LETTERS TO THE EDITOR

Tests for growth hormone secretion

SIR,—We were interested in the correspondence between Dr Addy and Professor Brook and Dr Hindmarsh on detecting organic illness through assessment of height velocity.^{1,2} The question, however, is academic and their arguments theoretical since, as we have recently shown, the assessment of height velocity in individuals is so imprecise as to be clinically meaningless. There is effectively no correlation between successive velocities, so that a 12 month velocity cannot possibly identify anyone.^{3,4}

The Wessex Growth Study provides a practical demonstration of the problem. Thirty (17%) of the original cohort of 174 school entrants below the third height centile had identifiable organic disease. Eighteen of these were monitored over a period of three years alongside a cohort of 78 short 'normal' children in whom all pathology had been excluded. The height velocity of four of the short 'normal' children and two of those with organic disease was deemed to be on or below the third centile for velocity after the first year. Over the next 12 months, two of the short 'normal' subjects, and three of those with organic disease, were growing at a rate below the third centile, but the identity of the 'poor growers' changed from year one to year two.

We should abandon the notion that low 12 month velocities will effectively identify pathology. The children in the Wessex Growth Study with organic causes of short stature were identified at the beginning of year one on the basis of height screening alone.

L D VOSS
The Wessex Growth Study,
Room CD53,
Southampton General Hospital,
Southampton SO9 4XY

1 Brook CGD, Hindmarsh PC. Tests for growth hormone secretion. *Arch Dis Child* 1991;66:85-7.

2 Addy DP. Tests for growth hormone secretion. *Arch Dis Child* 1991;66:749.

3 Voss LD, Bailey BJR, Cumming K, Wilkin TJ, Betts PR. The reliability of height measurement. *Arch Dis Child* 1990;65:1340-4.

4 Voss LD, Wilkin TJ, Bailey BJR, Betts PR. The reliability of height and height velocity in the assessment of growth (the Wessex Growth Study). *Arch Dis Child* 1991;66:833-7.

The reliability of height and height velocity in the assessment of growth

SIR,—Voss *et al* make a good point when they emphasise the fact that height velocity is much worse affected by measurement error than height itself, partly because it involves two measurements both subject to error and partly because the normal variability of the error free quantity is much smaller.¹ But it is not clear that their conclusion follows, that velocity charts are no more discriminating than height charts in the screening context that they consider. To establish such a conclusion it would be necessary to have information not

only on the normal children on which the charts are based but also on the abnormal children that the screening exercise is intended to detect.

Growth standard charts can be described as providing age specific normal ranges or reference values and their properties need to be assessed in terms such as sensitivity, specificity, and predictive values that are familiar in discussions of these topics. When only a single measurement is available it is usual to express it as a centile position on the height chart and to investigate the child if this position is below an arbitrary level, commonly the third centile. Such a procedure provides a protection against false positive errors; if applied to children from the normal population it ensures that not more than 3% of them will be unnecessarily investigated. It says nothing about the frequency with which children who are genuinely growth retarded will be missed by the screen. It is important to notice that the chart provides centiles for the *measured* height; the 'true' height of a child does not enter into the argument.

Exactly the same considerations apply to growth velocity. If children whose *measured* velocities fall below the third centile on the velocity chart are investigated, only 3% of those from the normal population will be included. Once again, the number of abnormal children picked up by such a screen is unknown, and once again the fact that a child's 'true' velocity may be rather far above (or below) its measured value is not to the point.

Only studies which include children known to be abnormal are capable of distinguishing between the properties of rival screening methodologies. It is natural to suppose that the two measurements included in a velocity are capable of providing more information than a single measurement; the question is whether the value of the extra information outweighs the delay which its acquisition involves.

M J R HEALY
17 Moreton Avenue,
Harpenden,
Herts AL5 2EU

1 Voss LD, Wilkin TJ, Bailey BJR, Betts PR. The reliability of height and height velocity in the assessment of growth (the Wessex Growth Study). *Arch Dis Child* 1991;66:833-7.

Mr Bailey and Ms Voss comment:

Professor Healy is right to stress that velocity could, in some cases, be a useful discriminator in a screening context, but in our paper we were concerned mainly with the estimation of height velocities, and we showed that the imprecision attached to these estimations can be considerable. Unfortunately, disease specific growth charts are rare and more are needed. In the case of Turner's syndrome such a chart is available and the mean velocity is shown to be lower than normal.^{1,2} If one were to screen for the disease by identifying all girls with a velocity less than the 3rd centile on the normal velocity chart, between the ages of 5-6 years, this would locate about 25% of girls with Turner's syndrome. On the other hand, screening for those below the 3rd centile for *height*, using the normal height chart at age 5 years, would pick out over 50% of these girls. (Actually, screening by height and then by velocity would be even better as girls with Turner's syndrome are on average shorter than normal and they also fall further behind

with increasing age. As Professor Healy points out, however, the extra information gained may not be worth the delay involved.)

The problem of choosing an appropriate method of screening is further demonstrated by our letter in this issue regarding the comments of Dr Addy.³ In this, we describe how children in the Wessex Growth Study with pathology could not be distinguished from healthy children by their velocity over a single 12 month period. Certainly much work is yet to be done, and data collected on a variety of organic diseases, before it is possible to evaluate rival screening methodologies.

1 Lyon AJ, Preece MA, Grant DB. Growth curve for girls with Turner's syndrome. *Arch Dis Child* 1985;60:932-5.

2 Ranke MB, Pfluger H, Rosendahl W, *et al*. Turner syndrome: spontaneous growth in 150 cases and review of literature. *Eur J Pediatr* 1983;141:81-8.

3 Addy DP. Tests for growth hormone secretion (letter). *Arch Dis Child* 1991;66:749.

Terbutaline powder in asthma exacerbations

SIR,—Inhaled β_2 agonists are the most efficient means of relieving acute bronchoconstriction in asthmatic children. However, inhalation technique with a metered dose inhaler is often unsatisfactory particularly in young dyspnoeic children. Spacers have been shown to be useful in this setting.^{1,2} Asthmatic children may be reluctant to carry spacers during daily activities because they are cumbersome. The Turbuhaler (Astra, Turbuhaler in the UK) is a new multidose breath actuated pure powder inhaler available for the administration of terbutaline. It can be triggered by an airflow of 22 l/min; this is reached by almost all children over 5 years old in a stable condition and even by those with moderately acute asthma.³ Terbutaline given with a Turbuhaler is effective in the treatment of exercise induced asthma.⁴ It has not been reported yet if terbutaline with Turbuhaler is effective in children with acute asthma.

Twenty two children attending the hospital with acute wheeze were included in an open, randomised, parallel group study comparing the efficacy of 0.5 mg of terbutaline given either with a Turbuhaler or with a metered dose inhaler attached to Nebuhaler (Astra). Administration of the drug was carefully supervised and consisted of one inhalation by the Turbuhaler or two consecutive puffs of terbutaline introduced separately by the Nebuhaler at one minute intervals as previously described.^{1,3} Before, 15 and 30 minutes after treatment we measured specific airway resistance (sRaw in cm H₂O/l/s, body plethysmograph 2800, Physiosystem), forced expiratory

Results in efficacy of the two systems after inhaling 500 µg of terbutaline. Results are mean (SD)

Variable	Nebuhaler	Turbuhaler
sRaw (cm H ₂ O/l/s):		
Initial	14.1 (3.5)	13.5 (3.4)
15 Minutes	7.4 (2.0)	6.4 (1.6)
30 Minutes	6.5 (1.7)	6.4 (1.9)
FEV ₁ (ml):		
Initial	1200 (390)	1610 (510)
15 Minutes	1530 (640)	1820 (610)
30 Minutes	1560 (600)	1830 (580)
PEFR (l/min):		
Initial	184 (47)	217 (74)
15 Minutes	214 (56)	265 (75)
30 Minutes	233 (54)	276 (85)

volume in one second (FEV₁ in ml, Pulmonet, Physiosystem), peak expiratory flow rate (PEFR in l/min, mini Wright), heart rate (pulses/min). Results as mean (SD) were compared by analysis of variance. The two groups (11 in each) did not significantly differ in age (Nebuhaler: 8.5 years, range 4.5–13 and Turbuhaler: 10 years, range 6–14). There was no difference between the baselines for any variables. Results in efficacy are presented in the table. Both treatments were effective at 15 minutes to improve lung function compared with baseline ($p < 0.01$ for all variables) with little further improvement at 30 minutes. No difference between treatments could be demonstrated at any time for these variables. No cardiovascular effect was observed in the Nebuhaler group. In the Turbuhaler group, a slight increase in heart rate (median: 80 to 86 pulses/min) was observed.

In conclusion, inhalation of terbutaline via Turbuhaler gave similar increase in lung function as a metered dose inhaler plus Nebuhaler in children above the age of 5 years with moderately acute exacerbation of asthma. The Turbuhaler is easy to use and to carry and can be recommended for paediatric use.

P RUFIN
M R BENOIST
J DE BLIC
G BRAUNSTEIN
P SCHEINMANN
*Service d'Allergologie et de
Pneumologie Infantiles,
Hôpital des Enfants Malades,
149 rue de Sévres,
75743 Paris and
Laboratoire Astra-France,
92000 Nanterre, France*

- 1 Pool JB, Greenough A, Gleeson JGA, Price JF. Inhaled bronchodilator treatment via the nebulizer in asthmatic patients. *Arch Dis Child* 1988;63:188–91.
- 2 Benoist MR, Rufin P, De Blic J, Scheinmann P. Nebuhaler in young asthmatic children. *Arch Dis Child* 1988;63:997.
- 3 Pedersen S, Hansen OR, Fuglsang G. Influence of inspiratory flow rate upon the effect of a turbuhaler. *Arch Dis Child* 1990;65:308–10.
- 4 Lopes Dos Santos JM, Costa H, Stahl E, Wiren JE. Bricanyl turbuhaler and ventolin rotahaler in exercise-induced asthma in children. *Allergy* 1991;46:203–5.

Evaluation of a pen injector system for growth hormone treatment

SIR,—We agree with many of the comments of Gluckman and Cutfield about convenience and compliance using a pen injector system (0.5 unit increments up to a maximum of 4.0 units per injection) and the important role of a nurse educator.¹ The authors have demonstrated that if convenient doses of growth hormone using a pen injection system are administered, such as 2 or 4 units (which by serendipity fit the 0.5 unit increments and divide into 16 with no residual) then indeed this pen system is accurate and efficient. However the authors have convincingly argued that traditional fixed dose regimens of 4 units three times a week are obsolete and that the dose of growth hormone should be related to the patient's size. If the dose schedule of growth hormone is related to either weight or surface area, then usually the resulting dose will not be convenient using this pen injector system, which may lead to wastage of growth hormone at the end of the cartridge vial. After four growth hormone injections of 3.5 units, what happens to the 2 units remaining in the cartridge vial?

Dosage for small children may prove diffi-

cult, because of 0.5 units per increment dose selection. For example, a child of 0.6 m² treated with a physiological replacement regimen of 15 units/m²/week as a daily injection, will necessitate large steps in dose schedule. The difference between 1.0 and 1.5 units per injection is the equivalent of dosages of 11.5 and 17.5 units/m²/week respectively, which makes an accurate dose schedule impossible to administer. Of course, there remains the possibility of having varying doses on different days of the week, but this would probably be counterproductive for both convenience and compliance. Although the optimum dose regimen for growth hormone administered during the pubertal growth spurt is unknown, many authors have recommended an increase in dose.² The limitation of this pen system to a maximum of 4 units per injection makes a daily regimen of 20 or 30 units/m²/week difficult to achieve in pubertal children. In a similar fashion, pharmacological doses of growth hormone using such a pen system for girls with Turner's syndrome will have severe limitations; because of the restriction of maximum dose, a schedule of 30 units/m²/week will restrict the use of this pen system to a child of less than 0.93 m² surface area.

We agree that pen injection systems are a considerable advance in convenience to patients. However, if optimum treatment regimens are prescribed, these should not be introduced in a system with inflexible dose selection which may be detrimental to accurate dose schedules and potentially wasteful of expensive resources.

G HAMILL
R STANHOPE
*Medical Unit,
Institute of Child Health,
30 Guilford Street,
London WC1N 1EH*

- 1 Gluckman PD, Cutfield WS. Evaluation of a pen injector system for growth hormone treatment. *Arch Dis Child* 1991;66:686–8.
- 2 Vanderschueren-Lodeweyckx M, van den Broeck J, Wolter R, Malvaux P. Early initiation of growth hormone treatment: influence on final height. *Acta Paediatr Scand* 1987;337 (suppl):4–11.

Dr Cutfield and Professor Gluckman comment: Sister Hamill and Dr Stanhope appear to have misinterpreted the major theme of our paper. We addressed patient perception and satisfaction of growth hormone delivery systems, not growth hormone dose regimens. Publications to date have largely ignored patients' perception of growth hormone delivery. As the primary goal of growth hormone treatment is to promote greater psychosocial wellbeing, achieved in part by attempting to increase adult height, it is essential to consider patient acceptance of the method of treatment. In our study most children and their families preferred a pen to a syringe delivery system. As children self administered at an earlier age with the pen than with the syringe, we presume these are real differences perceived by the patients. If the prime motive of treatment is the improvement in psychosocial wellbeing, then use of the injector pen, despite a minor compromise in dose regimen, must be considered by the physician in the choice of treatment modality.

If there is a real advantage to the extreme accuracy of the regimens proposed by Hamill and Stanhope, hopefully pharmaceutical companies will respond by producing vials of varying growth hormone concentrations to allow more precise titration of dose using pens or other easy use administration devices.

Day case ligation of patent ductus arteriosus in preterm infants

SIR,—I read with interest about the brave new world of day case ligation of patent ductus arteriosus (PDA) in preterm infants¹ and was relieved to learn that infants were not discharged home on the day of surgery. The authors are to be commended on developing a safe and efficient service but are not justified in concluding in their abstract that 'if it is carried out early [ligation of PDA] will reduce the time before extubation and discharge from the intensive care unit'. They present no control data to support this conclusion. Indeed they refer in their discussion to a multicentre comparative study which showed no significant difference in mortality, duration of respiratory support, and number of days in hospital between infants receiving medical or surgical treatment.²

My own experience (also uncontrolled) over the last 10 years in a neonatal intensive care unit serving approximately 5500 births a year is that surgical ligation of PDA in preterm infants is very rarely necessary, only one infant having been operated on in the neonatal period. During this time we cared for 492 infants of birth weight ≤ 1500 g of which 173 had birth weight ≤ 1000 g. Our survival rates compare favourably with the other four large Trent region centres,³ and long term ventilation (beyond 14 days) is now rarely needed.

Fluid restriction, early use of indomethacin, effective treatment of underlying lung disease including dexamethazone, and above all patience will allow the preterm infant's duct to close in all but exceptional cases. I am very worried at the apparent early resort to surgery which many appear to adopt.

It is not enough to show an operation is safe and readily available, it must also be shown to be necessary.

K L DODD
*Derbyshire Children's Hospital,
North Street,
Derby DE1 3BA*

- 1 Satur RM, Walker DR, Dickinson DF. Day case ligation of patent ductus arteriosus in preterm infants: a 10 year review. *Arch Dis Child* 1991;66:477–80.
- 2 Gersony WM, Peckham GJ, Elisson RC, Miettinen OS, Nadas AS. Effect of indomethacin in premature infants with patent ductus arteriosus: results of a national collaborative study. *J Pediatr* 1983;102:895–906.
- 3 Field D, Hodges S, Mason E, Burton P. Survival and place of treatment after premature delivery. *Arch Dis Child* 1991;66:408–11.

Drs Satur and Dickinson comment:

As cardiologists and cardiac surgeons at a supraregional centre for paediatric cardiac surgery we see a highly selected group of preterm infants with a patent arterial duct, namely those referred by paediatricians specifically for ligation of the duct because the measures suggested by Dr Dodd had either failed or were considered inappropriate. Our conclusions at the end of the paper relate only to this group of patients. We have shown that if a paediatrician feels that active surgical management of the duct is necessary he or she should not delay because of the perceived hazards of transportation and operation. However we would agree entirely with the statement that the operation must be shown to be necessary. Because of the selected nature of our patients we cannot address the wider issues relating to the management of the patent arterial duct in the neonatal unit. We