

# PostScript

## LETTERS TO THE EDITOR

### Variations in mortality in acute COPD may reflect nihilism as well as resources

I read with great interest the paper by Roberts *et al*<sup>1</sup> and the accompanying editorial by Rudolf.<sup>2</sup> The study highlights important variations in the outcomes of patients with a common chronic disease, and once more illustrates that doctor:patient ratios may be an important contributor to this. It is also likely that some of the observed variation may arise as a result of variations in decision making by individual clinicians.

A recent study carried out in the eight hospitals in the Heart of England Critical Care network interviewed 98 clinicians who made end of life decisions for patients with chronic obstructive pulmonary disease (COPD).<sup>3</sup> Each had made a median of 10 end of life decisions for COPD patients in the previous 12 months. There was considerable variability in the decision whether or not to admit identical patients to the critical care unit, with those choosing not to admit patients forming very pessimistic predictions of outcome compared with clinicians who would admit. It seems possible that poor outcomes for patients with COPD may not simply reflect a lack of resources, but also therapeutic nihilism that may have grown up over the years in response to the cognitive dissonance that arose when beds in critical care units could not be found for COPD patients in extremis. It seems likely that reversing variations in outcome will require both changes in resources and changes in clinicians' expectations. In this respect, the GMC guidance on withholding and withdrawing life prolonging treatments<sup>4</sup> may well be helpful, particularly section 20 which recommends that "where there is a reasonable degree of uncertainty about the appropriateness of providing a particular treatment, treatment which may be of some benefit to the patient should be started until a clearer assessment can be made". In the Heart of England Critical Care network study over one third of clinicians would not admit a 75 year old COPD patient with single organ respiratory failure, yet in a recent study of over 3700 admissions of COPD patients of median age 67.8 years to UK intensive care units, those with single organ respiratory failure had a hospital survival of over 70%.<sup>5</sup>

It is important that chest physicians continue to be strident advocates for COPD patients admitted as emergencies, and take every opportunity to point out to their colleagues in general medicine and intensive care how well patients with COPD can do with both invasive and non-invasive ventilation.

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### Authors' reply

We thank Dr Wildman for his letter suggesting a further possible reason for the variation in outcome that we reported for the acute care of COPD patients in different hospital centres. In a further unpublished multiple regression analysis of the RCP/BTS 2001 audit we found that 26% of the variation in the outcome of death at 90 days following admission could be accounted for by factors measured in the study that included patient characteristics such as performance status and resource and organisational issues, as described in our paper.<sup>1</sup> Dr Wildman suggests that individual clinicians might vary in determining admission to the ITU for COPD patients in respiratory failure, and suggests that respiratory physicians need to be advocates for their patients in this arena.

Attitudes and beliefs in what might be achieved are important but are difficult to measure in clinical practice. They might account for some of the variation in outcome but, if so, the therapeutic nihilism would have to vary systematically between whole hospitals to have been a factor in our study. Admission to the ITU depends on more than the individual attitude of the referring doctor. A lack of availability of beds may raise thresholds, and an institutional nihilism within the ITU may lead to rejection of suitable patients.

Perrin *et al*<sup>2</sup> reported a study in which questionnaires regarding initiation of mechanical ventilation in end stage COPD patients were completed by 350 doctors subdivided by speciality (intensivists, respiratory specialists and other physicians). As in the paper by Wildman *et al*,<sup>3</sup> there was

considerable individual variation in decision making but no overall difference between the three types of specialist studied. However, no analysis by hospital or trust was made to identify local patterns. We believe all respiratory physicians will share Dr Wildman's call that referring physicians should be advocates for their patients, and this has to be matched by a willingness of the ITU staff to accept such patients and the availability of beds within an ITU/HDU facility to accommodate them. Perrin's paper provides hope of a generic match although individual disagreements may still occur. It is, however, not only admission to the ITU that matters, as in many hospitals non-invasive ventilatory support is provided on general wards by respiratory units without input from intensivists.

In the BTS/RCP 2003 national audit of the acute care of COPD patients, 95% of all acute admitting sites have now registered to participate and data collection is nearing completion. Within the clinical data gathering there is a question that attempts to document clinical decision making when a patient eligible for ventilation on blood gas criteria does not receive ventilatory support. In addition, data regarding available resources such as ITU beds, bed occupancy, and numbers of ITU candidates transferred off site will be recorded. We may be in a position to shed further light on the issues of individual versus institutional nihilism or rationing in due course.

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### Do inhaled corticosteroids slow FEV<sub>1</sub> decline in COPD after all?

I question the findings of the meta-analysis by Sunderland *et al*<sup>1</sup> and the content of the associated editorial by Burge and Lewis.<sup>2</sup> The meta-analysis has drawn from available long term data from randomised controlled studies (RCTs) of inhaled corticosteroids (ICS) in chronic obstructive airways disease (COPD). The whole purpose of meta-analysis is to analyse such data systematically to answer a question. This study seems to use the data selectively to demonstrate an effect. Another recent meta-analysis—in my opinion properly conducted—drew on the same studies and reached the opposite conclusion.<sup>3</sup> The fact is that four long term, adequately powered RCTs have examined the effect of ICS. All of these studies showed no effect of ICS on the primary outcome measure of decline in forced expiratory volume in

1 second (FEV<sub>1</sub>). There may be a subset of people in whom the exacerbation rate is reduced, which was a secondary outcome in some of these studies.

In any case, as the authors point out, an annual difference of 7.7–9.9 ml in FEV<sub>1</sub> decline compared with placebo is of “debatable clinical importance”.<sup>1</sup> It is hardly something to shout about, as occurred following this publication (probably egged on by the editorial) which was quoted in the GP press as suggesting that current widespread ICS use (albeit “off-label”) was now clinically justified.<sup>5</sup>

Another major problem with this study is that it does not analyse harm. For example, the largest RCT showed a significant reduction in bone mineral density of the lumbar spine and femur in patients receiving inhaled triamcinolone.<sup>4</sup> People with COPD likely to receive ICS are frail and have poor mobility, so this finding raises particular concern as they are more likely to fall and falls could result in fracture. Even if inhaled triamcinolone is not used in the UK, fluticasone is. Fluticasone has been the subject of particular cautionary advice because of its ability to cause systemic effects at high doses.<sup>6</sup> If there is indeed a marginal clinical benefit from using these drugs, I think these people deserve a better assessment of risk and benefit than was presented in this meta-analysis and the accompanying editorial.<sup>2</sup> The editorial claimed that it is no longer ethical to do more long term trials: surely the conclusion is the opposite? We need better data to justify the widespread use of ICS in COPD.

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## Ethics of placebo controlled studies of inhaled steroids for COPD

The meta-analysis by Sutherland *et al*<sup>1</sup> of the effect of inhaled corticosteroids on the progression of airflow limitation in patients with chronic obstructive pulmonary disease (COPD) found a small improvement in forced expiratory volume in 1 second (FEV<sub>1</sub>) of –7.7 ml/year (95% CI –14.2 to –1.3) which is similar to the results of the meta-analysis

performed by Highland *et al*<sup>2</sup> (–5 ml/year (95% CI –11.2 to 1.2)) using a very similar data set. The meta-analyses employed slightly different study selection criteria and analytical techniques, and questioned the clinical significance of such small differences in FEV<sub>1</sub>. The selected primary studies suffered from potential drop-out bias and significant selection bias, in that almost all of the studies subjected to these meta-analyses excluded patients with a bronchodilator response.<sup>3</sup> Studies of asthma and COPD as separate entities are limited because asthma and COPD (observed in cross section) represent a continuum,<sup>3</sup> and the small number of available prospective observations indicates that asthma and COPD are sometimes different clinical manifestations of the same underlying aetiology evolving over time.<sup>3</sup> Given all the uncertainties, questions and limitations, Highland *et al*<sup>2</sup> concluded (correctly in my opinion) that “additional studies are needed to evaluate the effects on quality of life, risk for systemic side effects, dose-response relationships in corticosteroid-responsive patients, and the economic effect of inhaled corticosteroids”. On the other hand, in an editorial accompanying the paper by Sutherland *et al*, Burge and Lewis<sup>5</sup> state: “It is no longer ethical to do more long term placebo controlled studies [of inhaled corticosteroids in COPD]”. Given the uncertainties, questions and limitations which Burge and Lewis acknowledged, I was puzzled by this statement and would like to ask them why they reached this conclusion.

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## Authors' reply

To make randomised controlled studies ethical, the investigator must believe that neither treatment is known to be superior to the other. If the trial is to be placebo controlled, the investigator must believe that no non-allowed treatment is known to be of benefit. Both Drs Duerden and Hahn want more placebo controlled trials of inhaled corticosteroids (ICS) in COPD before they recommend their use. Our editorial pointed out that ICS were of established benefit in reducing exacerbations of COPD,<sup>1</sup> so any future placebo controlled study would need to be in

patients without a history of exacerbations. As exacerbations are associated with disease severity, and as about 80% of patients with an FEV<sub>1</sub> <50% predicted have exacerbations over a 3 year period,<sup>2</sup> any trial would need to be in those with early disease. The Copenhagen City Lung Study found that inhaled budesonide 800 µg/day had no benefit in a population of smokers selected with a reduced FEV<sub>1</sub>/FVC ratio, the majority of whom had an FEV<sub>1</sub> above 80% predicted.<sup>3</sup> This leaves the group with an FEV<sub>1</sub> between 50% and 80% predicted, many of whom have not been identified by their medical practitioners. This was the group included in the EUROSCOP and Lung Health 2 studies, where the results included in the meta-analysis were the most divergent, probably because of the relatively low dose of ICS used in the Lung Health study.<sup>4,5</sup> In the symptomatic patient with more severe disease, the combination of a long acting β agonist and an ICS has been shown to be superior to either alone and is now the treatment of choice.<sup>6,7</sup> This leaves the presymptomatic population in whom a decline in FEV<sub>1</sub> is the only practical outcome measure. No randomised study using an intention to treat analysis has shown a reduction in FEV<sub>1</sub> decline with any treatment in any disease, including ICS in asthma, although several studies have shown an improvement in FEV<sub>1</sub> with ICS in COPD.<sup>2,4,6</sup> Our editorial tried to explain why changes in FEV<sub>1</sub> decline were difficult to show in patients with COPD. Patients with progressive disease are likely to be given ICS by their clinicians outside any trial, reducing the power of any study.

Any treatment should weigh the potential risks against any benefit. Dr Duerden wants a better analysis of the risks of ICS in patients with COPD, particularly related to bone loss, and points out the reduced bone mineral density in the triamcinolone group in the Lung Health 2 study.<sup>5</sup> The reported results are in 359/412 of a convenience sample who had three measurements of bone density. After 3 years the lumbar spine density reduced from 0.988 to 0.985 g/cm<sup>2</sup> and the femoral neck from 0.762 to 0.747 g/cm<sup>2</sup> in the triamcinolone group. EUROSCOP studied bone density measurements in 194 subjects<sup>4</sup> and showed very small changes which were significantly less at the femoral trochanter in the budesonide group (0.04%/year *v* 0.36%/year in the placebo group). Randomised controlled studies are probably not the best method for assessing the extent of long term adverse effects, but the evidence from the randomised studies to date shows that the risks are relatively minor compared with the risks of death from the natural progression of the disease. Introducing ICS at an earlier stage may alter the risk/benefit ratios. The adverse effects on the bones are probably best studied in asthmatics of whom many are already taking long term ICS in equivalent doses.

There is a striking difference between the way that cardiac and respiratory physicians greet new treatments whose individual effects are present but relatively minor. There has been a meaningful reduction in cardiac deaths attributed to the combination of several treatments with modest individual effects. This has resulted in more smokers living to develop significant COPD. It is likely that improvements in the quality and quantity of life in patients with COPD will come from a combination of treatments, among which ICS have a place. The main

unanswered questions are—at which stage to start and what dose to use? Randomised trials in these areas are badly needed. They will require large numbers, enthusiasm from respiratory clinicians, and are likely to need public rather than pharmaceutical industry funding.

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## Delays in diagnosis of OSAHS

We very much enjoyed the first paper in the review series on sleep and admired Stradling and Davies's honest appraisal of the current difficulties in defining disease and the lack of a relationship between symptoms and the results of investigations.<sup>1</sup> One of the problems of truly determining the size of the health burden associated with the obstructive sleep apnoea/hypopnoea syndrome (OSAHS) is that much of the burden may occur before the diagnosis is made. Others have shown how use of hospital resources and use of cardiovascular medication is high in those with undiagnosed obstructive sleep apnoea.<sup>2,3</sup> We administered a questionnaire to 166 consecutive patients with diagnosed OSAHS on continuous positive airway pressure treatment and asked them to identify how long they could recall having symptoms at the time of diagnosis. In 155 cases (93.4%) someone had previously complained of the patient's loud snoring and first mention of this had been made a median of 12 years (range 2–52) before diagnosis of OSAHS. In 84.3% of respondents excessive daytime sleepiness had been present for a median of 8 years (range 0.5–62) and 133 patients (80.1%) reported that their bed partner had witnessed apnoeas a median of 8 years

(range 1–49) before diagnosis. We also found that, of the 119 (71.7%) who were drivers, 26 (21.8%) reported at least one or more automobile crashes in the previous 5 years, with seven respondents having had two and one having had four.

These results suggest a lack of awareness of sleep related breathing disorders among the general population and probably among health professionals. The delay in diagnosis is likely to have significant effects on morbidity, and in recent preliminary work it has been shown that those with OSASHS have structural changes in brain morphology compared with healthy controls.<sup>4</sup> In addition to the health and quality of life benefits to the individual to be gained by prompt diagnosis, there are also economic aspects in favour of prompt diagnosis and treatment<sup>5,6</sup> and early benefits in terms of driving performance.<sup>7</sup>

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## Prophylactic antibiotic treatment of bronchiectasis with azithromycin

Once a treatable cause of bronchiectasis such as hypogammaglobulinaemia has been excluded, management largely involves physiotherapy and treatment of infective exacerbations with appropriate antibiotics.<sup>1</sup> In a proportion of patients this is not adequate to prevent frequent infective exacerbations. Prophylactic antibiotic treatment can be used to try to prolong the exacerbation free period. This may be administered orally, via a nebuliser, or using a cyclical regimen of intravenous antibiotics. Prophylactic treatment may be problematic due to side effects and development of antibiotic resistance.<sup>2</sup> Macrolide antibiotics exhibit immunomodulating properties. Long term, low dose erythromycin has been shown in diffuse panbronchiolitis, a disease with some similarities to idiopathic bronchiectasis, to be

effective in controlling chronic suppurative airways disease.<sup>3</sup> Recently published research has shown benefits of long term azithromycin treatment in patients with cystic fibrosis.<sup>4</sup> These results led us to consider using azithromycin as prophylaxis in patients with non-cystic fibrosis bronchiectasis with frequent infective exacerbations.

Patients attending the outpatients department between February 1999 and April 2002 who fulfilled the following criteria were considered for azithromycin prophylaxis:

- bronchiectasis defined by CT scan;
- any causal condition had been treated if possible;
- general management optimised;
- >4 documented infective exacerbations requiring oral or intravenous antibiotic treatment during the last 12 months;
- *Pseudomonas aeruginosa* respiratory infection, if present, had not responded to nebulised antibiotic prophylaxis or this had not been tolerated;
- failure to control chronic symptoms.

Exclusions included allergy to macrolides and abnormal liver function tests. The dosing schedule was 500 mg once daily for 6 days, 250 mg once daily for 6 days, then 250 mg on Monday/Wednesday/Friday of each week. A safety blood examination was organised 1 month after starting treatment. The patients were fully reviewed at least 4 months after commencement of azithromycin prophylaxis and lung function tests repeated. Sputum culture results before and after starting prophylaxis were noted. Statistical analysis was performed using a paired *t* test and non-parametric Wilcoxon test.

Thirty nine patients were studied. Fifteen had idiopathic bronchiectasis and the remainder consisted of 13 with post childhood infections, five with primary ciliary dyskinesia, five with common variable immunodeficiency, and one with Young's syndrome. Their mean (SD) age was 51.9 (16.1) years (range 18–77) with a 2:1 female predominance. All patients had had more than four documented exacerbations during the previous 12 months. Six patients stopped taking the azithromycin prophylaxis because of side effects: abnormal liver function tests (*n* = 2), diarrhoea (*n* = 2), rash (*n* = 1), and tinnitus (*n* = 1). All occurred during the first month of treatment. Other side effects experienced were mild and mainly gastrointestinal. Five patients were on long term oral corticosteroids with no change in dosage, in two new inhaled corticosteroids were introduced, and one patient was given a short 7 day reducing course of oral corticosteroids. The mean (SD) length of time taking azithromycin, excluding those who stopped because of side effects, was 20 (10.1) months (range 4–38). Twenty six patients are continuing with the prophylaxis at the present time; in the other seven treatment was discontinued because of improvement in their condition.

Sputum culture results (all bacteria isolated) before commencement showed no growth (*n* = 13), *Pseudomonas aeruginosa* (*n* = 8), *Staphylococcus aureus* (*n* = 6), *Haemophilus influenzae* (*n* = 6), *Streptococcus pneumoniae* (*n* = 3), *Stenotrophomonas maltophilia* (*n* = 2), *Moraxella catarrhalis* (*n* = 1), not done (*n* = 4). After 4 months the results were no growth (*n* = 18), *P. aeruginosa* (*n* = 5),

**Table 1** Change in symptoms while taking azithromycin prophylaxis

	Mean	SD	SE	p value
Sputum volume	1.6	0.8	0.14	<0.001
Sputum colour	2.1	0.7	0.13	<0.001
Sputum consistency	2.5	0.6	0.11	0.006
Cough	2.4	0.7	0.12	0.001
Fatigue	2.1	1.0	0.18	0.001
Exercise tolerance	3.8	0.9	0.16	0.002
Wheeze	2.6	0.8	0.14	0.011
Breathlessness	2.3	0.7	0.13	0.002

Symptoms scored on a 5-point scale: 1 = large decrease, 2 = decrease, 3 = no change, 4 = increase, 5 = large increase in symptoms.

*S aureus* (n = 1), *S pneumoniae* (n = 1), not done (n = 10). In three patients who had cultured *P aeruginosa* before starting azithromycin prophylaxis the organism was not recultured at follow up.

In the 33 patients completing at least 4 months treatment there was a statistically significant reduction in infective exacerbations requiring oral antibiotics from a mean of 0.71 per month to 0.13 per month (p < 0.001). There was also a reduction in the requirement for intravenous antibiotics from a mean of 0.08 courses per month to 0.003 courses per month (p < 0.001). Subgroup analysis of patients with *P aeruginosa* isolated before starting azithromycin prophylaxis showed no difference compared with all patients included (p = 0.22). Twenty five patients had lung function tests before and after at least 4 months of treatment (range 4–20 months). There was an improvement in all lung function parameters but the improvement in carbon monoxide transfer factor (TLCO) was the only one to reach statistical significance (p = 0.01).

Symptom data were collected from 32 patients and scored on a 5-point scale (table 1). Statistical analysis using a non-parametric Wilcoxon test showed that there was a significant improvement in all symptoms.

The mechanism by which azithromycin reduces the number of infective exacerbations and chronic symptoms is unknown, but it is likely to be multifactorial. It may be due to downregulation of the host immune response by azithromycin, so decreasing host mediated tissue damage as postulated in the vicious circle hypothesis. It might also benefit patients by reducing bacterial load and therefore the stimulation for neutrophilic inflammation, or by influencing the pathogenic mechanisms of bacteria. Macrolide antibiotics have also been shown to reduce mucus secretion.<sup>1 5</sup>

Currie *et al* compared high dosage amoxicillin with placebo over an 8 month period and found a greater reduction in the volume of purulent sputum between exacerbations in the amoxicillin group (to 20% of pretreatment volume) than in the placebo group, but did not demonstrate any reduction in infective exacerbations.<sup>6</sup> The superior findings of our study suggest that the anti-inflammatory effects of azithromycin were important in achieving the results obtained. This study was performed with patients who were sufficiently unwell to preclude consideration of a placebo group. The patients therefore acted as their own controls. The results are sufficiently impressive to encourage the design of a randomised study, either enrolling less sick patients and having a placebo

comparator or using a comparator antibiotic without immunomodulating properties.

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## Early life antibiotics and asthma

Cullinan *et al*<sup>1</sup> present interesting data on the association between exposure to antibiotics in early life and the subsequent expression of atopy and asthma. In keeping with other studies, they report a positive association between antibiotic receipt over the first 5 years of life and asthma. The association was, however, largely accounted for by prescriptions issued for respiratory illnesses, and the authors conclude that reverse causation was the likely explanation for this association.

The inappropriate use of antibiotics for respiratory symptoms caused by unrecognised asthma is the main potential confounding factor in observational studies attempting to demonstrate a causal link between antibiotic receipt and atopic illnesses. It is certainly plausible that GPs may prescribe antibiotics in children with symptoms such as cough and wheeze in early life. Suggestions of a casual link are strengthened by demonstration of an association when antibiotics were used for symptoms not associated with asthma. The earlier study by Faroouqui and Hopkins<sup>2</sup> did, indeed, observe an association with non-respiratory use of antibiotics and asthma; in the study by

Cullinan *et al* the association between non-respiratory indicated antibiotics and atopic asthma narrowly failed to reach statistical significance. The authors acknowledge that the study was only powered to show a doubling of the odds ratio for the association between early life antibiotic use and asthma, so an association remains possible in this cohort.

The most important limitation of the study, however, is the timing of the observed early life events in relation to secular changes in asthma prevalence and antibiotic prescribing, and hence the applicability of the results to modern day settings. This study observed events occurring 30 or more years ago in the parents of the Ashford birth cohort. As is well described, the prevalence of asthma has increased greatly over the last 30 years.<sup>3</sup> There may also have been significant increases in antibiotic prescribing over this time. The subjects in this study received an average of 3.1 and a median of 3 antibiotic prescriptions over 5 years, while we found in a recent case-control study<sup>4</sup> of 37 children with atopy and wheezing and 37 without either that the average and median number of antibiotic courses received during the first 5 years of life was 9.9 and 7 for wheezers and 6.3 and 5 for non-wheezers. There is also evidence of earlier prescribing of antibiotics in recent times; in our study group 89% of wheezers and 68% of non-wheezers received one or more courses of antibiotics in the first year, while in the Ashford study only 396 prescriptions were issued to 746 subjects in the first year, so a maximum of 53% children received any antibiotics.

It seems likely from the data presented that antibiotic exposure did not play a major causal role in promoting the asthma phenotype 30 years ago when both the prevalence of asthma and antibiotic prescribing to young children were significantly less than they are now, but the question of whether it may now be a significant and potentially modifiable factor remains unanswered.

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## Recurrence of acute respiratory failure following use of waterproofing sprays

Between January and March 2003 six patients were admitted to hospital in the Lausanne area of Switzerland with acute respiratory failure following use of a waterproofing spray for clothes and leather. Within hours of exposure all patients developed a dry cough and rapidly progressive dyspnoea. The clinical picture included severe hypoxaemia, increased white blood cell count, raised C-reactive protein, and reduced carbon monoxide



**Figure 1** CT scan of thorax of a patient showing diffuse ground glass opacities.

transfer factor (TLco). All patients had diffuse bilateral ground glass opacities on a high resolution CT scan, most often sparing the subpleural areas (fig 1). Every patient improved following treatment with oral prednisone (0.5–0.9 mg/kg) but residual dyspnoea and reduced TLco (<80% of predicted value) could be seen for more than 2 weeks.

Acute respiratory failure was attributed to inhalation of the waterproofing spray in view of the sudden occurrence of symptoms following exposure, the diffuse ground glass opacities without other abnormalities on the CT scan, and the absence of any other detected cause. In particular, BAL fluid was sterile for bacteria, mycobacteria, viruses and fungi. Serological tests for chlamydia and mycoplasma were performed on two patients and were negative. A nasal swab for influenza was performed on one patient and was negative.

We were, however, surprised that the patients used three different spray brands. Waterproofing sprays contain three types of components—a propellant gas (propane butane), a waterproofing agent (fluorocarbon resin), and a solvent. It appeared that the manufacturer of the fluorinated resin changed during the summer of 2002 (the same for the three brands) and that the isopropanol solvent had to be replaced with a heptane solvent. Consumers started complaining of respiratory symptoms in October 2002 and the first severe case requiring admission was reported in January 2003. The three products were withdrawn from the market at the beginning of March. During this 6 month period 153 cases of respiratory symptoms related to waterproofing sprays were reported to the Swiss Toxicological Information Centre, whereas less than 10 cases per year had been reported in the previous 7 years.

The same fluorinated resin was also distributed in Germany, the Netherlands, and the UK. In Germany the waterproofing sprays were withdrawn before they reached the consumers. During the same period five patients were admitted to hospital in the Netherlands with the same complaints.<sup>1</sup> These sprays were also withdrawn from the Dutch market. Surprisingly, no case has yet been recorded in the UK.

However, only sprays for public use were withdrawn, not the industrial liquids. In Switzerland two additional patients developed a chemical pneumonitis with similar symptoms and diffuse bilateral ground glass opacities after using industrial waterproofing liquid with a nebuliser. Workers in the above mentioned countries should therefore be

warned not to use the liquid form with nebulisers.

In the past, several outbreaks of acute respiratory symptoms have been recorded in different countries including 550 in Oregon in 1992,<sup>2</sup> 3 in Pennsylvania and Virginia in 1993,<sup>4</sup> in Quebec in 1993,<sup>5</sup> and in Japan between 1992 and 1993.<sup>6</sup> Most of these epidemics followed a modification of the composition of the spray. One untreated patient developed a pulmonary fibrosis during a German outbreak in the 1980s<sup>7</sup> and one death was reported in Japan in the 1990s.<sup>8</sup>

Following these outbreaks, various suggestions were proposed to explain these intoxications.<sup>9</sup> In our opinion, the most likely explanation for the present outbreak is that the heptane solvent, which is more volatile than the previous one (isopropanol), allows the mist containing the new fluorinated resin to spread further in the tracheobronchial tree and to reach the alveoli where it might produce reactive metabolites inducing an alveolitis. However, the exact chemical reaction remains unknown. Because of the potentially lethal aspect of these intoxications and the possibility of new outbreaks, we consider that more research is needed on the effect of mist particle size and large analytical epidemiological studies are required to investigate this phenomenon further.

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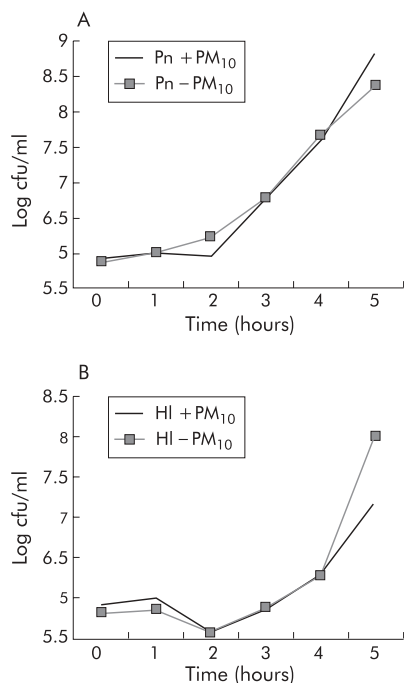
## Effect of PM<sub>10</sub> on *H influenzae* and *S pneumoniae*

That air pollution, and specifically particles, are harmful to health is well accepted,<sup>1</sup> causing direct effects such as lung inflammation resulting in exacerbations of lung and cardiac conditions<sup>2</sup> and being associated with admissions for pneumonia. In the 1960s Lawther *et al* showed that ambient particles stimulated the growth of *Haemophilus influenzae* in vitro,<sup>4</sup> suggesting a direct effect of particles on bacteria themselves. However, it is not known whether this remains so for modern ambient particles where the sources are different.

To address this we have assessed the effect of PM<sub>10</sub> (particles essentially less than 10 µm in diameter) on the respiratory pathogens commonly associated with acute exacerbations of chronic obstructive pulmonary disease (COPD) and pneumonia. The effect of dilutions of extracts of PM<sub>10</sub> on the growth of *H influenzae* and *Streptococcus pneumoniae* grown in liquid broth and the effect of PM<sub>10</sub> on microbial growth kinetics of *S pneumoniae* was assessed.

Fresh isolates of *H influenzae* and *S pneumoniae* obtained from clinical specimens and the control strains *H influenzae* NCTC 11931 and *S pneumoniae* ATCC 49619 were used. Particles were collected on a tapered element oscillating microbalance situated in central Birmingham, representative of an urban background site. To obtain a usable sample the surface of the filter was wetted and rinsed with two sequential aliquots of 0.5 ml saline using a Gilson pipette until visual inspection showed no more particles coming off the filter. The two aliquots were combined and sonicated for 2 minutes to disperse the particles and aggregates. This procedure usually gives a yield of 50–300 µg/ml particles (Donaldson, personal communication). It is not known for certain how these concentrations relate to likely concentrations in the epithelial lining fluid, but this approach has been used in previous in vitro studies of inflammatory responses which have shown pro-inflammatory effects.

In the first experiment a 1:20 dilution of PM<sub>10</sub> was made by adding 0.5 ml to 9.5 ml Iso sensitest broth (ISTA; Oxoid Ltd, Basingstoke, UK) supplemented with 5% horse blood and 20 µg/ml NAD. The same volume of normal saline was added to controls. Test and control bottles were inoculated with 0.5 ml of organism suspension at a density of 0.5 McFarland. A viable count was performed hourly for 5 hours while incubating at 37°C in 5% CO<sub>2</sub> using the Miles and Misra technique.<sup>5</sup> In the growth kinetic experiment equal volumes of PM<sub>10</sub> solution and ISTA broth (supplemented with 5% lysed horse blood and 20 µg/ml NAD) were added to the first column of a sterile microtitre tray. Serial broth dilutions to a final dilution of 1:64 were performed. Control wells contained only broth and wells for sterility checks contained PM<sub>10</sub> alone, broth alone and inoculum alone. Organism suspension, 50 µl *S pneumoniae* ATCC 49619, was added into each test and control column of the wells and incubated at 37°C in 5% CO<sub>2</sub> for 5 hours. The Miles and Misra technique<sup>5</sup> was used to estimate the viable count of organism in each well and the differences in log cfu/ml between test and control were plotted against serial dilutions of PM<sub>10</sub>. This test was repeated five times using the same strain to check for reproducibility.



**Figure 1** Growth curve against time with and without PM<sub>10</sub> solution for (A) *S pneumoniae* ATCC control strain and (B) *H influenzae* NCTC control strain.

In the first experiment the number of viable cells increased progressively and in the expected pattern over time (fig 1A and B), whether in the presence or absence of PM<sub>10</sub>, for both *H influenzae* and *S pneumoniae*. In the growth kinetics experiment the only consistent finding was an inhibition of growth at a PM<sub>10</sub>:broth medium dilution of 1:1 compared with the PM<sub>10</sub> free control.

Growth of *H influenzae* and *S pneumoniae* is therefore neither inhibited nor promoted by incubation with PM<sub>10</sub> at concentrations of diluted particles which are known to be able to exert pro-inflammatory effects in vitro. There was a constant inhibitory effect at a PM<sub>10</sub> dilution of 1:1, possibly due to the particles themselves or to dilution of the broth by the added saline. These findings suggest that the association of air pollution with hospital admissions for exacerbations of COPD and for pneumonia is probably not mediated through direct promotion of bacterial growth. If particles alone are responsible for these effects, they are likely to be mediated by particles causing lung inflammation, thus encouraging penetration and growth of bacteria in the respiratory tract. Alternatively, gaseous pollutants may be responsible for the epidemiological findings, either directly or in conjunction with

particles. This interactive mechanism is supported by the association of ambient nitrogen dioxide levels with admissions for croup, and is analogous to the potentiation of the airway response to inhaled allergen by both nitrogen dioxide<sup>6</sup> and ozone.<sup>7</sup> Finally, it is possible that the particles have an effect on bacterial virulence and toxin production rather than growth. This possibility has not been tested here but warrants further study.

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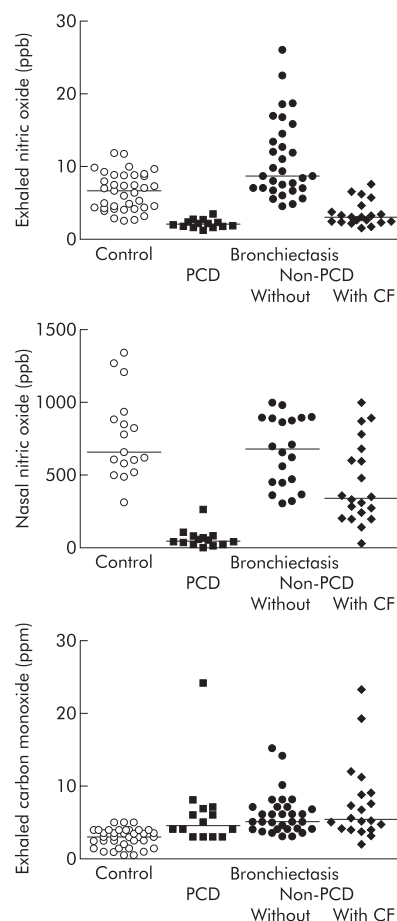
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**Figure 1** Exhaled NO, nasal NO and exhaled CO concentrations in normal subjects, patients with primary cell dyskinesia (PCD) with documented bronchiectasis, and patients with non-PCD bronchiectasis with and without CF. The Kruskal-Wallis test showed significant differences between mediator levels (p<0.0001).

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**CORRECTIONS**

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**PAPER BY HORVATH ET AL (THORAX 2003;58:68-72)**

In the paper entitled "Comparison of exhaled and nasal nitric oxide and exhaled carbon monoxide levels in bronchiectatic patients with and without primary ciliary dyskinesia" by I Horvath, S Loukides, T Wodehouse, et al published in the January 2003 issue of *Thorax* (2003;**58**:68-72), there was an error in the labelling of fig 1. The correct version of the figure is printed here. The publishers apologise for this error.

**PAPER BY BALDI ET AL (THORAX 2004;59:428-32)**

In the paper entitled "Prognostic significance of cyclooxygenase-2 (COX-2) and expression of cell cycle inhibitors p21 and p27 in human pleural malignant mesothelioma" by A Baldi, D Santini, F Vasaturo, et al published in the May 2004 issue of *Thorax* (2004;**59**:428-32) there was an error in the sentence beginning on line 14 of the left hand column on page 430. The sentence should have read "The median survival in patients with low p21 or p27 expression was shorter than in those with high p21 or p27 expression." The publishers apologise for this error.