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 neutrophil 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.

SIMON HART
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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 mean sputum cell counts in sputum or any other biological sample.

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Table 1 Mean absolute cell counts (cells/ml × 10^6) 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)

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>240</td>
<td>139</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>176</td>
<td>72.3</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>8.4</td>
<td>4.3</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>9.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Macrophages</td>
<td>47.0</td>
<td>19.8</td>
</tr>
<tr>
<td>Epithelial cells</td>
<td>2.6</td>
<td>3.2</td>
</tr>
</tbody>
</table>

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 SaO2, or lung function indices. There is little doubt that the aero-bronchial inflammation occurs in bronchiectasis, COPD and asthma, and plays an important role in the pathogenesis of these diseases.1,3 Although inhaled steroid therapy is undoubtably 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.4 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 therapy in COPD and bronchiectasis.

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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 di077 not 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,5 and there is some evidence that such patients respond particularly well to corticosteroids.6 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, 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 SaO2, 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 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 after 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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interception of trials of corticosteroid therapy in COPD will remain difficult.

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AUTHORS’ REPLY We would like to thank Drs Brightling and Pavord for their interesting comments. Although this was 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.

The second group was no overall change in the sputum eosinophil count after two months of treatment with beclomethasone dipropionate, we have analysed separately the subgroup of patients with COPD without sputum eosinophils.

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Coal mining and COPD

Professors Coggon and Newman Taylor 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 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.”

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 fact, the mean difference from baseline of the total cell count (cells/ml × 106) was 191 (51.8) (95% CI 68.3 to 314), and the mean difference from baseline of the neutrophils was 27 (1.7) (95% CI 22.9 to 31).2

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 eosinophils.


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AUTHORS’ REPLY We remain unconvincing 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.1 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. These deficits persist after cessation of exposure and are of similar magnitude in miners with and without symptoms of bronchitis.3 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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BOOK REVIEW


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 into 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 unapoposed 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 susceptibility, 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 Tirasci or Pam Walslawski, 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](https://example.com/figure2_corrected.png)

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 (α = 146; p = 0.008).