Thorax 1999;**54**:91–93

LETTERS TO THE EDITOR

Comparison of the in vitro and in vivo response to inhaled DNase in patients with cystic fibrosis

Recombinant human DNase has been shown to reduce sputum viscosity and improve pulmonary function in patients with cystic fibrosis.[1] The individual response is, however, highly variable with between one third and two thirds of patients showing an improvement in their forced expiratory volume in one second (FEV_1) of more than 10%.[1] In view of the high cost of this treatment and the lack of long term studies confirming its safety, prediction of the response of individual patients is an important issue. In a larger series of patients both baseline pulmonary function and the clinical status of the patient were unable to predict the outcome.

As part of a multicentre phase IIIb trial we have compared the in vitro response assessed by total DNA content and fragment length in sputum with the response in pulmonary function in 92 patients with cystic fibrosis after six weeks of treatment with DNase. The study population consisted of 42 males and 50 females with a mean (SD) age of 20.6 (7.7) years with moderate pulmonary disease reflected by a forced vital capacity (FVC) of 30–70% predicted (mean (SD) 54.9 (9.8)%). All patients were clinically stable and did not receive intravenous antibiotic therapy in the six weeks prior to the study. Most of the patients were chronically colonised with *Pseudomonas aeruginosa*. Sputum samples and pulmonary function tests were obtained at baseline and after six weeks of treatment with 2.5 mg DNase inhaled via a sidestream jet nebuliser with a Portaneb 50 compressor once daily. The median improvement in pulmonary function for the total group was +8% of baseline FEV_1 (range –25% to +138%) and +5.6% of baseline FVC (range –22 to +102%), similar to that reported in previous studies.[1] The median DNA content decreased from 0.53 to 0.3 mg/ml sputum, as reported previously.[2] A marked reduction in DNA fragment length was observed in the majority of cases but it remained unchanged in 18 patients. There was a small but significant difference in the change in FVC for patients with reduced DNA content compared with those in whom the DNA content remained unchanged (median FVC 8.1% versus 3.9%, p = 0.04, Wilcoxon test). No difference was found in the improvement in pulmonary function after six weeks of treatment in those patients with biochemical evidence of DNA fragmentation when compared with those with unaltered DNA fragment length (table 1). In addition, baseline DNA content and fragment length had no influence on the individual patient's pulmonary function after six weeks of treatment.

Assessment of sputum DNA content and fragment length are therefore not helpful in predicting the clinical response of patients receiving DNase treatment. Heterogeneity of the sputum sample or non-uniform distribution of inhaled DNase within the lung may be among the factors responsible for this finding.

FELIX RATJEN
Children's Hospital,
University of Essen,
Hufelandstrasse 55,
D-45122 Essen,
Germany

BURKHARDT TUMMLER
Children's Hospital,
University of Hannover,
Konstanty-Gutschow-Strasse 8,
D-30625 Hannover,
Germany

1 Fuchs HJ, Borowitz DS, Christiansen DH, *et al*. Effect of aerosolised recombinant human DNAse on exacerbations of respiratory symptoms and pulmonary function in patients with cystic fibrosis. *N Engl J Med* 1994;**331**:637–42.
2 Brandt T, Breitenstein S, von der Hardt H, *et al*. DNA concentration and length in sputum of patients with cystic fibrosis during inhalation with recombinant human DNAse. *Thorax* 1995;**50**:880–2.

Table 1 Median (range) response in pulmonary function with DNase treatment in relation to the biochemical response assessed by DNA fragment length in sputum

	Fragment length reduced (n = 74)	*Fragment length unchanged (n = 18)*
Age (years)	22	19
Male/female	33/41	9/9
FVC (% baseline)	56 (37–82)	59 (41–74)
FEV_1 (% baseline)	36 (14–70)	41 (21–67)
Improvement in FVC (%) 6 weeks	6.5 (–21 to +45)	3 (–22 to +26)
Improvement in FEV_1 (%) 6 weeks	8.5 (–25 to +59)	6.5 (–14 to +78)

Lung function parameters are given as a percentage of reference values.

Domiciliary NIPPV in COPD

I was surprised to find that the paper by Jones *et al*[1] did not come up to the normally high standard of the journal. Firstly, the study design itself lacks a control group and yet attempts to make a contribution to the debate about using non-invasive positive pressure ventilation (NIPPV) to improve survival in COPD. Clearly, comparing before and after treatment as a measure of survival can be misleading as it may introduce a "placebo effect" bias that may easily swamp out any physiological improvement. In these days of systematic reviews this evidence is flimsy and may well dilute the effect of good prospective controlled randomised studies.

There were a few minor errors in table 1 which, firstly, presents the transfer factor (TLCO) in non-SI units and offers no conversion factor as quoted in the instructions for authors. Secondly, the units for the transfer coefficient (KCO) are expressed in ml/min instead of mmol/min/kPa/l. I would also have preferred to see the lung volumes, that were expressed as percentage of predicted, have their measured units as litres instead of just "percentage" of predicted value.

Despite these shortcomings, I strongly support the final paragraph that more prospective studies on larger patient groups with clearly defined enrolment criteria are desperately needed to help secure essential funding to what providers of this service all believe is effective medical care.

B G COOPER
Chairman ARTP,
Lung Function Department,
City Hospital,
Nottingham NG5 1PB, UK

1 Jones SE, Packham S, Hebden M, *et al*. Domiciliary nocturnal intermittent positive pressure ventilation in patients with respiratory failure due to severe COPD: long term follow up and effect on survival. *Thorax* 1998;**53**:495–8.

AUTHORS' REPLY We thank Dr Cooper for his interest in our paper and agree that a control group might have strengthened our conclusions. However, to establish such a group with a sham device for NIPPV over the time periods involved would, in practice, be difficult. We are aware of only one study[1] in which a sham device was used. No improvements in arterial blood gas tensions were found over a three month follow up period but levels of pressure support were low in the treatment group with inspiratory pressures of 10 cm H_2O, there was not sufficient monitoring to allow correction of CO_2, and the starting Pa_{CO_2} was only mildly raised to a mean of 48.5 mm Hg. In our group of patients who had more severe COPD, inspiratory pressures of up to 20 cm H_2O were required and our mean status Pa_{CO_2} was 8.0 kPa. A technical intervention such as NIPPV might result in a reduction in hospital or general practitioner visits through a "placebo effect" (conversely, dependency on technology might have resulted in more attendances due to anxiety or technical failings). However, we do not accept that physiological measurements such as improved arterial blood gas tensions or worsening lung function are affected by placebo.

In an attempt to obtain a control group we compared our patients with those from the MRC and NOTT trials; these well recognised studies of LTOT investigated a population similar to our own in terms of baseline characteristics, as stated in our discussion. Without the option of NIPPV, our patients would have remained on LTOT which would have been insufficient to correct hypoxia.

The SI units for transfer factor are mmol/min/kPa; the conversion factor is to multiply by 0.335 or divide by 2.986. Transfer coefficient units are mmol/min/kPa/l. The lung volumes in table 1 are quoted in both litres and percentage predicted.

Finally, as Dr Cooper states, most of us working in this area who see the improvement NIPPV makes to patients with severe hypercapnic respiratory failure due to COPD believe that it is an effective medical treatment. Multicentre European trials comparing LTOT with LTOT and NIPPV are currently underway and the results should help to clarify the role of domiciliary NIPPV in COPD.

S E JONES
S M PACKHAM
M H HEBDEN
A P SMITH
Chest Department,
Llandough Hospital,
Penarth,
South Glamorgan,
CF64 2XX, UK

1 Gay PC, Hubmayr RD, Stroe RW. Efficacy of nocturnal nasal ventilation in stable severe chronic obstructive pulmonary disease during a three month controlled trial. *Mayo Clin Proc* 1996;**71**:533–42.

Burkholderia cepacia bronchiectasis

We read with interest the case report by Ledson *et al*[1] describing a non-cystic fibrosis individual with chronic *Burkholderia cepacia* bronchiectasis. Although *B cepacia* most commonly affects patients with cystic fibrosis, it is also known to infect patients with chronic ventilatory requirements or immunocompromised patients.[2] The immunocompromised patient population who appear most vulnerable to *B cepacia* infection are those with chronic granulomatous disease where the defect in neutrophil burst[3] predisposes them to infection by specific organisms. Although the patient described by Ledson *et al* had normal immunoglobulins, we wonder whether she has a defect in either neutrophil burst or chemotaxis to explain her unusual complaint.

S SURESH
IOLO DOULL
Cystic Fibrosis Respiratory Unit,
University Hospital of Wales,
Heath Park,
Cardiff CF4 4XW, UK

1 Ledson MJ, Gallagher MJ, Walshaw MJ. Chronic *Burkholderia cepacia* bronchiectasis in a non-cystic fibrosis individual. *Thorax* 1998;**53**:430–2.
2 Govan JR, Hughes JE, Vandamme P. *Burkholderia cepacia*: medical taxonomic and ecological issues. *J Med Microbiol* 1996;**45**:395–407.
3 Speert DP, Bond M, Woodman PC, *et al*. Infection with *Pseudomonas cepacia* with CGD: role of non oxidative killing by neutrophils in host defence. *J Infect Dis* 1994;**170**:1524–31.

AUTHORS' REPLY Drs Suresh and Doull suggest that the chronic *B cepacia* colonisation of the respiratory tract in our patient may be due to a peculiar defect in her immune system, specifically an abnormality of neutrophil burst or chemotaxis. We presume they base this speculation on their experience of chronic granulomatous disease in children where acute infections with *B cepacia* have been described. However, our patient is a mature adult who has had an unremarkable past medical history with no evidence of recurrent childhood infections. She has never required ventilation and, despite exhaustive testing, we have been unable to demonstrate any defect in her immune system.

Furthermore, we have tested her neutrophil burst function (using the nitroblue tetrazolium slide test[1]) and found it to be normal. We have not assessed her neutrophil chemotaxis since this is not easily performed. However, such disorders of neutrophil function predispose to infections with catalase positive organisms and usually present at an early age with staphylococcal or fungal infections, particularly of the skin and lung.[2] Our patient gives no such history and we are therefore confident that she does not have an abnormality of neutrophil chemotaxis.

We thank the authors for their comments and welcome any further suggestions that may throw light on the management of this difficult clinical problem.

MARTIN LEDSON
MARTIN WALSHAW
The Cardiothoracic Centre,
Thomas Drive,
Liverpool L14 3PE, UK

1 Bogomolski-Yaholom V, Matzner Y. Disorders of neutrophil function. *Blood Rev* 1995;**9**:183–90.
2 Weatherall DJ, Ledingham JGG, Worall DA, eds. *Oxford textbook of medicine*. 3rd edn. Oxford: Oxford University Press, 1996: 3560–1.

Childhood empyema

In October 1997 we reported an increase in the incidence of childhood empyema in Nottingham.[1] There had been no cases of childhood empyema in the city between April 1994 and April 1996, yet there had been 11 cases between April 1996 and April 1997. We have now reviewed the data for the following 12 months, from April 1997 to April 1998. During this period we have seen only three children with a diagnosis of empyema at the two paediatric departments in the city—Queen's Medical Centre and Nottingham City Hospital. During this period there have been no further reports of increased incidence of childhood empyema since the original report by Rees *et al*.[2] One of the children admitted to Nottingham City Hospital in January 1998 was treated with intrapleural fibrinolysis. She received eight doses of urokinase administered into the pleural space via a pigtail catheter at 12 hourly intervals. A dose of 40 000 U urokinase was diluted in 40 ml on normal saline and instilled via the catheter, which was clamped for four hours and then placed on low grade suction for a further eight hours. This patient received 13 days of intravenous antibiotics and remained in hospital for 14 days; both of these values are less than the median values for duration of intravenous antibiotics and length of hospital admission found previously (15.5 days and 17 days, respectively).

It is interesting to read of the increasing use of intrapleural fibrinolysis in children in the form of case reports and small series[3 4] where the treatment appears to be safe and effective. It is important, however, to emphasise the need for a randomised controlled trial of intrapleural fibrinolysis in children in order to demonstrate any benefit in terms of reducing hospital stay and preventing more invasive procedures.

S D PLAYFOR
R J STEWART
Paediatric Intensive Care Unit,
Queen's Medical Centre,
Nottingham NG7 2UH,
UK
C M SMITH
A R SMYTH
Department of Child Health,
City Hospital,
Nottingham NG5 1PB,
UK

Correspondence to: Dr S D Playfor.

1 Playfor SD, Smyth AR, Stewart RJ. Increase in incidence of childhood empyema. *Thorax* 1997;**52**:932.
2 Rees JHM, Spencer DA, Parikh D, *et al*. Increase in incidence of childhood empyema in West Midlands, UK. *Lancet* 1997;**349**:402.
3 Kornecki A, Sivan Y. Treatment of loculated pleural effusion with intrapleural urokinase in children. *J Pediatr Surg* 1997;**32**:1473–5.
4 Krishnan S, Amin N, Dozor AJ, *et al*. Urokinase in the management of complicated parapneumonic effusions in children. *Chest* 1997;**112**: 1579–83.

Adrenal function in asthmatic children

In a recent paper published in *Thorax* Fitzgerald and co-authors purport to have examined the effects of fluticasone propionate and beclomethasone dipropionate on adrenal function in children with asthma.[1] They state that they have used Dickstein's low dose ACTH test [2] to do this. However, the dose of ACTH (500 ng/1.73 m^2) used in Fitzgerald's paper is a dose taken from a different paper describing a dose-response relationship between ACTH and serum cortisol concentration published by Crowley *et al*[3] and a later paper by the same author comparing low dose with high dose ACTH cortisol secretory dynamics.[4] Dickstein's paper described a low dose ACTH test in adults using a test dose of 1 µg. This dose was not standardised for body surface area and is approximately twice the size of the dose used by Crowley *et al*. The cortisol secretory dynamics in the two low dose tests are likely therefore to differ as timing of the peak cortisol response is partly dependent on the dose of ACTH administered. The low dose ACTH test described by Crowley showed that 80% of the time the peak cortisol response after bolus intravenous injection of 500 ng/1.73 m^2 ACTH has occurred by 20 minutes, and the test protocol calls for sampling at five minute intervals from 10 to 30 minutes after injection to optimise identification of the peak cortisol response. It is also important to note that the rise in serum cortisol concentration at 20 minutes is identical after both high and low dose ACTH injection in normal volunteers. It is likely that, by taking samples at 30 and 60 minutes only, Fitzgerald has missed the peak cortisol response to 500 ng/1.73 m^2 ACTH. Taken in this context, the higher serum ACTH levels observed in the children during treatment with fluticasone may be important. Thus, Fitzgerald's findings regarding adrenal function may not be relevant and should be challenged.

SUZANNE CROWLEY
Department of Paediatric Respiratory Medicine and Intensive Care,
Royal Brompton Hospital,
Sydney Street,
London SW3 6NP,
UK

1 Fitzgerald D, van Asperen P, Mellis C, *et al*. Fluticasone propionate 750 µg/day versus beclomethasone dipropionate 1500 µg/day: comparison of efficacy and adrenal function in paediatric asthma. *Thorax* 1998;**53**:656–61.
2 Dickstein G, Shechner C, Wendell EN, Rosner *et al*. Adrenocorticotropin stimulation test: effects of basal cortisol level, time of day, and suggested new sensitive low dose test. *J Clin Endocrinol Metab* 1991;**72**:773–8.
3 Crowley S, Hindmarsh PC, Holownia P, *et al*. The use of low doses of ACTH in the investigation of adrenal function in man. *J Endocrinol* 1991;**130**:475–9.
4 Crowley S, Hindmarsh PC, Honour JW, *et al*. Reproducibility of the cortisol response to stimulation with a low dose of ACTH (1–24): the effect of basal cortisol levels and comparison of low-dose with high-dose secretory dynamics. *J Endocrinol* 1993;**136**:167–72.

AUTHORS' REPLY We thank Dr Crowley for her interest in our recent article regarding the use of a low dose synacthen test (LDST) in monitoring moderately severe paediatric asthmatic subjects with the potential for adrenal suppression.[1] Dr Crowley challenges the interpretation of our results based upon data in her two papers in "eight healthy young male volunteers aged 20–22 years"[2] and "six healthy adult males aged 20–22 years".[3]

Firstly, the ACTH dosing regime used in our study was arbitrarily chosen at the time of designing the study following communication with Dickstein's group in Israel. Dickstein and colleagues published papers in 1991 using ACTH doses of 1 µg in 20 adults[4] and in 1995 using 0.5 µg/1.73 m^2 in a population of healthy volunteers (n = 33) and asthmatic children and adults (n = 46).[5] In our paper[1] we referenced this work. We are aware of the work of Crowley *et al* from 1991[2] and 1993[3] using LDST (0.5 μg/1.73 m^2) and are happy to acknowledge their contribution of patients to the literature. However, the relevance of the papers by Crowley *et al*[2 3] to our paediatric asthmatic population is unclear. Indeed, the data presented by Crowley *et al* are not in asthmatics, nor in subjects chronically exposed to high dose inhaled and intermittent systemic corticosteroids. Whether their data are directly applicable to an entirely different cohort of paediatric patients with chronic disease should be further investigated.

In our study an additional cortisol sample 14 minutes after ACTH administration would have answered the question about a possible missed cortisol peak. However, Broide *et al*[5] measured serum cortisol levels at 20, 30, and 45 minutes after 0.5 μg/1.73 m^2 ACTH and found similar levels at 20 and 30 minutes in both healthy controls and asthmatic subjects on inhaled corticosteroids. Thus, we believe it unlikely that we have missed the peak cortisol response. Furthermore, we could not demonstrate a difference between treatment sequences in other measures of adrenal suppression including the baseline and 60 minute cortisol levels and the 24 hour urinary free cortisol levels. The marginally higher ACTH levels ($p<0.04$) in the subjects who did not receive systemic corticosteroids during the study whilst on fluticasone propionate therefore remain of uncertain significance.

We believe that to suggest our data are "largely irrelevant" seems harsh based upon the evidence currently available.

DOMINIC FITZGERALD
PETER VAN ASPEREN
CRAIG MELLIS
MAREEA HONNER
LUCIA SMITH
GEOFFREY AMBLER
The Royal Alexandra Hospital for Children
PO Box 3515,
Parramatta, Sydney,
New South Wales,
Australia 2124

1 Fitzgerald D, Van Asperen P, Mellis C, *et al*. Fluticasone propionate 750 μg/day versus beclomethasone dipropionate 1500 μg/day: comparison of efficacy and adrenal function in paediatric asthma. *Thorax* 1998;**53**:656–61.
2 Crowley S, Hindmarsh PC, Holownia JW, *et al*. The use of low doses of ACTH in the investigation of adrenal function in man. *J Endocrinol* 1991;**130**:475–9.
3 Crowley S, Hindmarsh PC, Honour JW, *et al*. Reproducibility of the cortisol response to stimulation with a low dose of ACTH (1–24): the effect of basal cortisol levels and comparison of low-dose with high-dose secretory dynamics. *J Endocrinol* 1993;**136**:167–72.
4 Dickstein G, Shechner C, Nicholson WE, *et al*. Adrenocorticotropin stimulation test: effects of basal cortisol level, time of day, and suggested low dose sensitive test. *J Clin Endocrinol Metab* 1991;**72**:773–8.
5 Broide J, Soferman S, Kivity S, *et al*. Low-dose adrenocortiotropin test reveals impaired adrenal function in patients taking inhaled corticosteroids. *J Clin Endocrinol Metab* 1995;**80**: 1243–6.

Serum angiotensin converting enzyme

Marshall and Shaw in their editorial[1] are correct to hypothesise that the normal range of serum angiotensin converting enzyme (SACE) would be narrower if ACE genotype (insertion/deletion; ID) is also taken into account. This would split its wide normal range into three narrower ranges defined by the genotypes II, ID and DD, with SACE concentrations rising co-dominantly with each copy of the D allele. However, they fail to realise that we have already shown that, not only is this the case, but also if SACE is measured in accordance with ACE genotype its diagnostic sensitivity in acute sarcoidosis is improved by 33.5%.[2]

In our paper we determined a genotype based normal range for SACE with 146 healthy white volunteers. Using this new normal range, SACE was measured in 29 patients with histologically proven sarcoidosis. The new SACE genotype based normal range identified 69% of these patients, an improvement of 33.5% on the previous normal range which identified only 51.7% of our patients with sarcoidosis.[2] Importantly, our work has also been independently confirmed.[3]

We suggest that the genotype based SACE normal range should be determined locally (especially for different racial populations[4]) to improve its sensitivity in the diagnosis of active sarcoidosis.

PANKAJ SHARMA
BHF Clinician Scientist
Clinical Pharmacology Unit,
University of Cambridge,
Cambridge, UK
IAN SMITH
JOHN SCHNEERSON
Papworth Hospital,
Papworth Everard,
Cambridge CB3 8RE, UK

1 Marshall BG, Shaw RJ. Association between angiotensin II receptor gene polymorphism and serum angiotensin converting enzyme (SACE) activity in patients with sarcoidosis. *Thorax* 1998;**53**:439–40.
2 Sharma P, Smith I, Maguire G, *et al*. Clinical value of ACE genotyping in diagnosis of sarcoidosis. *Lancet* 1997;**349**:1602–3.
3 Csaszar A, Halmos B, Palicz T, *et al*. Interpopulation effect of ACE I/D polymorphism on serum concentration of ACE in diagnosis of sarcoidosis. *Lancet* 1997;**350**:518.
4 Tozman ECS. Sarcoidosis: clinical manifestations, epidemiology, therapy, and pathophysiology. *Curr Opin Rheumatol* 1991;**3**:155–9.

AUTHORS' REPLY We thank Drs Smith and colleagues for their welcome comments regarding their excellent paper published in the *Lancet* last year. We are delighted that their findings concord with the hypothesis we raised in our editorial on serum angiotensin converting enzyme polymorphisms. We apologise for not referring to it in the text.

B G MARSHALL
Department of Respiratory Medicine,
National Heart and Lung Institute,
Imperial College School of Medicine,
London W2 1PG, UK

BOOK REVIEW

Lung Cancer. Second Edition. Roth JA, Cox JD, Hong WK, eds. (Pp 394, hardback; £75.00). UK: Blackwell Science, 1998. ISBN 0 8654 2573 6.

The editors of this second edition have created a series of detailed reviews of recent advances in lung cancer. Each chapter presents a succinct review of a relevant topic with a detailed and very useful reference list. There are chapters dealing with susceptibility and predisposition to lung cancer and clinical evaluation. Several chapters are devoted to recent advances in therapy, including surgery, radiotherapy, chemotherapy and combination therapy. Newer methods of detection are discussed in two chapters and finally novel experimental approaches to the treatment of lung cancer are discussed in three chapters. Most of the chapters are predominantly text with limited use of tables, graphics and images. However, each of the chapters is written in a succinct way that makes for easy reading.

This would be a useful text to bring one up to date with recent advances. In the preface the editors state that they "hope that this book will provide a succinct and timely summary of recent advances and new research in the field of lung cancer". They have fulfilled this aim admirably. —DB

NOTICES

Scadding-Morriston Davies Joint Fellowship in Respiratory Medicine 1999

This fellowship is available to support visits to medical centres in the UK or abroad for the purpose of undertaking studies related to respiratory medicine. Applications are invited from medical graduates practising in the UK, including consultants and irrespective of the number of years in that grade. There is no application form but a curriculum vitae should be submitted together with a detailed account of the duration and nature of the work and the centres to be visited, confirming that these have agreed to provide the facilities required. Please state the sum of money needed for travel and subsistence. A sum of up to £15 000 can be awarded to the successful candidate, or the sum may be divided to support two or more applications. Applications should be sent to Dr I A Campbell, Secretary to the Scadding-Morriston Davies Fellowship, Llandough Hospital, Penarth, Vale of Glamorgan CF64 2XX, UK by 31 January 1999.

Basic Clinical Allergy

The 13th course on Basic Clinical Allergy will be held at the National Heart & Lung Institute, Imperial College School of Medicine, London on 15–19 March 1999. CME approval has been sought (1998 course maximum 30 credits). The main topics will include: basic mechanisms in allergic disease; cells in allergic disease; immunotherapy; allergic rhinitis; asthma (aetiology and pathogenesis); recent trends in asthma research; treatment of asthma; major allergic problems. Further details can be obtained from the Education Centre, National Heart & Lung Institute, Imperial College School of Medicine, Dovehouse Street, London SW3 6LY, UK (telephone +44 171 351 8172; fax +44 171 351 8246; e-mail a.c.allen@ic.ac.uk; www.med.ic.ac.uk/dh/div/mtgs.htm).