LETTERS TO THE EDITOR

Effect of *N*-acetyl cysteine on thiol levels

We read with interest the article by Dr Bridgeman and colleagues on the effect of oral *N*-acetyl cysteine (NAC) on thiol levels in epithelial lining fluid (ELF) and lung tissue (July 1994;**49**:670–5). Their suggestion that NAC may not be the drug of choice to enhance the glutathione antioxidant potential of the lungs in chronic obstructive pulmonary disease (COPD) is not supported by their data, since levels of cysteine or glutathione in ELF, bronchoalveolar lavage (BAL) fluid, or lung tissue were not measured in these patients. In addition, they did not perform functional measurements.

Several studies have investigated the antioxidative capacity of NAC, 600 mg daily. In healthy smokers significant decreases in levels of lactoferrin, ECP, and chemotactic activity of neutrophils in BAL fluid, and of myeloperoxidase and elastase levels in serum, were found.[1,2] Treatment with NAC, 200 mg twice or three times daily for more than one year, was associated with a decrease in the number of bacteria, especially in patients with COPD.[3] The design of some of these studies precludes firm conclusions, but they at least suggest that conventional doses of NAC may influence the antioxidative capacity of the lung. This is of special relevance in those patients with a significantly disturbed pulmonary oxidative/antioxidative balance, such as patients with COPD and smokers. Indeed, Lundbäck *et al* recently showed that two years of treatment with NAC, 600 mg daily, reduced the annual decline in FEV_1 compared with a control group.[4] This effect was most pronounced in smoking patients over 50 years of age with already considerably decreased FEV_1.

Looking at the pharmacokinetic data, the authors showed in a group of patients consisting of smokers, ex-smokers and non-smokers that NAC, 600 mg daily for five days, increased levels of glutathione in BAL fluid by 180% 1–3 hours after the last dose ($p<0.05$), and by 24% 16–20 hours after the last dose (NS).[5] This "transient" increase in antioxidants in the lung apparently does not preclude a decrease in oxidative stress, or an improvement in antioxidative capacity of the lung, or both.

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2 Eklund A, Eriksson O, Hakansson L, *et al*. Oral N-acetylcysteine reduces selected humoral markers of inflammatory cell activity in BAL fluid from healthy smokers: correlation to effects on cellular variables. *Eur Respir J* 1988; 1:832–8.
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4 Lundbäck B, Lindström M, Andersson S, Nyström L, Rosenhall L, Stjernberg N. Possible effect of acetylcysteine on lung function. *Eur Respir J* 1992;5(Suppl 15):895.
5 Bridgeman MME, Marsden M, MacNee W, Flenley DC, Ryle AP. Cysteine and glutathione concentrations in plasma and bronchoalveolar lavage fluid after treatment with N-acetylcysteine. *Thorax* 1991;**46**:39–42.

AUTHORS' REPLY We thank Drs Dekhuijzen and van Herwaarden for their interest in our paper. We do not, however, agree with their conclusions. Although the patients in whom measurements of glutathione and cysteine in BAL fluid and lung tissue were performed were not specifically chosen as having COPD, these patients were all smokers or ex-smokers, as stated in the text, and table 1 clearly indicates that some had airflow limitation as shown by the predicted values for FEV_1. Thus, some of these patients had COPD. The results of measurements of thiol concentrations in plasma in our study also suggest that, even with high doses of *N*-acetyl cysteine, the plasma concentrations of thiols in patients with COPD were lower than in normal subjects. The lack of any significant changes in thiol concentrations in BAL fluid and lung tissue in this group of patients with minor airflow limitation suggests that levels in lung and BAL fluid would be even lower in patients with severe COPD.

The purpose of our study was not to assess any "functional" measurements but simply, as stated in the title, to determine whether there was a significant increase in thiol concentrations in plasma, BAL fluid, and lung tissue following administration of *N*-acetyl cysteine. We are aware of studies which suggest a decrease in exacerbation of symptoms in patients with COPD treated with *N*-acetyl cysteine. We are also aware, and state in the paper, that the beneficial effect on exacerbations of COPD has been shown in some, but not all, studies. The purpose of our study was to determine whether the possible beneficial effects of *N*-acetyl cysteine could be explained by a significant change in thiol concentrations – and hence the antioxidant potential – in BAL fluid and in the lungs.

Drs Dekhuijzen and van Herwaarden are clearly aware of our previous data. However, we were unable to confirm a sustained significant increase in glutathione levels in the lung or BAL fluid with high doses of *N*-acetyl cysteine. These studies therefore lead us to conclude that *N*-acetyl cysteine, even in high doses, failed to produce any sustained or significant increase in thiol concentrations in the lung. We must therefore seek an alternative explanation for the beneficial effects of *N*-acetyl cysteine shown in some studies in patients with COPD.

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Asthma publications

The incidence of asthma is high in most communities and possibly increasing,[1] and is associated with considerable morbidity.[2] Physicians have been aware of the links with allergy throughout most of this century and, in broad outline, the concept of the interaction between IgE and antigens in the bronchi is similar to that held in the 1970s. The fact that histological changes similar in quality to those found at post mortem examination are present even in mild asthma suggests that an immunological process is frequently going on in atopic subjects.[3] It is well recognised that apparent respiratory infections and exposures to some antigens, in particular the house dust mite,[4] is associated with an increase in the incidence of asthma.

Since for all diseases it is logical to consider that prevention is better than cure, one would expect that the major push in research in asthma would be towards finding methods to reduce antigen exposure. In 1993 *Thorax*, the journal of the British Thoracic Society, published 280 papers, 30·7% of which were on the subject of asthma. In the same year the *American Review of Respiratory Diseases*, the journal of the American Thoracic Society, published 540 papers of which 31·8% were on the same subject. The distribution of the type of asthma research published in the two journals is shown in the table, although naturally there are some areas of overlap. It can be seen that neither journal has published many papers on the household or external environment. The *American Review of Respiratory Diseases* has concentrated on allergy and general aspects of the disease, while *Thorax* has concentrated on the treatment.

It is natural that biological researchers should be interested in the details of pathophysiology and the exciting spectrum of lymphokines, adhesion molecules and mediators for their own sake, as well as the hope that in the future a cure for asthma might be found. Asthma patients and their physicians owe a great debt of gratitude to the pharmaceutical industry for the drugs they have produced, especially since the 1970s. When used correctly these have been of benefit to most patients and have been a rich resource for research as is obvious from the publications, especially in the British journal. I wonder, however, if, as physicians and not as researchers, we should be asking if the direction of asthma investigation has drifted too much away from the prevention of obvious excessive exposure to antigens.

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1 Burney PGJ. Asthma mortality in England and Wales: evidence for a further increase, 1974–84. *Lancet* 1986;ii:323–6.
2 Castle, Fuller R, Hall J, Palmer J. Serovent nationwide surveillance study: comparison of

Number (%) of papers on each aspect of asthma research published in Thorax and the American Review of Respiratory Diseases (ARRD) in 1993

Subject of paper	*Thorax*	*ARRD*	*Significance of difference*
Allergy	8 (9)	35 (20)	χ^2 4·7; df 1; $p<0.05$
General	27 (31)	77 (45)	χ^2 4·3; df 1; $p<0.05$
Therapy	46 (53)	47 (27)	χ^2 17·0; df 1; $p<0.001$
Housing	2 (2)	3 (2)	χ^2 0·1; df 1; $p>0.5$
Environment	3 (3)	11 (6)	χ^2 0·9; df 1; $p>0.5$
Total	86 (100)	173 (100)	