**LETTERS TO THE EDITOR**

**Effect of N-acetyl cysteine on thiol levels**

We read with interest the article by Dr Bridge-man and colleagues on the effect of oral N-acetyl cysteine (NAC) on thiol levels in epithelial lining fluid (ELF) and lung tissue (July 1994;49:670–75). Their suggestion that NAC may not be the drug of choice to enhance the glutathione 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 anti-oxidative capacity of NAC, 600 mg daily. In healthy smokers significant decreases in levels of lactoferrin, BCR, and chemotactic activity of neutrophils in BAL fluid, and of myeloperoxidase and elastase levels in serum, were found. Treatment with NAC, 200 mg twice or three times daily for more than one year, or three times daily for more than one year, was associated with a decrease in the number of bacteria, especially in patients with COPD.

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/anti oxidative balance, such as patients with COPD and smokers. Indeed, Lundback et al recently showed that two years of treatment with NAC, 600 mg daily, reduced the annual decline in FEV1, compared with a control group. This effect was most pronounced in smoking patients over 50 years of age with already considerably decreased FEV1.

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). 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.

**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, and none of the data clearly indicates that some had airflow limitation as shown by the predicted values for FEV1. 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 moderate airflow obstruction 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 also are 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 in antioxidative potential – in BAL fluid and in the lung. 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 in the BAL 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 patients with COPD.

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**Asthma publications**

The incidence of asthma is high in most communities and possibly increasing, and is associated with considerable morbidity. 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. It is well recognised that apparent respiratory infections and exposures to some antigens, in particular the house dust mites, is associated with an increase in the incidence of asthma. Since in 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 types of asthma research published in *Thorax* in 1993 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 Disease* 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 cytokines, 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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2. Castile, Pillar R, Hall J, Palmer J, Serenove nationwide surveillance study: comparison of...
Pulmonary Mycobacterium malmoense and Aspergillus infection

I read with great interest the paper by Dr FGE Bollett et al (May 1994;49:521-2). I recently described a case of pulmonary Mycobacterium malmoense with superadded Aspergillus infection and would like to make several additional comments.

I pointed out that coexisting infection was a problem and was associated with a poorer prognosis. Our patient died a few weeks after the initial evidence of fungal infection. Evidence of active pulmonary mycobacteriosis was assessed on post mortem examination after 20 months of antituberculous chemotherapy and thoracic surgery with residual signs of abscess cavities and pulmonary destruction. Aspergillus is likely to colonise these cavities and cause an aspergilloma as described in cases of tuberculosis.

Long term chemotherapy failed to sterilise the sputum and there was no evidence of clinical or radiological improvement of the mycobacterial infection. Surgery was performed, firstly, for mycobacteriosis as other authors have described, and, secondly, because of the aspergilloma. There was no evidence of fungal invasion but fungal hyphae were present in the cavity.

Aggressive treatment is indicated for the two infections: antituberculous (with ethambutol) and antifungal therapy (itraconazole) plus surgery if possible.

Endotoxin and the Lungs. Kenneth L Brahaim. (Pp 536; $175.00). New York: Marcel Dekker, 1994. 0 8247 9222 X.

This represents Volume 77 of the first clinical and scientific series published by Marcel Dekker entitled "Lung Biology in Health and Disease". These fine (principally) scientific monographs are on subjects of interest to thoracic physicians. In fact, the current volume represents nicely the historical and established overlap between pulmonary and critical care medicine in North America. There is an enormous literature on endotoxin, but the editor hopes that this volume will cast new light on the core of information about endotoxin relevant to clinical medicine by placing the scientific data in a clinical context. This review, I feel, has achieved this aim admirably. Chapters dealing with the chemical structure and biological activity of endotoxin are interspersed with those dealing with receptive and second messenger pathways. There is a first rate chapter on LPS-induced signal transduction in gene transcription and the chapter dealing with the effects of the anatomical and functional effects of endotoxin on the endothelium is very good. As lung injury and acute respiratory distress in adults (ARDS) are increasingly regarded by many authorities as only the pulmonary manifestation of a panendothelial insult, I would have liked to see more space devoted to the effects of endotoxin on systemic and peripheral and microvascular control mechanisms, although these are touched upon in a chapter dealing with sepsis. The chapter dealing with immunological therapy in endotoxaemia is disappointing - not in its content, but rather because of the failure of such approaches to produce any significant fall in the high mortality associated with these clinical conditions. Nevertheless, the volume ends on an up-beat note: the chapter on the prospects of gene therapy in this area is not only exciting but contains sufficient preliminary data to give us a glimpse of hope that real therapeutic advances may be in sight at last. - TWE


Rather than being a textbook, this is a record of conference proceedings. The chapters are a mixture of topical overview which vary in their degree of incisive comment and presentation of experimental data with attendant risks of subjectivity. Typographical errors are rare although grammatical structure, particularly of the transcribed "discussion" sections which follow most chapters, makes reading difficult.

Despite the general title, this book is selective in its coverage of this interesting topic. The introduction promises a more systematic approach than the book delivers, where some of the basic science is not discussed further in terms of physiological or pathophysiological mechanisms. The major topic of the book, however, concerns neuropeptide modulation of airway function which is dealt with comprehensively from general molecular biology through to potential therapeutic targets. Some other concepts and diseases discussed would have benefited from a similar methodological approach.

Other than in relation to asthma, we are given little insight into the clinical relevance of the neuropeptides. Their role in the selected diseases mentioned is discussed mainly in the context of mechanistic theories rather than potential therapeutic strategies. One obvious omission is any discussion on the role of neuropeptides in the pulmonary circulation or in relation to pulmonary vascular disease where a large body of work does exist.

The book does, however, contain a wealth of up-to-date reference material. As such, it is likely to be of most value to workers already engaged in related fields of research where the investment of $195 might be worthwhile. For the wider population of researchers and clinicians in respiratory medicine the book, like its subject matter, is mostly of uncertain relevance to current clinical practice. - RIC

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