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.1

In previous studies in neonates and children under two, referenced in the paper by Al Jarad et al., 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, 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 neonates1 and in Al Jarad’s study1 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 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.2

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 tuberculin 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.1 BCG vaccination of selective at risk groups, however, would still be required.

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AUTHOR’S REPLY To our knowledge our study1 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.3 and later by Ormerod and Palmer4 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 unacceptable high pressure on the handle to release the needles. We showed 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 tuberculin surveillance in the UK, but unfortunately we do not hold 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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Respiratory care units for non-invasive mechanical ventilation in motor neurone disease

We read with interest the review by Polkey et al.5 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.6 It is important to provide mechanical assistance 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 need 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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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...
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 made the point that most asthma deaths occurred outside hospitals, 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 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 and reports on 10 year and 15 year reviews of its progress were published in 1979 and 1987. 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 the conventional admission procedures.

The asthma self-admission scheme was widely welcomed as a measure which could save lives and was copied in many other hospitals, as well as promoting patient self-management to emphasise the use of normal referral services, as well as promoting patient self-management to emphasise the use of normal referral services, as well as promoting patient self-management to emphasise the use of normal referral services.

Published in 1979; 575.

Letters to the editor, Notice

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 was inaccurate and below acceptable standards for a major medical journal.

Nebulised fluticasone is frequently referred to, yet all the studies referenced1 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 “there is no uniform practice and it is possible that 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.1

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 Zeneva for presentations/lectures in the past five years. He has only received payment for research from GlaxoWellcome (fluticasone).

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inhalation with beclomethasone dipropionate 400 mcg/day in adult asthma. 
6 Agertoth I, Pedersen S. A randomised double-
blind dose reduction study to compare the
minimal effective dose of budesonide Turbo-
haler and fluticasone propionate Diskhaler. J
7 Dose of CFC-free inhaled beclomethasone
(Qvar). CSMA MACC Prof Prot Pharmacol-
8 O’Callaghan C, Barry P. Delivering inhaled
corticosteroids to patients. BMJ 1999;318:
110–1.
9 Lipworth BJ. Leukotriene-receptor antagonists.

AUTHOR’S REPLY The author thanks Dr Todd
for his constructive comments on her review article.1

There are few published randomised con-
trolled trials of nebulised fluticasone or budesonide in the treatment of asthma.2

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
be constructive.3 The author therefore thinks it is justifiable to review what evidence is
available, accepting its limitations in abstract form.

The author apologizes for incorrectly quoting a paper comparing the potency of
budesonide and fluticasone. The correct refer-
ce is cited below.4 However, the author had presumed that the readers of Thorax
would be well aware that data comparing dif-
ferent 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 neb-
uliser systems and drug solubility are well
taken. However, this was a short review of the
available clinical evidence for the use of ne-
bulised corticosteroids in the treatment of pa-
tients 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.

Dr Todd’s comments, particularly his view that 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 at-
tending meetings in the last three years.

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1 Hill JM. Nebulised corticosteroids in the

2 Barnes NC, Hallett C, Harris TAJ. Clinical

experience with fluticasone propionate in

asthma: a meta-analysis of efficacy and sys-
temic activity compared with beclomethasone and
beclomethasone dipropionate at half the ma-


Pyoderma gangrenosum

Wang et al report an interesting case of systemic pyoderma gangrenosum (PG) with
associated lung injury.1 They recognize the
importance of excluding Wegener’s granulo-
matosis (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-protease 3
(PR3).2

We are currently treating a 54 year old
ex-smoker who presented for investigation of
haemoptysis and who subsequently devel-
oped episcleritis and skin lesions resembling
PG. Initial investigations were Hb 11.5 g/dl,
WBC 9.4 x 10^9/L, platelets 401 x 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 inflam-
matives. Fibreoptic bronchoscopy and tran-
bronchial 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 sup-
ported a diagnosis of PG. One month into
treatment with pulsed intravenous methyl-
 prednisolone and cyclophosphamide the pa-
tient 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 associ-
ated with pANCA, 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.4

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1 Wang J, Wang JB, Zhu YL. Pyoderma gan-
2 Callen JP. Pyoderma gangrenosum. Lancet
3 Langford CA, Hoffman GS. Wegener’s granulo-

AUTHOR’S REPLY I would like to thank Dr Per-
kins 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 dis-

tinguish between WG and PG before that

time. The diagnosis of WG in our hospital
depends mainly on histopathological exam-

ination. In September 1999 the patient came
to our attention with haemoptysis, healing of the
pyoderma-like lesions, and a fall in the CRP to
21 mg/l.

Institutional ANCA assay was 

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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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 sal-
butamol dose of approximately 200 µg for
chlorofluorocarbon (CFC) or hydrofluoro-
alkane (HFA) pressurised metered dose inha-
lators (pMDIs).2 To construct a proper dose
response curve to estimate relative broncho-
dilator 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 in-
duced bronchoconstriction in patients with

mild to moderate asthma. However, in such

patients the dose response curve for broncho-


dilation is relatively shallow. For example,
in a recent study of 72 patients with mild to

moderate asthma a fourfold increment in the
dose of foromertol Turbohaler (from 6 µg to

24 µg) only resulted in a shift in the 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, as early

lung absorption profile in the first 20

minutes after inhalation, expressed as the

maximal plasma concentration (C_m), for the

samnominal dose.

We have therefore reviewed eight studies

performed in our laboratory using an identi-

cal design in which a nominal dose of 1200 µg
salbutamol was administered via different
devices in healthy volunteers.4 Where the

same device was evaluated in two or more

1 Hoffman GS, et al. Wegener’s granulomatosis: an


n91% of recipients; 75% experienced com-

plete 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 (with-

out renal injury) achieved sustained remis-

sion. 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 proto-

col, 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.
studies, the highest value for \( C_{\text{max}} \) was used. A

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reference in lung bioavailability between

2.96 ng/ml). 

250 ml metal spacer (Nebuchamber), and 145 ml plastic spacer (Aerochamber); and Sidestream

inhalers (Turbohaler, Diskhaler, Accuhaler); pMDI + 750 ml plastic spacer (Volumatic, Nebuhaler),

early lung absorption profile over the first 20 minutes following inhalation of a 1200 µg nominal dose

administered by nebuliser (C\(_{\text{max}}\) = 2.52 ng/ml) reflect the usual 2500 µg nominal dose

devices. However, if an adjustment is made to reduce the lung dose of bronchodilator response.iii

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 \( \beta \) adrenoceptor agonists delivered via chlorofluorocarbon-containing inhalers. The-


2 Clark DJ, Lipworth BJ. Dose-response of inhaled drugs in asthma. Clin Pharmacokinetics


3 Lipworth BJ, Tan S, Devlin M, et al. Effects of treatment with formoterol on bronchoprotec-


5 Clark DJ, Lipworth BJ. Effect of multiple actuations, delayed inhalation and antistatic treat-

6 Lipworth BJ, Clark DJ. Lung delivery of salbutamol by dry powder inhaler (Turbuhaler)

and small volume antistatic metal spacer (Aeromir CFC-free MDI plus Nebuchamber).


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 Centre, 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.

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