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 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.

Table 1 Mean absolute cell counts (cells/ml × 10^4) in induced sputum before and after treatment with inhaled beclomethasone dipropionate (1500 µg/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

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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 Sao_2 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 4] 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.[5–7] Similarly, little is known of the efficacy of inhaled steroid therapy in bronchiectasis despite its anti-inflammatory effects.[2 8] 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).
3 Lapa de Silva JR, Jones JAH, Cole PJ, *et al.* The immunological component of cellular inflammatory infiltrate in bronchiectasis. *Thorax* 1989;**44**:668–73.
4 Saetta M. Airway pathology of COPD compared with asthma. *Eur Respir Rev* 1997;7:29–33.
5 Bourbeau J, Rouleau MY, Boucher S. Randomised controlled trial of inhaled corticosteroids in patients with chronic obstructive pulmonary disease. *Thorax* 1998;**53**:477–82.
6 Van Schayck CP, Van Grunsven PM, Dekhuijzen PN. Do patients with COPD benefit from treatment with inhaled corticosteroids (editorial)? *Eur Respir J* 1996;**9**:1969–70.
7 Renkema TEJ, Schouten JP, Koeter GH, *et al.* Effects of long term treatment with corticosteroids in COPD. *Chest* 1996;**109**:1156–62.
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 Sao_2 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 al*[1] 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 FEV_1 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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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 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'Shaugnessy 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.[1] 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.[2 3]

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 FEV_1 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 $\times 10^4$) 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 subgroup 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.
2 Matsumoto K, Aizawa H, Inoue H, *et al.* Eosinophilic airway inflammation induced by repeated exposure to cigarette smoke. *Eur Respir J* 1998;**12**:387–94.
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 Taylor[1] 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 FEV_1."[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 FEV_1 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 FEV_1 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 FEV_1 between the ages of 20 and 30 in smokers is substantially less than that noted in non-smokers.[3–5] The second or rapid progressive decline in the FEV_1 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 FEV_1 in coal miners—that is to say, in the first 10 years.[6 7] 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 FEV_1 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 FEV_1 after they stop smoking.[8] 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.
3 Tager IB, Segal MR, Speizer FE, *et al.* The natural history of forced expiratory volumes. Effect of cigarette smoking and respiratory symptoms. *Am Rev Respir Dis* 1988;**138**:837–49.
4 Camilli AE, Burrows B, Knudson RJ, *et al.* Longitudinal changes in forced expiratory volume in one second. *Am Rev Respir Dis* 1987;**135**: 794–9.
5 Jaakkola MS, Ernst P, Jaakkola JJ, *et al.* Effect of cigarette smoking on evolution of ventilatory lung function in young adults: an eight year longitudinal study. *Thorax* 1991;**46**:907–13.
6 Seixas NS, Robins TG, Attfield MD, *et al.* Logitudinal and cross sectional analyses of exposure to coal mine dust and pulmonary function in new miners. *Br J Ind Med* 1993;**50**:929–37.
7 Carta P, Aru G, Barbieri MT, *et al.* Dust exposure, respiratory symptoms, and longitudinal decline of lung function in young coal miners. *Occup Environ Med* 1996;**53**:312–9.
8 Anthonisen NR, Connett JE, Kiley JP, *et al.* Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV_1. The Lung Health Study. *JAMA* 1994;**272**:1497–505.

AUTHORS' REPLY We remain unconvinced that bronchitis can explain other than at most a small part of the loss of FEV_1 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.[1] Professor Morgan refers to an early decline in FEV_1 in young smokers that is reversible and therefore cannot be attributable to emphysema, and also to a mean improvement in FEV_1 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 FEV_1 associated with coal mine dust, which average more than 225 ml in miners with heavy cumulative exposure.[2] These deficits persist after cessation of exposure and are of similar magnitude in miners with and without symptoms of bronchitis.[2]

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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1 Fletcher C, Peto R, Tinker C, *et al. The natural history of chronic bronchitis and emphysema.* Oxford: Oxford University Press, 1976.

2 Soutar CA, Hurley JF. Relation between dust exposure and lung function in miners and ex-miners. *Br J Ind Med* 1986;**43**:307–20.

BOOK REVIEW

Clinical and Biological Basis of Lung Cancer Prevention. Martinet Y, Hirsch FR, Martinet N, Vignaud J-M, Mulshine JL, eds. (Pp 322). Switzerland: Birkhäuser Verlag, 1998. ISBN 3-7643-5778-9.

This is a comprehensive and technically detailed book which will, I think, be of value to laboratory workers and perhaps some interested clinicians who wish to have authoritative accounts of research into the application of oncological biology to the early detection and, to a lesser extent, the prevention of lung cancer.

In 1996 the International Association for the Study of Lung Cancer (IASLC) sponsored two workshops on lung cancer prevention, the first focusing on clinical studies and the second—the subject of this book—focusing on basic laboratory work which was held in Nancy in France. This volume consists of 30 separate papers delivered at the workshop and edited for publication.

Although the title of the book emphasises prevention, to my mind the bulk of it essentially looks at laboratory investigations of risk factors and changes in the bronchial epithelium and the early evolution of tumours which might, with luck, be translated into strategies for early detection of lung cancer rather than its prevention. Of course this is a hugely important problem; 90% of lung cancers are caused by tobacco inhalation but it is unknown why only about 15% of smokers are susceptible to malignant change. Sadly, it is widely recognised that primary prevention—largely a matter of social policy and public pressure—is failing even in the developed world and, with the unopposed expansion of tobacco marketing in the third world, from a global perspective the lung cancer epidemic is set to continue for the foreseeable future and to be concentrated in communities where the prospects of using elaborate techniques for early detection or protection are bleak.

It is also well recognised that the lung cancer screening programmes using presently available techniques such as plain radiography and sputum cytology are not cost effective (unlike cancer of the cervix and cancer of the breast). This situation may change in some communities and there is now interest in portable spiral computed tomographic scanning, possibly coupled with the examination of chromosomal abnormalities in sputum in high risk individuals, which may to a certain extent bridge the gap between what is presently achievable and what the articles in this book hold out as tantalising promises.

The scope of laboratory work described here is wide. Amongst others, those that came to my attention included genetic subsectibility, chemoprevention, pre-malignant changes, inhibitory growth factors, and fluoroscopic bronchoscopy. For genetic susceptibility, I learnt that polymorphisms of a regulatory gene might determine the inducibility of two forms of cytochrome p450 by tobacco smoke which leads to a variable ability of tobacco smoke to convert pro-carcinogens into carcinogenic metabolites. Other polymorphisms may add to these risks. Sadly, the theoretical promise of primary chemoprevention using substances thought to inhibit carcinogenesis (β-carotenes and α-tocopherol) do not seem to have been borne out in clinical trials (Pastorino and Sasco).

Running throughout many chapters is the concept that there is a cascade of pre-malignant changes in bronchial epithelium involving genetic damage and which, if detected at an early stage, might allow more effective treatment. However, this hypothesis —although promising for squamous carcinoma—seems to be supported less strongly with respect to adenocarcinoma and small cell carcinoma. The particular value of studying these early genetic abnormalities is, it seems to me, that they may be reflected in sputum samples, and with a high proportion of carcinomas now presenting in the UK in ex-smokers as opposed to present smokers, in whom of course prevention is inappropriate, early treatment might be possible. A chapter discussing fluorescence bronchoscopy (Lam McAulay) shows that early lesions can be identified, but this particular volume does not include data showing that early detection in this way yields better survival figures. Not surprisingly, because of the possibility of improved therapy, there are papers on inhibitory growth factors such as metalloproteinases (Vignaud *et al*) and neuropeptides (Seckel and Rozengurt) in relation to small cell lung cancer which demonstrate how powerful synthetic inhibitors of these substances might be.

I came away from reading this book with a strong impression of the ingenuity and the variety of potential anti-cancer strategies that are being studied. It would be far too optimistic to suppose that the subjects of all of these 30 chapters will in due course be shown to be fundamental to a novel and important way of either detecting lung cancer earlier, preventing it, or inhibiting it. But only a pessimist would suppose that nowhere in this comprehensive book is there a discussion of an approach which will eventually be found to be clinically useful and justify the huge research effort so carefully described in these pages.—MM

NOTICES

Fleischner Society

The Fleischner Society's 29th Annual Conference on Chest Disease will be held on 18–21 April 1999 at the Loews Ventana Canyon Resort, Tucson, Arizona, USA. For further information contact Lynne Tiras or Pam Waslawski, International Meeting Managers Inc., 4550 Post Oak Place, Suite 342, Houston, Texas 77027, USA. Telephone +1 713 965 0566; Fax +1 713 960 0488.

The Dr H M (Bill) Foreman Memorial Fund

The Trustees of the Dr H M (Bill) Foreman Memorial Fund invite applications for grants related to study in respiratory disease and allied fields. Limited funds are available for registered medical practitioners to assist in travelling to countries other than their own to study respiratory disease and also for support for clinical research abroad. Intending applicants should write for further details to Dr Brian H Davies, Llandough Hospital, Penarth, Vale of Glamorgan CF64 2XX, UK.

CORRECTION

Long term treatment with salbutamol and salmeterol

In the paper entitled "Asthma control during long term treatment with regular inhaled salbutamol and salmeterol" by D R Taylor which appeared in the September 1998 issue of *Thorax* on pp 744–52, Figure 2 on page 749 was incorrect. A correct version of Figure 2 appears below.

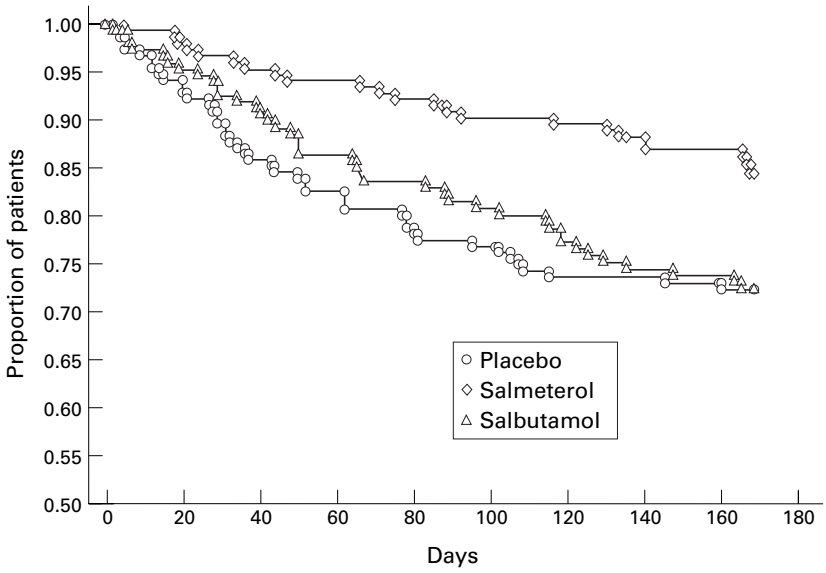

Figure 2 Kaplan-Meier plot showing the proportion of patients who remained free of exacerbations during each treatment period (days). This was significantly greater for salmeterol than for salbutamol compared with placebo in subjects for whom paired comparisons were possible (n = 146; p = 0.008).