

aggerated sensitivity to LTC₄ has been observed to be a characteristic of s-salbutamol in allergic animals.⁷

There can be no doubt that allergic hyperreactivity in the guinea pig is spasmogen selective, with LTC₄, LTE₄, and histamine being sensitive indicators of this phenomenon. However, following protracted (six days) exposure to salbutamol (1 mg/kg/day) there is a divergence of changed responsiveness such that it might be concluded from studies using LTC₄ or LTE₄ that airway responsiveness had increased whereas, at the same time and in the same animal, reduced responsiveness to histamine would favour a contrary conclusion. Hence, before categorising changes in airway responsiveness due to sympathomimetics as being small in asthmatic subjects, it would be prudent to examine a wider range of test spasmogens. When first investigated by use of sophisticated recording techniques, it was concluded that allergic airway hyperreactivity did not occur in the guinea pig.⁸ By giving consideration to alternative test spasmogens it is now possible to demonstrate substantial increased airway responsiveness during a modest allergic reaction in this species.³ Furthermore, it is possible to define circumstances whereby sustained exposure to sympathomimetics heightens susceptibility to certain allergic mediators so that the response to a low dose of antigen is transformed from a source of mild discomfort to sudden death. In the absence of experimental data, it cannot be presumed that this phenomenon cannot occur in asthma.

J MORLEY
Department of Applied Pharmacology,
Royal Brompton National Heart and
Lung Institute,
London SW3 6LY,
UK

- O'Connor BJ, Aikman SL, Barnes PJ. Tolerance to the nonbronchodilator effects of inhaled beta₂-agonists in asthma. *N Engl J Med* 1992; 327:1204-8.
- Cockcroft DW, McParland CM, Britto SA, Swystun VA, Rutherford BC. Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1994;342:833-7.
- Hoshiko K, Morley J. Allergic bronchospasm and airway hyperreactivity in the guinea-pig. *Japan J Pharmacol* 1993;63:151-7.
- Djukanovic R. Is airways hyperreactivity selective or non selective? *Agents Actions [Suppl]* 1993; 43:231-9.
- Hoshiko K, Morley J. Exacerbation of airway hyperreactivity by racemic salbutamol in sensitized guinea-pigs. *Japan J Pharmacol* 1993;63: 159-63.
- Chapman ID, Mazzoni L, Morley J. An anomalous effect of salbutamol in sensitized guinea-pigs. *Br J Pharmacol* 1990;99:66P.
- Morley J, Chapman ID, Foster A, Hoshiko K, Mazzoni L. Effects of (+) and racemic salbutamol on airway responses in the guinea-pig. *Br J Pharmacol* 1991;104:295P.
- Popa V, Douglas JS, Bouhuys A. Airway responses to histamine, acetylcholine and propranolol in anaphylactic hypersensitivity in guinea pigs. *J Allergy Clin Immunol* 1973;51:344-56.

AUTHORS' REPLY We thank Dr J Morley for his meaningful comment. We agree that our statement that the effect of sympathomimetics on bronchial hyperresponsiveness is relatively small was based upon studies in which histamine or methacholine were used. Other test spasmogens may indeed have other effects. Moreover, we believe that the clinical significance of the effects of spasmogens which are inhaled in natural circumstances (such as allergens) is much greater than that of provocative agents such as histamine or methacholine. The recently published study of Cockcroft *et al* points to this difference.¹ The results of the study of Cockcroft *et al*

and the other studies mentioned by Morley may be explained not only by the fact that other spasmogens were used, but also by the fact that the subjects involved were clearly sensitive to allergens. In other words, an increased bronchial hyperresponsiveness during continuous use of a bronchodilator may occur especially in allergic asthmatic patients. We have some information which supports this suggestion. In a secondary multivariate analysis of our study which showed an increased decline in lung function during continuous bronchodilator use² it was observed that only asthmatic patients who were both allergic and had a high reversibility of obstruction after a bronchodilator had an increased decline in lung function during continuous use of the sympathomimetic drug salbutamol. As this effect was independent of all other important characteristics (for example, baseline bronchial hyperresponsiveness, baseline lung function, peak flow variability, and smoking), it seems probable that reversibility and allergy were not merely measures of the severity of the disease but were real determinants of an increased decline in lung function during bronchodilator use. The enhanced airway response to allergens may be caused by enhanced mediator release from mast cells, possibly due to mast cell β -receptor downregulation.¹ This would mean that regular use of sympathomimetics in conjunction with exposure to allergens would induce inflammation, which in turn is an important determinant for an increased decline in lung function.³ It would also explain why β_2 agonists induce an increase in hyperresponsiveness in some patients and not in others in our study.

It seems paradoxical that particularly allergic patients should be careful in using sympathomimetics chronically, as these patients will in general benefit most from the acute bronchodilating effect of these drugs. This allows for a second explanation for the possibly deleterious effects of bronchodilators, namely a masking effect of the drug.⁴ If a patient is sensitive to an antigen and wheezes or gets dyspnoea on exposure, his natural tendency will be to stay away from it. The bronchoconstrictive reaction to antigens will warn him against repeated exposure. If, however, the patient is given effective bronchodilator medication that allows him to "carry on a normal life", he will quickly learn to get rid of the wheezing when it starts or to prevent it altogether by taking the bronchodilator in advance. Since the sympathomimetic drug does not interfere with the late reaction to the inhaled substance, patients may eventually develop a progressive inflammatory airway disease with increasing bronchial hyperresponsiveness. We observed earlier that there was a correlation between the decline in lung function and the increase in bronchial symptoms in patients who had been treated on demand, but that there was no correlation at all in patients who were treated with bronchodilators continuously.⁵ A poor perception of the severity of asthma seems to be a predictor of severe asthma, and it may be possible that these drugs have an influence on afferent signalling and its processing in the brain.⁶

C P VAN SCHAYCK
Department of General Practice,
Nijmegen University, PO Box 9101, 6500 HB
Nijmegen,
The Netherlands
C L A VAN HERWAARDEN
Department of Pulmonology,
University Lung Centre, Dekkerswald,
The Netherlands

- Cockcroft DW, McParland CP, Britto SA, Swystun VA, Rutherford BC. Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1993;342:833-7.
- Schayck CP van, Dompeling E, Herwaarden CLA van, *et al*. Bronchodilator treatment in moderate asthma or chronic bronchitis: continuous or on demand? A randomised controlled study. *BMJ* 1991;303:1426-31.
- Schayck CP van, Dompeling E, Herwaarden CLA van, Wever AMJ, Weel C van. Interacting effects of atopy and bronchial hyperresponsiveness on the annual decline in lung function and the exacerbation rate in asthma. *Am Rev Respir Dis* 1991;144:1297-301.
- Whitelaw WA. Asthma deaths. *Chest* 1991;99: 1507-10.
- Schayck CP van, Folgering H, Otter JJ den, Tizimanna P, Weel C van. Does the continuous use of bronchodilators mask the progression of asthma or chronic bronchitis? *Fam Pract* 1992;9:397-404.
- Barnes PJ. Blunted perception and death from asthma. *N Engl J Med* 1994;330:1329-34.

Bronchodilators in COPD

In their recent paper (April 1994;49:332-4) Fink and coworkers found, in a group of 22 patients with severe COPD (FEV₁ <50% predicted), that theophylline therapy induced a small but statistically significant increase in maximal voluntary ventilation (from 43.0 l/min with placebo to 46.7 l/min) resulting in an improvement in peak exercise capacity. Since at the same time there was no change in FEV₁ (from 1.05 to 1.1 l), they speculated that theophylline was probably acting on the respiratory muscles, either directly or via a central stimulatory pathway. The finding of a statistically significant improvement in arterial blood gases at rest favoured the second hypothesis.

However, we think that they have not paid enough attention to another of their findings - namely, the increase in FVC from 2.28 l to 2.38 l. Although of small magnitude, this change may well indicate beneficial bronchodilating effects of theophylline not reflected in FEV₁. Other workers have previously shown a reduction in the work of breathing,¹ a decrease in trapped gas volume, and an increase in slow vital capacity² without concomitant change in FEV₁ in patients with COPD receiving theophylline. We have also recently found such dichotomous responses to bronchodilators in COPD after betamimetic inhalations^{3,4}; significant decreases in specific airway resistance and sometimes increases in maximal inspiratory flows can occur in the absence of significant increases in FEV₁. Such a finding should not come as a surprise, however, since no change or only a small change in FEV₁ after administration of bronchodilators is somewhere included in the definition of COPD!

We suggest that, for evaluating bronchodilators, we should stop concentrating only on FEV₁ measurements and should look at other indices of airway function such as specific airway resistance, maximal inspiratory flows, and even the slow vital capacity.⁵

J C YERNAULT
A NOSEDA
Chest Department,
Erasmus University Hospital,
B-1070 Brussels,
Belgium