LETTERS TO THE EDITOR

BCG vaccination by multipuncture method

I write in response to the article by Al Jarad *et al*[1] on this topic. The first study to compare the efficacy of BCG vaccination and its side effects using the Bignal multipuncture device with the reusable handle and disposable heads was the pilot study of neonatal BCG vaccination carried out in 1992 for the Department of Health in our health authority.[2]

In previous studies in neonates and children under two, referenced in the paper by Al Jarad *et al*,[1] an 18–20 needle percutaneous head gave approximately the same degree of tuberculin conversion as did intradermal vaccination but, to achieve this in older children and adults, 36–40 punctures were required. This would require either a 40 needle head or a double vaccination with two × 18–20 needles. This is why percutaneous BCG is currently only licensed for children aged under two years. Although in neonates[2] and in Al Jarad's study[1] in older children the rate of tuberculin conversion was lower with percutaneous than with intradermal vaccination, tuberculin conversion does not necessarily equate to lower efficacy. In the early studies on intradermal BCG the protective efficacy of the vaccination was related to the presence of a scar after vaccination, but not to the tuberculin test result after vaccination. Those with a BCG scar but a negative post vaccination tuberculin test—that is, no tuberculin conversion—had the same degree of protection against tuberculosis over the 15 years following vaccination as did those with a scar and a positive post vaccination tuberculin test.[3]

The multipuncture method is undoubtedly easier to use in neonates because their very thin skin makes intradermal vaccination difficult, and also in nervous teenagers. Further long term studies on large numbers of subjects would be required to determine whether the technique using only 18 needles in older children is as effective as intradermal vaccination. Such studies may well prove to be unnecessary. The PHLS system for enhanced tuberculosis surveillance begun this year should, with sufficient cooperation, be able to give the relevant information by the end of 2001 to show whether England and Wales meet the internationally recommended criteria for discontinuation of unselective BCG vaccination in low prevalence countries.[4] BCG vaccination of selective at risk groups, however, would still be required.

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1 Al Jarad N, Empey DW, Duckworth G. Administration of the BCG vaccination using the multipuncture method in schoolchildren: a comparison with the intradermal method. *Thorax* 1999;**54**:762–4.
2 Ormerod LP, Palmer C. Tuberculin reactivity after neonatal percutaneous BCG immunisation. *Arch Dis Child* 1993;**69**:155.
3 D'Arcy Hart P, Sutherland I, Thomas J. The immunity conferred by effective BCG and vole bacillus vaccines in relation to individual variation in induced tuberculin sensitivity and to technical variations in the vaccines. *Tubercle* 1967;**48**:201–10.
4 International Union against Tuberculosis and Lung Diseases. Criteria for discontinuation of vaccination programmes using Bacille Calmette-Guerin (BCG) in countries with a low prevalence of tuberculosis. *Tuberc Lung Dis* 1994;**75**:179–80.

AUTHORS' REPLY To our knowledge our study[1] was the first to compare the Bignal device with the conventional device in the multipuncture technique in schoolchildren. We were interested in assessing its efficacy in this particular group as we felt that the multipuncture technique would allow us to protect more schoolchildren in a part of London where it is difficult to access this population. The studies by Cundall *et al*[2] and later by Ormerod and Palmer[3] made the same comparison in neonates and small children.

We agree (and stated) that the 18 needle device may not be sufficient to convey a similar conversion rate of the tuberculin test. The manufacturers were unable to produce 40 needle heads as they would require an unacceptably high pressure on the handle to release the needles. We feel that applying two successive punctures with an 18 needle head on the same skin area would not be practicable as the head comes off and would need to be changed after each application. In addition, schoolchildren (and the operators) would not appreciate two applications.

Dr Ormerod's statement on the BCG scar being a predictor of protection may be appropriate for the intradermal method. In our study the BCG scar in children who received the multipuncture method was not visible in under one fifth of children.

Dr Ormerod is in agreement with our statement that the conversion of the tuberculin test does not equate to protection from tuberculosis, but it is frequently used as an indirect measure of the efficacy of BCG vaccination.

We strongly support the PHLS system for enhanced tuberculosis surveillance in the UK, but unfortunately we do not hold out Dr Ormerod's optimism that it will indicate that unselective BCG vaccination can be discontinued in boroughs and countries where notification rates of tuberculosis are high. Further studies on the protective values of multipuncture BCG may still be appropriate.

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2 Cundall DB, Ashelford DJ, Pearson SB. BCG immunisation of infants by percutaneous multiple puncture. *BMJ* 1988;**279**:1173–4.
3 Ormerod LP, Palmer C. Tuberculin reactivity after neonatal percutaneous BCG immunisation. *Arch Dis Child* 1993;**69**:155.

Respiratory care units for non-invasive mechanical ventilation in motor neurone disease

We read with interest the review by Polkey *et al*[1] pointing out the need to use all means possible to enable patients with motor neurone disease to achieve the best quality of life.

The authors state that, in order to maintain 24 hour ventilatory support, nasal ventilation must be complemented with alternative strategies during the day that are not suitable for widespread use in district general hospitals. We consider that it is possible to maintain 24 hour non-invasive ventilation in patients with motor neurone disease if nasal ventilation is combined with other non-invasive techniques such as mouth piece ventilation or a pneumobelt, and with manual or mechanical expiratory muscle aids to clear secretions in those patients whose weakness makes spontaneous coughing ineffective.[2] It is important to provide these techniques because they can delay tracheostomy and additional problems in most patients with motor neurone disease and are the only way for those patients who reject tracheostomy but not ventilatory support. However, we are in agreement with Polkey *et al* that this treatment must be performed by trained staff in respiratory care units. Moreover, these units are the best place to prevent respiratory morbidity and mortality, to enhance cooperation between patients, relatives and caregivers, and to manage clinical and psychological problems during the terminal phase of the disease.

In our experience the care of patients with motor neurone disease outside respiratory care units needs to be improved. These patients must not be negatively discriminated against compared with other chronic patients receiving even more expensive but socially accepted treatment. We must therefore try to ensure that all patients with motor neurone disease have access to management in a respiratory care unit in order to receive standardised quality care both in hospital and at home.

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1 Polkey M, Lyall R, Davidson A, *et al*. Ethical and clinical issues in the use of home non-invasive mechanical ventilation for the palliation of breathlessness in motor neurone disease. *Thorax* 1999;**54**:367–71.
2 Bach JR. Prevention of morbidity and mortality with the use of physical medicine aids. In: Bach JR, ed. *Pulmonary rehabilitation. The obstructive and paralytic conditions.* Philadelphia: Hanley & Belfus, 1996: 303–29.

AUTHOR'S REPLY We thank Dr Servera and colleagues for their interest in our paper. We agree that patients with motor neurone disease should have access to specialist expertise where this is necessary. However, we are also conscious that travel can be difficult for some patients with advanced disease and our experience is that, in many cases, satisfactory palliation can be achieved using non-invasive positive pressure ventilation alone. This treatment could theoretically be

provided by an interested chest physician working in a district general hospital. We recognise that, in practice, it may be difficult to identify the necessary resources and that, conversely, an under-resourced service may lead to suboptimal care; however, this is true both of district hospitals and specialist centres.

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Asthma deaths in Scotland and in Wales

It is surprising to say the least that, although the two inquiries into asthma deaths published recently in *Thorax*[1 2] made the point that most asthma deaths occurred outside hospital (the Welsh study commented on the "relative rarity" of deaths in hospital), neither addressed the question as to whether more prompt admission to a hospital with respiratory intensive care facilities could have prevented some, or even many, of the domestic deaths.

The Respiratory Unit at the Northern General Hospital in Edinburgh first addressed that question as long ago as 1968[3] when it inaugurated a self-admission scheme for patients known by the unit to be subject to life threatening attacks of asthma, whereby the often long delays inherent in conventional admission procedures were bypassed with the willing cooperation of their general practitioners. The scheme was more fully described in 1975[4] and reports on 10 year and 15 year reviews of its progress were published in 1979[5] and 1987.[6] These showed that the death rate in patients admitted under the scheme was only 0.3%, substantially lower than that recorded in asthmatic patients admitted to other Edinburgh hospitals which relied on conventional admission procedures.

The asthma self-admission scheme was widely welcomed as a measure which could save lives and was copied in many other countries, including Australia. Yet in neither of the studies reported in the November 1999 issue of *Thorax* was this important initiative even mentioned. May I ask the authors why?

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1 Bucknall CE, Slack R, Godley CC, *et al*. Scottish Confidential Inquiry into Asthma Deaths (SCIAD) 1994–6. *Thorax* 1999;**54**:978–84.
2 Burr ML, Davies BH, Hoare A, *et al*. A confidential inquiry into asthma deaths in Wales. *Thorax* 1999;**54**: 985–9.
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AUTHORS' REPLY Dr Grant's comments are welcome and highlight the impossibility of including all the information obtained in a study such as SCIAD[1] in a paper of suitable length for publication. The sudden deterioration of previously well patients, so called "brittle asthma", was not a major feature of the deaths studied, raising the possibility that there may be relatively fewer such patients or that patients who die suddenly in the community, even with a history of asthma, are certified with other causes of death. It is noteworthy that the routine management of patients studied, including the use of inhaled steroids, was appropriate in the majority of cases, so it may be that, with a general improvement in standards of asthma care, there are fewer patients with brittle disease than there were previously. Review of the cases where delays were cited as a factor showed no case where delay in reaching hospital was the only factor in patients in whom a sudden onset of symptoms was reported; poor compliance was also commented on in these few patients. A review of the cases where death occurred in A&E likewise revealed no case of sudden deterioration (within hours) definitely due to sudden onset of severe asthma; in most cases a number of other factors including aspiration of vomit and the use of non-prescribed drugs was a factor. There is therefore no evidence of deaths which would have been prevented by fast track admission and, with the more widespread administration of oxygen and nebulised bronchodilators by paramedical ambulance crews, there are other reasons for emphasising the use of normal referral services, as well as promoting patient self-management to minimise the occurrence of such episodes.

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1 Bucknall CE, Slack R, Godley CC, *et al*. Scottish Confidential Inquiry into Asthma Deaths (SCIAD) 1994–6. *Thorax* 1999;**54**:978–84

AUTHORS' REPLY We are aware of the work to which Dr Grant refers, and agree that self-admission schemes can prevent asthma deaths by avoiding the delays that sometimes occur with conventional admission procedures. Different versions of self-admission schemes operate throughout Wales, but there is no uniform practice and it is possible that a few deaths in our series might have been prevented had such a scheme operated everywhere. However, in most cases it is unlikely that the outcome would have been different, particularly when patients failed to take their illness seriously, were not under the care of a respiratory physician, or had no prior history of severe attacks.

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Nebulised fluticasone

The place of nebulised inhaled corticosteroids in the treatment of patients with asthma is difficult to assess, but Dr J M Hill's editorial in *Thorax*[1] was inaccurate and below accepted standards for a major medical journal.

Nebulised fluticasone is frequently referred to, yet all the studies referenced[2–4] have only been published as abstracts (sponsored by the manufacturers of fluticasone) in supplements to journals. There are insufficient details for these papers to be properly scrutinised. They have not been subject to proper peer review and should have no place as the sole references for a new treatment for asthma in the editorial of a major medical journal.

Dr Hill states that "it is clear from a number of studies that fluticasone is twice as potent as budesonide at a mg for mg dose" but references this with a study which compares fluticasone with beclomethasone[5] and not budesonide.

This is clearly incorrect. She forgets that different inhaling devices influence potency ratios. Thus, fluticasone in a Diskhaler may be equipotent with budesonide in a Turbohaler[6] and fluticasone in a metered dose inhaler may be equipotent with beclomethasone in the newer, smaller particle, CFC free inhaler (Qvar).[7]

As far as nebulised steroids are concerned, she seems unaware that even different nebuliser systems may affect the amount delivered to the lung by a factor of four or more.[8] Is this not important to mention? Also, the respirable fraction of nebulised steroid depends on the physical properties of the steroid molecule. For example, beclomethasone might be equipotent with budesonide in metered dose inhalers, but beclomethasone solution nebulises poorly and has been withdrawn from use. So, what is the potency ratio between nebulised fluticasone and budesonide? The answer is unknown, simply because there are no comparative studies. Yet Dr Hill confidently assumes a 1:2 potency ratio when giving the costs of each treatment—and fluticasone appears to be one half the price of budesonide.

Finally, any article, editorial or otherwise—and especially one that makes unfavourable comparisons between drugs—should be accompanied by a declaration of competing interests. There is nothing wrong with having a competing interest but readers need to know. Dr Hill should have stated these interests (if any) in the same detail as reported recently in a review article on asthma drugs in the *BMJ*.[9]

Conflict of interests: neither Dr Todd nor his spouse have shares in any pharmaceutical company. He has received payment from Astra, Boehringer, 3M, Forest Laboratories (USA), GlaxoWellcome, MSD and Zeneca for presentations/lectures in the past five years. He has only received payment for research from GlaxoWellcome (fluticasone).

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1 Hill JM. Nebulised corticosteroids in the treatment of patients with asthma. *Thorax* 1999;**54**:661–663.
2 Efthimiou J, Westbrook J, Saarelainen S, *et al*. Oral steroid-sparing effect of nebulised fluticasone propionate at two dose levels with placebo over a 3 month period in patients with severe asthma. *Am J Respir Crit Care Med* 1998;**157**: A404.
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AUTHOR'S REPLY The author thanks Dr Todd for his constructive comments on her review article.[1]

There are few published randomised controlled trials of nebulised fluticasone or budesonide in the treatment of asthma. Despite this, these agents are being actively marketed by the pharmaceutical industry so it is vital that the debate about the place of these agents in the treatment of asthma should begin. The author therefore thinks that it is justifiable to review what evidence is available, accepting its limitations in abstract form.

The author apologises for incorrectly quoting a paper comparing the potency of budesonide and fluticasone. The correct reference is cited below.[2] However, the author had presumed that the readers of *Thorax* would be well aware that data comparing different inhaled corticosteroids apply only to the type of inhaler used in any comparison, and that this basic principle did not require explanation.

Dr Todd's comments about different nebuliser systems and drug solubility are well taken. However, this was a short review of the available clinical evidence for the use of nebulised corticosteroids in the treatment of patients with asthma. It was not possible to, nor did I, review nebuliser pharmacokinetics and, as Dr Todd states, there are no comparative studies of the potency ratio of nebulised budesonide and fluticasone.

Finally, neither Dr Hill nor her spouse has shares in any pharmaceutical company manufacturing asthma treatments. She has received payment from GlaxoWellcome, Boehringer, Bayer, Abbott Laboratories and Astra for presentations/lectures and for attending meetings in the last three years.

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1 Hill JM. Nebulised corticosteroids in the treatment of patients with asthma. *Thorax* 1999;**54**:661–3.
2 Barnes NC, Hallett C, Harris TAJ. Clinical experience with fluticasone propionate in asthma: a meta-analysis of efficacy and systemic activity compared with budesonide and beclomethasone dipropionate at half the microgram dose or less. *Respir Med* 1998;**92**:95–104.

Pyoderma gangrenosum

Wang *et al* report an interesting case of systemic pyoderma gangrenosum (PG) with associated lung injury.[1] They recognise the importance of excluding Wegener's granulomatosis (WG) in patients with respiratory symptoms and cutaneous ulceration, but in their case seem only to have done this on clinical and histopathological grounds. A more complete assessment should include testing for cANCA and anti-proteinase 3 (PR3).[2]

We are currently treating a 54 year old ex-smoker who presented for investigation of haemoptysis and who subsequently developed episcleritis and skin lesions resembling PG. Initial investigations were Hb 11.3 g/dl, WBC 9.4×10^9/l, platelets 401×10^9/l, ESR 86 mm/h, and CRP 181 mg/l. Renal function was normal. The chest radiograph showed alveolar shadowing in the left lower zone and an HRCT scan confirmed pulmonary infiltrates. Fibreoptic bronchoscopy and transbronchial biopsy specimens were normal. Skin biopsy specimens showed epithelial cell necrosis and acute inflammatory changes with no evidence of vasculitis or granulomas, consistent with PG. The ANCA assay was positive with a cytoplasmic distribution and was directed against the proteinase 3 epitope. Despite the absence of histological evidence, the clinical features and positive ANCA supported a diagnosis of WG. One month into treatment with pulsed intravenous methylprednisolone and cyclophosphamide the patient is clinically better with resolution of haemoptysis, healing of the pyoderma-like lesions, and a fall in the CRP to 21 mg/l.

Patients with WG frequently present with non-specific signs and symptoms and a high index of suspicion is important.[3] This case highlights the importance of testing for ANCA in patients with PG and respiratory tract symptoms as the treatment of WG requires prolonged immunosuppression for at least a year. Whilst PG itself may be associated with pANCA,[2] the presence of cANCA directed against PR3 is highly suggestive of WG. The histological features of WG are often patchy in distribution and the absence of the characteristic findings of vasculitis, granulomas, and necrosis does not exclude the diagnosis.[3]

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1 Wang JL, Wang JB, Zhu YJ. Pyoderma gangrenosum with lung injury. *Thorax* 1999;**54**:953–5.
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3 Langford CA, Hoffman GS. Wegener's granulomatosis. *Thorax* 1999;**54**:629–37.

AUTHOR'S REPLY I would like to thank Dr Perkins and colleagues for their interest in our article and for their suggestions. The ANCA assay was only introduced in our hospital in 1997 so we could not use this method to distinguish between WG and PG before that time. The diagnosis of WG in our hospital depends mainly on histopathological examination. In September 1999 the patient came for re-examination. All drugs had been stopped for more than four months, she had no symptoms, and all investigations (including chest radiograph, ESR, and CRP) were normal.

Hoffman *et al* reported the treatment outcome of 158 patients with WG.[1] One hundred and thirty three patients received standard treatment of daily low dose cyclophosphamide (2 mg/kg/day) plus prednisone (1 mg/kg/day). This protocol produced marked improvement or partial remission in 91% of recipients; 75% experienced complete remission with a median time of 12 months. Less than 10% of patients so treated experienced remission as late as six years after beginning the protocol. However, 10 cases received corticosteroid only. In this group only two of six cases with limited WG (without renal injury) achieved sustained remission. The authors concluded that the course of WG had been dramatically improved by daily treatment with cyclophosphamide and a corticosteroid; other treatment regimens had not achieved such high rates of remission and successful maintenance.

Compared with Hoffman's standard protocol, the dosage of cyclophosphamide and the duration of treatment in our patient were lower and shorter, respectively. We feel it is unlikely that the clinical picture would have improved so significantly within 10 days if the diagnosis was WG. Of course, the best way is to perform an ANCA test and we intend to do so.

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1 Hoffman GS, *et al*. Wegener's granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992;**116**:488.

Therapeutic equivalence of inhaled salbutamol

The meta-analysis by Hughes *et al* was hindered by difficulties in comparing trials that were often flawed and of varied design.[1] The authors correctly pointed out that, in most of the studies, the use of equivalence as the null hypothesis was invalid. In addition, all but two of the studies looked at the bronchodilator effects in the presence of basal airway tone, when the top of the dose response curve for bronchodilator response occurs in mild to moderate asthma at a salbutamol dose of approximately 200 µg for chlorofluorocarbon (CFC) or hydrofluoralkane (HFA) pressurised metered dose inhalers (pMDIs).[2] To construct a proper dose response curve to estimate relative bronchodilator potency would therefore necessitate the use of doses much lower than 200 µg or evaluation of patients with more severe asthma. Two of the cited studies evaluated functional antagonism against histamine induced bronchoconstriction in patients with mild to moderate asthma. However, in such patients the dose response curve for bronchoprotection is relatively shallow. For example, in a recent study of 72 patients with mild to moderate asthma a fourfold increment in the dose of formoterol Turbohaler (from 6 µg to 24 µg) only resulted in a shift in methacholine hyperresponsiveness of one doubling dose.[3]

One simple way of evaluating bioequivalent doses of inhaled salbutamol is to evaluate the relative respirable lung dose, which can be quantified as lung bioavailability from the early lung absorption profile in the first 20 minutes after inhalation, expressed as the maximal plasma concentration (C_{max}), for the same nominal dose.

We have therefore reviewed eight studies performed in our laboratory using an identical design in which a nominal dose of 1200 µg salbutamol was administered via different devices in healthy volunteers.[4–11] Where the same device was evaluated in two or more

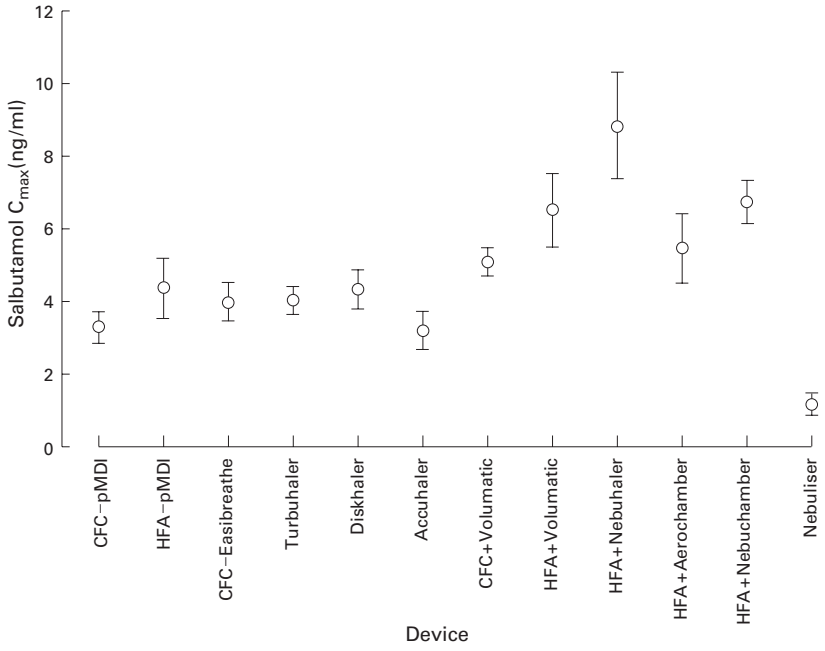

Figure 1 Relative lung dose, shown as maximal plasma salbutamol concentration (C_{max}), from the early lung absorption profile over the first 20 minutes following inhalation of a 1200 µg nominal dose of salbutamol. Values are shown as mean and 95% CI for ordinary (CFC: Ventolin, HFA: Airomir) or breath actuated (Ventolin Easibreathe) pressurised metered dose inhalers (pMDI); dry powder inhalers (Turbohaler, Diskhaler, Accuhaler); pMDI + 750 ml plastic spacer (Volumatic, Nebuhaler), 250 ml metal spacer (Nebuchamber), and 145 ml plastic spacer (Aerochamber); and Sidestream nebuliser.

studies, the highest value for C_{max} was used. A significant difference between devices was assumed where respective 95% confidence intervals did not overlap. The results are shown in fig 1.

There were no differences in lung dose between CFC-pMDI, HFA-pMDI, and the dry powder inhalers, although the Accuhaler produced lower levels than the Diskhaler. As expected, the addition of a Volumatic spacer increased the lung delivery for both CFC-pMDIs and HFA-pMDIs. When used in combination with a Volumatic spacer there was greater delivery with HFA than with CFC. The Sidestream nebuliser resulted in a lower relative lung dose than any of the other devices. However, if an adjustment is made to reflect the usual 2500 µg nominal dose administered by nebuliser (C_{max} = 2.52 ng/ml), the lung dose is similar to the adjusted value for a 400 µg nominal dose from a Nebuhaler spacer with HFA-pMDI (C_{max} = 2.96 ng/ml).

Although decreased airway calibre in asthmatic patients will reduce the lung dose of salbutamol from a given device,[12] the relative difference in lung bioavailability between devices will remain the same and is related to the bronchodilator response.[13]

Measurement of the lung bioavailability of salbutamol in healthy subjects may therefore represent a simple in vivo method for preliminary quantification of the relative lung dose from different inhaler devices to select rational doses for subsequent clinical equivalence studies in asthmatic patients.

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1 Hughes DA, Woodcock A, Walley T. Review of therapeutically equivalent alternatives to short acting β_2 adrenoceptor agonists delivered via chlorofluorocarbon-containing inhalers. *Thorax* 1999;**54**:1087–92.
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NOTICE

International Pediatric Respiratory and Allergy Congress

The International Pediatric Respiratory and Allergy Congress will be held on 1–4 April 2001 at the Prague Congress Center, Prague, Czech Republic. For further information contact the Congress Secretariat at the Congress Centre, Czech Medical Society, JEP Sokolská 31, CZ-120 26 Prague, Czech Republic. Telephone +4202 296889 or +4202 297271; fax +4202 294610 or +4202 24216836. Email: lonekova@cls.cz