

LETTERS TO THE EDITOR

Inhaled corticosteroids in COPD

The importance of presenting absolute cell numbers when counting cells in biological samples is illustrated by the potentially misleading interpretation of data in the paper by Marco Confalonieri and colleagues.¹ The authors concluded that, in addition to reduced sputum neutrophilia, the number of sputum macrophages increased significantly following treatment with inhaled beclomethasone dipropionate in patients with COPD. However, the observed increase in the proportion of sputum macrophages from 19.6% before treatment to 35.8% following treatment is entirely attributable to the reduced number of sputum neutrophils. From the data presented in the paper, the absolute numbers of different cells in the sputum can be calculated (table 1), revealing that the absolute sputum macrophage count was essentially unchanged following treatment. It is important that the absolute numbers of cells, and not simply their proportions, are presented when measuring differential cell counts in sputum or any other biological sample.

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- 1 Confalonieri M, Mainardi E, Della Porta R, et al. Inhaled corticosteroids reduce neutrophilic bronchial inflammation in patients with chronic obstructive pulmonary disease. *Thorax* 1998;53:583-5.

AUTHORS' REPLY We would like to thank Dr Hart for his useful comment. We agree that it is important that the absolute numbers of cells are presented when measuring differential cell count in a biological sample. In fact, fig 1 of our paper illustrated the reduction of sputum neutrophils as absolute cell numbers. We thank Dr Hart for the table where the data have been presented as mean absolute cell counts, showing no difference in the absolute number of macrophages after treatment and confirming that the increase in the proportion of sputum macrophages following treatment is attributable to the reduced number of sputum neutrophils. However, the presentation of data as absolute cell numbers

Table 1 Mean absolute cell counts (cells/ml $\times 10^6$) in induced sputum before and after treatment with inhaled beclomethasone dipropionate (1500 μ g/day for eight weeks) in patients with COPD (numbers calculated from table 2 of Confalonieri et al)

Cell type	Before treatment	After treatment
Total	240	139
Neutrophils	176	72.3
Eosinophils	8.4	4.3
Lymphocytes	9.1	5.4
Macrophages	47.0	49.8
Epithelial cells	2.6	3.2

did not change the major conclusion of our article that a two month course of treatment with high dose inhaled beclomethasone dipropionate significantly reduces the sputum neutrophil cell count in patients with clinically stable, smoking related COPD.

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I was very interested to read the article by Confalonieri et al published recently in *Thorax*.¹ It is interesting that the sputum neutrophil count was reduced after two months of treatment with inhaled beclomethasone with no parallel improvement in spirometric parameters and blood gas data. My group has recently completed a study on the effects of inhaled fluticasone (500 mg twice daily) via the Accuhaler device on 24 patients with steady state bronchiectasis in a double blind, placebo controlled manner.² After eight weeks of treatment we also found a significant reduction ($p < 0.05$) in the sputum neutrophil density and the levels of interleukin (IL)-1, IL-8, and leukotriene B₄, but no parallel changes in Sa_o2 or lung function indices. There is little doubt that tracheobronchial inflammation occurs in bronchiectasis, COPD and asthma, and plays an important role in the pathogenesis of these diseases.³ Although inhaled steroid therapy is undoubtedly efficacious in asthma, its use in COPD has not shown any clinical benefits from the trials reported to date.⁴ Similarly, little is known of the efficacy of inhaled steroid therapy in bronchiectasis despite its anti-inflammatory effects.⁵ It is possible that the clinical benefits of inhaled steroid therapy in COPD and bronchiectasis will only be shown by long term studies in large numbers of subjects in view of the more "fixed" damage in these two conditions. The similarity of the findings of Confalonieri et al and my group is exciting and should lead to further research in the use of anti-inflammatory treatment in COPD and bronchiectasis.

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- 1 Confalonieri M, Mainardi E, Della Porta R, et al. Inhaled corticosteroids reduce neutrophilic bronchial inflammation in patients with chronic obstructive pulmonary disease. *Thorax* 1998;53:583-5.
- 2 Tsang KWT, Ho PL, Lam WK, et al. Fluticasone reduces sputum inflammatory indices in bronchiectasis. *Am J Respir Crit Care Med* 1998 (in press).
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- 8 Elborn JS, Johnston B, Allen F, et al. Inhaled steroids in patients with bronchiectasis. *Respir Med* 1992;86:121-4.

AUTHORS' REPLY We would like to thank Dr Tsang for his interesting comment. We appreciate his finding of a similar effect of inhaled corticosteroids both on cells and inflammatory mediators in a group of patients with bronchiectasis without any parallel changes in Sa_o2 or lung function indices. We agree with Dr Tsang on the necessity of long term trials with a sufficient number of subjects to show any beneficial effect of inhaled corticosteroids on inflammatory airway diseases other than asthma. In fact, as mentioned in our paper, Stanescu et al¹ showed that airway obstruction as well as accelerated decline in lung function are associated with increased numbers of neutrophils in the sputum. This suggests that a reduction in airway inflammation (neutrophils) might influence the decline in lung function only over a long period of time. Further research on the effect of corticosteroids on airway inflammation could also clarify the similarities and differences in distinct airway diseases with fixed obstruction.

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- 1 Stanescu D, Sanna A, Veriter C, et al. Airway obstruction, chronic expectoration, and rapid decline of FEV₁ in smokers are associated with increased levels of sputum neutrophils. *Thorax* 1996;51:267-71.

We read with interest the effect of inhaled corticosteroids in reducing the neutrophil count in patients with chronic obstructive pulmonary disease (COPD).¹ This highlights the value of sputum induction as a tool in the study of airway inflammation in a diverse range of airway diseases. The authors have concentrated on the effect of beclomethasone dipropionate on neutrophilic inflammation, but we note that in both the control and treatment groups the mean sputum eosinophil count was outside the normal range of our laboratory and others (sputum eosinophils 0-2%). The authors did not comment on whether this eosinophilia was significantly different from the normal subjects they studied. Do they have any explanation for this apparently high sputum eosinophil count? Did any of the subjects have a previous history of asthma?

We have recently described a population of patients with fixed airway obstruction and a marked sputum eosinophilia,² and there is some evidence that such patients respond particularly well to corticosteroids.³ Although there was no overall change in the sputum eosinophil count, we wonder whether some of the patients reported by Confalonieri and co-workers fit into this category and whether the effect of beclomethasone dipropionate was different in these patients.

Until we clearly establish whether sputum evidence of an eosinophilic bronchitis predicts a response to corticosteroids and determine how common it is in patients with COPD,

interpretation of trials of corticosteroid therapy in COPD will remain difficult.

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- 2 Pavord ID, Pizzichini MMM, Pizzichini E, et al. Eosinophilic bronchitis with fixed airflow obstruction. *Am J Respir Crit Care Med*. 1998;157:A624.
- 3 Chanez P, Vignola AM, O'Shaughnessy T, et al. Corticosteroid reversibility in COPD is related to features of asthma. *Am J Respir Crit Care Med* 1997;155:1529-34.

AUTHORS' REPLY We would like to thank Drs Brightling and Pavord for their interesting comments. As stated in our article, we enrolled only patients with stable COPD, diagnosed according to a recent European Consensus Conference, and none of them had a previous history of asthma. The percentage of sputum eosinophils in the global COPD study population (34 subjects; mean (SE) 2.7 (0.7)) was not significantly different from that of the healthy subjects (16 subjects; mean (SE) 0.98 (0.2)) by the Mann-Whitney U test ($p = 0.08$). Indeed, if we consider the treated and control groups separately, a significant increase in the proportion of sputum eosinophils is seen in both COPD groups compared with the healthy subjects ($p = 0.02$).

We suggest that the sputum eosinophilia in our patients with smoking related COPD could be explained by their current smoking habit. In fact, recent experimental and clinical data seem to support the hypothesis that exposure to cigarette smoke can induce eosinophilic airway inflammation both in animals and humans.^{1,2}

Although there was no overall change in the sputum eosinophil count after two months of treatment with beclomethasone dipropionate, we have analysed separately the seven subjects with eosinophils of >2% in the treated group. In these subjects, not only neutrophils but also sputum eosinophils decreased (from a mean (SE) of 4.5 (1.2)% to 2.0 (0.4)%) after two months of treatment, although the difference did not reach statistical significance ($p = 0.06$). Moreover, these subjects did not show a significant increase in FEV₁ after two months of treatment with inhaled corticosteroids (from 60.1 (5.6)% to 64.9 (4.1)% predicted).

We also analysed separately the subgroup of treated patients with COPD with sputum eosinophils <2% in order to verify the changes in sputum neutrophils after two months of treatment with inhaled beclomethasone dipropionate. These patients showed a significant reduction in both total cell and neutrophil counts after treatment. In fact, the mean difference from baseline of the total cell count (cells/ml $\times 10^7$) was 191 (51.8) (95% CI 68.5 to 314), and the mean difference from baseline of the neutrophils was 27 (1.7) (95% CI 22.9 to 31.1).

We are grateful to the authors of this letter for their careful consideration that provides a good insight into our paper. Nevertheless, the results of our study do not change since a reduction in sputum neutrophils also occurred after treatment with high dose inhaled beclomethasone dipropionate in the sub-

group of patients with COPD without sputum eosinophilia.

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- 1 Siafakas NM, Vermeire P, Pride NB, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1995;8:1398-420.
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- 3 Pesci A, Balbi B, Majori M, et al. Inflammatory cells and mediators in bronchial lavage of patients with chronic obstructive pulmonary disease. *Eur Respir J* 1998;12:380-6.

Coal mining and COPD

Professors Coggon and Newman Taylor¹ correctly state that it is my opinion that the adverse effects of cigarette smoking vary markedly with only around 15-20% of smokers being affected, while the effects of coal mine dust are distributed much more evenly. They find my arguments unconvincing because Fletcher and coworkers' "seminal longitudinal study into the natural history of COPD found that the presence of chronic bronchitis had no independent influence on the decline of the FEV₁".²

I yield to none in my admiration for the work of Fletcher and his coworkers, but it needs to be pointed out that the men they selected were "aged 30 to 59 years since younger men were thought unlikely to have developed airflow obstruction by this age". In this connection their assumption was incorrect. While non-smoking men aged 23-35 show either an extended plateau or a period of slow continued growth, at about the age of 35 they start to lose FEV₁ due to ageing. In contrast, male smokers show a plateau or a minimal increase between the ages of 23 and 30 but a decline in the FEV₁ at the start of the third decade, with the rate being slightly greater than that for non-smokers over the age of 35. In addition, the increase in the FEV₁ between the ages of 20 and 30 in smokers is substantially less than that noted in non-smokers.³ The second or rapid progressive decline in the FEV₁ of smokers occurs later, around the age of 40-45 years. The early decline in young persons appears completely reversible and cannot be attributed to emphysema. Moreover, it is known that many young smokers have what is termed a "smoker's cough" with the production of sputum. In this connection Coggon and Newman Taylor quote two papers, both of which claim to show the early onset of a reduction in the FEV₁ in coal miners—that is to say, in the first 10 years.^{4,5} None of these early changes would have been apparent in the studies of Fletcher and colleagues.

Clearly some thought must be given to explaining the early decline in the FEV₁ that occurs in the 20-30 age group, be they non-miners who smoke or miners exposed to either dust or cigarette smoke, or both. Emphysema cannot account for this reduction and some other mechanism must be sought. It will not do to torture the data until they confess so that some other statistical explanation becomes apparent. Perhaps Coggon and Newman Taylor would also explain

why older smokers with established chronic airflow limitation show a mean improvement of around 50 ml in the FEV₁ after they stop smoking.⁶ Presumably the emphysema does not improve but we know that their smoker's cough and sputum usually do—that is, their bronchitis disappears.

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- 1 Coggon D, Newman Taylor A. Coal mining and chronic obstructive pulmonary disease: a review of the evidence. *Thorax* 1998;53:398-407.
- 2 Fletcher C, Peto R, Tinker C, et al. *The natural history of chronic bronchitis and emphysema*. Oxford: Oxford University Press, 1976.
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AUTHORS' REPLY We remain unconvinced that bronchitis can explain other than at most a small part of the loss of FEV₁ associated with exposure to coal mine dust. If bronchitis had a major influence on airflow, we would have expected it to be apparent in Fletcher's study.² Professor Morgan refers to an early decline in FEV₁ in young smokers that is reversible and therefore cannot be attributable to emphysema, and also to a mean improvement in FEV₁ of 50 ml among older smokers with established chronic airflow obstruction who stop smoking. However, he does not indicate that these effects are restricted to, or even more prominent in, subjects with symptoms of bronchitis. Moreover, the improvement of 50 ml is small in comparison with the deficits of FEV₁ associated with coal mine dust, which average more than 225 ml in miners with heavy cumulative exposure.³ These deficits persist after cessation of exposure and are of similar magnitude in miners with and without symptoms of bronchitis.⁴

For these reasons and the others set out in our review, we stand by our conclusion that there is strong evidence that coal mine dust can have a critical influence on health in an important number of people.

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