

## LETTERS TO THE EDITOR

### Reform of the Public Health Act

We agree with Richard Coker<sup>1</sup> that the vast majority of non-compliant cases of tuberculosis can be dealt with by a mixture of directly observed therapy (DOT) and inducements. However, when DOT fails in a few cases each year, despite intensive team effort and carrots such as housing or food vouchers, the Public Health Act may have to be invoked. We have had recourse to this measure four times in the past six months but, though providing valuable breathing space, it is extremely costly and proved ineffectual as a solution each time.

Once the patient is admitted there are still potential problems. Treatment cannot be enforced and patients can abscond. There have also been instances of patients assaulting staff, physically and sexually, issuing death threats, breaking hospital property, and terrorising other patients, even interfering with others' oxygen therapy. Dealing with such patients puts hospital staff and patients under unacceptable pressure and requires extra staffing for security purposes. NHS hospitals were not designed for, nor are they staffed adequately for, custodial purposes.

There is an urgent need to review the Public Health Act and make provisions for small specialist units staffed by nurses with training in and an aptitude for interpersonal skills. Admission to the unit would usually only be required for short periods of time until precipitating circumstances were resolved and alternative arrangements made. The threat of compulsory admission, or a short period thereof, may induce a behavioural change in the patient, allowing DOT to be successful after failing previously. In addition, a centrally based mobile unit of trained staff could be available to help tide teams over emergencies and could reduce the need for the specialist unit, enabling more non-adherent patients to be managed in the community.

We call upon the Department of Health to examine and implement these proposals.

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1 Coker RJ. Carrots, sticks and tuberculosis. *Thorax* 1999;54:95-7.

### Pulsed dose oxygen delivery system

Dr Garrod and colleagues have described a pulsed flow oxygen delivery system for use during exercise by patients with chronic obstructive pulmonary disease (COPD).<sup>1</sup> They found the device to be four times as economical as nasal cannulae for the same increase in walking distance. On the debit side, the weight of equipment carried by the patient was increased from 2.9 kg to 3.7 kg, and at a cost of £410.

Old fashioned remedies are often looked down on, but an equal benefit could have been achieved, without the disadvantages, by using a mask of the type designed by Haldane in 1917.<sup>2</sup>

By comparison with nasal cannulae, this device similarly resulted in fourfold economy when maintaining a raised alveolar oxygen tension in normal subjects.<sup>3</sup> Its use led to a significantly greater improvement in walking distance in patients with COPD compared with the other devices which were tested.<sup>4,5</sup>

The Haldane type mask fell out of use because, with a limited demand and low price, the manufacturer had little incentive to maintain a stock. Now, with greater awareness of the likely benefit, there might be a case for trying again.

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- 1 Garrod R, Bestall JC, Paul E, *et al*. Evaluation of pulsed dose oxygen delivery during exercise in patients with severe chronic obstructive pulmonary disease. *Thorax* 1999;54:242-4.
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- 5 Cotes JE, Matthews CR, Tasker PM. Continuous versus intermittent administration of oxygen during exercise in patients with chronic lung disease. *Lancet* 1963;i:1075-7.

### Simian virus 40 and human pleural mesothelioma

Mulatero *et al*<sup>1</sup> report failure to detect Simian virus 40 (SV40) DNA in 12 British mesotheliomas. They propose that their negative results indicate that the previous positive findings are probably a consequence of PCR contamination. Since Mulatero *et al* submitted their paper, several laboratories have further confirmed the association of SV40 with human mesothelioma and other types of human tumours.<sup>2,3</sup> Furthermore, the International Mesothelioma Interest Group has published results of their multilaboratory investigation confirming consistent association of SV40 DNA with mesotheliomas.<sup>4</sup> Additional recent studies (reviewed by Butel and Lednický<sup>5</sup>) have shown SV40 DNA to exist in an integrated form in human tumours and to be associated with expression of SV40 large T antigen as demonstrated by RNA in situ hybridisation, Western blotting, and immunostaining. These results therefore contradict the PCR contamination theory. The negative findings of Mulatero *et al* may be explained by technical or demographic differences.<sup>2-4</sup> The authors state that the sensitivity of their assay is one SV40 genome per cell based on a PCR methodology capable of

detecting HPV. This level of sensitivity is below the threshold for detecting SV40 in human mesothelioma, partly because of the usual low proportion of tumour cells included in mesothelioma biopsy specimens and partly because of the low copy number (<1 copy/tumour cell) of SV40 genome estimated to be associated with this tumour type.<sup>2-4</sup> In this context, the adequacy of method sensitivity claimed by the authors based on its comparability with sensitivity of an assay capable of detecting HPV in cervical cancer is potentially misleading. Cervical cancer is not only a more cellular tumour but is known to be associated with several to hundreds of viral genomic copies per tumour cell. We therefore suggest that the specimens of Mulatero *et al* should be re-tested using a more sensitive methodology to establish whether their negative findings are related to technical or demographic differences.

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- 1 Mulatero C, Suretheran T, Breuer J, *et al*. Simian virus 40 and human pleural mesothelioma. *Thorax* 1999;54:60-1.
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- 3 Huang H, Reis R, Yonekawa Y, *et al*. Identification in human brain tumours of DNA sequences specific for SV40 large T antigen. *Brain Pathol* 1999;30 January: 1-12.
- 4 Testa JR, Carbone M, Hirvonen A, *et al*. A multi-institutional study confirms the presence and expression of Simian virus 40 in human malignant mesotheliomas. *Cancer Res* 1998;58:4505-9.

**AUTHORS' REPLY** Dr Jasani misquotes us when he says we suggested that previous positive findings are probably a consequence of PCR contamination; we listed laboratory contamination of samples as one of several possible explanations for differing results.

Dr Jasani suggests that our failure to identify SV40 may be due to inadequate sensitivity and he states that the sensitivity of our assay, which we reported at one copy of SV40 per cell, is below the threshold for detecting SV40 in human mesothelioma. We do not reject the possibility that he may be correct, but he does not identify any evidence to support his assertion. The studies which have identified SV40 in mesothelioma to which he refers, including one of which he was a co-author,<sup>1</sup> did not report sensitivity of more than one copy per cell.

The multi-institutional study to which Dr Jasani refers<sup>2</sup> examined only 12 cases of mesothelioma from one hospital in New York, but the samples were analysed in four laboratories including one in Finland which had previously reported negative results for SV40 in local mesotheliomas. All four laboratories identified SV40 in 10 of the 12 New York cases. However, in their discussion the authors stated that the Finnish group subsequently confirmed the absence of SV40 in mesothelioma cases from Finland and speculated that this was because SV40 contaminated vaccines had not been used in Finland. This evidence points to demographic differences rather than lack of sensitivity as a more likely explanation for differing results from different series.

It appears from the collective results of various studies that the prevalence of SV40 in mesothelioma may be greater in the USA than in Europe, possibly as a consequence of

more widespread use of contaminated polio vaccine in the USA. However, epidemiological evidence indicates that the incidence of mesothelioma in the USA has peaked,<sup>3</sup> whereas a continuing increase in incidence over the next 20 years is expected in Europe.<sup>4</sup> These observations, together with evidence that so far there is no increase in the incidence of mesothelioma in individuals who received SV40 contaminated polio vaccine,<sup>5</sup> do not suggest that SV40 is important in the causation of human mesothelioma.

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- 4 Peto J, Decarli A, La Vecchia C, *et al*. The European mesothelioma epidemic. *Br J Cancer* 1999;79:666-72.
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## Acronyms

I write to protest against the use of unexplained acronyms in your editorial entitled "EUROSCOP, ISOLDE and the Copenhagen City Lung Study".<sup>1</sup> Acronyms are useful and often necessary because they simplify and accelerate modern communication.<sup>2</sup> But when first mentioned in any biomedical journals, acronyms must be explained fully.<sup>3</sup> Furthermore, abbreviations are prohibited in a title.<sup>4</sup>

Specialists often take for granted that certain "trade terms" are so evident that they do not bother to define them. I thought that cardiologists, of which I am one, are notorious for using or inventing acronyms.<sup>2</sup> Acronymia is contagious. Please do not let our colleagues in respiratory medicine catch this terrible disease.

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- 1 Sherwood Burge P. EUROSCOP, ISOLDE and the Copenhagen City Lung Study. *Thorax* 1999;54:287-8.
- 2 Cheng TO. Acronyms of clinical trials in cardiology—1998. *Am Heart J* 1999;137:726-65.
- 3 International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *JAMA* 1993;269:2282-6.
- 4 Cheng TO. No abbreviations in title, please. *J Emerg Med* 1997;15:379.

## Cystic fibrosis and diabetes

Yung *et al* present important data on cystic fibrosis related diabetes (CFRD) and suggest a selective approach for screening and diagnosis.<sup>1</sup> Although the majority of patients with CFRD may be identified using this approach, over 8% would remain undiagnosed.

CFRD is associated with substantial morbidity and mortality. Analysis of 21 000

patients followed by the Cystic Fibrosis Foundation Registry shows a sixfold increase in mortality for CFRD with more severe pulmonary disease.<sup>2</sup>

Once insulin treatment begins, FEV<sub>1</sub> and FVC increase and are comparable to non-diabetic patients by two years. The number of pulmonary infections with *Haemophilus influenzae* and *Staphylococcus aureus* fall and body mass index increases sharply within three months of starting treatment.<sup>3</sup> Consequently, many may judge the risk for patients undiagnosed by the selective approach to be too high.

Recommendations from the 1998 Consensus Conference on CFRD<sup>2</sup> state that the fasting glucose and oral glucose tolerance test (OGTT) should be performed in all patients with symptoms of diabetes, particularly as measurement of glycosylated haemoglobin (HbA1c) has been shown to be unreliable in the diagnosis of new CFRD. The major discrepancy between the findings of Lanng *et al*<sup>3</sup> and the Brompton group<sup>1</sup> emphasises this point.

Clear distinction needs to be made between screening and diagnosis. Many tests of glucose control in CFRD lack the sensitivity and specificity to identify most new cases. The approach used by Yung *et al* may prove to be a suitable screening test since the majority of cases were identified.

The OGTT is currently recommended as the test of choice in the diagnosis of CFRD which aids in prompt and accurate identification of the disease. Otherwise, an entirely treatable cause of pulmonary decline may be missed.

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- 1 Yung B, Kemp M, Hooper J, *et al*. Diagnosis of cystic fibrosis related diabetes: a selective approach in performing the oral glucose tolerance test based on a combination of clinical and biochemical criteria. *Thorax* 1999;54:40-3.
- 2 Moran A. Highlights of the February 1998 consensus conference on CFRD. *Pediatr Pulmonol* 1998;17:104-5.
- 3 Lanng S, Thorsteinsson B, Nerup J, *et al*. Diabetes mellitus in cystic fibrosis: effect of insulin therapy on lung function and infections. *Acta Paediatr* 1994;83:849-53.

**AUTHOR'S REPLY** I thank Drs Pirzada and Wales for their interest in our paper and would like to make two points in response. Firstly, I agree entirely with Drs Pirzada and Wales that the oral glucose tolerance test (OGTT) should be the test of choice in the diagnosis of cystic fibrosis related diabetes (CFRD). The selective use of OGTT in the diagnosis of CFRD as described by us may indeed miss a few cases of CFRD, but it represents an alternative approach to the diagnosis of CFRD in large cystic fibrosis centres where it may not be practical to perform OGTTs on all patients. As stated in our paper, patients with CFRD missed by our selective approach are those with normal random blood glucose levels, glycosylated haemoglobin, and those asymptomatic of hyperglycaemia. We speculate that the clinical and metabolic consequences of their diabetes may not be as great as those diabetics with one or more of the abnormal criteria cited above. As most adult patients are reviewed at least three monthly, these patients are likely to be identified at a later date.

Secondly, whether the development of CFRD is associated with a deterioration of clinical status remains unresolved. The evi-

dence in the literature on this issue is conflicting.<sup>1-3</sup> CFRD may cause a decline in patients' clinical status or it may merely be a marker of poor clinical and nutritional status. The latter may explain the apparent high mortality of CFRD patients as reported by the Cystic Fibrosis Foundation. In the management of patients with CFRD, every effort should continue to be made to improve the clinical and nutritional status of patients so that the impact of the development of CFRD is kept to a minimum.

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- 1 Rodman HM, Doershuk CF, Roland JM. The interaction of two diseases: diabetes mellitus and cystic fibrosis. *Medicine* 1986;65:389-97.
- 2 Finkelstein SM, Wielinski CL, Elliott GR, *et al*. Diabetes mellitus associated with cystic fibrosis. *J Pediatr* 1988;112:373-7.
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## Methacholine challenge and sputum induction

Spanevello and colleagues claim that a methacholine inhalation challenge carried out one hour before sputum induction in patients with stable asthma does not significantly alter the cellular, eosinophil cationic protein (ECP), or albumin constituents of sputum.<sup>1</sup> These results, if correct, are important for both clinical practice and clinical trials where information regarding airway hyperresponsiveness and inflammation is needed. Being able to perform a methacholine challenge and sputum induction on the same day would be convenient.

Sixteen subjects with asthma were studied on two days within a week. Sputum induction was performed alone on one day and one hour after a methacholine challenge on the other. Cell counts and the biochemical markers of the two sputum samples were compared using the Wilcoxon signed rank test and a value of  $p < 0.05$  was considered statistically significant.

The small sample size, variability in the data, and  $p$  values near significance for neutrophils ( $p = 0.06$ ) and macrophages ( $p = 0.08$ ) led us to determine the power of the study. The results of a power analysis for paired continuous data showed that the study only had a 36%, 29%, 10%, 6.6%, and 19.5% chance of detecting a difference for macrophage, neutrophil, eosinophil, lymphocyte and epithelial cell counts, respectively, and 6.0% and 15.3% for ECP and albumin. Hence, while methacholine may not influence sputum cell counts, this study is too underpowered to reach this conclusion.

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- 1 Spanevello A, Vignola AM, Bonnano A, *et al*. Effect of methacholine challenge on cellular composition of sputum induction. *Thorax* 1999;54:37-9.

**AUTHORS' REPLY** We would like to thank Drs Labiris and Hargreave for their interesting comments on our article. They have emphasised the variability in the data and the fact that the p values for neutrophils and macrophages were near significance. Moreover, they have provided the results of a power analysis for paired continuous data showing that the study is underpowered to reach solid conclusions.

We agree that their comments are valid both for the variability of the data and that the p value was near significance for neutrophils and macrophages. However, the p value for eosinophils was far from the significance level ( $p = 0.49$ ). This is important because the aim of the study was to evaluate the influence of methacholine challenge on overall sputum cellularity but, in particular, on eosinophils which are considered the most relevant inflammatory cell in bronchial asthma.

We are confident that a methacholine inhalation challenge carried out one hour before sputum induction in asthmatic subjects does not alter the eosinophil count in induced sputum, and that this result is important for both clinical practice and clinical trials involving patients with asthma.

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defined criteria for its use: patients over five years of age,  $FEV_1 < 70\%$  predicted, and more than one course of intravenous antibiotics during the previous year. In 1995 12 (17%) of patients receiving DNase did not appear to meet these clinical criteria. A further 36 patients who were eligible under these criteria were not receiving the drug.

Innes<sup>2</sup> rightly emphasises the responsibility of carers to target this treatment effectively—it is also important that treatment is seen to be equitable and not dependent on postcode. Our experience illustrates that a regional cystic fibrosis database can be a clinically relevant and cost effective device for targeting appropriate treatment. The annual cost of DNase for two patients would be sufficient to fund a regional audit to monitor and influence this and other expensive treatments in patients with cystic fibrosis.

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1 Milla CE. Long term effects of aerosolised rhDNase in cystic fibrosis. *Thorax* 1998;53:1014-7.

2 Innes JA. DNase in cystic fibrosis: the challenge of assessing response and maximising benefit. *Thorax* 1998;53:1003-4.

## rhDNase in cystic fibrosis

Cystic fibrosis is a disease that is relatively rare but expensive for patients, families, and carers. The introduction of rhDNase has been associated with controversy as to its benefits and costs. Milla describes the experience in a centre that prescribed this drug to patients, 60% of whom had an  $FEV_1$  of more than 80% predicted at the time of prescription.<sup>1</sup> Overall, the group had an accelerated decline in lung function following its introduction. This study illustrates the importance of patient selection and follow up in the prescription of rhDNase.

Paediatricians and chest physicians from the South & West Region of the UK have audited their use of DNase as part of their contribution to the South & West Cystic Fibrosis database. In 1995 78 (12%) of the 664 patients receiving care within the region had been prescribed DNase. This had risen to 143 (22%) in 1996. We subsequently

tion instructions, it ran efficiently on a 266 MHz based laptop from the hard disc or CD-ROM drive. The search functions were easy to use with helpful cross referencing links and section content outlines. The initial cost is approximately £300 for the first year with the CD-ROM being regularly updated throughout the year.

Have they succeeded in their aim? Overall, the answer is yes.

Useful practical advice is given on simple but irritatingly difficult questions to answer—for example, provision of oxygen during air travel, the choice of agent for chemical pleurodesis, the role of inhaled steroids in chronic obstructive pulmonary disease, etc. However, the programme is slanted toward the American market, as highlighted in the section on long term oxygen therapy (LTOT) which gives, in detail, the billing mechanism. Similarly, nasal calcitonin suggested for the treatment of steroid induced osteoporotic bone pain is not licensed in the UK.

Its functionality makes it a valuable tool in the outpatient setting, being described by one trainee as "really helpful". This programme would be best suited to hospitals and practices with adequate provision for computing facilities in the clinical area, ideally over a local area network and not locked away in the library. The added bonus for the chest physician with a commitment to general medicine is that the disc also has sections on cardiology, gastroenterology, and other main stream disciplines of similar quality. This programme sets a formidable standard for the UK government's proposed NICE (National Institute for Clinical Excellence) clinical information system.—SPH

## BOOK REVIEW

**Up to Date in Pulmonary and Critical Care.** Steven E Weinberger. USA: American Thoracic Society.

*Up To Date in Pulmonary and Critical Care*, a product from the stable of the American Thoracic Society, is one of a rising tide of PC based medical texts. The programme is based on the concept of providing quick and authoritative answers to common specific questions that arise during specialist clinical practice but not as a resource to use when faced with a rare disease.

Presented on CD-ROM for Windows or Macintosh and supported by clear installa-

## NOTICE

### MICRO 2000

Following the success of MICRO 98, the Royal Microscopical Society has announced that a MICRO 2000 international microscopy exhibition and conference will be held on 11-13 April 2000 in London. Further information will be available shortly from the Exhibition Organiser, Royal Microscopical Society, 37/38 St Clements, Oxford OX4 1AJ, UK. e-mail: exhibitions@rms.org.uk