LETTERS TO THE EDITOR

Inhaled fluticasone

I read with interest the article on the effects of inhaled fluticasone propionate and oral prednisolone on markers of airway inflammation in asthma recently published in *Thorax* by Meijer *et al*.[1] In particular, it was interesting to read that the magnitude of reduction in airway hyperresponsiveness after fluticasone was more pronounced for adenosine 5'-monophosphate (AMP) than for methacholine. Ketchell *et al*[2] have recently reported that sensitive prediction of the AMP response to inhaled corticosteroids is already apparent as early as 48 hours. Taken together, these findings further support the use of adenosine challenge as a sensitive and convenient non-invasive test of asthmatic inflammation for potential use in diagnosis, monitoring disease activity, and evaluating treatment efficacy.[3]

In asthma the ability of this test to discriminate the changes in airway reactivity with anti-inflammatory treatment better than histamine or methacholine has also been validated with inhaled budesonide and the new corticosteroid ciclesonide.[4 5] In contrast, in patients with chronic obstructive pulmonary disease (COPD) adenosine appears to be as insensitive as methacholine in detecting changes in airway reactivity after treatment with high dose inhaled steroids.[6] This diversity is of diagnostic interest as it may indicate an additional way by which adenosine challenge may be useful in differentiating asthma from "true" COPD .

In contrast to the work by Meijer *et al*,[1] Taylor *et al*[6] have shown that adenosine challenge offers substantial advantages (especially in terms of sensitivity) over that of other non-invasive tests, including induced sputum. The premise for this is that adenosine elicits bronchoconstriction by stimulating the release of bronchoconstrictor mediators from cells/nerves within the airway, and thus may be sensitive to the underlying inflammatory state of the airway. The capacity of adenosine to elicit a much greater bronchoconstrictor response and mediator release from mast cells in atopic subjects than in non-atopic subjects[7 8] indicates that atopic status is an important determinant of the response.

Current GINA guidelines recommend careful monitoring of asthma symptoms and pulmonary function and recognise the need for "developing non-invasive test(s) of airway inflammation for use in diagnosis, monitoring the disorder's activity, and evaluating treatments". Despite the emerging view that adenosine bronchoprovocation may be useful for monitoring disease severity, it is important that well planned and well conducted large clinical trials be performed to confirm that information gained from this test will lead to improved patient management.

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1 Meijer RJ, Kerstjens HAM, Arends LR, *et al*. Effect of inhaled fluticasone and oral prednisolone on clinical and inflammatory parameters in patients with asthma. *Thorax* 1999;**54**:894–9.
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AUTHORS' REPLY We have read the letter by Dr Polosa with great interest. We support his view that adenosine challenge appears to be a sensitive non-invasive test of asthmatic inflammation with potential use in diagnosis, monitoring disease activity, and evaluating treatment efficacy in asthma. We have previously shown the latter in a head to head comparison of treatment with 250 µg fluticasone and 50 µg salmeterol twice daily for six weeks.[1] In that study the mean (SD) improvement in PC_{20} methacholine, expressed in doubling concentrations (DC), was 2.1 (0.5) DC for fluticasone and 1.5 (0.5) DC for salmeterol (fig 1). Therapeutic effects on PC_{20} AMP were greater, with an improvement of 4.5 (0.9) DC for fluticasone and 2.9 (0.9) DC for salmeterol. Usually bronchial hyperresponsiveness is measured during the treatment,[2–4] in our study twice daily.

We have measured treatment efficacy, not only during treatment but also 12 hours after stopping the drugs, which allowed the β agonist bronchodilator effect to be removed (unpublished data). At that time, however, a significant improvement in forced expiratory volume in one second (FEV_1) was still seen in both regimens. The improvements in PC_{20} methacholine were similar to those seen during treatment for both fluticasone and salmeterol. In contrast, the improvement in PC_{20} AMP with salmeterol had decreased to 2.2 (0.9) DC, while for fluticasone it remained 5.0 (1.1) DC.

Treatment with fluticasone produced a significantly larger bronchoprotective effect to AMP than salmeterol, whereas both drugs had a comparable effect to conventional parameters—that is, PC_{20} methacholine and FEV_1—12 hours after stopping treatment. Given these observations, the results of our study would have led to the conclusion that salmeterol produces effective asthma control after six weeks of treatment, even when given as monotherapy. This would be in accordance with the interantional guidelines[5] which state that efficient asthma therapy should be related to symptoms and airway obstruction. Yet, a considerable treatment difference was detectable in favour of fluticasone when the effects were tested with AMP.

AMP is more specific in assessing changes in different components of airway wall inflammation than methacholine. Improvement in PC_{20} AMP might therefore be a better predictor of efficient anti-asthma therapy

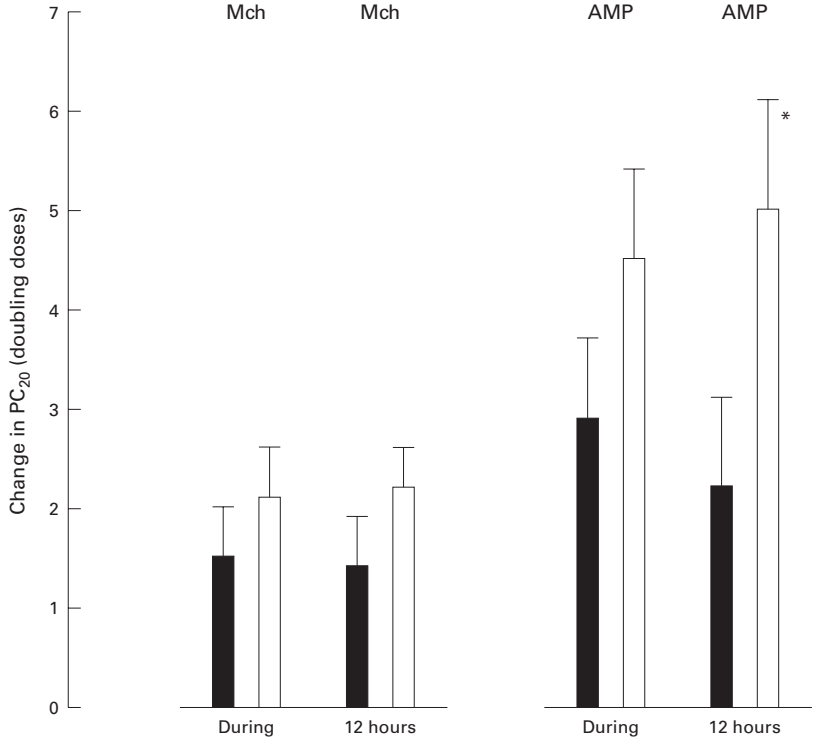

*Figure 1 Improvement in PC_{20} methacholine and AMP with salmeterol (solid bars) and fluticasone (open bars) both during active treatment and 12 hours after stopping the drugs. *p<0.05, fluticasone versus salmeterol.*

than changes in the conventionally used parameters, as advised in current guidelines.

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1 Weersink EJM, Douma WR, Postma DS, *et al.* Fluticasone propionate, salmeterol xinafoate and their combination: treatment of asthmatics with nocturnal airway obstruction. *Am J Respir Crit Care Med* 19976;**155**:1241–6.
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Gender differences in airway behaviour

We were surprised to read in the exhaustive and, some might say, exhausting review of gender differences in airway behaviour by Becklake and Kauffmann[1] that the most common respiratory symptom—namely, cough—deserved only a single sentence and was then dismissed. In fact, the most dramatic gender difference in airway sensitivity is seen with the cough reflex. We studied 163 consecutive, healthy, non-smoking volunteers (90 women, mean age 32 years) with an inhalation cough challenge of five one-second inhalations of 10% citric acid delivered from a Mefar dosimeter. Women coughed over 50% more than men (mean total cough score 19.1 versus 12.0, $p<0.001$). This confirms several other observations in the literature with both acid[2] and capsaicin[3 4] inhalation.

It could be argued that the smaller airways of women allow for greater deposition of the protussive agent, but this cannot explain the twofold difference between the sexes in the incidence of ACE inhibitor-induced cough.[5]

Unlike many of the observations quoted in their review, this gender difference in the cough reflex sensitivity has important clinical implications. In the Hull Cough Clinic we see twice as many women as men (64 versus 33 completed episodes last year). Other reported series have similar experiences.[6 7]

The fact that a review of 20 pages and 211 references did not comment on these observations is alarming. Surely the objective is to sift the literature, or is the policy now to publish gargantuan articles of the kind seen earlier last year on cytokines in asthma[8] in order to enhance the journal's impact factor?

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1 Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human life span. *Thorax* 1999;**54**:1119–38.
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8 Chung KF, Barnes PJ. Cytokines in asthma. *Thorax* 1999;**54**:825–57.

AUTHORS' REPLY In our review[1] we used the term "airway behaviour" to refer to the dimensions, structure, and function of the airways and we examined the extent to which these accounted for the gender differences in obstructive airway disease. As Professor Morice and colleagues point out, cough as a variant of asthma should have been included, particularly since, as two of their references suggest,[2 3] the lower threshold for cough in response to inhaling a tussive agent in women does not appear to be accounted for by methodological differences resulting from larger doses of the agent being delivered to their airways because of their smaller airway size.

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.[3] Our review would have predicted the opposite, based on the higher rates of asthma incidence in women during their reproductive years than in men, with reversal of these differences after the menopause. We attributed these changes to the hormonal effects on the airways of women. This paradox is one that invites further study.

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1 Becklake MR, Kauffmann, F. Gender differences in airway behaviour over the human life span. *Thorax* 1999;**54**:1119–38.
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3 Fujimura M, Kasahara K, Kamio Y, *et al.* Female gender as a determinant of cough threshold to inhaled capsaicin. *Eur Respir J* 1996;**9**:1624–6.

EDITORS' REPLY The editors appreciate the time that Professor Morice has taken to read both of these articles,[1 2] despite their length.

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Executive Editors

1 Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human life span. *Thorax* 1999;**54**:1119–38.
2 Chung KF, Barnes PJ. Cytokines in asthma. *Thorax* 1999;**54**:825–57.

Cell and cytokine markers in COPD

We read with interest the paper by Dr Wedzicha and colleagues on cell and cytokine measurements in exacerbations of COPD.[1] We feel there are two factors which are worthy of comment. The authors described their patients as being predominantly those with chronic bronchitis. They presented with an exacerbation that consisted of the cardinal features described by Anthonisen and colleagues—namely, combinations of increased breathlessness, increased sputum volume, and increased sputum purulence.[2] In view of the fact that increased sputum purulence is a feature of exacerbations, we are surprised at the lack of increase in neutrophils seen in the exacerbations described in the paper. Even if half the patients did not have purulent sputum, we would have expected to have seen an overall increase in the number of neutrophils in the samples obtained.

In addition, the authors used sputum induction when most of the patients must have presented with spontaneous sputum production in order to have increased sputum volume or sputum purulence. Surely the use of sputum induction in such patients would lead only to dilution of the bronchial secretion obtained, and this may explain some of the negative neutrophil results. Indeed, in our own studies of approximately 140 exacerbations in a similar setting, two thirds of them were purulent in nature and were associated with increases in cytokines in the spontaneously expectorated sample. The purulent samples were associated with an increase in myeloperoxidase concentration and in neutrophil numbers seen on Gram staining. We would have expected the same findings in the paper by Wedzicha and colleagues if the exacerbations were similar.

We consider that it may be appropriate to stratify exacerbations, particularly when trying to assess the role of intervention treatments and the nature of the cytokines present.

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1 Bhowmik A, Seemungal TAR, Sapsford RJ, *et al.* Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. *Thorax* 2000;**55**:114–20.
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AUTHORS' REPLY We appreciate the comments of Professor Stockley and Dr Hill that neutrophils should increase during COPD exacerbations and their hypothesis that this was not found in our study because of a possible dilutional effect of the induced sputum technique on lower airway secretions.

Eleven of the 37 sampled exacerbations (29.7%) in our study[1] were associated with purulent sputum, whereas 24 (64.7%) were associated with increased sputum volume and 10 patients had no sputum production at exacerbation. This indicates that about 33% of COPD exacerbations are not associated with sputum production.

We have shown previously that the number of viable cells was greater in induced sputum than in spontaneous sputum (65% versus

41.2%, p = 0.001).[2] In the latter study we found no difference in total or differential cell counts between spontaneous and induced sputum. There is therefore no evidence for a diluting effect of induced sputum relative to spontaneous sputum in patients with COPD. Rather, the use of the induced sputum technique allowed us to obtain standardised samples from all our patients at exacerbation, whether or not they were sputum producers.

In our study there was a tendency for patients with purulent sputum to have a greater increase in neutrophils at exacerbation (rho = 0.416, p = 0.068) but there was clearly no significant overall change in neutrophils (p = 0.771). Furthermore, there was great variability in the neutrophil counts at COPD exacerbation (IQR 1.18–4.67 × 10^6 cells/g sputum). We sampled our patients early in the course of the exacerbation (median of three days after onset), so a later rise in neutrophil count may not have been detected in our study.

Examination of induced sputum has been used for some years as a diagnostic technique to investigate lower airway inflammation.[3 4] In asthma this technique is now well established as a relatively safe, non-invasive, repeatable, and valid method[5] and we have shown that it is useful and safe in patients with COPD.[2] It is unlikely that a dilutional effect of induced sputum is important in patients with COPD. The variability in neutrophil counts may reflect heterogeneity in the exacerbations sampled as well as the timing of sampling in the course of an exacerbation.

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Diagnosis and assessment of DPLD

In this excellent report[1] the transfer factor (TL) in untreated cryptogenic fibrosing alveolitis is reported as reflecting the extent of fibrosis; it is noted that KCO (TL/VA) does not. Given more space, the authors might have added that KCO can mislead by being normal or increased when alveolar volume is restricted. This is because KCO is based on a proportional model that does not make valid allowance for alveolar volume. An alternative linear model is available and should be used instead.[2]

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1 British Thoracic Society. The diagnosis, assessment and treatment of diffuse parenchymal lung disease in adults. *Thorax* 1999;**54**(Suppl 1):S1–30.
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BOOK REVIEW

Lung Development. Claude Gaultier, Jacques R Bourbon, Martin Post eds. (Pp 451; $89.50). USA: Oxford University Press, 1999. ISBN 0 19 511278-4

This book represents the ninth publication in the Clinical Physiology series published for the American Physiological Society and provides a comprehensive review of the multiple facets of lung growth and development in both health and disease. Particular emphasis has been placed on recent advances at the cellular and molecular level with respect to the complex series of controlled interactions involving genetic, hormonal, and cell-cell interactions that are required for lung development. Each chapter is extensively referenced and presents a succinct review of selected topics relevant to lung development by experts in the field.

Inevitably with a multi-author book such as this, there is considerable variability in presentation style with some chapters more accessible to the non-specialist than others. The inclusion of a glossary would have been beneficial in view of the increasing use of abbreviations in this field. Nevertheless, most of the authors have provided an excellent review of their topic and have clearly indicated, not only the current state of knowledge and the clinical significance of recent research findings, but what still needs to be investigated.

The first part of the book is devoted to lung branching morphogenesis, development of the lung elastic matrix and the importance of elastin in lung structure and function, differentiation of airway epithelial cells, and gene expression in alveolar development. Lung development and angiogenesis, including sections which emphasise the importance of postnatal microvascular maturation and the potential impact of exogenous risk factors such as impaired nutrition and glucocorticoid therapy on lung development and alveolisation, are the subject of an important chapter. Other authors have reviewed the developmental aspects of the pulmonary vasculature and circulation, cellular host defence mechanisms, lung epithelial ion transport (including a fascinating overview of its dysfunction in neonatal lung diseases), cell growth and tissue repair, and the role of bioactive peptides.

The last part of the book concentrates on the pathophysiology of neonatal and paediatric pulmonary disorders including discussions of new treatments for surfactant deficiency, the role of nutrition in lung development, the development of lung hypoplasia, and the effects of oxygen toxicity. The final chapter is devoted to a review of current knowledge regarding growth and development of the lung following lung transplantation, including the fact that lung growth can continue when an immature lung is transplanted into either an immature or adult recipient.

The strength of this publication lies in the eclectic mix of topics that are not always covered in books on lung development, and it provides a succinct summary of recent advances and new research in the field. There is now increased awareness that adverse influences on lung development during prenatal and early postnatal life may have lifelong effects. This book should therefore be of potential interest, not only to paediatric pulmonologists, neonatologists, ICU physicians and obstetricians, but also to chest phyisicians and surgeons dealing with older patients.—JS

NOTICES

COPD: New Developments and Therapeutic Options

A course on "COPD: New Developments and Therapeutic Options" organised by Professors Peter Barnes and Neil Pride will be held on 26–28 September 2000 at Imperial College School of Medicine at the National Heart & Lung Institute in collaboration with the Royal Brompton Hospital, Dovehouse Street, London SW3 6LY. Enquiries to: Postgraduate Education Centre, National Heart & Lung Institute, Imperial College School of Medicine, Dovehouse Street, London SW3 6LY, UK. Telephone: 020 7351 8172. Fax: 020 7351 8246. Email: shortcourses.nhli@ic.ac.uk

Pharmacology of Asthma

A course on "Pharmacology of Asthma" organised by Professor Peter Barnes will be held on 20–23 November 2000 at Imperial College School of Medicine at the National Heart & Lung Institute in collaboration with the Royal Brompton Hospital, Dovehouse Street, London SW3 6LY. Enquiries to: Postgraduate Education Centre, National Heart & Lung Institute, Imperial College School of Medicine, Dovehouse Street, London SW3 6LY, UK. Telephone: 020 7351 8172. Fax: 020 7351 8246. Email: shortcourses.nhli@ic.ac.uk