

## LETTERS TO THE EDITOR

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### Palivizumab and RSV prevention

EDITOR,—The letters from Drs Deshpande and Nicholl, in relation to the Impact-RSV study and the UK guidance for the use of palivizumab in the prevention of serious RSV infections, raise interesting questions that need to be addressed.

I believe Dr Deshpande "has got it wrong" in that he fails to realise that the primary objective of the IMPact study was to investigate whether palivizumab reduced RSV hospitalisations in high risk infants. It was never intended that this study would address the severity of RSV infections, the need for paediatric intensive care, the need for mechanical ventilation, or a reduction in death rate. It is unreasonable to suggest that because the study didn't show these then it is not valid. To show such benefits would require a totally different protocol, the numbers of patients being such that the study could never have been undertaken.

To reiterate the findings of the IMPact study, there was a 55% reduction in hospital admission rate for RSV proven disease—a significant result, however one wishes to interpret it. Those high risk patients admitted with RSV infection spent fewer days in hospital, had less need for oxygen treatment, and had lower respiratory infection clinical scores if they received palivizumab.

The study was designed in association with and with the approval of the licensing authorities to grant a marketing licence for the medication. It was not designed to provide economic data on the cost effectiveness of the product. Both Deshpande and Nicholl fail to realise that if they want this information then different studies are needed.

Does anyone know the lifelong cost of RSV disease in infancy? What is the relationship between RSV hospitalisation in the first year of life, recurrent wheezing in childhood, or indeed the possible development of chronic obstructive pulmonary disease in later adult life? To develop a relevant, long term, cost effectiveness plan, all these points

need to be taken into consideration. In an attempt to help with this there are two ongoing studies that Deshpande, Nicholl, and others, may find helpful. One is taking place in four centres in the UK and the other is a follow up study from the IMPact trial. Both are attempting to identify the health service costs over a three year period following hospitalisation for RSV disease, and it is hoped the results will be available later on this year.

The UK guidance on the use of palivizumab does not advocate universal usage of the product, but makes recommendations on how infants may benefit. It is the role of clinicians in local hospitals to discuss with their managers, the local health authority, and the individual primary care group or trust, which specific patients they feel should receive palivizumab. These decisions may well differ between centres depending on budgets, the morbidity of their patients and interpretations of evidence both research and clinical.

RSV bronchiolitis remains the greatest annual epidemic disease to hit paediatric departments in Europe, the USA, and Australasia.<sup>1</sup> The treatment of the symptoms is unsatisfactory in that the only proven benefit is oxygen. Each year, vast amounts of money are wasted on bronchodilators, steroids, ipratropium bromide, and antibiotics. Palivizumab, the first monoclonal antibody to be developed specifically for use in paediatrics, has been shown to be effective in reducing hospital admission in high risk infants. To dismiss it out of hand seems churlish. To rationalise its use in those whom it may most benefit seems clinically sensible. All new treatments need to be considered with caution. However, I believe that if clinicians take a back seat view whilst awaiting definitive confirmation of absolute cost effectiveness, we will continue to deny our most vulnerable patients the benefits of scientific advance.

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1 Simoes EAF. Respiratory syncytial virus infection. *Lancet* 1999;354:847-52.

EDITOR,—I am writing in reply to the recent correspondence regarding the use of palivizumab (Synagis),<sup>1,2</sup> a monoclonal antibody licensed for the prophylaxis of respiratory syncytial virus (RSV) infection in premature infants. RSV is a disease that affects 50% to 70% of all infants within the first year of life, and causes significant morbidity and mortality, particularly in a number of well defined high risk groups.

The major trial demonstrating the safety and efficacy of palivizumab was the IMPact-RSV trial,<sup>3</sup> a randomised, double blind, placebo controlled, multicentre trial that enrolled 1502 children with prematurity ( $\leq 35$  weeks gestation) or bronchopulmonary dysplasia (BPD). One hundred and twenty three of the children enrolled were from 11 UK centres. The primary end point of the IMPact-RSV study was hospitalisation due to confirmed RSV disease. The study was not powered to demonstrate a reduction in mortality, neither was it designed as a pharmaco-economic study. The average gestation of all the infants was 29 weeks and the placebo (n=500) and palivizumab (n=1002) groups were well matched for both demo-

graphic parameters and RSV risk factors. The study demonstrated a relative reduction in RSV related hospitalisation of 55% (10.6% placebo *v* 4.8% palivizumab  $p=0.0004$ ). A significant reduction in RSV hospitalisation was seen irrespective of gestational age, diagnoses of BPD, weight, or gender. Of all the children in both groups admitted with RSV infection, 27.7% were admitted to intensive treatment units (this figure was similar in both groups). There was however a significant reduction in the overall incidence of RSV related intensive treatment unit admission in the palivizumab group (3% placebo *v* 1.3% palivizumab  $p=0.026$ ).

The placebo RSV hospitalisation rate of 10.6% reported in the IMPact-RSV trial was lower than that seen in previous controlled trials which have reported rates of 13.5%,<sup>4</sup> 20%,<sup>5</sup> 22.4%,<sup>6</sup> and 37%.<sup>7</sup> Further reported rates of hospitalisation vary depending on the risk group studied, and data from the US demonstrate that it is possible to predict subgroups who have considerably higher hospitalisation rates.<sup>8</sup>

Further data from both Europe<sup>9</sup> and the US<sup>10</sup> reported RSV readmission rates in large numbers of premature children receiving palivizumab prophylaxis over the 1998/9 RSV season (neither study had a placebo arm). Of the 565 European infants enrolled, 1.2% had confirmed RSV hospitalisation, whilst two US groups of 1839 and 7013 children had RSV hospitalisation rates of 2.3% and 1.5% respectively. Despite the lack of comparator arms, these data do suggest that the IMPact-RSV trial may have underestimated the true efficacy of palivizumab.

The generation of pharmaco-economic arguments directly from the IMPact-RSV data very much oversimplifies what is an extremely complex issue. Hospitalisation rates vary considerably between risk groups, and measuring the true economic cost of RSV hospitalisation requires long term follow up, both of hospital, community, and parental costs.

Despite its relatively high costs, modern neonatal care has led to dramatic improvements in the outlook of premature infants. Advances such as surfactant therapy and mechanical ventilation seem expensive on the face of it, but both controlled trials<sup>11</sup> and clinical experience have shown the investment to be worthwhile.

Dr Deshpande refers to the guidance document reflecting the outcome of a consensus committee of a number of UK clinicians,<sup>1</sup> and issued by ourselves. Many were aware of the guidelines published by the American Academy of Pediatrics regarding RSV prophylaxis and the use of palivizumab,<sup>12</sup> and felt that whilst they were very useful, UK guidelines should be formulated at a local level, taking into account local risk groups and epidemiology. For these reasons, the UK guidance document deliberately avoids being too prescriptive and whilst describing the two major risk groups (premature infants,  $\leq 35$  weeks gestation, and those with BPD), it emphasises that treatment priorities are likely to vary locally and that decisions regarding which preterm infants to treat will be individualised.

Abbott Laboratories are continuing to work with many in the paediatric community in order to help better define many of the issues. We strongly feel that palivizumab is an important breakthrough in the battle against RSV infection, a disease that continues to

cause high levels of morbidity and significant mortality in high risk infants.

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- 1 Deshpande S. RSV prevention. *Arch Dis Child* 2000;82:88-90.
- 2 Nicholl RM. RSV prevention. *Arch Dis Child* 2000;82:88-90.
- 3 Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMPACT-RSV Study Group. *Pediatrics* 1998;102:531-7.
- 4 Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. The PREVENT Study Group. *Pediatrics* 1997;99:93-9.
- 5 Groothuis JR, Simoes EAF, Levin MJ. Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. The Respiratory Syncytial Virus Immune Globulin Study Group. *N Engl J Med* 1993;329:1524-30.
- 6 Groothuis JR, Simoes EAF, Hemming VG. Respiratory syncytial virus (RSV) infection in pre-term infants and the protective effects of RSV immune globulin (RSVIG). The Respiratory Syncytial Virus Immune Globulin Study Group. *Pediatrics* 1995;95:463-7.
- 7 Groothuis JR, Gutierrez KM, Lauer BA. Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. *Pediatrics* 1988;82:199-203.
- 8 Joffe S, Escobar GJ, Balck SB *et al*. Rehospitalization for respiratory syncytial virus among premature infants. *Pediatrics* 1999;104:894-9.
- 9 Law BJ, Patrick A, Baarsma R *et al*. Palivizumab (Synagis)—Expanded access study in 1998-9—Northern Hemisphere [abstract, p 25]. Second World Congress of Pediatric Infectious Diseases; 1999 Nov 2-6.
- 10 Cohen A, Hirsch RL, Sorrentino M *et al*. First year experience using Synagis (palivizumab), humanised antibody for protection from RSV lower respiratory tract infection [abstract A1.6]. Second World Congress of Pediatric Infectious Diseases; 1999 Nov 2-6.
- 11 Soll RF, Jacobs J, Pashko S *et al*. Cost effectiveness of beractant in the prevention of respiratory distress syndrome. *Pharmacoeconomics* 1993;4:278-86.
- 12 American Academy of Pediatrics Committee on Infectious Diseases and Committee of Fetus and Newborn. Prevention of respiratory syncytial virus infections: indications for the use of palivizumab and update on the use of RSV-IGIV. *Pediatrics* 1998;102:1211-16.

#### The editor comments:

In her letter, Dr Carnegie refers to a guidance document reflecting the outcome of a consensus committee of a number of UK clinicians and issued by Abbott Laboratories Ltd.

Earlier this year, we received as a submission for publication such a document, headed by the names of a number of distinguished paediatricians and neonatologists. I was puzzled because it was addressed from a public relations company. I contacted all those named to ask who the corresponding author was. I learned that they did not know the paper was to be submitted to a peer reviewed journal.

Consequently, I invited the PR company to withdraw the submission, which they did. The paper, itself, was marked as having been produced with the aid of an educational grant from Abbott Laboratories.

In general, *Archives of Disease in Childhood* is reluctant to publish the results of consensus groups, unless the methods by which they arrived at their conclusions are totally transparent. This case illustrates one reason why we believe it is right to be cautious.

HARVEY MARCOVITCH  
Editor in Chief

#### Dietary products used in infants for treatment and prevention of food allergy

EDITOR,—The joint statement of the European Society for Paediatric Allergology and Clinical Immunology (ESPACI) and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN),<sup>1</sup> deserves some comment.

Firstly, on the use of soy based formulas for the treatment, as well as for the prevention of food allergy: I was disappointed that no word about this subject appeared in the conclusions of the statement. Many have claimed that the use of soy bean formulas in infancy is an efficient way of treating or preventing food allergic disorders, but more recent prospective and randomised clinical studies have shown that soy protein is as allergenic as cow's milk protein.<sup>2</sup> As the matter remains controversial,<sup>3</sup> I believe that the conclusions should have been that soy based formulas are not recommended for the treatment or prevention of food allergy until more data are available.

The second issue concerns the use of partially hydrolysed formulas for preventing food allergy. A recent five year follow up prospective, randomised, and controlled study by Chandra,<sup>4</sup> which showed a beneficial preventive effect of a partial whey hydrolysed formula in high risk infants, was ignored. The only study where the preventive effect of an extensively hydrolysed formula was compared with the effect of a partially hydrolysed one, showed that the former was superior to the second.<sup>5</sup> This paper, however, has a possible methodological shortcoming: the manufacturer (Mead Johnson, Evansville, Indiana, USA) provided both a commercially available extensively hydrolysed formula (Nutramigen) and a non-commercially available (at least in Sweden where the study was undertaken) partially hydrolysed formula, prepared by mild (how mild?) enzymatic hydrolysis. In future, such studies should only use commercially available formulas of either the same or different brands. I consider that current data are insufficient to allow a firm view. Therefore, I believe the conclusions should have stated that no clear recommendation can be made for the use of a partially hydrolysed formula to prevent food allergy.

Conclusions of consensus statements are generally considered as guidelines for the practitioner. Omissions, as in the case of soy based formulas, or ambiguities, as in the case of partially hydrolysed formulas, do not clarify the issues so should be avoided. I believe that modified conclusions, as referred to above, would have been more in agreement with the literature and more helpful to the reader.

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- 1 Host A, Koletzko B, Dreborg S, *et al*. Dietary products used in infants for treatment and prevention of food allergy. Joint Statement of the European Society for Paediatric Allergology and Clinical Immunology (ESPACI) Committee on Hypoallergenic Formulas and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition. *Arch Dis Child* 1999;81:80-4.
- 2 Kerner JA. Use of infant formulas in preventing or postponing atopic manifestations. *J Pediatr Gastroenterol Nutr* 1997;24:442-6.
- 3 Cantani A, Lucenti P. Natural history of soy allergy and/or intolerance in children, and clinical use of soy-protein formulas. *Pediatr Allergy Immunol* 1997;8:59-74.

- 4 Chandra RK. Five-year follow-up of high risk infants with family history of allergy who were exclusively breast-fed or fed partial whey hydrolysate, soy, and conventional cow's milk formulas. *J Pediatr Gastroenterol Nutr* 1997;24:380-8.
- 5 Oldaeus G, Anjou K, Bjorksten B, *et al*. Extensively and partially hydrolysed infant formulas for allergy prophylaxis. *Arch Dis Child* 1997;77:4-10.

#### Drs Koletzko and Host comment:

We thank Professor Salazar-de-Sousa for his insightful comments on the joint comment of ESPACI and ESPGHAN.

We kept our conclusions brief and did not repeat all the considerations discussed earlier in the text but, rather, focused on the practically most relevant advisable measures to treat and prevent food allergy. In the text of the comment it is stated that, based on information currently available, we do not recommend the use of soy protein based formulas as a first line choice to prevent food allergy in infants. However, we also note that different views exist on this issue and that further studies may be useful to extend the rather limited database available, in order to clarify the allergenicity of soy formulas in infants with allergy risks.

The data presented in one of the studies by Chandra<sup>1</sup> referred to by Professor Salazar-de-Sousa were not ignored. However the committee felt that neither this study, nor many similar studies allowed definitive conclusions on all the issues. Since our comment was not intended to be an extensive review of all available publications, we did not cite this particular paper or the many other original papers on this topic, but referred to a recent editorial considering these and other data.<sup>2</sup>

We agree with Professor Salazar-de-Sousa that currently available data are insufficient to allow a firm conclusion on the relative effects of partially versus extensively hydrolysed formulas for the prevention of food allergy, an important issue for clinical practice. Hence, we concluded that more studies are needed.

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- 1 Chandra RK. Five-year follow-up of high risk infants with family history of allergy who were exclusively breast-fed or fed partial whey hydrolysate, soy, and conventional cow's milk formula. *J Pediatr Gastroenterol Nutr* 1997;24:380-8.
- 2 Kerner JA. Use of infant formulas in preventing or postponing atopic manifestations. *J Pediatr Gastroenterol Nutr* 1997;24:442-6.

#### Health care needs for travellers

EDITOR,—The article recently published by van Cleemput has made a valuable contribution to the health care needs of travellers and has drawn attention to a very deprived section of our community.<sup>1</sup> However, the assertion that childhood asthma is more common in travellers is not based on sound evidence. This suggestion was based on a study by Anderson, who reported on the health concerns and needs of traveller families.<sup>2</sup> The selection criterion for Anderson's study was families with children of less than 5 years of age. The traveller families had a mean of six children aged 1 to 15 years. The control

affluent families had a mean of 1.7 children aged 1 to 3 years, and the control inner city families had a mean of 1.9 children aged 1 to 4 years. Anderson reported that asthma was a concern to 30% of travellers compared with 11% of inner city families and 4.5% of affluent families, using a questionnaire that seemed to tackle parental concerns only, and was not validated for asthma incidence. Yet, van Cleemput extrapolated a high incidence of asthma in travellers' children from this study, and did not comment on questionnaire validation or the confounding factors of age and transient early wheezing.

We used the ISAAC (International Study of Asthma and Allergies in Childhood) questionnaire to compare the prevalence of asthma in schoolboys, aged 6 to 12 years, from travellers' families with settled controls.<sup>3</sup> The parent reported prevalence of wheezing and related symptoms were all more common in schoolboys from the control group than in traveller schoolboys. The values were significant for wheeze in the last year (31.3% *v* 14.8%, OR 5.6, *p*=0.025), and for doctor diagnosed asthma (25.6% *v* 11.1%, OR 5.1, *p*=0.04). We concluded that the experience of the travelling lifestyle may be a protective factor in the development of asthma.

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- 1 Van Cleemput P. Health care needs of travellers. *Arch Dis Child* 2000;**82**:5-9.
- 2 Anderson E. Health concerns and needs of traveller families. *Health Visitor* 1997;**70**:148-50.
- 3 Kearney PM, Kearney PJ. The prevalence of asthma in schoolboys of traveller families. *Irish Medical Journal* 1998;**91**:203-6.

### Fits, pyridoxine, and hyperprolinaemia type II

EDITOR,—There are currently two types of measurements that are used to assess vitamin B6 status. These are measurements of vitamin B6 and its metabolites, and activation of vitamin B6 dependent enzymes and associated amino acids. Tryptophan loading test is also used to reveal the subtle defects by stressing the B6 metabolic pathway. None of them is ideal, and a combination of them is recommended.

Additionally, there is no concordance between these indices. Transaminase activity in serum and red blood cells (functional index) decreases along with plasma pyridoxal phosphate, urine B6, and pyridoxal acid (direct chemical index) within one week of the removal of vitamin B6 from the diet. Electromyographic abnormalities appear within three weeks.<sup>1</sup> Some population groups have a suboptimal intake with or without excess protein intake, although severe vitamin B6 deficiency is not common in man.<sup>2</sup>

Epileptiform convulsions are a common finding in young vitamin B6 deficient subjects.<sup>1</sup> These (sub)clinical deficiencies can be routinely screened by a clinical laboratory if simple tests like transaminases are used. Vitamin B6 deficiency in a well nourished child with an autosomal recessively inherited  $\Delta^1$ -pyrroline-5-carboxylate dehydrogenase deficiency led to childhood fits, because of binding of the proline metabolite, pyrroline-5-carboxylate with vitamin B6, as reported by Walker *et al.*<sup>3</sup> It would be interesting to know if and how the authors had measured the

transaminases. Their results could indicate if this is a cost and clinically effective screening test.

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- 1 McCormick DB, Green HL. Vitamins. In: Burtis CA, Ashwood ER, editors. *Tietz textbook of clinical chemistry*, 3rd ed. Pennsylvania: WB Saunders, 1999:1016-18.
- 2 Bates CJ. Vitamin analysis. *Ann Clin Biochem* 1997;**34**:599-626.
- 3 Walker V, Mills GA, Petrs SA, *et al.* Fits, pyridoxine, and hyperprolinaemia type II. *Arch Dis Child* 2000;**82**:236-7.

### LHRH analogue and growth hormone did not improve the final height of a patient with juvenile hypothyroidism accompanied by precocious puberty

EDITOR,—We report an 11 years 8 months old girl with juvenile hypothyroidism and precocious puberty who failed to respond to thyroxine, growth hormone, and luteinising hormone releasing hormone (LHRH) analogue. The patient was considered to be hypothyroid for about two years before the therapy was started. She had a very low serum thyroxine concentration, a height SD score of -3 SD, and a bone age of 10 years 3 months. Her pubertal development was graded as Tanner stage IV of breasts and Tanner stage II of pubic hair. Her menarche occurred at the age of 10 years 3 months. The enlarged pituitary gland reduced in size with the thyroxine treatment (100  $\mu$ g/day). In addition to thyroxine, she was treated for 31 months with an LHRH analogue (30  $\mu$ g/kg, once a month) and growth hormone (0.5 U/kg/wk divided into six doses) to avoid the progression of puberty and improve the final height. She reached the final height at the age of 15 years 1 month (-2.8 SD), which was the same as before the treatment (fig 1).

Minamitani *et al* reported that treatment with LHRH analogue and growth hormone in addition to thyroxine was successful in improving the final height and avoiding pubertal growth of patients with juvenile hypothyroidism in the prepubertal stage.<sup>1</sup> Difference between the report of Minamitani *et al* and our case is that our patient already had the advanced bone age relative to height age and the progression of puberty at the start

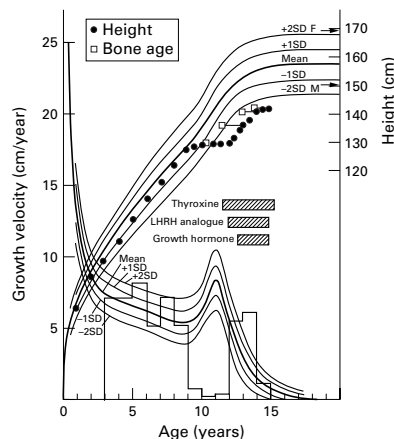


Figure 1 Treatment, bone age, and height of the patient, plotted on a cross sectional growth chart for girls (0-19 y). Height, bone age, and growth velocity of the patient are shown. F, father's height; M, mother's height.

of treatment, to which our failure to improve the final height with the combination therapy might have been ascribed. To improve the final height, we should have increased the dose of LHRH analogue and growth hormone. During the combination therapy, peak serum insulin like growth factor 1 was 710 ng/ml (normal: 370-896 ng/ml), and peak concentrations of LH and FSH were completely suppressed in response to gonadotropin releasing hormone. Although her menstruation was successfully suppressed, bone maturation was not inhibited.

We concluded that patients with juvenile hypothyroidism who are often found to be in progressive pubertal development may not be indicated for treatment with LHRH analogue and growth hormone. An early diagnosis may therefore be of utmost importance in improving the final height. In Japan, schoolchildren are biannually measured for height and weight. It is therefore strongly urged to educate school nurses to direct their attention to the evaluation of height measurements and also thelarche and to consult paediatric endocrinologists. Although a number of possibilities have been raised for failure in attainment of desired height in the patient, the early medical attention would have been expected to lead to the possible prevention of short stature.

This work was supported by grants from the Ministry of Health and Welfare of Japan, the Ministry of Education, Science, and Culture, the Japan Private School Promotion Foundation, and the Mami Mizutani Foundation.

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- 1 Minamitani K, Murata A, Ohnishi H, Wataki K, Yasuda T, Niimi H. Attainment of normal height in severe juvenile hypothyroidism. *Arch Dis Child* 1994;**70**:429-31.

### Intraosseous access in infant resuscitation

EDITOR,—We believe that intraosseous access to the circulation in infant resuscitation is undervalued and therefore under utilised.

Intraosseous cannulation is a simple and effective technique that can be performed both quickly and safely in resuscitation.<sup>1-4</sup> There have been relatively few complications reported with this technique.<sup>5</sup>

In a laboratory study, we compared the average flow rates through a range of intravenous cannulae with that of an 18 gauge intraosseous cannula. We purged intravenous Hartmann's solution through the various devices, at a constant pressure of 300 mm Hg, recording the average volumes over one minute intervals. The results and calculated infusion time for a 20 ml/kg bolus in a 5 kg baby are shown in table 1.

Administration of intravenous fluid is an essential component of infant resuscitation. Fluid boluses have to be infused under pressure through an intravenous cannula placed in a peripheral vein. Successful cannulation can be a technical challenge in collapsed infants. Small veins are prone to damage when fluids are rapidly purged through them. Central venous access is not usually established in infants in the immediate resuscitation period and larger intravenous

Table 1 Results and calculated infusion time for a bolus in a 5 kg baby

Access device	Gauge	Flow rate (ml/min)	Infusion time for 100 ml bolus (minutes)
Yellow venflon*	24	35.6	2.81
Blue venflon*	22	60.6	1.65
Pink venflon*	20	126.8	0.79
Green venflon*	18	161.2	0.62
Intraosseous needle	18	248	0.40

\* BOC Ohmeda AB, SE-25106 Helsingborg, Sweden.

cannulae (22 and 20 gauge) can be difficult to site in small infants presenting with circulatory failure.

Our simple experiment has shown that fluids can be infused through an intraosseous cannula at a significantly higher rate to that of the intravenous devices. The resistance to flow in situ has not been calculated, but one could reasonably expect the capacitance of the marrow cavity to be greater than that of an infant's peripheral vein. These factors, in addition to the ease and success of placement of intraosseous over intravenous cannulae, leads us to advocate that greater emphasis is placed on the value of intraosseous cannulation during the early phase of resuscitation in infants.

This is an important issue that should be addressed both locally and nationally, as well as through advanced life support provider courses (APLS/PALS).

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- Ellemunter H, Simma B, Trawoger R, *et al.* Intraosseous lines in preterm and full term neonates. *Arch Dis Child Fetal Neonatal Ed* 1999;80:F74-5.
- Rieger A, Berman JM, Striebel HW. Initial resuscitation and vascular access. *Int Anesthesiol Clin* 1994;32:47-77.
- Neufeld JD, Marx JA, Moore EE, *et al.* Comparison of intraosseous, central, and peripheral routes of crystalloid infusion for resuscitation of hemorrhagic shock in a swine model. *J Trauma* 1993;34:422-8.
- Guy J, Haley K, Zuspan SJ. Use of intraosseous infusion in the pediatric trauma patient. *J Pediatr Surg* 1993;28:158-61.
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### Natural history of glutaric aciduria type 1

EDITOR.—In their retrospective study, Monavari and Naughten (*Arch Dis Child* 2000;82:67-70) suggest that early intensive management can alter the natural history of glutaric aciduria type 1. However, the pathogenesis of this disorder is poorly understood and just what is responsible for the better outcome is not clear. In several families in which the first child has the classical phenotype, we have noted a marked difference in outcome of siblings without any specific treatment.

**Family 1**—In this Jordanian family the first child had a severe movement disorder and died. The second has macrocephaly and mild gait disturbance but is attending normal school.

**Family 2**—This first child of Nigerian and West Indian parents has a severe dyskinetic cerebral palsy. Her sister has minimal symptoms and attends a normal school.

**Family 3**—This family are Irish travellers and they have had three affected children. The first died with a severe movement disorder and the third, although he was known to be at risk, had an episode of decompensation at 6 weeks. He developed a severe movement disorder and died suddenly and unexpectedly at the age of 13 months. The second child has had some speech delay but has minimal problems and attends a normal school.

None of these children were receiving any specific dietary treatment or medication. While we would agree that early diagnosis is essential, the diet is a significant imposition and all that may be needed is intensive treatment during intercurrent infections.

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### Gastrointestinal symptoms in asthmatic patients

EDITOR.—Caffarelli *et al* comment on several immunological mechanisms by which gastrointestinal symptoms could occur in asthma.<sup>1</sup> They do not comment on whether they excluded cystic fibrosis (CF). This is relevant as there are an increasing number of mild phenotypes of CF presenting as asthma.<sup>2</sup> CF could be a unifying diagnosis in the "asthmatic" with gastrointestinal symptoms.

The important clinical message is to consider a diagnosis of CF in difficult cases of asthma.

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- Caffarelli C. Gastrointestinal symptoms in patients with asthma. *Arch Dis Child* 2000;82:131-5.
- Aznarez I. Increased frequency of CFTR mutations and variants among asthma patients. *Ped Pulmon* 1999;208 (Suppl 19): poster 155.

*Drs Caffarelli and Atherton comment:*

We appreciate the comments made by Dr Furness, and we would certainly concur with his view that one must consider a diagnosis of CF in any child presenting with the combination of asthma and gastrointestinal symptoms.

We accept that a diagnosis of CF may not always be obvious on clinical criteria alone, but it remains the case that there is no simple cheap screening test for CF, and we must therefore continue to test only those children in whom there is at least some clinical basis for suspecting this diagnosis. We believe that we did adequately consider CF in the children that participated in our study according to clinical criteria, but sweat testing was not undertaken routinely, nor did we

screen for CF mutations. While it is possible that we may have missed a child in whom the combination of asthma and respiratory symptoms was due to CF, we consider it exceedingly improbable that such omission would have substantially prejudiced our results.

The finding that gastrointestinal symptoms, for most of which there was no simple explanation, are common both in children with atopic eczema and in children with asthma, suggests that these symptoms are a reflection of the patients' atopic status itself, and undiagnosed CF is unlikely to be a significant contributory factor. Neither do we believe that these symptoms can merely be dismissed as being due to food allergy, any more than one could dismiss either atopic eczema or asthma themselves as being caused exclusively by food allergies. The precise aetiologies of these conditions remain to be clarified.

CARLO CAFFARELLI

DAVID J ATHERTON

## BOOKS

**National Study of Health and Growth.** By Rona RJ, Chinn S. (Pp 133, hardback; £49.50.) Oxford: Oxford University Press, 1999. ISBN 0 19262 919 0

The youth of today are not what they were: they are bigger. Rona and Chinn, in their long and meticulous study of the health and growth of some 87 000 children, have documented the continuing trend to increasing height for age in primary school children over a 20 year period. This is generally thought to be a good thing and indicative of ever improving health and nutrition. The trend has been rumoured to be at an end many times, but in fact continues. Similarly, poverty was thought to be at an end in the 1970s when this study had its beginnings, only to be reluctantly rediscovered after the Black report. The two clearly go hand in hand: when there is no more poverty and perfect health and nutrition have been achieved, there will be no further gain in height. The effect of poverty is illustrated in this study, as in many others, by the social class gradient in height. Yet the exact mechanism of the relationship is mysterious as most of the gradient disappears after adjustment for parental height. The authors argue that most of the variation must therefore be genetic, others argue that there has been overadjustment.

The other secular trend observed has been of increasing obesity: a worrying trend in light of the much larger epidemic in adult obesity. But then again all is not what it seems. Mean weight for height is referred to throughout as "obesity". Yet, as this is the age when children pass through the thinnest phase of their growth, few if any will be actually obese and presumably a proportion were actually underweight. When does less undernutrition become too much overnutrition, and how do we tell? So a paradox: the secular trend to increasing height is good and is due to improved overall nutrition. The parallel trend

to increasing weight for height is bad and is due to improved overall nutrition.

No dataset can provide all the answers. By collating their long work and summarising all their analyses in this well structured and admirably slim volume, the authors make it possible for the idle and speculative like myself to argue with their conclusions. The range of the work is vast: from heart disease risk factors and asthma prevalence, to the prevalence of enuresis and food intolerance. It may come as no surprise that the last has a strong inverse relation with level of education, but the adverse impact of food exclusion on height certainly surprised me. No doubt future generations will dip into this rich dataset and pick out many more plums to inform both research and practice. We can be grateful to Rona and Chinn for making it possible.

CHARLOTTE WRIGHT

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**Using the Internet in Healthcare.** Tyrrell S. (Pp 168, paperback; £17.95.) Radcliffe Medical Press, 1999. ISBN 1 85775 366 6

**MedLine: a Guide to Effective Searching.** Katcher BS. (Pp 148, paperback; \$29.) Ashbury Press. ISBN 01 96734 450 6

Good, I thought, as these books dropped through the letterbox.

The day before I'd been party to a family receiving an antenatal diagnosis of gastroschisis, and the father had commented on "looking it up on the Internet". I wanted to learn more about the condition myself, and reckoned I'd follow the man's example.

*Using the Internet in Healthcare* sounded an ideal title; disappointingly it wasn't. It's a book about the basics of the Internet, which isn't bad, but is presented better in other books (for example, *Internet for dummies*).

It's "medical" legitimacy comes from a good summary of NHSnet and a crumb of information about healthcare searches on the Web. (Embarrassingly, it was *MedLine: a guide to effective searching* that contained the nicest www resources.)

*MedLine: a guide to effective searching* was also a let down. It's beautifully written, starts with a lovely summary of the history of MedLine, but annoys with drawn out explanations of Boolean logic and historical access systems. In explaining PubMed, it doesn't even mention the excellent "Clinical queries" search page ([www.ncbi.nlm.nih.gov/PubMed/clinical.html](http://www.ncbi.nlm.nih.gov/PubMed/clinical.html)), based on the work of Brian Haynes and colleagues.

For clinicians, there are better summaries of framing questions and effective database searching in Sackett's book.<sup>1</sup> For researchers, there are better databases for citation searching than MedLine.

My own searches found a wonderful paediatric patient information site (<http://www.birthdefects.org/MAIN.HTM>), a site telling the story of a young lad with gastroschisis (<http://www.geocities.com/Heartland/Flats/1558/>), and an excellent study of outcome (using the PubMed/Haynes filters). I wonder how the father of our latest pre-surgical patient fared...

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<sup>1</sup> Sackett D. *Evidence-based medicine*. 2nd edition. 1999.

**Information for evidence-based care.** By Roberts R. (Pp 79, paperback; £17.95.) Oxford: Radcliffe Medical Press, 1999. ISBN 1 85775 356 9

Evidence based care is upon us, whether we like it or not. There is a multitude of books on the subject, so how is this one different? This is the first in the "Harnessing health information series", and summarises how evidence based care has evolved into mainstream NHS policy. It does appear to achieve what the series purports to do, as it harnesses health information on the subject. The reader is gently guided around the different organisations set up to implement evidence based care, and the different policies in each of the countries of the United Kingdom are described. Many useful resources are highlighted, and the reader feels that he or she can make sense of all the jargon in current usage.

There is a brief introduction to the practice of evidence based care, with an overview of the types of research, including qualitative research, and their advantages and disadvantages for answering different sorts of questions. The book does not set out to duplicate the many "How to..." books, but, rather, points the reader in the right direction. There is a useful chapter on information sources on the Internet, and a comprehensive chapter on guidelines, describing most of the arguments for and against. Again, the reader is continually pointed in the direction of other useful information, without it being duplicated in this book. Patient information is covered in another chapter, and this is interesting and thought provoking reading. Audit, and where it fits into the system, is also included. Finally, clinical quality and clinical governance are brought into the picture, and it all makes sense.

Ruth Roberts is a nurse, and she emphasises the importance of multidisciplinary working. This is an easy book to digest, making common sense of what sometimes seems a complex system. It gives a "warts and all" description of evidence based care. The reader is not put off, but, rather, is left with the feeling, "I can do this".

This will be a useful resource for managers, nurses, doctors, and clinical quality coordinators. It will be useful for senior staff with a good understanding of the health service and its current requirements, as well as being a good starting point for more junior staff who are trying to make sense of white paper recommendations, and the national organisations set up to implement those recommendations. It can be read in a couple of hours, and will no doubt become pre-interview reading for would be consultants and specialist registrars.

MAUD MEATES  
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**Essential paediatrics.** Edited by Hull D, Johnston DI. (Pp 400, paperback; £24.95.) Churchill Livingstone, 1999. ISBN 0 44305 958 6

After coming to this country some years ago, I decided to take up paediatrics. I remember asking a senior colleague for advice regarding any textbook that would give me an introduction to the subject. She gave me a choice, but recommended that *Essential paediatrics*, then in its third edition, would make easy reading. I must say I found this sound advice. Of course, as a postgraduate, one had to progress

rapidly on to other textbooks considered the bibles of paediatrics. Hence, when I was asked to review the fourth edition, I was overwhelmed as it brought back memories of my first few months in paediatrics.

As the editors have noted in their preface, this book is meant for medical students. I find that this has been maintained with regard to the manner in which different subjects have been handled with easy to understand language and diagrams. I continue to find the first chapter, "The ill child", the most impressive and compelling to read, and would not hesitate to recommend this to postgraduate doctors intending to take up a first paediatric post. A similar chapter that needs special mention is that on emotions and behaviour, which, in a brief but concise manner, describes children that we meet daily. It teaches us the importance of careful history taking, including social and family histories.

The book has been updated in many areas, especially in terms of management, in keeping with an evidence based approach. The addition of the British Thoracic Society guidelines on the management of chronic asthma is commendable. However, I cannot understand why the importance of the peak flow meter has been downplayed, unlike the previous edition which also featured a graph of normal PEF values related to height.

On the whole, *Essential paediatrics* can be described as user friendly, with numerous relevant line drawings and important information in the margin and in highlighted boxes. Interesting and useful x rays have also been included in this edition.

Yet why does one get the feeling that this may not be the first choice textbook for many medical students? One reason, I would think, is the limited number of colour photographs compared with some other books on the market. Another reason, I would suggest, is the lack of adequate definitions of some of the common disorders—for example, coeliac disease and ulcerative colitis.

Despite some drawbacks, I find that *Essential paediatrics* is invaluable and have no qualms about recommending it to medical students as essential reading.

MINI MARGARET NELSON  
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**Eating disorders: a parents' guide.**

Bryant-Waugh R, Lask B. (Pp 222, paperback; £7.99.) London: Penguin. ISBN 0 14026 371 3

Their children's eating disorders pose serious problems for parents. They may seek professional help, but services in the United Kingdom are fragmented and under developed; therefore, any book that is designed specifically for parents must be welcome.

My clinical experience is that parents appear bemused and shocked by the realisation that their daughter or son has an eating problem. They are often confused and may be angry or in denial. Parents may turn to the popular press, in which articles are sometimes sensible, sometimes sensationalist, worrying, or misleading. High profile cases, such as those of Princess Diana or Lena Zavaroni tend to dominate.

The authors have obviously recognised the lack of sensible self help and advice for parents of younger children and adolescents. This book, therefore, is timely and fills an important gap. A lot of the information is

derived from their previous book, *Eating disorders in early adolescents* (Psychology Press 1999).

One of the main premises of the authors is that parents are the best people to help their child, and they set about informing them how to be in a better position to do so. There are seven main chapters, which cover subjects such as "What are eating disorders?", "Causes", "What to do", "General principles of treatment", and "Collaboration with professionals". There are case vignettes, outlines of overall care, therapeutic treatments, and a very sensible dietary plan. A glossary of the terms commonly used in the treatment of eating disorders is provided.

It is difficult to judge at what level to set a book like this. There is a danger of being either too complicated or simplistic and patronising. This book is probably set correctly, but the text is a little heavy, and with only seven figures, mostly graphs, can appear a little dense. At 222 pages, it is not too long and can be read in sections, which is helpful for parents going through a particular stage of treatment or assessment. Naturally enough, the book concentrates upon the treatment plans the authors have used with good effect at Great Ormond Street Hospital.

Overall, I can recommend the sympathetic and caring approach taken by the authors, which will reassure parents.

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#### Immediate care of the critically ill child.

By Macnab AJ, Macrae D, Henning R. (Pp 660, paperback; £45.) Edinburgh: Churchill Livingstone, 1999. ISBN 0 443 05394 4

Few would disagree that in the past two decades, world leaders in the relatively young specialty of paediatric intensive care have emerged in Australia, Canada, and the United Kingdom. It is a welcome pleasure, therefore, that the exceptional talents of many of the individuals working in these centres have been brought together to create a much needed practical text encompassing the principles and practice of caring for critically ill and injured children.

The major strength of this book is that it takes into account one of the most important aspects of paediatric critical care, namely that the initial management of these children takes place in a wide diversity of settings. For many children ultimately admitted to a paediatric intensive care unit (PICU), the first few hours of care may have the most significant impact on their clinical course and outcome. This book targets the practitioners most likely to be involved in these situations, and provides key information and a problem based approach that is difficult to achieve in standard texts.

Like most multidisciplinary texts, the bulk of the book is divided into systems, and by and large system *disease* and *failure* are addressed separately. This distinction doesn't always work, and the inevitable repetition and need for cross referencing can be distracting. Some sections seem to assume no prior

knowledge of paediatrics, and others appear to be aimed at the experienced paediatrician. In spite of this, there is a reasonable and logical flow to the text, and many extremely useful tables and diagrams. Key learning points and common errors are highlighted in most chapters, and constitute a list of useful tips based on the considerable collective experience of the authors. This sort of approach is as close to bedside teaching that you can get in a textbook, and will be appreciated by trainees in particular.

Areas that stand out include the management of fluid and nutritional problems, toxicological and metabolic emergencies, and the diagnostic investigation of children with cardiac and neuromuscular problems. It is always difficult to do justice to non-clinical topics like the ethical and psychosocial aspects of critical care, but, at least by including them, the emphasis on the whole patient remains intact. Due attention is given to non-accidental injury and the challenges of transporting patients, the latter reflecting modern, increasingly centralised paediatric intensive care.

In a subspecialty defined by rapid intervention and practical procedures, it is especially difficult to strike the appropriate balance between background detail and clinical practice. On the whole, this book accomplishes this very well. It is not a comprehensive reference text for tertiary care paediatric intensivists, but covers first line treatment to optimise the transition from emergency patient to PICU patient. Until recently, this was mainly undertaken by specialist registrars and consultant anaesthetists, but, in the United Kingdom at least, the next generation of consultant paediatricians will increasingly be called upon to manage critically ill children in those crucial first hours. That group, however reluctantly, will particularly benefit from this useful text.

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#### Abnormal cortical development and epilepsy: from basic to clinical science.

Edited by Spreafico R, Avanzini G, Andermann F. (Pp 324, hardback; £39) London: John Libbey, 1999. ISBN 0 86916 579 5

In his chapter in this book entitled "Neuronal migration disorder and epilepsy in infancy", Vigeveno emphasises that brain malformations represent a causal factor in 3–4% of all epilepsies, although this percentage increases to 18–20% in drug resistant epilepsies. With every new generation of MRI scanner, more and more patients with epilepsy are recognised to have a cortical developmental abnormality, and the aetiological significance of these to the development of epilepsy has opened up exciting new fields in the understanding of the pathophysiology of epilepsy and its treatment. This book is a compilation of papers presented at a meeting on epileptogenic cortical developmental abnormalities, organised by the editors. As with books

produced in this way there are strengths and weaknesses, with a bias towards specific topics of interest.

The book starts with a short introduction by Frederick Andermann, followed by several chapters on cortical development and animal models. These early chapters are not easy reading but persistence is rewarded by information of direct clinical relevance from the dry basic scientific details—for example, I learnt that work with animal models has shown that pathological changes continue for years after the initial insult, explaining the delay in the development of clinical epilepsy. Furthermore, the progressive maturation of the neurotransmitter pathways could explain why neonatal encephalopathies are often catastrophic, and why children can grow out of their epileptic tendency, even with lesional epilepsy.

The later chapters on electroclinical imaging, neuropathological studies, genetics, and surgery are more relevant for the clinician. In this section, several of the authors emphasise the error of using the term "neuronal migration disorders" for all dysplasias, when the disturbance can be of neuronal proliferation or organisation and not always an arrest of neuronal migration. Of particular interest to me were the chapters on neuroradiology of malformations, neuronal migration disorders and epilepsy in infancy, schizencephaly: clinical and genetic findings, and periventricular nodular heterotopia, especially the genetic implications of recognising these various malformations. I also enjoyed Guerrini's excellent chapter on the development of polymicrogyria. As in his other publications, he points out that polymicrogyria is the only cortical developmental abnormality which can produce ESES with eventual spontaneous remission, and when this pathology is identified on neuroimaging, surgery should be avoided. This leads us to the two chapters on the problems of resective surgery in focal developmental abnormalities and epilepsy; the first by the Montreal group and the second outlining the Italian/French experience. Both emphasise the specific difficulties of deciding the demarcation of surgical resection in these patients. I was particularly interested in the approach of Munari *et al* to two step surgery, reoperating with more invasive electrocorticography if the seizures do not stop with lesionectomy alone. While acknowledging that cortical dysplasias can be intrinsically epileptogenic, Munari *et al* state that, in practice, the epileptogenic zone is often wider than the MRI limits of the lesion, suggesting either that the adjacent cortex is also epileptogenic or that microscopic pathology extends further than that seen on MRI images.

The book is a useful addition to the literature on cortical dysplasias. It does not aim to be a comprehensive review of the topic and the reader would need considerable prior knowledge of the subject to find the book useful.

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