LETTERS TO THE EDITOR

Adrenocortical activity in children

I read with interest the report on adrenocortical activity in children receiving inhaled corticosteroids by Lipworth and colleagues[1] but am perplexed by the relevance to clinical practice. Although it is possible to demonstrate biochemical evidence of suppression of the hypothalamo-pituitary-adrenal axis with sensitive tests such as the measurement of overnight urinary cortisol excretion, this is likely to have little clinical significance. There is to date no evidence that inhaled corticosteroids taken at recommended doses have caused clinically significant adrenal suppression.

The major side effect of inhaled corticosteroids in childhood is growth suppression.[2 3] In a group of children aged 7–9 years who received beclomethasone dipropionate at a dose of 400 μg/day there was no significant effect on overnight urinary cortisol. Despite this, there was clinically relevant growth suppression in those children who received beclomethasone dipropionate (difference of 1 cm in growth over seven months of study).[3]

I therefore feel that the authors' conclusions are premature as no conclusions on the safety profile of either budesonide or fluticasone propionate can be derived from this study.

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1 Lipworth BJ, Clark DJ, McFarlane LC. Adrenocortical activity with repeated twice daily dosing of fluticasone propionate and budesonide given via a large volume spacer to asthmatic school children. *Thorax* 1997;**52**:686–9.
2 Tinkelman DG, Reed CE, Nelson HS, Offord KP. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. *Pediatrics* 1993;**92**:64–77.
3 Doull IJM, Freezer NJ, Holgate ST. Growth of prepubertal children with mild asthma treated with inhaled beclomethasone dipropionate. *Am J Respir Crit Care Med* 1995;**151**:1715–9.

AUTHOR'S REPLY Adrenal suppression, and particularly overnight urinary cortisol, is a sensitive marker of potential systemic bioactivity with inhaled corticosteroids.[1] It has been shown that suppression of 24 hour urinary cortisol was associated with a blunted dynamic response to stimulation with low dose (0.5 μg) ACTH in children receiving inhaled corticosteroids.[2] Inhaled fluticasone propionate is licensed to be used in children at doses up to 200 μg/day although many paediatricians and general practitioners use higher doses which have been shown to exhibit significant adrenal suppression.[3]

The observed effects of beclomethasone dipropionate on growth in the study reported by Doull *et al*[4] over a seven month period are rather short term and do not take into account intermittent growth spurts which occur in the longer term over several years during normal childhood. Indeed, in a meta-analysis of studies with inhaled beclomethasone dipropionate there was no association between its use and the adverse effect of diminished stature.[5] This is supported by a large six year cohort follow up study with budesonide where there was no significant effect on growth velocity at doses up to 400 μg/day.[6] Furthermore, inhaled corticosteroids do not appear to exert any effect on final height achieved in adulthood.[7]

I therefore remain firmly of the opinion that, at conventional doses of up to 400 μg/day, inhaled corticosteroids have a high therapeutic ratio with little if any long term risk for significant systemic toxicity in children. The potential for any degree of systemic bioactivity will be minimised by stepping down in order to achieve the lowest possible maintenance dose required to achieve effective asthma control and quality of life.

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1 Lipworth BJ, Seckl JR. Measures for detecting systemic bioactivity with inhaled and intranasal corticosteroids. *Thorax* 1997;**52**:476–82.
2 Broide J, Soferman R, Kivity F, *et al*. Low dose adrenocorticotropin tests reveal impaired adrenal function in patients taking inhaled corticosteroids. *J Clin Endocrinol Metab* 1995;**80**:1243–6.
3 Clark DJ, Clark RA, Lipworth BJ. Adrenal suppression with inhaled budesonide and fluticasone propionate given by a large volume spacer to asthmatic children. *Thorax* 1996;**51**:941–3.
4 Doull IJM, Freezer NJ, Holgate ST. Growth of prepubertal children with mild asthma treated with inhaled beclomethasone dipropionate. *Am J Respir Crit Care Med* 1995;**151**:1715–9.
5 Allen DB, Mullen M, Mullen B. A meta-analysis of the effect of oral and inhaled corticosteroids on growth. *J Allergy Clin Immunol* 1994;**93**:967–76.
6 Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;**88**:373–81.
7 Silverstein JW, Yunginger CE, Reed T, Patterson D, Zimmerman JT, O'Fallon WM. Attained adult height after childhood asthma: effect of glucocorticoid therapy. *J Allergy Clin Immunol* 1997;**99**:466–74.

Fenoterol and asthma deaths

After reading the correspondence on this vexatious topic published in the August issue of *Thorax*[1 2] I am more deeply puzzled than ever by the acrimony displayed by the Wellington and Auckland medical schools over the role played by fenoterol in the 1977/82 "epidemic" of asthma deaths in New Zealand.

I visited that country in 1982 at the invitation of its Asthma Foundation which hoped I might be able to shed some light on the cause of the "epidemic" that had given rise to serious public concern. I suspected that a therapeutic innovation, available without prescription, analogous to that of Medihaler Iso Forte – a high dose preparation of isoprenaline that had been implicated the earlier UK "epidemic" – might be responsible. Thus, when I was informed that vast numbers of nebulisers delivering large doses of salbutamol or terbutaline were being used in excess by patients with severe asthma anxious to avoid or at least defer the payment of doctors' fees, I felt it was not unreasonable for me to blame the indiscriminate and uncontrolled use of these nebulisers for the increased asthma mortality. My views on that matter, published in both the British and New Zealand medical journals,[3 4] evoked heated criticism to which I responded vigorously.[5] I gave no further thought to the controversy until it was claimed by the Wellington medical school in 1989 that fenoterol by inhalation was the principal cause of that "epidemic" of asthma deaths. That may or may not be the case, but in retrospect I find it incomprehensible that the words "fenoterol" (or "Berotec") did not cross the lips of any of the many respiratory physicians I met during my visit to New Zealand in 1982. I was clearly given to understand that the only β_2 agonists used in the treatment of asthma at that time were salbutamol and terbutaline. Had I been informed of the widespread prescription of fenoterol inhalers during the 1977/82 "epidemic" I would certainly have questioned its safety.

As I pointed out in a letter to the *New Zealand Medical Journal* published on 11 April 1990, one metered dose (then 200 μg) of fenoterol was equivalent to four metered doses (400 μg) of salbutamol and overuse of a fenoterol inhaler would be four times more dangerous in terms of adverse cardiac and metabolic side effects than similar use of a salbutamol inhaler. In effect, therefore, overuse of a fenoterol inhaler in patients with severe acute asthma must have carried a similar risk to that of overuse of other β_2 agonists delivered by nebuliser and overuse of Medihaler Iso Forte in the 1970s which must all have contributed to "epidemics" of asthma deaths.

I would urge my colleagues in New Zealand to accept that view, which may seem simplistic but carries more conviction with practical clinicians than the sterile semantics that have occupied so much space in medical journals during the past few years.

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1 Pearce N, Burgess C, Crane J, Beasley R. Fenoterol, asthma deaths, and asthma severity: confounding or confusion? *Thorax* 1997;**52**:750.
2 Garrett JE, Lanes S, Rea HH, Kolbe J. Fenoterol, asthma deaths, and asthma severity: confounding or confusion? *Thorax* 1997;**52**:750–1.
3 Grant IWB. For debate: asthma in New Zealand. *BMJ* 1983;**286**:374–7.
4 Grant IWB. For debate: asthma in New Zealand. *NZ Med J* 1983;**96**:167–70.
5 Grant IWB. Asthma in New Zealand. *BMJ* 1983;**286**:718.

Home environment and asthma

Butland and colleagues found that increased use of non-feather pillows was the only domestic indoor exposure that appeared to explain a 20% increase in the population prevalence odds of wheeze in children in Croydon, London between 1978 and 1991.[1] This extends their previous epidemiological studies on synthetic material-filled pillows as a risk factor for severe asthma in adolescence.[2] In that study they hypothesised that synthetic material-filled pillows may release volatile organic compounds, possibly influencing the airway response to inhaled allergens.

In their latest study no hypothesis for the association between wheezing and the use of non-feather pillows is put forward. Environmental exposures to allergens were not directly examined and, in particular, levels of the major house dust mite allergen Der p 1 in feather and non-feather pillows were not available. They discard the possibility that house dust mite allergens could be a reason for the increased prevalence of wheeze based on a study that showed no change in domestic reservoir levels of Der p 1 between 1979 and 1989.[3] However, in that study Der p 1 levels were measured in dust samples from mattresses, bedroom floors, and living room carpets, not from pillows.

We have recently demonstrated and confirmed in a follow up study that synthetic pillows contain a mean of eight times more total Der p 1 allergen than feather pillows.[4 5] Given that people spend many hours in close contact with pillows, it could be argued that exposure to higher levels of Der p 1 in non-feather pillows may explain the findings of Butland and colleagues relating the increased use of non-feather pillows with an increase in the prevalence of wheeze. Recent evidence shows clear correlations between exposure to house dust mite allergens in the bed and the severity of various parameters used in the measurement of asthma severity.[6]

We agree with Butland and colleagues that further studies are required to explain the link between increased wheeze and the use of non-feather pillows – not only toxicological and epidemiological studies, as suggested by the authors, but further investigations of allergen levels in different types of pillows to determine whether our New Zealand based findings are applicable in the UK and elsewhere.

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1 Butland BK, Strachan DP, Anderson HR. The home environment and asthma symptoms in childhood: two population based case-control studies 13 years apart. *Thorax* 1997;**52**:618–24.
2 Strachan DP, Carey IM. Home environment and severe asthma in adolescence: a population based case-control study. *BMJ* 1995;**311**:1053–6.
3 Sporik R, Holgate ST, Platts-Mills TAE, Cogswell JJ. Exposure to house-dust mite allergen (Der p 1) and the development of asthma in childhood. *N Engl J Med* 1990;**323**:502–7.
4 Kemp TJ, Siebers RW, Fishwick D, O'Grady GB, Fitzharris P, Crane J. House dust mite allergen in pillows. *BMJ* 1996;**313**:916.
5 Crane J, Kemp T, Siebers R, Rains N, Fishwick D, Fitzharris P. Increased house dust mite allergen in synthetic pillows may explain increased wheezing. *BMJ* 1997;**314**:1763–4.
6 Custovic A, Taggart S, Francis H, Chapman M, Woodcock A. Exposure to house dust mite allergens and the clinical activity of asthma. *J Allergy Clin Immunol* 1996;**98**:64–72.

NOTICES

Sixth Bronchitis Symposium

The Sixth Bronchitis Symposium on the link between asthma and COPD will be held in Groningen, The Netherlands on 24–26 August 1998. For further information contact the Secretariat Department of Pulmonary Diseases, PO Box 30.001, 9700 RB Groningen, The Netherlands. Telephone: +31 50 361 2357 or 3532. Fax: +31 50 361 9320. E mail: e.piek@int.azg.nl or c.w.verver@int.azg.nl.

COPD: New Developments and Therapeutic Opportunities

A course on "COPD: New Developments and Therapeutic Opportunities" organised by Professor Peter Barnes will be held at Imperial College School of Medicine at the National Heart & Lung Institute in collaboration with the Royal Brompton Hospital on 7–8 July 1998. For further information please contact the Postgraduate Education Centre, National Heart & Lung Institute, Dovehouse Street, London S3 6LY, UK. Telephone: 0171 351 8172. Fax: 0171 376 3442.

CORRECTION

Survival of patients with severe α_1-antitrypsin deficiency

In a paper entitled "Survival of patients with severe α_1-antitrypsin deficiency with special reference to non-index cases" by Seersholm, Kok-Jensen and Dirksen published in *Thorax* in 1994 [1] it has been pointed out by Dr James K Stoller of the Cleveland Clinic, Cleveland, Ohio, USA that the labels on the key of figure 1 on page 696 were transposed. A correct version of the figure is shown below.

1 Seersholm N, Kok-Jensen A, Dirksen A. Survival of patients with severe α_1-antitrypsin deficiency with special reference to non-index cases. *Thorax* 1994;**49**:695–8.

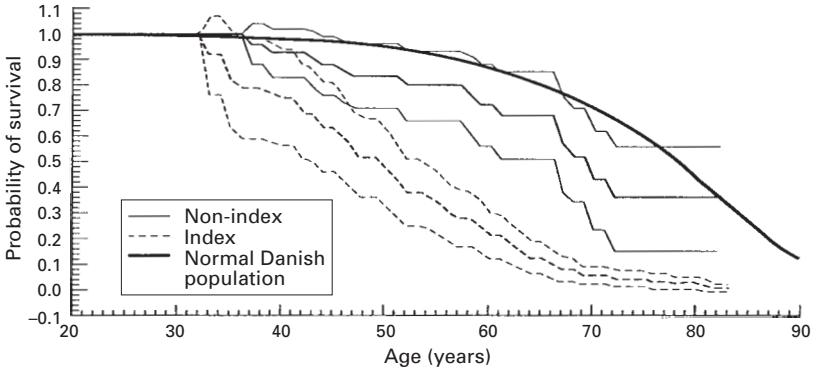

Figure 1 Cumulative probability of the survival time of index cases and non-index cases with 95% confidence intervals. Survival of the normal Danish population is shown for comparison.