

Delays in managing lung cancer

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Efforts to reduce delays in lung cancer management should not cease even though they may not affect the prognosis

It is universally acknowledged that the prognosis of lung cancer is very poor, with overall 5 year survival figures of about 5–10% worldwide.¹ What is less well recognised is that the picture has changed very little over the last 20 years, and that this is in sharp distinction to other solid tumours where not only are survival rates better—in the order of 60–90%—but they have been increasing (improving) fairly rapidly and continue to do so over a comparable time. For example, in our region of the UK, comprehensive population based registry data for 2 year survival of the 5000 patients diagnosed with lung cancer in 1999 was 13% compared with 60%, 79%, 87% and 92% for colorectal, cervix, prostate, and breast cancer, respectively.² There is merit therefore in considering what might influence and be responsible for this poor outcome.

FACTORS AFFECTING PROGNOSIS IN LUNG CANCER

The factors which affect the prognosis in lung cancer are principally the stage and related performance status at presentation, histology (that is, the biological activity of the tumour), co-morbidity, age, sex, and the time interval between first symptom and treatment.

Some of these factors are not modifiable. In theory, however, reducing intervals between presentation and treatment might downstage patients and allow an improvement in survival. There are excellent data to show that early stage disease has better survival;³ there is less good but nevertheless fairly convincing evidence that very early stage disease (that is, small asymptomatic lesions) have an even better prognosis.

There are, of course, other ways of reducing lung cancer mortality. In the very long term, over a period of decades, prevention is clearly key. In the longer term, over a 5–10 year time span, the identification and treatment of very early asymptomatic disease offers good prospects of cure (screening).⁴ At the present time, however, efforts to improve lung cancer mortality have to reside in reducing delays to treatment

and ensuring better access to specialist appropriate care.⁵ However, since the best appropriate care for cure is surgery, and this modality has not changed appreciably—although now technically more adroit—for many years,⁶ and because the cure rate will remain low unless a higher proportion of patients present and can be managed while at stage I and stage II, the question of interval delays and their effect on prognosis is of great importance.

STAGES IN THE DIAGNOSIS OF LUNG CANCER

In considering the life history of a tumour and points at which medical intervention can take place, four intervals are pertinent:

- between first malignant change and first symptom;
- between first symptom and presentation;
- between first presentation and confirmation of diagnosis;
- between diagnosis and staging/treatment.

Interval between first malignant change and first symptom

This is the very long asymptomatic period between the first malignant change in the bronchial epithelium and the first symptom. It is a reasonable assumption that the change from Tx to T1 and then T2 is not only a local increase in size, but an increase in metastatic potential—that is, there is a greater chance that, as the tumour enlarges, the stage will increase to N1, N2, N3 or from M0 to M1. There are reasonably good data, particularly from Japanese studies, that this is the case, certainly for tumours between 0.5 and 3 cm.^{7,8} For example, in a study by Oda *et al*⁸ the proportion of the 409 resected specimens which had nodal disease (N1, N2, N3) was 0% for primary tumours <10 mm in diameter, 21% for tumours of 11–20 mm, 23% for those of 21–30 mm, and 48% for tumours of >30 mm in diameter. Unfortunately, most T1 lesions are asymptomatic. Tumours can enlarge markedly within

lung tissue and remain silent clinically. Many of these have metastatic potential and do metastasise when they achieve a size of about 1 cm. Thus, when the first symptoms begin there is, in practice, a high chance that the tumour will be at an advanced stage, either locally invasive T3 or T4 with nodal involvement N1–N2–N3, or it will present with a metastatic symptom such as back pain.

Interval between first symptom and presentation

The interval between the patient's first cancer symptom and presentation (within patient delay) is currently under intense investigation as a possible target for health education action. The reasons why patients present when they do and with the symptoms they do is a highly complex phenomenon which is influenced by various factors such as age and health expectations, background symptoms, fear, and their impressions about health care.⁹ However, as we discuss below, it is likely that attempts to shorten this interval will increase the survival chances of only a few patients with an eventual diagnosis of lung cancer.

Interval between first presentation and confirmation of diagnosis

The third interval is between first presentation to any doctor and a confirmed diagnosis in secondary care. A considerable amount of activity is presently taking place to encourage primary care practitioners to recognise potential cancer symptoms and to expedite referral to specialists and for the specialists to rapidly diagnose and stage these patients. In the UK at present, and in parallel with other healthcare systems such as in Scandinavia, there are national recommendations for these pathways which are predicated on the assumption that reducing these intervals, as well as reducing patient distress, will improve survival.¹⁰

Interval between diagnosis and staging/treatment

The fourth interval is between a confirmed diagnosis—that is, when the patient is managed as a case of lung cancer—and staging/treatment. Once again, healthcare systems are investing considerable resources in reducing this and making it uniform. There is convincing evidence that, for some patients who are potentially curable, delays at this point can decrease their chances of survival.¹¹ Furthermore, the exponential growth pattern of tumours suggests that stage migration—that is, the change in a tumour staging from, for example, I to II, II to III, or III to IV is likely to be a far more rapid event when the primary

tumour is large or when there is early nodal disease than when the tumour is, for example, a small T1 lesion.¹²

These points, based upon considerations of tumour biology, suggest that survival should be improved if within-patient and within-health system delays are short.

STUDY BY MYRDAL *ET AL*¹³

The paper by Myrdal *et al* in this issue of *Thorax*¹³ examines the impact of delay in diagnosis and treatment on the prognosis for lung cancer patients. It retrospectively analyses Swedish registry data on patients diagnosed with non-small cell lung cancer (NSCLC) over a 5 year period. Patients were excluded if they were first diagnosed at necropsy or if they received no cancer specific treatment (38% of patients diagnosed with NSCLC in the study period). Two types of delay were studied: (1) symptom to treatment delay, defined as the length of time from first onset of symptoms to the start of treatment, and (2) hospital delay, defined as the length of time from the first hospital visit to the start of treatment. The impact of these separate delays on survival was then assessed.

The results showed that the mean first symptom to treatment delay was 5.8 months and was shortest in those patients with advanced disease (3.9 months). Only 9% of patients with stage I–II disease were treated within 3 months of first symptoms. Mean hospital delay was 2.5 months and appeared to be longer for those patients with potentially curable lung cancer, but the difference was not statistically significant. On average, treatment was started 1.4 months earlier in patients with stage IV disease than in those with stage I–II disease. Survival was negatively influenced by a short delay time between first onset of symptoms and treatment: 3 year survival was 11% for patients treated within 3 months and 35% for delays of more than 6 months. Similarly, patients with the shortest hospital delay (<30 days) had a poorer prognosis.

The main conclusions of Myrdal *et al* were that delays in the investigation and treatment of lung cancer exceeded the recommended time scales advised by the Swedish Lung Cancer Study Group in the majority of their patients. They state that neither patient nor hospital delay appeared to negatively influence survival. Patients with advanced tumour stage who presented and received treatment within 30 days of the first hospital visit fared less well than those with a longer delay. They also suggest that, as NSCLC tumours have both varied cell doubling times and aggressiveness, further information is needed to allow

identification of patients who have tumours that would benefit particularly from prompt treatment.

In this retrospective analysis, 42% of patients had adenocarcinoma—a figure probably three times higher than in comparable UK populations. This may influence the overall natural history of this group of patients with NSCLC. The exclusion of the 190 patients (38%) who did not receive active treatment seems wrong. There is no reason to presume that, if they had not been diagnosed earlier, they would not have been suitable for inclusion: they could have been confirmed not to have had another cancer and to have a compatible clinical picture and to have died from their cancer. Recall of first symptoms is likely to be difficult for patients (as pointed out by the authors), given this serious diagnosis, and will probably add bias to the analysis: 34% of patients could not recall their first symptom. The authors make no comment about those people who presented with an incidental finding on a chest radiograph. This group is more likely to be operable (small peripheral tumour not causing any symptoms) and it would be interesting to know if stage I/II is over-represented in these patients. If so, this would introduce another bias into the analysis.

Other groups have identified similar delays in the diagnosis and treatment of NSCLC. A review of the literature by Jensen *et al*¹⁴ showed that the time intervals between first symptom and contacting a doctor varied widely from a median of 7 days to 6 months. Studies examining doctor (hospital) delays are difficult to compare because of the different end points used. They vary widely from 48 days (referral to treatment)¹⁵ to 189 days (first symptom to treatment or decision not to treat)¹⁶ with a median delay of only 9 days from first visit to specialist to diagnosis for one centre.¹⁶ In a UK regional study in 1995 Billing *et al*¹⁷ showed that the mean total delay from presentation to operation for NSCLC was 109 days, including 1 month for pre-hospital delay and 2 months for physician delay. Overall, delays in the diagnosis of lung cancer vary widely at every step on the diagnostic/treatment pathway and the paper by Myrdal *et al* reflects this.

The effect of delay on prognosis has also been examined before. Bozcuk *et al*¹⁵ studied the prognostic consequences of delays in diagnosing and treating lung cancer and, like Myrdal *et al*, found that treatment (hospital delay) did not affect survival, regardless of disease stage. Billing *et al*¹⁷ found that the length of delay did not correlate with tumour stage for potentially resectable patients. However, setting up a quick access two

stop clinic in one centre led to a substantial increase in the number of patients who had successful surgical resection.¹⁸ O'Rourke and Edwards¹¹ found that six out of 29 patients on a UK regional waiting list for radical radiotherapy developed progressive disease so that they were later deemed unsuitable for this, which implies that even a modest delay decreased their chance of cure. However, delays in palliative treatment may not always be so crucial. For asymptomatic patients with stage III/IV lung cancer, delaying palliative radiotherapy treatment did not negatively affect quality of life, symptom control, or survival.¹⁹

The trend in these surveys showing longer hospital delay for patients with early stage lung cancer seems contradictory. However, patients with advanced disease are usually easily diagnosed by pleural fluid cytology, fine needle aspiration of a lymph node, or bronchoscopy—that is, they have an easily accessible tumour. In those patients who may be operable, diagnosis, staging and work up often involve extra steps in the diagnostic pathway, thereby adding extra hospital delay time. In one study, staging for potentially operable patients required a mean of 5.1 diagnostic tests per patient (mainly to exclude metastasis) necessitating on average an extra 20 days in the diagnostic work up.²⁰ Patients suitable for surgery also need more detailed work up which may include cardiopulmonary exercise testing, mediastinoscopy, etc.

The study by Myrdal *et al* suggests that increased delay (patient or hospital) has no negative influence on survival and this is probably true for the majority of patients because of the high proportion of patients who present with stage III/IV disease. However, for those with a large but potentially radically treatable tumour, delay may be crucial. It is these patients perhaps who need to be identified and “fast tracked” through the diagnostic pathway. Identifying these people is inherently difficult but should be based on tumour size and location, performance status, and lack of constitutional symptoms such as weight loss.

FUTURE CONSIDERATIONS

So, in the light of these results, should we modify present efforts to reduce delays in patients with lung cancer? As discussed earlier, the delay between appearance of the first symptom and treatment is dependent on many factors. Presentation of the patient to the GP, decision by the GP to refer or for radiography, and waiting time to see a specialist make up the steps in the delay

to a first hospital visit. The symptoms of lung cancer may be vague and non-specific. A history of haemoptysis without obvious infection will generally alert both patient and clinician. Cough is a less robust symptom but significant new persistent cough (that is, more than 3 weeks) should arouse suspicion. Many patients with lung cancer have COPD, so increasing breathlessness is part of their overall clinical progression and may not be a reliable specific symptom for lung cancer. Half of all patients do not have symptoms in primary care which suggest a diagnosis of lung cancer.² It is therefore difficult to see how earlier referral to a chest physician can be achieved. In secondary care some centres use direct referrals from a radiologist to a chest physician. At our centre patients attend the chest clinic for an exclusion radiograph at the request of the GP. A chest physician reads these every day and relevant urgent appointments and investigations are implemented directly by the physician.

To reduce hospital delay time further will require an increase in resources and the re-engineering of clinical services (for example, "one stop" clinics). However, in some patients it will still necessarily take longer to obtain the diagnosis as they may need several investigations before a positive diagnosis is made.

The paradoxical results of Myrdal's study do not mean that we should cease our efforts to reduce delays. There are three reasons for this. Firstly, the psychological stress on patients and their families who have a possible

diagnosis of lung cancer is enormous. Delays only serve to worsen this. Secondly, there is a small group of patients with potentially radically treatable disease (especially those in whom this may be a borderline decision) who may have a different outcome if delays occur. Thirdly, there should be large rewards from being able to identify patients at an early (asymptomatic) stage when radical treatment is possible.

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Antioxidants and asthma

The developing story of antioxidants and asthma

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Antioxidant genotype may predict response to antioxidant supplements for asthma

The extent to which diet may have an impact on either the aetiology or the severity of asthma is a question that has generated much interest over the past decade.^{1–2} A number of observational studies have suggested that various dietary components—including higher levels of antioxidants,^{3–4} magnesium,⁵ and fish,⁶—have a protective influence on the risk of asthma. The implication of these findings is that, by changing our diet, we may be able to

alter our risk of developing asthma or modify the severity of the disease, and these hypotheses have now been tested in a number of randomised controlled trials. Most intervention studies have included subjects with a diagnosis of asthma and hypothesised that nutrient manipulation may improve disease activity. To date there have been only a limited number of long term randomised controlled trials of dietary interventions in patients with asthma, with

those using antioxidants such as vitamin C and vitamin E tending to suggest a benefit,^{7–9} while others using fish oil supplements have been disappointing.¹⁰ The study of dietary intervention for the prevention and treatment of asthma is still in its infancy and further clinical trials are required to enhance our understanding of the relationship between diet, the individual, and asthma.

Exposure to the pollutant ozone places an oxidative burden on the airways which, in turn, leads to airway inflammation and bronchoconstriction. In this issue of *Thorax* Romieu *et al* report on the use of this "model" of asthma to show in a clinical trial setting that dietary supplementation with the antioxidants vitamin C and E can ameliorate the deterioration in lung function that ozone exposure produces in children living in Mexico City.¹¹ These results are consistent with existing data,^{8–12–13} and together these studies provide evidence that the adverse effects of an oxidative stress can be counteracted by dietary antioxidants, and that

the beneficial effects of diet can be measured in terms of outcomes relevant to asthma. This model therefore provides a good opportunity to study the relationship between oxidative exposure, diet, host, and asthma outcome.

Romieu *et al* used data from their previous randomised controlled trial⁹ to show that host factors, particularly genotype, may have an important influence on the efficacy of dietary supplementation with vitamins C and E in preventing ozone provoked bronchoconstriction.¹¹ The glutathione S-transferase supergene family is an important part of the cellular enzymic defence against endogenous and exogenous chemicals, and acts by conjugating the numerous byproducts of oxidative stress with glutathione.¹⁴ The full function of these enzymes is not understood, but those with the homozygous deletion polymorphism (*GSTM1* null) are known to have diminished enzyme activity. Romieu *et al* hypothesised that, since the metabolic enzyme glutathione S-transferase (*GSTM1*) may help to protect against the adverse effects of ozone, children who have a homozygous deletion of the *GSTM1* gene, and hence diminished endogenous antioxidant activity, may be particularly susceptible to the effects of ozone, and thus have the potential to benefit more from antioxidant supplementation. Their results showed that 39% of the trial participants, all of whom had asthma, had the null genotype and hence decreased enzyme activity. In children who received placebo there was an adverse impact of ozone on lung function, but this was restricted to children with the *GSTM1* null genotype and no association was present in children with the active *GSTM1* gene. In addition, the authors report that, in children with the *GSTM1* null genotype who received placebo, the adverse effect of ozone was more marked in those with more severe asthma, although the criteria for defining asthma severity are not reported. Ozone did not reduce lung function in children who received antioxidant supplementation regardless of *GSTM1* genotype. The authors conclude that *GSTM1* has a role in protecting the airways against oxidative stress and that those children with diminished enzyme levels are more vulnerable to the effects of ozone. The importance of these findings is that, if replicated, they suggest that a sizeable proportion of the children in Mexico City are particu-

larly vulnerable to the adverse effects of ozone, but that this increased risk can readily be counteracted by simple dietary supplementation methods. These data may be relevant to subjects in the UK since the 24 hour mean ozone concentrations reported in Mexico City are comparable to those recorded in Westminster, London during August 2003.¹⁵

The study by Romieu *et al* does have limitations which are acknowledged by the authors. The sample size was relatively small and not powered to allow formal tests of interaction between dietary supplementation, genotype, and outcome. In addition, data on the effect of genotype and dietary supplementation on symptoms are not reported. However, the findings suggest that, by identifying genes involved in relevant metabolic processes that are also related to asthma outcomes, we may be able to understand the importance of diet more clearly. This should lead to more appropriately designed epidemiological studies and interventional trials. The findings of Romieu *et al* are consistent with other studies which have shown that the adverse effect of in utero exposure to tobacco smoke on childhood wheezing illness is largely restricted to children of *GSTM1* null genotype.¹⁶ Furthermore, polymorphisms at the locus of another member of the glutathione S-transferase supergene family (*GSTP1*) are associated with a sixfold lower risk of asthma.¹⁷ However, it is noteworthy that, in this latter study, no association was found between asthma and the *GSTM1* genotype, in contrast to the findings of Romieu *et al*.

The understanding of how a "good diet" may help to reduce the prevalence and severity of asthma is still at an early stage, but the findings reported by Romieu *et al* are interesting and should stimulate more work in this field. As more antioxidant enzymes are genotyped and this knowledge is incorporated into both clinical trial and observational dietary datasets, we will understand better the interactions between diet, oxidative stress, and asthma. In the meantime it is tempting to speculate that all of us would be better off eating a healthy diet containing large amounts of fresh fruit and vegetables.

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Sleep disordered breathing awoken

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Introducing a new series on obstructive sleep apnoea/hypopnoea syndrome in *Thorax*

In 1997 Dr Wright and colleagues published a systematic review on the health effects of obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and the effectiveness of treatment with continuous positive airway pressure (CPAP).¹ They concluded that there was limited evidence of increased mortality or morbidity in patients with OSAHS, and that the evidence linking the condition to cardiac arrhythmias, ischaemic heart disease, left and right ventricular dysfunction, systemic and pulmonary hypertension, stroke, and automobile crashes was conflicting and inconclusive. They also concluded that, although CPAP had been shown to improve daytime sleepiness, there were insufficient data to determine its effect on quality of life, morbidity, or mortality. This review generated much controversy but was a wake up call² to investigators in this field that all were not convinced that OSAHS was an important condition that always warranted treatment. At that time our understanding of the natural history of OSAHS and the impact of treatment was at a similar stage to where we were with systemic hypertension and hypercholesterolaemia several decades ago. Considerable progress has been made in the past six years since the publication of this review, and many of the issues which it raised have started to be addressed. Long term population based prospective cohort studies have been initiated to examine the association of OSAHS with morbidity and mortality. Additional studies have been performed to determine the link between OSAHS and automobile crashes. A variety of large, well designed, randomised controlled trials have been completed or are in progress to determine the indications, benefits, and risks of treatment of OSAHS.

An important first step in this process was performed by an international task force in 1997 which developed definitions of sleep disordered breathing (SDB) and recommendations for measurement techniques.³ OSAHS was characterised as recurrent episodes of partial or complete upper airway obstruction during sleep. The diagnostic criteria for

OSAHS were >5 apnoeas or hypopnoeas/h during sleep (the apnoea/hypopnoea index, AHI) and the presence of either excessive daytime sleepiness or two other symptoms (nocturnal choking, recurrent awakening, unrefreshing sleep, daytime fatigue, or impaired concentration). Nasal pressure or respiratory inductance plethysmography were recommended as the preferred techniques for measuring apnoea and hypopnoea. Apnoeas or hypopnoeas were defined as events of 10 seconds or longer with either a >50% decrease in amplitude of a valid measure of breathing during sleep or a <50% decrease with either a 3% desaturation or arousal. The severity of OSAHS was determined by two components—severity of daytime sleepiness and overnight monitoring (mild 5–15 events/h, moderate 15–30 events/h, severe >30 events/h)—with the final rating for the severity of the syndrome based on the most severe component.

The Wisconsin Sleep Cohort Study is a prospective community population based study initiated in 1988 which has estimated that 4% of middle aged men and 2% of women have OSAHS.⁴ Analysis of 709 participants studied for 4 years and 184 participants studied for 8 years revealed a dose-response association between SDB at baseline and the development of systemic hypertension that was independent of known confounding factors.⁵ A cross sectional study of 1741 subjects in Pennsylvania also found an independent association between SDB and systemic hypertension in young and middle aged individuals.⁶ The Sleep Heart Health Study (SHHS) is a prospective cohort study of 6424 individuals recruited between 1995 and 1998 designed to determine whether SDB is a risk factor for cardiovascular and cerebrovascular diseases. The initial cross sectional analysis⁷ was compatible with modest to moderate effects of OSAHS on a variety of manifestations of cardiovascular disease. If similar results are found in the prospective analysis, this will provide conclusive evidence linking OSAHS to the premature development of cardiovascular disease. A number of cross

sectional studies based either on patient self-reports or examination of motor vehicle records have reported increased automobile crashes in patients with OSAHS.^{8–10} Examination of all traffic violations and accidents in 913 participants in the Wisconsin Sleep Cohort Study revealed that men with an AHI of >5/h were significantly more likely to have at least one automobile crash in 5 years than participants without OSAHS. Men and women combined with an AHI of >15/h were significantly more likely to have multiple automobile crashes in 5 years. However, many of these studies have been subject to selection or information bias and to date there have been no prospective studies to prove that OSAHS results in increased automobile crashes.

Until the mid to late 1990s the majority of studies of the effectiveness of treatment in OSAHS were small, short term, uncontrolled, and retrospective. More recently the quality of clinical research into the treatment of OSAHS has become more rigorous. A recent meta-analysis of randomised controlled trials of CPAP in patients with OSAHS included 12 trials of 738 patients and concluded that nasal CPAP significantly improves subjective and objective sleepiness across a broad range of OSAHS severity.¹¹ Several short term, randomised, double blind, placebo controlled trials have also shown that nasal CPAP reduces systemic blood pressure.^{12–13} A recent meta-analysis of randomised controlled trials of oral appliances in patients with OSAHS identified 12 trials involving 509 participants with OSAHS of varying severity.¹⁴ This review concluded that there was some evidence that oral appliances improve subjective sleepiness and AHI compared with an inactive control and that nasal CPAP appears to be more effective in improving OSAHS than oral appliances. Cheyne-Stokes breathing syndrome is another type of SDB characterised by cyclic fluctuations in breathing with periods of central apnoea or hypopnoea alternating with periods of hyperpnoea.³ Cheyne-Stokes breathing syndrome is common in patients with congestive heart failure and there is increasing evidence that nasal CPAP reduces the combined rate of mortality and cardiac transplantation in these patients.¹⁵

Several large randomised controlled multicentre trials are currently either in progress or about to start recruitment, which will provide important data concerning the effectiveness of nasal CPAP in the treatment of SDB. The Apnea Positive Pressure Long-term Efficacy Study (APPLES) is a randomised, double blind, sham controlled, multicentre trial of 1100 patients with OSAHS

performed over 6 months to evaluate the long term effectiveness of nasal CPAP on neurocognitive function and quality of life. The impact of CPAP on functional outcomes in milder OSA (CAT-NAP) is a randomised, double blind, placebo controlled, multicentre trial of 270 patients with mild to moderate OSAHS over 8 weeks to determine whether CPAP treatment enhances functional status and reduces daytime sleepiness and systemic blood pressure. The Canadian CPAP trial for congestive heart failure patients with central sleep apnoea (CANPAP) is a randomised, controlled, multicentre, long term trial to determine the impact of nasal CPAP on transplant free survival in 400 patients with congestive heart failure and Cheyne-Stokes breathing.¹⁶ The effectiveness of treatment for other common conditions such as hypertension or hypercholesterolaemia has required trials of thousands of patients studied over many years. Additional trials will be required to determine which groups of patients with SDB are most likely to benefit from all the currently proposed treatments, how these patients can be identified, how much benefit can be achieved, and with what cost, side effects and complications.

In this issue of *Thorax* we publish the first of 10 articles by a group of international experts on OSAHS which will review these issues in more depth. The first article outlines the definitions, epidemiology, and natural history of OSAHS. Subsequent articles will review the pathophysiology, clinical presenta-

tion, and diagnosis of the condition. The relationship between OSAHS and sleepiness, cognitive function, quality of life, automobile crashes, and systemic hypertension will be examined in three articles. The role of nasal CPAP, oral appliances, and upper airway surgery in the treatment of OSAHS will also be addressed. The final article in the series will discuss paediatric OSAHS.

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Reviewers

Thank you to all *Thorax* reviewers

J A Wedzicha, S L Johnston, D M Mitchell

Acknowledgement of the contribution of peer reviewers to the success of *Thorax*

Thorax had a very successful year in 2003 with an increase in submissions and an impact factor which now stands at 4.08.¹ The invaluable resource of our dedicated peer reviewers has allowed *Thorax* to maintain its high standards.^{2–4} Peer review has been used in journals for over 300 years⁵ and is an important part of the editorial process, as constructive criticism during the peer review process leads to improvements in the final published paper.⁶

In this issue of *Thorax* we publish the names of all the peer reviewers who

have reviewed papers for the journal over the past year (see page 86). We would like to thank all our reviewers from all over the world who have signed up on our online submission site for availability for peer review and who have so generously given up their valuable time to improve the quality of papers in *Thorax*. We are very grateful to all those reviewers who have written such critical and thoughtful reviews and returned them on time.

The availability of the online system has allowed a faster peer review process,

and we hope that this has made it easier for our reviewers to access the papers and submit the reviews. During peer review we maintain strict confidentiality with respect to the identity of our reviewers. At the time of the decision, the online site enables reviewers to view the other reviews on the paper, although even at that stage they do not know the identity of these other reviewers. In order to improve the statistical aspects of our papers, all potentially acceptable manuscripts also undergo formal statistical review.

We encourage authors when submitting papers to name up to four peer reviewers, although the Editors and Associate Editors use their discretion on reviewer selection and will also use reviewers who have not been suggested by the authors. Reviewers for a particular paper are not aware of whether or not they have been named by the authors. During the year the online system has enabled us to develop a very large database of reviewers with their particular expertise registered. Like all

journals, a small minority of invited reviewers persistently decline our invitations to review or never return the review, and we strongly urge them to join their colleagues in this most important scientific effort which we are sure they will find challenging and rewarding.

It is vital for the success of the journal that all our reviewers continue their work, and we would also like to encourage younger reviewers to come forward to take part in the process. Please let us know if you are interested. Peer review also has its faults and at some time all of us have received an "unfair review" of our paper from a journal. However, it is still regarded as the best way to assess the originality,

validity, importance, and reliability of research work published in a paper. So we ask all our reviewers to continue with their important work and contribute to improving the quality of the scientific papers that we publish in *Thorax*. Your efforts are ultimately of great benefit to the global respiratory community.

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LUNG ALERT

The use of opioids for palliative care in refractory dyspnoea

▲ Abernethy AP, Currow DC, Frith P, *et al*. Randomised, double blind, placebo controlled crossover trial of sustained releases morphine for the management of refractory dyspnoea. *BMJ* 2003;**327**:523–6

Dyspnoea is a disabling and distressing problem for many patients and carers. Clinicians are often reluctant to prescribe opioids for such patients because of concerns of adverse effects—particularly respiratory depression and sedation—and paucity of evidence of clinical benefit.

Abernethy and colleagues conducted a small (n = 48) double blind, placebo controlled, crossover study. Patients, most of whom had chronic obstructive pulmonary disease (n = 42), were randomised to receive 20 mg/day sustained release morphine or identical placebo. No washout period between the 4 day treatment periods was employed, although the authors acknowledge some carryover effect in patients receiving morphine first in sequence. Patients reported significantly less dyspnoea according to a visual analogue scale and had less sleep disturbance when using active treatment. More patients experienced constipation when receiving morphine, while no differences in other adverse effects, including sedation and depressed respiratory rate, were observed between treatments. The study concluded that sustained release morphine was useful in relieving refractory dyspnoea with reassuring data concerning adverse effects other than troublesome constipation. The authors comment that opioids should be used with caution as the study was not sufficiently powered to detect significant differences in adverse effects.

Although limited by the small number of patients completing the study (n = 38) and uncertain clinical significance of observed effects upon the visual analogue scale, this study provides reassuring evidence of the potential benefits of opioids in relieving intractable dyspnoea. This short trial should pave the way for further large scale studies to investigate the optimum dose of sustained release morphine and to identify which patients benefit most, while also incorporating a rigorous evaluation of adverse effects.

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