

## LETTERS

## An integrated home oxygen service saves £130 000 per year on home oxygen tariffs

In February 2006 the Department of Health introduced a new home oxygen service with the aim of improving the assessment of patients on oxygen and allowing access to newer technologies such as ambulatory oxygen. Oxygen is provided following completion of a home oxygen order form and is allocated a predetermined tariff according to the delivery device and usage. In South East Essex there are currently 554 patients receiving home oxygen with an annual cost of £668 546.

In response to these changes, South East Essex PCT and Southend Acute Trust set up an oxygen implementation group leading to the establishment of an integrated home oxygen service. This service comprises four respiratory consultants, one respiratory physiotherapist and three respiratory nurse specialists (one of whom is based in the community and was the only new post). The role of this service is to identify patients requiring home oxygen, to provide formalised oxygen assessments and home or out-patient monitoring once oxygen is ordered, as well as ensuring that existing patients receiving home oxygen have the correct oxygen order for their needs.

The cost of home oxygen was highlighted by the home oxygen service. In order to investigate high oxygen order costs, 22 patients who were on a higher tariff were identified from the supplier monthly statement of December 2006 for review either by a respiratory consultant in outpatients, formal long-term oxygen treatment (LTOT) assessment or a home visit by a nurse specialist. Of these, 4 had the correct order, 3 no longer required home oxygen, 1 was unwilling to change his order and 14 had their order altered to a more appropriate usage requirement resulting in recategorisation to a lower tariff. This resulted in an annual saving of £76 993.

Over the following 6 months, during the course of routine monitoring a further 43 patients had their home oxygen order altered to reflect their actual oxygen requirements more accurately; 8 no longer required home oxygen and 35 were recategorised to a lower tariff with an annual cost saving of £52 819.

Increased awareness of the need to regularly re-evaluate patients on home oxygen therefore resulted in the recategorisation to a lower tariff of 65 patients at an annual cost saving of £129 812. A cost saving of £76 993 was made by targeting the 22 patients on the highest tariff out of a total of 554 patients on home oxygen.

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## Early detection of cancer: lessons from lung cancer CT screening

Black *et al*<sup>1</sup> reviewed 12 studies of CT screening for lung cancer published up to 2004 and concluded that there is insufficient evidence that CT screening might be clinically effective in reducing mortality from lung cancer.

This study was published immediately after two discordant studies by Henschke *et al*<sup>2</sup> and Bach *et al*.<sup>3</sup> The first study, in spite of the lack of total or disease-specific mortality rates for the screened population, concluded that low-dose CT screening could lead to a therapeutic strategy that resulted in a 10-year survival of 88% for patients with stage I disease.<sup>2</sup> The second, in line with Black *et al*,<sup>1</sup> concluded that there is no evidence that CT screening reduces deaths from lung cancer.<sup>3</sup> In this study, despite annual screening, most of the individuals who died from lung cancer did not have their cancer detected at an early stage when cure was possible. However, the survival of patients with stage I disease was equivalent to the survival in the study by Henschke *et al*,<sup>2</sup> but the proportion of patients with stage I disease fell dramatically after the second year and the cumulative mortality from lung cancer at 5 years was very close to that expected without screening.

A reasonable explanation is that radiological screening can detect early stage, slow growing or indolent disease, but is unable to prevent more aggressive and early metastatic lung cancer. Indeed, autopsy studies recognise inconsequential lung cancers.<sup>4</sup> As a possible consequence, some individuals—even those enrolled in screening trials—will live and die with their lung cancer.

The major finding of these studies is that the natural history of lung cancers detected by CT scanning is unknown. According to the current view on the carcinogenesis of non-small cell lung cancer, it cannot be assumed that the biological behaviour of cancer parallels the anatomical size of the tumour or that small lesions are equivalent to early stage disease. No data are available to confirm that a primary lung tumour of 5 mm has a significantly better prognosis than tumours of 10 mm or even 30 mm.<sup>5</sup> In different studies, approximately 60% of patients with clinical (radiographically detected) stage I disease (<3 cm) died from lung cancer within 5 years despite appropriate treatment.<sup>6</sup> This suggests that a high percentage of patients have disseminated occult disease at the time of presentation.

With newer and more sensitive methods of detection, sites of isolated tumour cells and

micrometastases may now become apparent. Indeed, clinical studies have confirmed that patients with small tumours can harbour malignant cells in lymph nodes of normal appearance detectable only by PCR assay.<sup>7</sup> Other investigations have found tumour cells or circulating endothelial progenitor cells in the peripheral blood and bone marrow of patients with lung cancers of all sizes and stages.<sup>8</sup>

As the debate on lung cancer screening continues, it appears that we must learn more about the biology of this disease and integrate this knowledge with early diagnostic strategies including genomics and/or proteomics.

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## Gene expression of IL17 and IL23 in the lungs of patients with active tuberculosis

Immunity to tuberculosis is dependent on type 1 responses (interferon (IFN) $\gamma$ , interleukin (IL)12, tumour necrosis factor (TNF) $\alpha$ ) but these do not provide a complete

explanation for the regulation of the immune response seen. Additional effector or regulatory mechanisms need to be sought.<sup>1</sup> Recently, a new T cell subset, IL-17 producing CD4+ Th cells (Th17), has been described.<sup>2</sup> In the mouse at least, IL-17 secreting cells may be distinct from conventional Th1, Th2 and regulatory T cells.<sup>2</sup> These IL-17-secreting T cells drive secretion of TNF $\alpha$ , IL1 $\beta$  and IL6, as well as chemokines CXCL1, 2 and 8, and enhance inflammation and influx of neutrophils.<sup>2</sup> IL17 has tentatively been implicated in mouse models of immunity to mycobacteria.<sup>3,4</sup> However, there are no data from the human lung or from patients with tuberculosis (TB).

To ascertain whether Th17 related cytokines are expressed in tuberculous lungs and to evaluate the anatomical (blood vs lung) and cellular (CD4 vs CD8) compartmentalisation of these cytokines, we measured expression of genes encoding IL4, IFN $\gamma$ , IL17 and IL23 (a cytokine that increases expression of IL17 by T cells) in bronchoalveolar lavage (BAL) cells (unfractionated) of 14 HIV negative culture positive TB patients and 14 matched controls with no laboratory evidence of latent TB infection (determined by antigen specific IFN $\gamma$  responses; T SPOT TB), and correlated these findings with

clinical parameters. Blood was obtained from all participants, and BAL from all TB patients but only from six control subjects. Bronchoscopy, isolation of cells and qRT-PCR (normalised to a validated reference after quality control of RNA), were performed as previously described.<sup>1</sup> Blood derived peripheral mononuclear cells were separated into CD3, CD4 and CD8 fractions.

We showed previously using the same samples that IFN $\gamma$  and IL4 levels were significantly elevated in BAL fluid of patients compared with controls.<sup>1</sup> Here we show that this is also true for IL23 mRNA (fig 1A). In contrast, patients had reduced IL23 mRNA levels in blood, suggesting that in TB there is sequestration of IL23 expressing cells in the lung (fig 1B). However, IL17 mRNA levels were similar in patients and controls, both in blood and BAL fluid (fig 1B). In blood, IL17 was expressed predominantly in CD8 rather than CD4 cells of TB patients (fig 1C). Neither IL17 nor IL23 mRNA levels correlated radiological disease extent or presence of cavitation on chest radiography ( $p = 0.09$ ).

In the mouse, IL17 secreting CD4+ cells have been considered to be a distinct helper T cell lineage.<sup>2</sup> Nevertheless, in mice infected with *M tuberculosis*, most of the IL17 was

expressed by  $\gamma/\delta$  T cells.<sup>4</sup> In humans, the situation is even more confusing. IL17 can be expressed in both naïve and memory T cells after non-specific stimulation, in CD8+ cells and in cells simultaneously expressing IFN $\gamma$  or transforming growth factor  $\beta$ , suggesting Th1-like and regulatory properties, respectively.<sup>5</sup> There might not be a distinct Th17 lineage. Thus although we did not observe altered expression of IL17 in TB, it will be essential to study in detail the effect of counter-regulatory cytokines and the phenotypes of the IL17 expressing cells, since this might be altered even though the overall levels of IL17 mRNA were not. Furthermore, an apparently "normal" IL17 expression profile does not preclude its importance in the early stages of infection. Answering these questions will require a new study because the stored clinical material is now exhausted. A limitation of this preliminary study is the measurement of mRNA and not protein levels. However, measurement of biomarker protein levels, due to massive dilution and lack of a reliable normalisation strategy, is problematic in BAL fluid.<sup>1</sup>

In conclusion, although similarly expressed in patients and controls, IL17 may be a potentially important cytokine in the immunopathogenesis of TB. Increased IL23 expression in TB lung is likely to be inducing IL17 expression by some cell types that now need to be identified.

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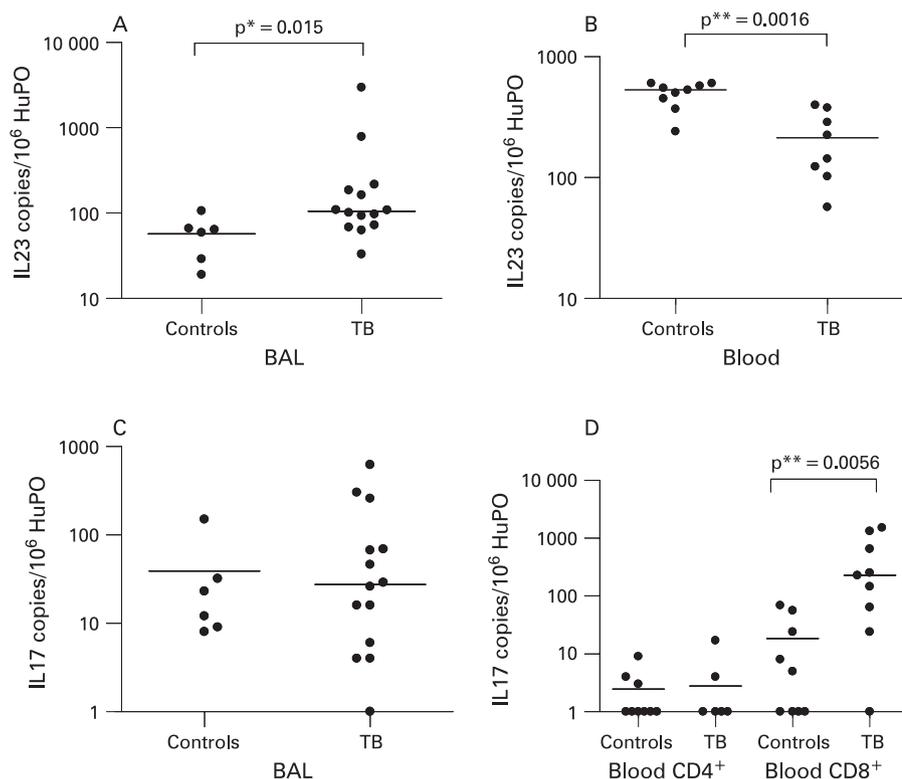
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**Figure 1** Gene expression profiles of interleukin (IL)17 and IL23 in whole blood and bronchoalveolar lavage (BAL) cells of patients with tuberculosis (TB) compared with controls. IL23 mRNA levels were significantly higher in TB patients in BAL cells (A) but not in peripheral blood (B); IL17 mRNA levels were not significantly different in blood or BAL cells (C) but were prominently expressed in CD8+ T cells (D). RNA was qualitatively and quantitatively assessed using a bioanalyser and mRNA values were normalised to 1 million copies of HuPO, a validated reference gene.

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## Accuracy in suspicious lung infiltrations

We read with interest the paper by Targowski *et al*.<sup>1</sup> Suspicious lung infiltrations such as malignant tumours are always difficult to diagnose in clinical practice. Transthoracic fine needle biopsy (TFNB) may be a useful procedure despite a high risk of false negative results. To improve the accuracy of the technique, telomerase activity in combination with TFNB was investigated in the study by Targowski *et al*.

We suggest that alternative options such as positron tomography scanning (CT-PET) should be evaluated, which may provide better imaging quality and accurate guidance for performing TFNB, increasing the accuracy of lung cancer diagnosis.

In the Continuing Observation of Smoking Subjects (COSMOS) study recently published by Veronesi *et al*<sup>2</sup> involving 5200 current or former smokers, CT-PET had a sensitivity of 100% in the diagnosis of solid pulmonary nodules of 10 mm or more. In this study, TFNB was not part of the clinical routine. In contrast, the sensitivity of the combination of TFNB with telomerase activity used by Targowski *et al* was lower at 89.3% and the mean size of suspected lesions was not described.

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## Authors' reply

We read with interest the comment by Dr Carbone *et al* on our article<sup>1</sup> and agree that nowadays CT-PET is the best imaging method for visualisation of suspected pulmonary nodules.

Transthoracic fine needle aspiration (TFNB) under CT-PET control could improve the accuracy of lung cancer diagnosis, especially in cases of solid lesions with a smaller standardised uptake value (SUV). Some data suggest that even 50% of pulmonary nodules with SUV <2.5 are benign.<sup>2</sup>

In the Continuing Observation of Smoking Subjects (COSMOS) study by Veronesi *et al*,<sup>3</sup> CT-PET had a sensitivity of 100% in the diagnosis of solid pulmonary nodules of 10 mm and more. In our study the mean size of suspected lesions (described at the beginning of the Results section) was 2.4 cm (95% CI 2.2 to 2.5), which was comparable to data in the study by Veronesi *et al* (2.5 cm, range 0.6–6 cm), but the indication for TFNB was not only restricted to solid nodules. The sensitivity, specificity and accuracy of cytological and telomerase activity examinations in our study was adequate (89.3%, 96.9%, 90%, respectively) and was similar to the overall results achieved by Veronesi *et al* (88%, 93% and 91%, respectively). The diagnostic value of telomerase activity assessments in pulmonary tumours is only one of many benefits. Data show that telomerase activity in material derived from pulmonary nodules is also a prognostic factor for survival<sup>4</sup> and could be a target for antitelomerase treatment.<sup>5</sup>

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## Dysfunctional breathing in patients with asthma

We recognise and applaud the efforts of Holloway and West<sup>1</sup> and are encouraged by their findings. We agree that further investigation is warranted but that greater scientific methodology needs to be applied. Hyperventilation appears to be the only form of dysfunctional breathing that most physicians recognise yet even within this label, acute and chronic hyperventilation are physiologically distinct.<sup>2</sup> Efforts must be made to further elucidate the nature of dysfunctional breathing in its many forms<sup>3</sup>

and direct appropriate therapy towards appropriate patients. It is a reasonable assumption that breathing retraining will be efficacious only in those patients where dysfunctional breathing exists. This lends support to the positive results of Holloway and West,<sup>1</sup> given the unselected nature of the cohort of subjects recruited. It is hardly surprising that many trials of breathing retraining in unselected asthmatics prove equivocal. We liken this approach to a trial of thrombolytic therapy in unselected chest pain patients.

As a sub-note, we would guard against making assumptions on the basis of a reduction in Nijmegen scores. The Nijmegen questionnaire has only ever been validated in primary hyperventilation and even then the gold standard was physician interpreted typical symptoms.<sup>4</sup> It was only described as a threshold value for the diagnosis of hyperventilation and there is no evidence that there is a graded correlation between Nijmegen scores and symptom severity. The domains within the questionnaire overlap with asthma symptoms. We have found it not to be predictive of capnography in patients with severe asthma. Since there is a trend towards improved spirometric values in the study group of Holloway and West,<sup>1</sup> we would suggest caution in interpreting a reduction in Nijmegen scores as a positive signal of reduced dysfunctional breathing.

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## Use of long-acting $\beta_2$ agonists in arginine-16 homozygous patients with asthma

We read with interest the study by Palmer and colleagues.<sup>1</sup> Their findings suggest that patients who are Arg/Arg homozygous at position 16 of the  $\beta_2$  adrenoceptor may be at increased risk of asthma exacerbations,