LETTERS TO THE EDITOR

Montelukast and Churg-Strauss syndrome

I read with interest the case report by Tuggey and Hosker where Churg-Strauss syndrome was associated with the use of montelukast in an asthmatic patient in whom there was no recent exposure to oral corticosteroid.1 However, it is worth noting that the patient was using a high dose of inhaled fluticasone propionate (1.5 mg/day) via a large volume spacer prior to the introduction of montelukast. In this respect, a large volume spacer has been shown to double the systemic bioavailability of fluticasone propionate compared with a metered dose inhaler, in terms of its propensity for adrenal suppression.2 In a dose ranging study in asthmatic patients a comparison was made between inhaled fluticasone propionate via a 750 ml large volume spacer (Volumatic) and oral prednisolone.3 Regression analysis showed significant (p<0.05) dose-response relationships with both drugs for suppression of peripheral blood eosinophils (fig 1), in keeping with their systemic bioavailability. At the highest doses studied for prednisolone (20 mg/day) and fluticasone propionate (2 mg/day nominal dose) there was a 1.5-fold (95% CI 0.8 to 2.7) greater suppression of blood eosinophils with prednisolone than with fluticasone although, as indicated by the confidence interval (which included unity), this did not represent a significant difference between the drugs. Our data are in keeping with those of Toogood et al who also showed dose related suppression of blood eosinophils with inhaled budesonide and oral prednisolone.4

It is therefore evident that a high dose of inhaled fluticasone via a spacer, as reported in the case of Tuggey and Hosker, might have been suppressing the eosinophil count and therefore masking previously undiagnosed Churg-Strauss syndrome prior to starting montelukast. Indeed, it has been shown in a previous meta-analysis of 13 studies that, in terms of relative systemic bioactivity for



Figure 1 Dose response for suppression of peripheral blood eosinophils with inhaled fluticasone propionate (FP) given via large volume spacer and oral prednisolone (Pred) compared with placebo (PL). Significant dose related suppression of eosinophils was accompanied by other systemic bioactivity markers including serum osteocalcin and plasma cortisol. Doses of FP are shown ex-actuator, with 1.76 mg/day ex-actuator corresponding to 2.0 mg/day ex-valve (nominal dose).³ producing suppression of early morning plasma cortisol, 1 mg inhaled fluticasone is approximately equivalent to 10 mg oral prednisolone.⁵

The learning point here is that high doses of inhaled corticosteroid may exhibit sufficient systemic bioactivity as a class effect to suppress previously undiagnosed Churg-Strauss syndrome in the same way as low doses of oral corticosteroids. Furthermore, the revised package insert for fluticasone propionate (as Flovent, GlaxoWellcome Inc, Research Triangle Park, North Carolina, USA) now has an insertion in the section on precautions and adverse reactions stating that "in rare cases patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome. These events usually but not always have been associated with the reduction and/or withdrawal of oral corticosteroids following the introduction of fluticasone propionate. A causal relationship between fluticasone propionate and these underlying conditions has not been established". It is also difficult to understand, in the case described by Tuggey and Hosker, how the introduction of montelukast may have precipitated Churg-Strauss syndrome and a peripheral eosinophilia, given that studies have shown montelukast actually to suppress the peripheral blood eosinophil count.6

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AUTHORS' REPLY We are grateful to Professor Lipworth and Dr Wilson for their interest in our case report. Their main point seems to be that the dose of inhaled fluticasone via a Volumatic might have suppressed the eosinophil count and masked previously undiagnosed Churg-Strauss syndrome before starting treatment with montelukast. Several points can be made against this argument: (1) the blood eosinophil count was normal before the patient received any systemic or inhaled steroids (including fluticasone); (2) there was no dose reduction in inhaled fluticasone before the sudden development of systemic symptoms and profound peripheral eosinophilia; and (3) the features of vasculitis developed very rapidly with a close temporal relationship to the commencement of montelukast therapy.

Professor Lipworth and Dr Wilson also point out that montelukast is normally associated with suppression of the peripheral blood cosinophil count. However, this does not preclude the possibility of an eosinophilic vasculitis developing as a consequence of montelukast therapy.

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We read with interest the case report by Tuggey et al1 of a woman who developed Churg-Strauss syndrome associated with montelukast therapy in the absence of corticosteroid withdrawal. We have recently seen a similar case of a 65 year old man who was admitted acutely to hospital with malaise, general polymyalgia, and weakness associated with a dry cough. He was known to have nasal polyps and asthma for which his general practitioner had started treatment with montelukast 10 mg daily four months previously due to poor control, despite treatment with beclomethasone 400 µg daily. He was not on oral prednisolone and had not received any courses previously. Clinical examination revealed a fever of 37.8°C and generalised muscle tenderness. The rest of the examination was unremarkable. Blood tests revealed a raised white cell count of 15×10^9 /l of which the eosinophil count was 8×10^{9} /l. The chest radiograph showed left basal infiltration. Discontinuation of montelukast brought about temporary improvement, but he then deteriorated with severe myalgia and paraesthesia in his toes and soles of the feet. Chest examination revealed basal crepitations. The eosinophil count had increased to 13.8 × 10% and he had moderately positive P-ANCA (titre of 1/160) against myeloperoxidase. The clinical and biochemical tests were in keeping with the diagnosis of Churg-Strauss syndrome which we believe to be associated with montelukast therapy in this asthmatic patient in whom prednisolone had not been previously used. He was started on prednisolone 40 mg/day with prompt clinical improvement and his eosinophil count decreased to $1.5 \times 10^{\circ}/l$. We would therefore like to reinforce the message of Tuggey et al that clinicians need to be vigilant in patients developing systemic symptoms after starting treatment with a leukotriene antagonist.

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 Tuggey JM, Hosker HSR. Churg-Strauss syndrome associated with montelukast therapy. *Thorax* 2000;55:805–6.

Montelukast sodium in cystic fibrosis

Many older patients with cystic fibrosis (CF) describe a component of their condition as "asthma" despite a lack of objective bronchial lability. We undertook a therapeutic trial of the leukotriene antagonist montelukast sodium in one such patient and observed a marked improvement in symptoms and peak expiratory flow rate (PEFR). Subsequently

Table 1 Subjective and objective changes during observation and montelukast treatment periods

Measurement	Run in	Change with montelukast	p value
Exercise tolerance	5.6 (1.0 to 10.0)	1.4 (0.0 to 3.8)	0.008
FEV, (1)	2.4 (0.7 to 4.2)	0.1 (-0.2 to 0.6)	NS
PEFR morning (l/min)	390 (180 to 545)	22.8 (1.0 to 63.0)	0.003
Diurnal PEFR variability (1/min)	34.3 (8.3 to 101.0)	-10.3 (-44.0 to 0.0)	0.008
Day to day variability in morning PEFR (l/min)	24.0 (5.7 to 68.0)	-9.1 (-44.0 to 1.4)	0.008

Values are mean (95% confidence interval). The statistical analysis was made using Wilcoxon signed ranks test.

FEV₁ = forced expiratory volume in one second; PEFR = peak expiratory flow rate.

we performed an open label study in adult patients attending the Hull Adult Cystic Fibrosis Clinic.

Eleven patients (eight male) of mean (range) age 25.9 (16–44) years with stable CF and no pulmonary infective exacerbations for at least four weeks entered a two week observation period during which they recorded a daily symptom score on a scale of 1–10 and twice daily PEFR. Each patient was also asked to define a desirable and achievable individual outcome from the new therapy. After the observation period patients received montelukast sodium 10 mg nightly (Singulair; Merck Sharp & Dohme, Herts, UK) for a further two weeks.

All patients finished the study without adverse events. There was a significant augmentation in subjective symptoms score, with most pronounced improvement in exercise tolerance. Morning PEFR and PEFR variability were significantly improved (table 1). There was a positive correlation (Spearman's correlation coefficient $(r_s) = 0.834$) between the improvement in the day to day morning PEFR variability and percentage change in forced expiratory volume in one second (FEV,) following montelukast (p=0.01). Eight patients achieved their objective aims. Five of these patients had a positive immunological response to Aspergillus fumigatus and FEV1 of less than 65% of predicted.

Montelukast is a specific LTD₄ receptor antagonist which has been shown to reduce symptoms and improve lung function in several large randomised controlled trials in asthma. Leukotrienes have been found in the sputum of patients with CF.1-3 Cysteinyl leukotrienes were also shown to correlate with the severity of pulmonary disease in CF.4 Our study suggests that LTD₄ may have a clinically important role in the pathophysiology of CF. That the patients who benefited the most had positive Aspergillus serology provides further evidence as to a possible mechanism. Two thirds of adults with CF develop an immune response to Aspergillus, usually by the IgE, mast cell, eosinophil system.5 It has been hypothesised that injured respiratory epithelium in CF allows access of aeroallergens and the presence of Aspergillus fumigatus in the mucus may stimulate the immunological response by activating local immune cells including T helper 2 (Th2) cells.

In most patients with CF, however, as in our small study population, there is insufficient bronchial lability to meet the diagnostic criteria for asthma. These patients also do not meet the diagnostic criteria for allergic bronchopulmonary aspergillosis. We believe that colonisation of the CF airway by *Aspergillus* stimulates Th2 inflammation and thus leukotriene synthesis. Such a Th2 mediated immune response is also characteristic of asthma.⁷ The confirmation of this hypothesis in randomised studies of

leukotriene antagonists may have important implications for the treatment of this large subgroup of patients with CF.

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Declining incidence of episodes of asthma

With great interest we read the thought provoking contribution by Fleming *et al* on general practice consultation patterns for asthma.¹ We would like to offer some alternative viewpoints to those posed by the authors.

First of all, we wonder whether the choice of statistical techniques obscures the view of what happened to respiratory morbidity. Given the sudden rise in asthma episodes at the end of 1991 and the subsequent fall after 1994, a step function would be more appropriate. Besides, the amplitude within the years studied appears to increase during the period 1991–4. This can be modelled by adding an interaction term season*time to the model. Furthermore, given the nature of the data, Poisson regression would be preferable to linear regression techniques.

Secondly, it is unclear whether the trend is specific for asthma and bronchitis or is relevant for all respiratory morbidity or, even broader, applies to all morbidity. In the discussion paragraph the authors point out that the broader category of respiratory infections shows the same trend, but they fail to explore the possible implications of this finding. How do their data compare with hospital data over the years? How about general practice consultation patterns?

Thirdly, the distinction between new episodes and repeat consultations may be a difficult one, especially for chronic diseases like asthma. Subtle changes in registration routines may have affected the outcomes of this study.

Apart from practice nurses, we wonder whether the introduction of asthma facilitators² may be possible causes for the trends that are shown.

The authors suggest that the observed trends are due to fluctuations in prevalence. There is no evidence for this. The rise in consultations in the years 1991–4 could be due to a temporary increase in complaints in roughly the same number of prevalent asthma patients.

We invite the authors to explore these and other alternative hypotheses to explain or elucidate their findings.

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- Fleming DM, Sunderland R, Cross KW, et al. Declining incidence of episodes of asthma: a study of trends in new episodes presenting to general practitioners in the period 1989–98. *Thorax* 2000;55:657–61.
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AUTHORS' REPLY We note the comments of Drs Bernsen and van der Wouden. With regard to their first point, the graphs clearly show the changing incidence of new episodes of asthma and acute bronchitis. We isolated and modelled the trend by other methods which gave similar results. However, we acknowledge that the sudden rise in asthma during 1991 (though not evident for acute bronchitis) was not allowed for in our model, and we cannot explain this feature. It may be that the 1989 and 1990 values were, for some reason, unduly low as is supported by the graphs of annual new episode rates over the last 20 years displayed by the LAIA (fact sheet 2000/1 included as an insert in the same edition of Thorax) using the same data base. Whatever view is taken, the new episode rates for both asthma and bronchitis peaked in 1993/4, and rates at the end of the decade were marginally lower than at the beginning.

We referred in the text of the paper to a peaking of total respiratory infections in 1994, but we can only speculate as to the cause. Clearly, there is a strong relationship between acute respiratory infections and asthma attacks.

For asthma, the distinction between new episodes and ongoing consultations is difficult. However, for acute bronchitis there are comparatively few ongoing consultations and our findings are not obscured by this difficulty. While we cannot rule out the possibility of changes in the behaviour of doctors with regard to the allocation of episode type, we know that, individually, doctors are consistent in their recording behaviour.

We can confirm that nationally the number of hospital admissions per annum with a diagnosis of asthma peaked in 1993 for adults and in 1990 for children (Department of Health reports from finished consultant episodes), although caution is needed when interpreting these data since persons treated in accident and emergency departments (especially children) are not necessarily admitted.

The role of nurse facilitators and the relationship between asthma attacks and prevalence has been addressed in the paper. We agree with Drs Bernsen and van der Wouden that the explanation of the findings remains elusive.

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I was particularly interested to read the paper by Fleming and colleagues1 in which they described evidence for a peaking of the UK asthma epidemic in about 1993 and a decline in incidence thereafter. In speculating about possible causes they exclude improvements in pollution, exposure to allergens, or diet at the relevant time.

In 1994 my colleagues and I proposed that dietary change-specifically, the observed reductions in average intake of fresh fruit, vegetables and fish-had been responsible for making the populations of advanced countries more susceptible to allergy,² and that this was the explanation for the increases in the prevalence of asthma observed worldwide. Since then we have published three studies, all different but all showing evidence of a 3-7-fold increase in risk of wheezy illness in relation to the lowest intakes of foods containing antioxidant vitamins.³⁻⁵ A poor diet does indeed appear to be an important risk factor for asthma.

In the final sentence of our original paper we stated "... if the dietary hypothesis is correct, the favourable trend in eating habits between 1985 and 1991 may already be having a beneficial effect". The trend we referred to was a clear increase in intake of the three foods referred to above, as recorded in the annual national household food consumption and expenditure surveys. We had in mind a decrease in the prevalence of asthma in 10-12 year olds from about the mid 1990s

The paper by Fleming and colleagues seems to give some further indirect support to our hypothesis. My colleagues and I are currently investigating the influence of maternal diet during pregnancy on allergy in the child, including in these studies fatty acids as well as antioxidants. We believe that a dietary hypothesis for the actiology of asthma is worthy of very serious scientific investigation, not least because it points to an obvious and simple public heath strategy for prevention.

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- 1 Fleming DM, Sunderland R, Cross KW, et al. Declining incidence of episodes of asthma: a study of trends in new episodes presenting to
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AUTHORS' REPLY We note Professor Seaton's comments in relation to the potential benefits of an improved diet. We find it difficult to reconcile the very diffuse changes in the incidence of episodes of asthma and of acute bronchitis in all age groups peaking at roughly the same time with a diet based hypothesis. It is unlikely that dietary deterioration in the 1980s and improvement in the 1990s would have occurred simultaneously in all age groups and all regions of the country. The seasonal pattern of asthma attacks shows a relationship to pollens (a well recognised allergenic factor), but an even stronger relationship to viral respiratory infections, where the links with allergy are much weaker.

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The paper by Fleming et al1 reporting the decline in the incidence of asthma episodes raises some interesting questions. While they discuss possible reasons for the decline, we suggest the authors have underestimated the impact of trained asthma nurses.

There has been a threefold rise in whole time equivalent practice nurse numbers since 1988 following the new GP contract and the introduction of payment for asthma chronic disease management (CDM) clinics in the early 1990s. While we agree that historically the nurse's role did not include disease diagnosis, the level of asthma care they provide has increased.2 Nurse responsibility for CDM ranges from supporting the GP to the diagnosis and management of asthma; specialist training is recognised as important.

The 1992-4 peak in the mean weekly episodes, both by quarter and by region, may reflect increased nurse involvement at that time. Completion of a recognised asthma course has been shown to be associated with favourable patterns of structure, process, and clinical outcomes in general practice,3 as well as reductions in asthma symptoms and numbers of acute attacks where a specialist asthma nurse was employed.4 Evidence of improved management in hospitals5 by trained asthma nurses has also been reported. Recognised training, as well as the British Thoracic Society's asthma guidelines, have facilitated a more structured management approach and nurses now diagnose and treat new episodes of asthma and suggest appropriate treatment, leading to the development of asthma management protocols and their implementation in primary and secondary care.6

We propose that the decrease in the incidence of asthma episodes reported by Fleming et al may reflect better management of asthma by GPs as well as increased and improved asthma management by nurses. Although the introduction of specialist nurses would not have had a significant effect on numbers of consultations for new episodes of asthma, improved management is likely to have substantially reduced numbers of asthma exacerbations. We therefore suggest that the impact of nurses' specialist training on reducing episodes of asthma is greater than is currently recognised.

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- 1 Fleming DM, Sunderland R, Cross KW, et al. Declining incidence of episodes of asthma: a study of trends in new episodes presenting to general practitioners in the period 1989-98 Thorax 2000:55:657-61.
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AUTHORS' REPLY The introduction of trained nurse based management programmes for asthma has undoubtedly been good for asthmatic patients. The contribution made to the changing incidence of new episodes of asthma is difficult to estimate but, as the writers recognise, it is likely to be small. We suspect the main factors associated with the decline are linked with those associated with the increase in the 1980s and with those factors associated with the decline in acute bronchitis-a condition much more frequent than asthma and not generally associated with nurse based care.

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CORRECTION

In the reply by Becklake and Kauffmann to the letter by Morice et al entitled "Gender differences in airway behaviour" which appears on page 629 of the July 2000 issue of Thorax, an error occurred in the second paragraph. This paragraph should have read: "We thank them for their references. Of particular interest to us was the observation that the cough was higher in premenopausal than in postmenopausal women, an observation in line with our own findings". The authors apologise for this error.