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

There can be no doubt that allergic hyperreactivity in the guinea pig is spasmogen selective, with LTC₄, LTE₄ and histamine being sensitizers 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 results with 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 categorizing any change 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. By giving consideration to alternative test spasmogens it is now possible to demonstrate substantial increased airway responsiveness to a modest allergic reaction in this species. Furthermore, it is possible to define circumstances whereby sustained exposure to sympathomimetics heightens susceptibility to certain allergic mediators so that even to a low dose of allergen 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.

The first investigated by Cockcroft and colleagues was the probable action of theophylline on 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. By giving consideration to alternative test spasmogens it is now possible to demonstrate substantial increased airway responsiveness to a modest allergic reaction in this species. Furthermore, it is possible to define circumstances whereby sustained exposure to sympathomimetics heightens susceptibility to certain allergic mediators so that even to a low dose of allergen 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.

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 sympathomimetic 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), it was suggested 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 2.281 to 2.381. 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, a decrease in trapped gas volume, and an increase in slow vital capacity 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; 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.
Bioavailability of salbutamol

We read with interest the paper of Hindle and Chrystyn (May 1994, 49: 549-53) in which they claimed that the lung bioavailability of salbutamol (Ventolin, Allen & Hanburys, Uxbridge, UK) was increased 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 β₂-mediated effects of inhaled salbutamol.

On the basis of the data of Hindle et al one might predict that the use of the Nebuhaler will increase the systemic β₂ effects of salbutamol in comparison with a metered dose inhaler. This was not found to be the case, however, in the study where systemic β₂ 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. 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 β₂-mediated effects of inhaled salbutamol.

That lung bioavailability determines systemic effects is supported by two studies. 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 β₂ effects of salbutamol in comparison with a metered dose inhaler. This was not found to be the case, however, in the study where systemic β₂ 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. 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 β₂-mediated effects of inhaled salbutamol.

The finding of greater deposition to the lung when a Nebuhaler was used with a metered dose inhaler (MDI) by Hindle et al is consistent with that reported by others. During our study we did not measure systemic effects of salbutamol but subjects did report that tremor, between 5 and 20 minutes after inhalation, was more marked when spacers were used. Lipworth and Grove cannot find an explanation for the greater lung deposition with spacers because a previous report has shown that extrapulmonary β₂ adrenoceptor responses were the same when an MDI was used with and without a spacer. 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 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 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 and those which demonstrate greater lung depositions with the Nebuhaler.

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 and that an efficient technique must be selected by subjective methods. 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 a 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 biopharmaceutical 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 CHRISTY
Professor of Pharmacy Practice, University of Bradford, Bradford BD7 1DF, UK

Bronchodilators in COPD.

J C Yernault and A Noseda

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