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). They found the device to be four times as economical as nasal cannulae for the same increase in walking distance in patients with COPD compared with the other devices which were tested. The Haldane type mask fell out of use because of its very 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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Simian virus 40 and human pleural mesothelioma

Mulatero et al 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. Furthermore, the International Mesothelioma Interest Group has published results of their multinational investigation confirming consistent association of SV40 DNA with mesotheliomas. Additional recent studies (reviewed by Butel and Lednicky) 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 amplification theory. The negative findings of Mulatero et al may be explained by technical or demographic differences. 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 per cell) which is estimated to be associated with this tumour type. In this context, the adequacy of method sensitivity claimed by the authors based on its comparison 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 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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AUTHORS’ REPLY
Dr Jasani misquotes us when he says we suggested that the laboratories’ 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. Any laboratory that does 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 mesotheliomas all used different detection strategies and laboratories may differ in their methods and conclusions.

The multi-institutional study to which Dr Jasani refers 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 laboratories claimed to have 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, whereas a continuing increase in incidence over the next 20 years is expected in Europe. The observations, together with evidence that so far there is no increase in the incidence of mesothelioma in individuals who received SV40 contaminated polio vaccine, do not suggest that SV40 is important in the causation of human mesothelioma.

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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”. Acronyms are useful and often necessary because they simplify and accelerate modern communication. But when first mentioned in any biomedical journals, acronyms must be explained fully. Furthermore, abbreviations are prohibited in a title. Specialists often take for granted that certain “trade terms” are so evident that they do not bother to define them. I thought that certain “trade terms” are so evident that they do not need to be defined. I am not aware of any reports to suggest that the abbreviation CF has any different meaning than the word cystic fibrosis. Whether the abbreviation CFRD has any different meaning than the word cystic fibrosis related diabetes (CFRD) is suggested by the selective approach to screening and diagnosis. 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.

Once insulin treatment begins, FEV1 and FVC increase and are comparable to non-diabetic patients by the number of pulmonary infections with Haemophilus influenzae and Staphylococcus aureus fall and body mass index increases sharply within three months of starting treatment. 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 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 and the Brompton group 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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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 constitutents of sputum. 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 advantageous.

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 biocidal properties 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, which would have consisted of 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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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 FEV1 of more than 80% predicted at the time of prescription. 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 defined criteria for its use: patients over five years of age, FEV1 <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 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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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