affinity which are stimulatory, and A_2 receptors of low affinity which are inhibitory [5]. Thus, therapeutic levels *in vivo* could actually lead to increased superoxide generation by activated neutrophils.

RENKEMA *et al.* [1] suggest that oral prednisolone may have a beneficial effect in patients with emphysema, through inhibition of superoxide generation. Whereas this may be true, corticosteroids have, more importantly, been shown to have an inhibitory effect on other key neutrophil functions, chemotaxis and connective tissue degradation by proteinases [6]. These effects may have more relevance in the pathogenesis of chronic destructive lung diseases, and explain the protective role of corticosteroids.

The authors have concentrated on the role of superoxides, because they were unable to demonstrate an increased release of elastase by neutrophils in patients with emphysema in an earlier study [7]. Other studies suggest, however, that it is proteinase-mediated connective tissue degradation that is the key to emphysema. In support of this, we have previously shown an increase in elastase release from neutrophils in some patients compared to controls [8]. The discrepancy of our data with the authors previous work may relate to the subjects studied, but the fact that the authors were unable to show increased elastase release does not preclude the importance of this enzyme. Actively metabolizing neutrophils release only a very small proportion of their total elastase content when they effect proteolysis of extracellular connective tissue proteins [9]. We have also shown that neutrophils from patients with chronic obstructive bronchitis show enhanced chemotaxis [10], possibly resulting in greater recruitment to the lung and, thereby, increasing the elastase burden. This has also been reported by other workers [11]. Furthermore, the cells were able to degrade more connective tissue by release of elastase than healthy controls, [10] indicating a greater potential to cause tissue damage. The evidence suggests that this process is effected wholly by elastase, and that superoxide radicals play no direct part [9]. We believe, therefore, that neutrophil-mediated connective tissue damage in chronic obstructive bronchitis is largely due to proteinases, especially elastase, and that corticosteroids may have a beneficial effect on these mechanisms.

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CORRESPONDENCE

Nedocromil sodium effective treatment for asthma

To the Editor:

We wish to respond to the recent editorial [1] concerning our paper entitled "The clinical efficacy of inhaled nedocromil sodium (Tilade®) in the treatment of asthma" [2]. We would like to emphasize certain statements made in the paper: we included all placebo-controlled, double-blind trials that have been supplied and analysed by Fisons. We were not selective in any way other than to exclude centres (not studies) that contributed less than nine patients per treatment group. The results presented gave a fair and unbiased assessment of nedocromil sodium compared with placebo.

We have conducted an additional analysis, that

demonstrates the concept of publication bias. The 127 centres included in the meta-analysis represent 62 separate trials. Of these, 22 trials (54 centres) have been published, 40 trials (73 centres) have not been published.

The beneficial effect of nedocromil sodium compared with placebo is numerically greater in the published trials than in the unpublished trials for the six efficacy variables included in the meta-analysis. All variables significantly favour ($p<0.05$) nedocromil sodium, irrespective of published or unpublished status. However, for two of these variables (day and night asthma (Appendix 1) and patient opinion), the differences between published and unpublished trials are significantly ($p<0.05$) in favour of the published trials.

The inclusion of the unpublished trials in our full analysis [2], therefore, diluted the size of the effect that would be perceived by published trials alone.

We suggest that this illustrates the desirability that, at a certain stage after the introduction of a new drug, the originating company should be encouraged, or required, to publish an overview analysis of all trials in order to allow prescribing doctors to make a rational judgement of therapy.

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Appendix 1

Example. Day and night asthma: the mean difference between nedocromil sodium and placebo is 0.45 (95% CI 0.32: 0.59) for unpublished trials, and 0.67 (95% CI 0.51: 0.82) for published trials.

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1. O'Byrne P, Cook D. – Is nedocromil sodium effective treament for asthma? *Eur Respir J* 1993; 6 (1): 5–6.
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