoracoabdominal respiration.

Fully instrumented patients in the study are, by definition, obligate mouth breathers and, for the reasons offered, this may provide the sole explanation for the findings of the persistent breathlessness. The relevance of the time honoured practice of measuring ventilation with a mouthpiece and noseclip needs to be carefully reviewed in the future.

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Authors' reply

We are grateful for Dr Williams' positive comments about our study which was primarily designed to evaluate the relationship between the physiological effects of supplementary oxygen in normoxaemic COPD patients and the intensity of their dyspnoea when oxygen was administered after a standardised exercise stimulus.¹ The difference between the instrumented and non-instrumented patients was not a primary outcome and should therefore be interpreted with some caution, at least from the statistical point of view. Nonetheless, we agree that stimulation of upper airway receptors can be an important mechanism for modifying respiratory sensation, as we suggested several years ago when we found that administering cold air during exercise reduced the intensity of exercise induced dyspnoea.² We can confirm that breathing with a noseclip and mouthpiece modifies the pattern of regional chest wall ventilation in COPD patients compared with non-instrumented breathing when assessed by optoelectronic plethysmography. These changes at rest did not modify the pattern of chest wall movement during exercise that we recently described,³ and this would argue against Dr Williams' suggestion that the breathing route is a major contributory factor to dyspnoea intensity. It is possible that the switch to mouth breathing reflects a need to reduce inspiratory resistance and is thus an adaptive response in these patients. Further work in this interesting area will be needed to resolve these important issues.

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α_1 -Antitrypsin genotype unaffected by age

In a recent otherwise excellent editorial in *Thorax*,¹ Dr Seersholm indicated that our previous results on the decline in forced expiratory volume in 1 second (FEV₁) based on the Copenhagen City Heart Study² are biased. We disagree, and rather believe that our study of the general population is prone to less bias than case-control or family based studies.

Dr Seersholm argues that, because we genotyped study participants after measurement of FEV₁ in 1976-8, 1981-4, and 1991-4, our results are biased.¹ Certainly, if conventional risk factors are measured after

development of disease, the disease might be the cause of the risk factor rather than vice versa. However, an α_1 -antitrypsin MZ genotype in a newborn does not change into a ZZ genotype by age. Therefore, the Pi MZ genotype preceded FEV₁ outcomes in our study, even though genotypes were determined after FEV₁ measurements. Using identical logic, the genotype preceded outcomes in a similar manner in other previous studies.³⁻⁶

Selection bias could potentially be a reason for discrepancies between studies on Pi MZ and COPD.^{1,7} In our study, where genotype distribution was in Hardy-Weinberg equilibrium, we found no evidence for selection against any α_1 -antitrypsin genotype.^{2,8} Therefore, as also pointed out by Dr Seersholm,¹ selection bias is more likely in case-control and family based studies than in cohort studies of the general population.

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Authors' reply

Drs Dahl and Nordestgaard argue against selection bias if genotyping is performed after lung function tests because a newborn with a Pi MZ genotype does not change to Pi ZZ later in life. The latter is obviously true and not the issue. The reason for possible selection bias is that some people may fail to have genotype performed due to a characteristic of the lung function tests under study, and this may affect the result of a longitudinal study.

If we assume that subjects with a Pi MZ genotype have a very fast decline in forced expiratory volume in 1 second (FEV₁) with premature death, a number of them may have attended the first examinations but did not live long enough to attend the last visit with genotyping. They would not therefore be included in the analysis of FEV₁ decline and the result would be an underestimate of the decline in FEV₁ with the possible conclusion

that Pi MZ is not a risk factor for lung disease. This is usually called a “survivor effect”.

The opposite may also be true. Suppose there is a reverse relationship between pulmonary function and compliance with study visits—that is, subjects with a normal FEV₁, normal FEV₁ decline, and no lung symptoms may not attend the last visit because they feel well. This would tend to exaggerate any increased decline in FEV₁ and the conclusion could be that Pi MZ is an important risk factor for lung disease.

These are just two of many examples of possible biases. They show that, even if the risk factor (Pi MZ) is present from birth, it is vital to postpone the collection of tests for analysis after genotyping has been performed.

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Exhaled breath condensate in chronic cough

We read with interest the recent article by Niimi *et al* reporting low levels of exhaled breath condensate (EBC) pH in patients with chronic cough.¹ We and others have described low EBC pH in association with airway inflammation in allergic asthma, cystic fibrosis, and chronic obstructive pulmonary disease.^{2–4} In these studies there is a relatively close association between inflammation and low pH which is shown by the further fall in pH during exacerbations.² However, in non-asthmatic chronic cough, while there is a low grade inflammation present in some subjects, this is much less than would be required to invoke inflammation as the major cause of airway acidification.

It is unclear from the description of the assessment protocol how patients were allotted their individual diagnostic categories. A positive methacholine challenge test is not infrequently found in patients with reflux⁵ and, even in classical asthma, reflux is a common phenomenon.⁶ We suggest that there has been a significant underdiagnosis of reflux disease in this cohort because of the lack of a structured history, the non-uniform application of investigations, and the failure to perform full oesophageal assessment, particularly manometry. We have shown that, when oesophageal manometry is not performed, a significant number of patients with reflux cough will be missed.⁷ Proton pump inhibitors at conventional doses only temporarily increase the pH of gastric reflux and do not prevent reflux per se and, unsurprisingly, only improve symptoms in a proportion of patients with reflux cough. A failure of cough to improve with proton pump inhibitors does not therefore adequately rule out reflux cough.

The simplest explanation for the low airway pH observed by Niimi *et al* would be that a large proportion of the subjects had laryngopharyngeal reflux. This would also explain the otherwise surprising finding of similar EBC pH across the authors' diagnostic categories.

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- 7 Kastelik JA, Redington AE, Aziz I, *et al*. Abnormal oesophageal motility in patients with chronic cough. *Thorax* 2003;**58**:699–702.

Authors' reply

We thank Professor Morice and his colleagues for their interest in our paper. The main issue they raise concerns the possibility that we may have missed gastro-oesophageal disorders such as reflux and dysmotility in our cohort of patients with chronic cough. In our assessment protocol we state that we used oesophageal pH measurements in most patients (32 of 50), together with a trial of proton pump inhibitors. We are pleased to read from Professor Morice that proton pump inhibitors “only improve symptoms in a proportion of patients with reflux cough”, when they reported previously a very excellent 82% therapeutic response in this group treated with “proton pump inhibitors, alginate and conventional advice regarding diet and posture”.¹ We agree entirely that proton pump inhibitors are not very efficacious in reflux cough. We have not performed oesophageal manometry and are aware of Professor Morice's interesting observations. They also report that patients with abnormal oesophageal manometry respond to proton pump inhibition, and therefore we would have picked up such patients with a trial of proton pump inhibitor treatment. However, the direct link between oesophageal dysmotility and chronic cough still remains to be established.

We do not believe we have missed reflux as an associated cause of the cough and therefore do not agree with the explanation that the reduced exhaled breath condensate pH is a reflection of laryngopharyngeal reflux throughout the diagnostic categories. Rather, this is likely to be related to the chronic inflammatory and remodelling process that is present in the submucosa of chronic cough patients, associated with both asthma and non-asthmatic causes.^{2–4} We must emphasise that we are assuming that exhaled breath condensate is a reflection of the epithelial surface liquid, which needs to be confirmed.

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Bilateral non-traumatic second rib fracture after bilateral first rib resection for TOS

Thoracic outlet syndrome (TOS), which is caused by osseous and soft tissue abnormalities and presents as tingling, paraesthesia, and weakness of the extremity, is a controversial subject. Surgical treatment for TOS is seen as the last resort and involves resection of the first rib and scalenotomy and leads to an overall improvement of 70% over a period of 5 years.¹ The most common postoperative complications are pneumothorax, injury to the subclavian artery and vein, or brachial plexus and long thoracic nerve.² Second rib fracture as a complication after surgery for TOS has not previously been described.

A 54 year old woman had been symptomatic with bilateral constant numbness, tingling, paraesthesia, and weakness exacerbated by sports and exercises for well over 10 years. Numerous attempts at conservative treatment had failed. She also had bilateral omarthrosis which had been treated by previous acromioclavicular joint resection and subacromial decompression. Nevertheless, the symptoms persisted and increased in both ulnar innervated segments of the arm. The hyperabduction test (Wright) was positive on both sides. In conjunction with her other symptoms, a diagnosis of bilateral neurovascular TOS was established and the patient underwent transaxillary first rib resection on the right side. Any injury to the second rib during surgery could be ruled out. Her recovery was uneventful and both pain and numbness were greatly improved.

Two months later transaxillary first rib resection was performed on the left side. Again the symptoms improved. Three weeks after this operation the patient felt a sudden crack and tenderness in her left shoulder girdle with no previous minor or major trauma. Radiographs showed an anterolateral left second rib fracture. Two months later the patient developed sudden tenderness in her right shoulder, again with no previous trauma, and a posterolateral second rib fracture was diagnosed by radiography. An osteodensitometric study showed only a slightly deficient calcium intake of estimated 1150 mg instead of 1500 mg per day. T-scores were within the normal range and no diagnosis of osteoporosis could be established. A technetium-99m bone scan and a SPECT showed increased pathological activity in both second ribs consistent with the fractures, but no other abnormalities (fig 1). The patient was treated conservatively and recovered very well; she has had no further problems.

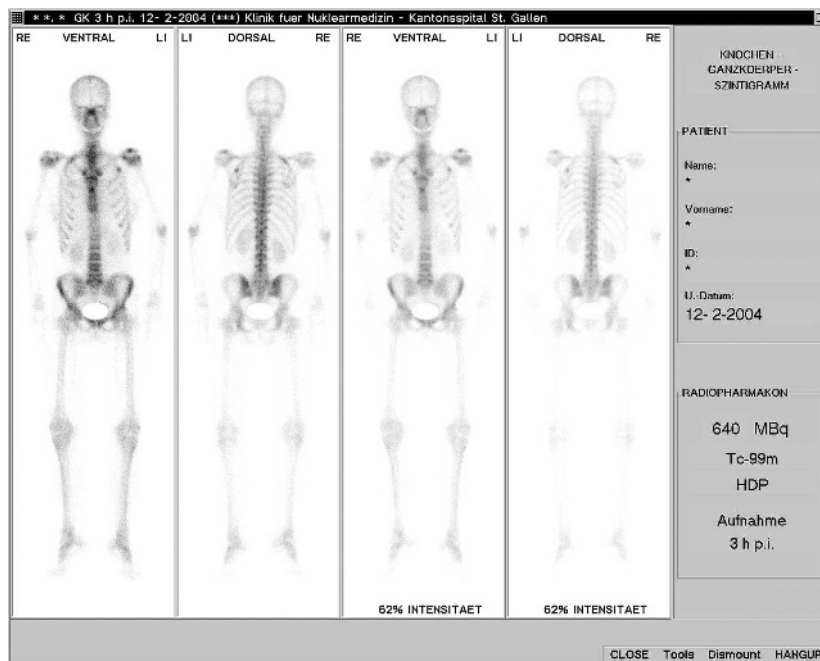


Figure 1 Tc-99m bone scan of patient.

Fractures of the first rib are very rare and bilateral fractures are even more uncommon.³⁻⁹ Bilateral fracture of the second rib has not been described previously. After first rib resection the second rib becomes the most cranial rib and thus takes the place of the former first rib. Second rib fracture after first rib resection can therefore be compared with first rib fractures in patients who have not undergone first rib resection. Several theories on the aetiology of first rib fractures exist.^{6,7} Traumatic fractures usually involve not only the first rib but also the clavicle or scapula. Considerable force is required to fracture the first rib since it is protected very well by soft tissue and the clavicle and scapula. Non-traumatic fractures occur without adequate trauma and are regarded as stress fractures and usually can be found in the weakest portion of the rib.³⁻⁸ Fractures present with upper chest pain and tenderness.³ Some authors have doubted the existence of this type of fracture and classify it as a congenital anomaly.¹⁰

Most authors explain the stress fracture by the anatomy of the first rib.³⁻⁸ The rib is broad and flat and weakened by the groove where the subclavian artery crosses it. The scalene muscles produce a bending force in the rib causing it to fracture. This theory has been questioned since it would mean that all fractures would occur at the same location.³ After first rib resection for TOS the second rib takes the place of the first rib and faces the same stress as the former first rib. The second rib is thinner and not as wide as the first rib, leaving it even more vulnerable to stress. This can explain the relatively short time between first rib resection and fracture of the second rib on the left side in our patient. This left the rib with insufficient time to adapt to the increased force after first rib resection. The clavicle may exert pressure on the second rib, particularly when carrying heavy loads. Our patient denied vigorous exercise before the fracture. The fracture of the right second rib may be explained by increased stress due to

impaired movement of the left shoulder. Furthermore, scar remodelling around the rib may have impaired motion leaving the rib prone to fracture. The two fractures occurred in different parts of the rib. We conclude that there is no point of least resistance in the second rib. Also, no muscle insertion on the rib is responsible for the fracture. A pathological fracture resulting from bone metastases was ruled out and there was no osteoporosis which would have made the bones more prone to trauma. We classify the fractures as spontaneous non-traumatic fractures in an otherwise healthy patient.

Spontaneous non-traumatic fractures of the first and second ribs remain a controversial topic. The fractures presented with pain and tenderness. Upper chest pain is the only symptom in such patients, and a second rib fracture should be considered in patients who develop chest pain after first rib resection.

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BOOK REVIEW

Chronic Obstructive Pulmonary Disease: Second Edition

P M A Calverley, W MacNee, N B Pride, P M Rennard, Editors. London: Arnold, 2003, £110.00. ISBN 0 340 807180

If I want to find the latest research papers quickly, the internet is the place to go. For advice on management there is no shortage of reputable guidelines. So what use is the old style textbook? The editors of the second edition of *Chronic Obstructive Pulmonary Disease* touch on this question as they introduce their own book and suggest that what they offer is time and depth. A textbook allows consideration of all aspects of a disease—not just the latest trials in COPD but the development and pathophysiology of the condition—and time to address the full background to active research topics even if the very latest advances cannot be incorporated. Contributors to a textbook have the opportunity to present a detailed exposition of a topic in a way that few readers could manage themselves via a trawl of the internet.

So has this opportunity been taken in *Chronic Obstructive Pulmonary Disease*? Overall, I think it has. No textbook is meant to be read from cover to cover and I haven't tried, but I did start at the beginning and, if thoughtful consideration is the hallmark of a textbook, then the opening chapter on definitions certainly sets the correct tone. Anyone who weaves Alice in Wonderland and Karl Popper into the first few pages of a medical book is doing rather more than going through the motions. This is a nice start, but perhaps the real test of any textbook is how well it explains the topics on which the reader is ignorant. I found myself worryingly spoilt for choice but decided to start with the chapters on "Oxidative Stress" and "Airway Repair", both of which are written by members of the editorial team. The styles are different but I learned from both. The chapter on "Oxidative Stress" is certainly detailed but worth the effort, and the briefer chapter on "Airway Repair" provided an extremely useful summary for an uninitiated person like myself. Several other chapters also brought rewards, not least those on "Lung Mechanics" and "Exercise" and the well written summary of "Pulmonary Rehabilitation". The smaller number of chapters whose subject matter I like to think I know well inevitably seemed a little less informative, but there are none anywhere near poor enough to be highlighted here. There is far more to applaud than to be disappointed with.

No-one will believe a review free of complaints, so I should list some. I think the editors might consider the balance of the chapters. Should there be seven pages on “ α_1 -Antitrypsin” when the whole “Pathology” chapter only gets the same? Or just nine pages on “Inflammation” when “Oxidative Stress” contains 20? There are also a few omissions. Despite the explanation in the Preface, I think it would be nice to have a chapter summarising the role of cigarette smoking and the mechanisms underlying this (a chapter on “Smoking Cessation” compensates in part). A good chapter on “Oxygen Therapy” offers little about short burst oxygen, and I struggled to find anything on the current debate regarding the role of inhaled steroids in preventing a decline in FEV₁ (it’s actually under the slightly misleading subheading “Short-term Treatment with Inhaled Corticosteroids”).

But these are minor quibbles. The package as a whole is of high quality and pitched at a level which will be appreciated by respiratory trainees, consultants, and the interested general physician.

A walk through the average medical school or hospital library suggests that there is still an appetite for textbook learning, and those wishing to know more about COPD will be well served by this title.

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CORRECTION

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Asthma exacerbation in children immediately following stressful life events

In the paper entitled “Asthma exacerbations in children immediately following stressful life events: a Cox’s hierarchical regression” by S Sandberg *et al* which appeared in the December issue of *Thorax* (2004; **59**:1046–51),

some of the statistics have been incorrectly presented.

In the Results section of the abstract on page 1046, the first sentence should read: “An immediate effect evident within the first 2 days following a severely negative life event increased the risk of a new asthma attack by a factor of 4.69, 95% confidence interval 2.33 to 9.44 ($p < 0.001$)”. The third sentence should read: “In addition to the immediate effect, an increased risk of 1.81 (95% confidence interval 1.24 to 2.65) was found 5–7 weeks after a severe event ($p = 0.002$)”.

On page 1049 the third paragraph should read: “The effect of a severely negative life event was as follows. The immediate effect corresponding to 1–2 days after the event increased the risk of a new asthma exacerbation by a factor of 4.69 (95% confidence interval 2.33 to 9.44) which was statistically significant ($p < 0.001$), whereas the effect for days 3–10 after the event was not statistically significant ($p = 0.5$). The risk of an asthma attack varied considerably between children; the frailty term was highly significant ($p < 0.001$).”