

## LETTERS TO THE EDITOR

### Does growth hormone treatment improve final height attainment of children with intrauterine growth retardation?

SIR,—The potential indications for the therapeutic use of growth hormone have widened with the availability of more abundant supplies of growth hormone. For some of the new potential indications such as Turner's syndrome, intrauterine growth retardation (IUGR), etc, the growth-promoting benefits of growth hormone have usually been assessed in the short term by comparing the changes in height velocity SD score during the first treatment year and the pretreatment year, and, in some instances, by quantitating the psychological benefit gained by improved growth during the middle childhood years. In the long term the benefits of growth hormone can be assessed by comparing final height in a treated group with either that achieved in an untreated group or with the original pretreatment height prediction of the treated group.

In their recent article on the use of growth hormone in children with IUGR, Stanhope *et al* present three year growth data and suggest that the results are rather disappointing.<sup>1</sup> This conclusion is based on the fact that the height for bone age score did not change significantly over the three years of the study. With knowledge of the natural history of IUGR, Stanhope *et al* do, however, still believe that their growth hormone treated children may attain a greater final height than would have been the case if they had remained untreated. In their discussion Stanhope *et al* state that 'only the continuation of clinical trials such as this until final height will answer the question'. Others might feel that the current results are sufficiently disappointing for the study to be concluded now.

Certainly if the design of the study remains in its present form then, as the authors acknowledge, there is a real possibility that growth hormone treatment will reduce the duration of puberty and compromise final height prognosis. Thus, I would suggest that, if the study is to continue, one of their groups of IUGR children, who received growth hormone during prepubertal life, should not receive growth hormone during puberty. Furthermore, their results emphasise that individual children with IUGR seen by paediatricians around the UK should not be offered growth hormone on an *ad hoc* basis.

Finally, if the authors believe that possible growth hormone treatment induced gain in height for IUGR children can only be interpreted when the children attain final height, is much learnt by publishing the three year growth data?

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1 Stanhope R, Preece MA, Hamill G. Does growth hormone treatment improve final height attainment of children with intrauterine growth retardation? *Arch Dis Child* 1991;66:1180-3.

### Dr Stanhope and Professor Preece comment:

We agree with Dr Shalet that there are many subgroups of children with short stature who may benefit from growth hormone treatment. However the only proved indication to final height is growth hormone deficiency.<sup>1</sup> The reason why we published our three year data of growth hormone treatment in children with intrauterine growth retardation (IUGR) was to emphasise that at the present time such treatment should remain part of a clinical trial and not be offered on an *ad hoc* basis. Height prediction depends on epiphyseal maturation, which is relatively inaccurate over short periods of time, especially in dysmorphic syndromes. However, we believe the natural history of the growth of children with IUGR is sufficiently disappointing to allow our trial to continue.<sup>2</sup>

Our study has been modified after one year,<sup>3</sup> when the results from the lower dose growth hormone regimen were disappointing in terms of short term growth rate, and we may modify our trial again. Although growth hormone treatment may increase the rate of pubertal progress in a dose dependent fashion, this phenomenon has only been described in children with isolated growth hormone deficiency.<sup>4</sup> Although growth hormone insufficiency is common among children with IUGR,<sup>5</sup> our patients were carefully screened to avoid this ambiguity.

We believe that the continuation of this trial is justifiable and having done so, it is our duty to report the findings.

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- 2 Davis PSW, Valley R, Preece MA. Adolescent growth and pubertal progress in the Silver-Russell syndrome. *Arch Dis Child* 1988;63:130-5.
- 3 Stanhope R, Ackland F, Hamill G, Clayton J, Jones J, Preece MA. Physiological growth hormone secretion in response to growth hormone treatment in children with short stature and intrauterine growth retardation. *Acta Paediatr Scand* 1989; suppl 349:47-52.
- 4 Stanhope R, Uruena M, Hindmarsh P, Leiper AD, Brook CGD. Management of growth hormone deficiency through puberty. *Acta Paediatr Scand* 1991; suppl 372:47-52.
- 5 Ackland FM, Stanhope R, Eyre C, Hamill G, Jones J, Preece MA. Physiological growth hormone secretion in children with short stature and intra-uterine growth retardation. *Horm Res* 1988;30:241-5.

### Kawasaki disease

SIR,—I read with interest the annotation on Kawasaki disease by Levin *et al*.<sup>1</sup> I would like to draw attention to the fact that this disease, like any other vasculitis, can have a predominantly neurological presentation, with an encephalopathic/encephalitic illness. I have seen three such patients who all presented with high fever, diminished consciousness, a minimal increase in lymphocytes in the cerebrospinal fluid with normal protein and glucose, and a rash. In one child, a 7 year old, the most striking physical sign was bilateral papilloedema.

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1 Levin M, Tizard EJ, Dillon MJ. Kawasaki disease: recent advances. *Arch Dis Child* 1991; 66:1369-72.

### Late intravenous gammaglobulin treatment in Kawasaki syndrome

SIR,—We wish to comment on the interesting article on intravenous gammaglobulin treatment for Kawasaki disease in which the Archivist mentioned it seems reasonable to treat if the disease is still active.<sup>1</sup> Indeed, the results published by Marasini *et al* suggest a favourable effect of gammaglobulins on established coronary abnormalities, at least in the midterm follow up.<sup>2</sup>

They studied two groups of children with a similar image of coronary abnormalities. The first group (nine children) was treated with aspirin (100 mg/kg/day) until the fever disappeared, followed by aspirin (5 mg/kg/day) and dipyridamole (5 mg/kg/day). The second group (seven children) received intravenous gammaglobulins (400 mg/kg/day) for five days after the 10th day from the onset of the disease, when coronary artery abnormalities had already developed.

In the first group four patients had a complete resolution of their abnormalities. Five had persistent abnormalities including three with myocardial infarction (one died from his myocardial infarction). In the second group, all coronary abnormalities had resolved during follow up.

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- 1 Archivist . . . and while on the subject. *Arch Dis Child* 1991;66:1407.
- 2 Marasini M, Pongiglione G, Gazzolo D, Campelli A, Ribaldone D, Caponnetto S. Late IV gammaglobulin treatment in infants and children with Kawasaki disease and coronary artery abnormalities. *Am J Cardiol* 1991;68:796-7.

### Inherited metabolic diseases in the sudden infant death syndrome

SIR,—Holton and his coworkers set out to investigate among other causes the prevalence of medium chain acyl CoA dehydrogenase deficiency (MCAD) in cases of sudden infant death syndrome (SIDS).<sup>1</sup> They assert that the claim 'MCAD deficiency could cause 3% of cases of SIDS' is not supported by their findings.

Unfortunately their work, while exhaustive in its scope, demonstrates the difficulty in looking for rare events in small samples. Using binomial probability theorem

$$P(r) = \frac{n!}{r!(n-r)!} p^r q^{(n-r)}$$

the chance of finding 0 cases in a sample of 70 with a true population prevalence of 3% is 0.118. What the authors can say from their work is that with a 0.05 confidence, the true prevalence of MCAD in cases of SIDS is less than 4.2% and using a 0.01 confidence they can state the prevalence is less than 6.4%.

Support for their claim of a low prevalence rate of MCAD in SIDS is found in a recent report of carrier rate of the K 329E mutation for MCAD in population screening.<sup>2,3</sup> These estimate the carrier rate to be between 1/40

and 1/107. It is regrettable that the authors' considerable effort in searching for metabolic cause of SIDS was let down by some basic mathematics.

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- Holton JB, Allen JT, Green CA, Partington S, Gilbert RE, Berry PJ. Inherited metabolic diseases in the sudden infant death syndrome. *Arch Dis Child* 1991;66:1315-7.
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- Matsubara Y, Narisawa K, Tada K, et al. Prevalence of K329E mutation in medium-chain acyl-CoA dehydrogenase gene determined from Guthrie cards. *Lancet* 1991;338:552-3.

#### Dr Holton and colleagues comment:

Dr Smith is quite correct in pointing out that our negative results in testing for MCAD deficiency in cultured skin fibroblasts from 70 cases of SIDS were not incompatible with claims of a true prevalence of 3%. However, our paper made it clear that our claims that the incidence was less than 3% were based on our findings and those of others, the report of the Lyon group being cited in particular.<sup>1</sup> In an almost identical study to our own, the French workers found no positive findings in 107 SIDS cases. If our results are combined, the binomial probability theorem indicates that the incidence of MCAD is less than 1.7% with 95% confidence, or 2.6% with 99% confidence. On this basis, our claim was not unreasonable.

Perhaps it would be useful to summarise further work relating to the prevalence of MCAD deficiency in SIDS. Two other studies similar to those referred to above have been completed. In Sheffield, 160 SIDS cases (E Worthy, personal communication) and in Edinburgh 120 cases (G T N Besley, personal communication) were tested for MCAD deficiency, all with negative results. If all our results are pooled (457 cases) the prevalence of MCAD deficiency is calculated to be less than 0.65 or 1.00%, with 95 or 99% confidence respectively.

Dr Smith concludes that recent reports of population screening for the common MCAD deficiency mutation found carrier frequencies which supported our claim. In addition, the K329E mutation has been sought in DNA extracted from the liver of more than a 100 SIDS cases without finding any homozygotes for the defect.<sup>2</sup> Although it is important to appreciate that MCAD deficiency is a cause of sudden, unexplained death, the presentation is not typical of SIDS and it is a rare occurrence.

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- Chinsky J, Tolsma T, Cowan T, Blitzer M. Medium chain acyl CoA dehydrogenase (MCAD) deficiency and SIDS: an analysis of post-mortem liver samples for the presence of the common MCAD mutant allele. *Am J Hum Genet* 1991;49 suppl:183.

#### Reducing the risk of cot death

SIR,—The nationwide campaign urging mothers to lay their babies on their backs to sleep is open to question. It would be unfortu-

nate if the leaflets from the Foundation for the Study of Infant Deaths (FSID)<sup>1</sup> and its counterpart from the Department of Health with the unambiguous slogan 'Back To Sleep'<sup>2</sup> are taken to represent the views of paediatricians generally.

The assertion that 'there is no evidence that babies are likely to choke when lying on their backs' belies the considerable research into gastro-oesophageal reflux and laryngeal spasm, which is one of the major aetiological hypotheses. Altogether 70% of normal babies have been shown to have reflux during active sleep with 24 hour pH probes.<sup>3</sup> A high incidence of reflux has also been demonstrated in 'near miss' cases using barium swallows, pH probes, and isotope milk scans.<sup>4 5</sup>

Because the prone position is unsafe it does not follow that the supine position is safe. This latest U turn merely replaces one bad position with another. All horizontal positions encourage reflux with the risk of laryngeal spasm. What really matters is to raise the head of the cot. All studies of the supine-versus-prone position have neglected the important effect of gravity on reflux. The ideal sleeping position is with the head raised<sup>5</sup> but if babies must lie flat, the side is probably safer than the front or back. Better still, babies' cot mattresses should be wedge shaped.

Many parents are very worried by the risk of a cot death even if they do not voice their fears. The recommendations I have used for many years are:

- Lay your baby to sleep on one or other side, never the front or back
- Prop up the head of the cot by 10–12 cm (4–5")
- Keep the cot beside your bed in the first six months
- Learn to give the kiss of life
- Get medical advice if your baby is unwell

A nationwide campaign to reduce cot deaths is undoubtedly long overdue. However if it is to succeed, it is important that the recommendations are simple, sensible, and sound. I am seriously concerned about the widely publicised FSID and Department of Health guidelines.

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- Foundation for the Study of Infant Deaths. *Reduce the risks of cot death*. London: FSID, 1992.
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#### Imposed upper airway obstruction in small children

SIR,—Surveillance of one of the 14 cases described by Samuels and his colleagues<sup>1</sup> was undertaken in the department of child health in this hospital with their advice and support.

In addition to the videos they describe, we recorded sound as well and found this to be of considerable importance. Although perpetrators do not know that they are being watched, they are certainly aware of the possibility of being interrupted by someone entering the room. They may go to considerable lengths to disguise what they are about and this was certainly true in our case. As a result, it may not be easy to demonstrate what is happening on video alone. Some of the most compelling evidence which led to a successful outcome of the case arose from the ability to compare what we could see being done to the child with what the perpetrator was saying at the time. In addition, the audible change in a child's cry as the airway is obstructed is unmistakable even if the way in which that obstruction is being achieved is subtle.

Samuels and his colleagues describe the very careful preparation required for covert video surveillance. I would also emphasise the importance of continuing support for all the professionals involved, be they doctors, nurses, or police officers. Surveillance may be necessary for many days—all involved are only too well aware of the possible consequences of a few moments inattention, of any failure of communication, or indeed, of inadvertently betraying to the perpetrator that surveillance is being undertaken.

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- Samuels MP, McCloughlin W, Jacobson RR, et al. Fourteen cases of imposed upper airway obstruction. *Arch Dis Child* 1992;67:162-70.

#### ABC of child abuse

SIR,—Torn frenula in children have been said to be 'virtually diagnostic' of non-accidental injury (NAI).<sup>1</sup> However, two recent cases indicate that this is not always so.

The first case was a 1 year old boy, whose sister was attending our casualty department for an unrelated reason. The boy was walking around the waiting room and fell flat onto his face. Examination of the crying child revealed a torn frenulum of the upper lip. The whole incident was witnessed by professional nursing staff and so the innocence of the incident cannot be doubted.

The second case involves the 14 month daughter of the author. After attempting to climb a vegetable rack, my daughter fell backwards, pulling the vegetable rack onto herself. Rapid investigation of the source of the subsequent bleeding confirmed my worst fears—she had a torn frenulum of the upper lip, presumably where it had been caught on the wire basket. I'm afraid that readers will have to take my word as to the innocence of this injury (what self respecting paediatrician would ever dare take such an injury to their local casualty department!). A torn frenulum is classically said to occur when a bottle or spoon is forced into the mouth of a child.<sup>2</sup> This association is probably strong enough to warrant the usual inquiries by the child protection agencies to see if NAI has occurred. However, before guilt of the child carers is assumed, it should be borne in mind that a torn frenulum is no more pathognomonic of