aggerated sensitivity to LTC_4 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 LTC_4, LTE_4, 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 LTC_4 or LTE_4 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

1 O'Connor BJ, Aikman SL, Barnes PJ. Tolerence to the nonbronchodilator effects of inhaled beta$_2$-agonists in asthma. *N Engl J Med* 1992; **327**:1204–8.
2 Cockcroft DW, McParland CM, Britto SA, Swystun VA, Rutherford BC, Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1994;**342**:833–7.
3 Hoshiko K, Morley J. Allergic bronchospasm and airway hyperreactivity in the guinea-pig. *Japan J Pharmacol* 1993;**63**:151–7.
4 Djukanovik R. Is airways hyperreactivity selective or non selective? *Agents Actions* [*Suppl*] 1993; **43**:231–9.
5 Hoshiko K, Morley J. Exacerbation of airway hyperreactivity by racemic salbutamol in sensitized guinea-pigs. *Japan J Pharmacol* 1993;**63**: 159–63.
6 Chapman ID, Mazzoni L, Morley J. An anomalous effect of salbutamol in sensitised guinea-pigs. *Br J Pharmacol* 1990;**99**:66P.
7 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.
8 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 use[2] 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

1 Cockcroft DW, McParland CP, Britto SA, Swystun VA, Rutherford BC. Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1993;**342**:833–7.
2 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.
3 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;**44**:1297–301.
4 Whitelaw WA. Asthma deaths. *Chest* 1991;**99**: 1507–10.
5 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.
6 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 (FEV_1 <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 FEV_1 (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 FEV_1. 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 capacity[2] without concomitant change in FEV_1 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 FEV_1. Such a finding should not come as a surprise, however, since no change or only a small change in FEV_1 after administration of bronchodilators is somewhere included in the definition of COPD!

We suggest that, for evaluating bronchodilators, we should stop concentrating only on FEV_1 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, Erasme University Hospital, B-1070 Brussels, Belgium

1 Jenne JW, Siever JR, Druz WS, Solano JV, Cohen SM, Sharp JT. The effect of maintenance theophylline therapy on lung work in severe chronic obstructive pulmonary disease while standing and walking. *Am Rev Respir Dis* 1984;**130**: 600–5.
2 Chrystyn H, Mulley BA, Peake MD. Dose response relation to oral theophylline in severe chronic obstructive airways disease. *BMJ* 1988;**297**:1506–10.
3 Noseda A, Schmerber J, Prigogine T, Yernault JC. Perceived effect of shortness of breath of an acute inhalation of saline or terbutaline: variability and sensitivity of a visual analogue scale in patients with asthma or COPD. *Eur Respir J* 1992;**5**:1043–53.
4 Noseda A, Schmerber J, Prigogine T, Yernault JC. How do patients with asthma or COPD perceive an acute bronchodilation? *Eur Respir J* 1993;**6**:636–44.
5 Yernault JC. Rationale and assessment of acute drug trials in asthma. *Eur Respir Rev* 1991;1: 51–6.

Bioavailability of salbutamol

We read with interest the paper of Hindle and Chrystyn (May 1994;**49**:549–53) in which the lung bioavailability of salbutamol (Ventolin, Allen & Hanburys, Uxbridge, UK) was augmented by 53·4% by using a Nebuhaler (Astra Pharmaceuticals, Kings Langley, UK) as assessed by 30 minute urinary excretion of salbutamol in normal volunteers. In this respect, measuring the plasma concentration of salbutamol, peak levels occur within five minutes of inhalation, in keeping with rapid lung absorption, and it is this which will therefore largely determine systemic β_2-mediated effects of inhaled salbutamol.[1,2] That lung bioavailability determines systemic effects is supported by two studies.[3,4] Firstly, salbutamol given by inhalation but not by mouth spraying produces a tachycardia and, secondly, mouth washing does not attenuate the systemic effects of inhaled salbutamol.

On the basis of the data of Hindle *et al* one might predict that the use of the Nebuhaler should increase the systemic β_2 effects of salbutamol in comparison with a metered dose inhaler. This was not found to be the case, however, in the study where systemic β_2 responses to cumulative doubling doses of salbutamol (100–2000 μg) were compared in normal subjects using a metered dose inhaler and Nebuhaler as no differences were seen between the systemic dose-response curves.[5] Although it may not be possible to extrapolate between the two studies, the inference is that measurements of 30 minute urinary salbutamol excretion may not be a true reflection of lung bioavailability, which may be directly measured using peak plasma concentration. Indeed, this is supported by a study where the increased plasma salbutamol concentration with a modified actuator device compared with a metered dose inhaler was associated with a left shift in the dose-response curve for a number of β_2-mediated systemic effects.[2]

There have been recent concerns regarding the bioequivalence of generic salbutamol metered dose formulations, particularly with regard to safety evaluation in terms of systemic β_2 effects. Thus, if it is required to quantify the systemic bioequivalence of generic inhaled salbutamol formulations, the use of direct pharmacokinetic evaluation of lung bioavailability using plasma salbutamol concentration along with measurement of systemic β_2 responses may be more appropriate than using an indirect surrogate pharmacokinetic parameter such as 30 minute urinary salbutamol excretion.

B J LIPWORTH
A GROVE
Department of Pharmacology and Clinical Pharmacology, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK

1 Newnham DM, Wheeldon NM, Lipworth BJ, McDevitt DG. Single dosing comparison of relative cardiac β_1/β_2 activity of inhaled fenoterol and salbutamol in normal subjects. *Thorax* 1993;**48**:656–8.
2 Newnham DM, McDevitt DG, Lipworth BJ. Comparison of the extrapulmonary β_2-adrenoceptor responses and pharmacokinetics of salbutamol given by standard metered dose inhaler and modified actuator device. *Br J Clin Pharmacol* 1993;**36**:445–50.
3 Collier JG, Dobbs RJ, Williams I. Salbutamol aerosol causes a tachycardia due to the inhaled rather than the swallowed fraction. *Br J Clin Pharmacol* 1980;**9**:273–4.
4 Kung M, Croley SW, Phillips BA. Systemic cardiovascular and metabolic effects associated with the inhalation of an increased dose of albuterol; influence of mouth rinsing and gargling. *Chest* 1987;**91**:383–7.
5 Lipworth BJ, McDevitt DG, Struthers AD. Systemic β-adrenoceptor responses to salbutamol given by metered dose inhaler alone and with pear shaped spacer attachment: comparison of electrocardiographic hypokalaemic and haemodynamic effects. *Br J Clin Pharmacol* 1989;**27**:837–42.

AUTHOR'S REPLY The amount of salbutamol eliminated in the urine during the first 30 minutes after inhalation is an index of the dose delivered to the lungs, hence the term "relative bioavailability" to the lung.[1] It is useful for the comparison of two inhaled products or methods when used by a patient. Furthermore, the method can differentiate between the fractions of dose delivered to the body by the pulmonary and oral routes. This is also true for plasma salbutamol concentrations,[2] when measured after the inhalation of a first dose rather than following cumulative dosing. Peak plasma concentrations five minutes after inhalation,[2] together with the polar and basic properties of salbutamol, are consistent with the large renal excretion we have reported in the first 30 minutes after an inhalation.[1] Measurement of plasma salbutamol concentrations and the urinary excretion method do not indicate regional deposition in the lung and, therefore, are both indirect techniques.

The finding of greater deposition to the lung when a Nebuhaler was used with a metered dose inhaler (MDI) by Hindle *et al*[3] is consistent with that reported by others.[4,5] During our study[3] we did not measure systemic effects of salbutamol but subjects did report that tremor, between 5 and 20 minutes after inhalation, was greater when spacers were used. Lipworth and Grove cannot find an explanation for the greater lung deposition with spacers[3–5] because a previous report has shown that extrapulmonary β_2 adrenoceptor responses were the same when an MDI was used with and without a spacer.[6] This may be due to the specially prepared MDIs delivering 100 and 500 μg per actuation used in their studies which could have affected the in vivo respirable fractions with and without the Nebuhaler. Furthermore, a cumulative dosing schedule was used and the systemic effects could be influenced by the total delivery of salbutamol to the body from the modified MDIs via pulmonary and oral routes. Lipworth *et al*[6] do refer to this in their conclusion by stating that "improved lung delivery with a pear-shaped spacer (PSS) may have compensated for reduced oropharyngeal deposition and gut absorption". Hence, without a measurement of the amount of salbutamol delivered to the body no comparison can be made between the study of Lipworth *et al*[6] and those which demonstrate greater lung depositions with the Nebuhaler.[3–5]

Finally, we sympathise with the concerns of Lipworth and Grove with respect to the bioequivalence of inhaled products. We have shown that, using the same MDI, a variation in the technique significantly alters the amount of drug delivered to the lungs[7] and that an efficient technique cannot be detected by subjective methods.[8] If this occurred during a clinical study, especially the four period, two sequence randomised crossover design proposed by the FDA, then the issue of bioequivalence could be misrepresented. The need to carry out some simultaneous measure of lung deposition is highlighted by the confusion of Lipworth and Grove. Direct methods of measuring lung deposition require a modification to the aerosol and thus cannot be used in bioequivalence studies. Although the plasma salbutamol concentration measurements and the urinary excretion method are indirect methods, they do provide an indication of the relative in vivo respirable fractions delivered to the patient.

H CHRYSTYN
Professor of Pharmacy Practice, University of Bradford, Bradford BD7 1DP, UK

1 Hindle M, Chrystyn H. Determination of the relative bioavailability of salbutamol to the lung following inhalation. *Br J Clin Pharmacol* 1992; **34**:311–5.
2 Newnham DM, McDevitt DG, Lipworth BJ. Comparison of the extrapulmonary β_2 adrenoceptor responses and pharmacokinetics of salbutamol given by standard metered dose inhaler and modified actuator device. *Br J Clin Pharmacol* 1993;**36**:445–50.
3 Hindle M, Chrystyn H. Relative bioavailability of salbutamol to the lung following inhalation using metered dose inhalation methods and spacer devices. *Thorax* 1994;**49**:549–53.
4 Vidgren MT, Paronen TP, Karkkainen A, Karjalianen P. Effect of extension devices on the drug deposition from inhalation aerosols. *Int J Pharm* 1987;**39**:107–12.
5 Newman SP, Miller AB, Lennard-Jones TR, Moren F, Clarke SW. Improvement of pressurised aerosol deposition with a Nebuhaler spacer device. *Thorax* 1984;**39**:935–41.
6 Lipworth BJ, McDevitt D, Struthers AD. Systemic β-adrenoceptor responses to salbutamol given by a metered dose inhaler alone and with pear-shaped spacer attachment: comparison of electrocardiographic hypokalaemic and haemodynamic effects. *Br J Clin Pharmacol* 1989;**27**:837–42.
7 Hindle M, Newton PAG, Chrystyn H. Investigations of an optimal inhaler technique using urinary salbutamol as a measure of relative bioavailability to the lung. *Thorax* 1993; **48**:506–11.
8 Hindle M, Chrystyn H. Metered dose inhalers. *Pharm J* 1991;**246**:722.