LETTERS TO THE EDITOR

The risks and benefits of cisapride

EDITOR,—I read with interest the annotation by Lander and Desai discussing cisapride.¹ They conclude that the case against cisapride as a safe and useful agent in premature neonates has not been proved.

As the three main indications for cisapride in the newborn (gastro-oesophageal reflux, postoperative ileus, and intestinal dysmotility of prematurity) are self resolving with time, the only useful study design is a randomised controlled trial (RCT).

There are two small published RCTs on the use of cisapride in the newborn. Enriquez *et al* randomised infants at the initiation of feeds and reported no difference between cisapride and placebo in the time taken to full feeds.² Lander *et al* randomised neonates > 32 weeks' gestation with postoperative ileus to cisapride or placebo for seven days.³ They noted a significant increase in the mean net enteral balance with cisapride. While this is encouraging, the trial design did not permit comparison of time to full feeds or hospital discharge, and it was not analysed as intention to treat. There are no published trials on the use of cisapride in premature neonates with gastro-oesophageal reflux.

It is certainly too early to state that cisapride is unsafe in premature infants; however, there is insufficient evidence of its efficacy in the newborn. It is surely no longer acceptable that a drug with no objective evidence of efficacy and potentially serious side effects should be in widespread use.

Large placebo controlled trials with clinically important outcome measures are needed to establish whether cisapride is an effective treatment for neonates with gastro-oesophageal reflux, postoperative ileus, or intestinal dysmotility of prematurity. Prospective monitoring of the QTc interval with drug discontinuation in the event of prolongation should allow measurement of cardiac risk without jeopardising the health of any infant.

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- 1 Lander A, Desai A. The risks and benefits of cisapride in premature neonates, infants, and children [annotation]. *Arch Dis Child* 1998;79:469-70.
- 2 Enriquez A, Bolisetty S, Patole S, Garvey PA, Campbell PJ. Randomised controlled trial of cisapride in feed intolerance in preterm infants. *Arch Dis Child* 1998;79:F110-13.
- 3 Lander A, Redkar R, Nicholls G. Cisapride reduces neonatal postoperative ileus: randomised placebo controlled trial. *Arch Dis Child* 1997;77:F119-22.

Dr Lander replies:

Dr Cairns is right—robust, placebo controlled trials of cisapride are needed in both the premature and mature newborn, especially for those with problematic reflux or postoperative ileus. Unfortunately, the contraindication by the Committee on Safety of Medicines (CSM)⁴ will deter clinicians, ethics committees, and parents from these crucial

trials. The British Association of Paediatric Surgeons abandoned plans for a multicentre study of cisapride against placebo after the repair of gastroschisis for this very reason. We are now looking at the efficacy of erythromycin in these children.

Measures of clinical outcome are the most useful end points in trials, but of equal importance in interpreting the clinical usefulness of results are entry criteria. How do the subjects compare with those one needs to treat? In self resolving conditions there is no need to treat routinely unless the morbidity of the time to resolution is likely to be clinically important. Cairns cites Enriquez *et al* who reported no significant difference in the time to establishing enteral feeds between placebo and cisapride when used routinely in 34 preterm infants.² However, the following were noted: seven of 18 infants given cisapride had no significant gastric residue at any time compared with only one of 16 given placebo ($p = 0.04$); and only two of 18 given cisapride developed regurgitation compared with eight of 16 given placebo ($p = 0.02$). These observations are important. Furthermore, two babies with regurgitation were removed from their study and treated openly with cisapride with success. Although they cannot be included in the analysis, they show that the study population was limited to less worrying infants.

Unless the CSM revisits the question of prematurity, robust trials with cisapride, which is still widely used,³ will not get ethical approval and a good drug may be lost.

- 1 CSM/MCA. *Pharmacovigilance* 1998;24 (August).
- 2 Enriquez A, Bolisetty S, Patole S, Garvey PA, Campbell PJ. Randomised controlled trial of cisapride in feed intolerance in preterm infants. *Arch Dis Child* 1998;79:F110-13.
- 3 Ward RM, Lemons JA, Molteni RA. Cisapride: a survey of the frequency of use and adverse events in premature newborns. *Pediatrics* 1999;103:469-72.

Editors' comment

Please see "Randomised controlled trial of cisapride in preterm infants" by R J McClure, J H Kristensen, A Grauaug in the May issue of *Fetal and Neonatal* edition (*Arch Dis Child* 1999;80:F174-8).

Serum bicarbonate and the severity of dehydration in gastroenteritis

EDITOR,—I read with interest Booth's comments¹ on my article² and I take this opportunity to clarify our findings. Mackenzie *et al*'s study³ was fundamentally different from ours. The degree of dehydration was assessed by junior doctors and not specialists; all children were inpatients "thought to be" 5% to 10% dehydrated (only 25% were) and no cases of severe dehydration were included. Most were "social" admissions.

During rehydration, children were not fed, and weight loss from catabolism may have led to underestimation of the degree of dehydration. Children's weight may vary tremendously with voiding or defecation and those factors were not included; therefore, the weight increase after admission may not be the "gold standard". Nine years later, successive editions of major paediatric textbooks from both sides of the Atlantic still rely on clinical parameters to estimate the severity of dehydration, although they are not perfect.

At Booth's suggestion, we looked at the percentage of weight gain 24 hours after

admission for the 64 children who were admitted to hospital, and compared it with their serum CO₂ on admission: those with a weight increase of $\leq 5\%$ had a CO₂ on admission of 17 mmol/l (range 11-22); those with a weight increase of 5-10% had a CO₂ on admission of 16 mmol/l (11 to 19); and those who gained > 10% had a mean CO₂ of 19 mmol/l (range 12-20). There was also a poor correlation between weight gain and the degree of dehydration as assessed clinically.

The ideal parameter to estimate the severity of dehydration would be the difference between admission and pre-admission weight. As the latter is often lacking, physicians can rely only on clinical parameters. I would be interested to learn how Booth immediately assesses the degree of fluid loss in a dehydrated child. Perhaps all textbooks will need to be modified if his methods prove to be scientifically valid.

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- 1 Booth IW. Serum bicarbonate and the severity of dehydration in gastroenteritis [letter]. *Arch Dis Child* 1998;79:379.
- 2 Narchi H. Serum bicarbonate and dehydration severity in gastroenteritis. *Arch Dis Child* 1998;78:70-1.
- 3 Mackenzie A, Barnes G, Shann F. Clinical signs of dehydration in children. *Lancet* 1989;iii:605-7.

Cancer in Sotos syndrome

EDITOR,—We greatly enjoyed reading the article by Cole on overgrowth disorders in childhood.¹ While the article alluded to the increased risk of malignant disease among children with Beckwith-Wiedeman syndrome (BWS) no mention was made of the increased risk of cancer in Sotos syndrome.²

We recently treated a 3 year old boy with Sotos syndrome for abdominal B cell lymphoblastic lymphoma (Murphy stage III) in accordance with United Kingdom children's cancer study group protocol 9002. Although his lymphoma exhibited only a partial response to standard chemotherapy, he remains disease free two years later following second look surgery and subsequent high dose treatment with autologous bone marrow rescue.

Non-Hodgkin's lymphoma has also been reported in three other patients with Sotos syndrome.^{2,3} Malignant disease in this condition is not restricted to lymphoproliferative disorders and several other types of cancer including Wilms's tumour, neuroblastoma, hepatocellular carcinoma, and acute lymphoblastic leukaemia have been described. The risk of malignant disease in Sotos syndrome has been estimated as 1 in 41 under the age of four years.²

The literature suggests that the incidence of specific tumour types may differ between individual overgrowth syndromes. In Sotos syndrome, non-Hodgkin's lymphoma constitutes almost one quarter of reported cases; a very different pattern has been observed in children with BWS in whom Wilms's tumour, hepatoblastoma, and neuroblastoma are responsible for the vast majority of observed cancers.⁴ Although subject to reporting bias these figures suggest that specific overgrowth syndromes are associated with differing, albeit overlapping, patterns of tumour formation. Such an observation may

result from differences in the aetiology of the cancers involved. Dr Cole's annotation details the relation between overexpression of insulin-like growth factor II and BWS.¹ This discovery has stimulated considerable interest in the role of this peptide and its binding proteins in the aetiology of many human cancers including Wilms's tumour, hepatoblastoma, and neuroblastoma. The idea that overexpression of insulin-like growth factor II is important in the aetiology of these malignancies is an attractive hypothesis that may partially explain the observed differences in the incidence of individual tumour types between BWS and other overgrowth disorders.

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- 1 Cole TRP. Growing interest in overgrowth. *Arch Dis Child* 1998;78:200-4.
- 2 Hersh JH, Cole TRP, Bloom AS, et al. Risk of malignancy in Sotos syndrome. *J Pediatr* 1992;120:572-4.
- 3 Corsello G, Giuffrè M, Carcione A, et al. Lymphoproliferative disorders in Sotos syndrome: observation of two cases. *Am J Med Genet* 1996;64:588-93.
- 4 DeBaun MR, Tucker MA. Risk of cancer during the first four years of life in children from the Beckwith-Wiedemann syndrome registry. *J Pediatr* 1998;132:398-400.

Influence of five years of antenatal screening on the paediatric cystic fibrosis population in one region

EDITOR.—The paper describing screening for cystic fibrosis (CF) by Cunningham and Marshall¹ has a number of important flaws. Any screening programme is targeted at a defined population. The title refers to a "population in one region" without being geographically precise, but the study is of children born in two hospitals. If the total number of screened pregnancies in the hospitals had been stated then the incidence of CF conceptions in this group could have been calculated.

The paper quotes without referencing a CF "gene frequency", but the authors clearly mean CF carrier frequency of nearly 1 in 20. This gives an incidence of 1 in 1600 live births (not 1 in 2000). The only published long term population data estimating CF incidence in Scotland are the UK data, which at the time of this study was fractionally under 1 in 2500 live births.² Thus, the authors suppose that the CF incidence is 50% higher than this. This has important consequences, which the authors have ignored in the interpretation of their results.

The births to Edinburgh residents is not helpful because this was not the population screened. Given the number of cases found per year prescreening (approximately five), and assuming the UK incidence, there should have been about 12 500 live births per year. The births in Edinburgh were about 5000 per year, suggesting about two CF cases per year. This discrepancy warrants comment by the authors.

The prescreening data raise more issues that they solve. The direct reduction in CF live births is given by the number of abortions. This can only be converted to incidence if the exact population studied is known. Historical comparisons, with small numbers of cases, risks misinterpreting random variations and can magnify the effects of bias.

While it is helpful to know what peoples' reproductive intentions are, the overall effect of neonatal screening on reproductive behav-

iour can only be determined by long term population studies of disease incidence and gene frequency. As the members of a population become better informed about the nature and scope of antenatal screening they will adopt more sophisticated strategies to exploit its potential for their own benefit. It is difficult to anticipate the net effect of these strategies.

Organisations such as the UK National Screening Committee are more likely to accept the case for CF screening if scrupulously accurate data, properly analysed and clearly interpreted, are available. Anything less leads to confusion and can only damage the case.

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- 1 Cunningham S, Marshall T. Influence of five years of antenatal screening on the paediatric cystic fibrosis population in one region. *Arch Dis Child* 1998;78:345-8.
- 2 Dodge JA, Morison S, Lewis PA, et al. Cystic fibrosis in the United Kingdom 1968-1988, incidence, population and survival. *Perinatal and Paediatric Epidemiology* 1993;7:157-166.

Drs Cunningham and Marshall reply:

Information with regard to carrier frequency in this region has recently been reported.¹ The 1 in 20 frequency quoted was a general introductory statement that we did not attach to this region and did not use in any calculation.

The numbers of screened pregnancies² in this area have previously been reported by Professor Brock. Our paper attempted to mirror the time period and population used in Professor Brock's report, to allow the reader to collate both pieces of information. Edinburgh Sick Children's Hospital CF centre serves the population of south east Scotland. Even when considering this whole region, the effect of antenatal screening stated in our paper remains true. In the seven years before screening there were 39 children born with CF (mean 5.57) and in the seven years after screening was initiated (in Edinburgh only) there were 20 children with CF born in the south east of Scotland (mean 2.85) (including two children born in 1996 and four in 1997 not included in our original paper).

We accept that the data of births to Edinburgh residents (used to intimate stable demographics) may have been misinterpreted, as they do not represent the total number of births in the city (which is more typically 8500 per annum).

Potential discrepancies in our data as a result of small numbers of births were highlighted as the most likely explanation for differences in observed and expected numbers of CF births, other possible causes were discussed in recognition of this. As no other area in the world has a routine antenatal screening programme for CF we were unable to amalgamate data. Our aim was to highlight that we now have approximately 20 fewer children with CF under 6 years old in our clinic than we might have expected, information that we consider will be further able to inform the debate on antenatal and postnatal screening for CF.

- 1 Brock DJ, Gilfillan A, Holloway S. The incidence of cystic fibrosis in Scotland calculated from heterozygote frequencies. *Clin Genet* 1998;53:47-49.
- 2 Brock DJ. Prenatal screening for cystic fibrosis: 5 years' experience reviewed. *Lancet* 1996;347:148-50.

BOOK REVIEWS

Injury in the Young. Edited by MP Ward Platt, RA Little. (Pp 317 hardback; £55.) Cambridge University Press, 1998. ISBN 0 521 48117 1.

Paediatricians tend to forget that injury is the most common cause of death in school age children, responsible for just over a third of deaths in this age group. Even in children aged 1 to 4 years, nearly a quarter of deaths are traumatic in origin. In the past decade there has been increasing interest in the prevention and epidemiology of childhood injuries with advances in initial resuscitation and treatment, which depend on a basic understanding of the underlying pathophysiological processes.

Some deaths from trauma result from overwhelming damage and are inevitable. Children with less severe injuries may deteriorate quite rapidly and develop respiratory, circulatory or secondary brain problems with death occurring within several hours. The changes in training of paramedics and improved resuscitation training of doctors and hospital staff have helped improve the outlook for these children while advances in intensive care, improved interhospital transport, and faster high quality imaging have also been of benefit. Finally, there is a smaller number of children who die later from infection, multiple organ failure or brain damage secondary to raised intracranial pressure—some of these are preventable.

Therefore it is timely for *Injury in the Young*, which tries to bring together the mechanisms of injury and some of the abnormal physiological processes that supervene. The authors review experimental and empirical data to look at more rational treatment regimens for injured children. A wide panel of experts have been brought together in this well edited book, from disciplines including paediatrics, accident and emergency medicine, anaesthetics, and paediatric public health. Although the list of contributors is named and their work place stated it would have been helpful to have details of the authors' current posts to give readers an idea of the diversity of their skills.

The editors have had a difficult job squeezing all this information into a book of just over 300 pages, so they have rightly concentrated on the most common life threatening injuries in children including head injury, near drowning, burns, and chest injury. Unfortunately, they omit severe abdominal trauma; there should have been two or three pages of text about immediate treatment as ruptured spleen, liver or viscus can cause major diagnostic problems and death in the multiply injured child.

What about child abuse? This is covered in almost two pages of text with just two references, one to fractures caused by child abuse and another general review of the subject from the *BMJ* in 1995. This is disappointing, although the final chapter is on children's rights and child protection.

Overall the book is well laid out and carefully produced. The authors state its targets as accident and emergency specialists, paediatric surgeons, anaesthetists, and intensive care specialists, as well as paediatricians. There is no doubt that trainees in these disciplines will find the book a useful reference

source. My preference would have been for more illustrations to complement the text. The academic approach to many topics, such as acute respiratory distress syndrome, will mean that this text is useful for researchers.

The emphasis on primary prevention is covered well. Reducing injury from road traffic accidents is of major interest to community paediatricians. Other paediatricians are likely to be involved in initial resuscitation during the first hour or so of admission to hospital. In many units they will have an ongoing role in the acute management of some patients, such as those with severe head injury. Indeed, injury treatment is rapidly becoming multidisciplinary and no particular doctor has all the answers. If there are to be advances in management, basic mechanisms of injury and secondary damage must be understood. This book helps with this process and will be useful to staff in units treating paediatric trauma patients.

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Young Carers and their Families. By Becker S, Aldridge J, Dearden C. (Pp 144; paperback £14.99.) Blackwell Science, 1998. ISBN 0 632 04966 9.

"... it is not uncommon for the day to start at 5.30 am with preparation of breakfast and attendance to the personal needs of the parent. The child may call home at midday to toilet the parent and prepare lunch. In the evening shopping, cooking and cleaning may take priority over school homework. Often a child puts the parent to bed and sleeps in the same room in order to turn her during the night. The involvement in personal care such as changing of sanitary towels and catheter management has also been reported."

A day in the life of a child caring for a parent with multiple sclerosis.

Children caring for their parents or other children in the family are familiar to those who have worked in the third world but even with the UK's welfare service and safety net there are between 15 and 40 000 child carers nationwide. Oddly, just before starting to read this book I attended a meeting at a local school where we have begun a system of multiagency review of pupils not in school; the first young person discussed was caring for a parent and grandparent. We need to be more aware of this problem—hence this academic overview is welcomed.

Written by a trio of sociologists the book comes from a community and family based perspective but there is much of value to paediatricians.

The authors first describe three perspectives on child carers: the impact of disability on the family, which is mainly medical; the children's rights angle; and the view of the disability rights movement. The first is viewed rather negatively as being narrow, but to me portrays the emotional and educational impact on the child of being a carer: "Every child needs to grow up in a stable environment characterised by consistent relationships. Many children are instead subjected to unending crises stemming from a parent's illness and repeated hospitalisation which provoke chronic uncertainty and unresolved grief that can be more stressful to a child than the loss of a parent through divorce or death." Thus the role of carer can restrict the child's education, can create physical burdens that their bodies are unprepared for, and confront them with a picture of suffering that has long term harm.

The children as carers literature tells why children take on care giving roles: a major factor is lone parenthood, another is reluctance of their father to take on caring activity; sadly the failure of services to recognise the needs of children and indeed sometimes to withdraw their provision is a notable factor. Inevitably, poverty is an ever present contributor. We learn of the involvement of young carers in intimate tasks; one girl cared for her father from the age of 9 following a stroke: "I did stop showering him at about 14 or 15, but recently that's started again. I didn't like showering him any more. You know, I thought 'I want my privacy, I'm sure he wants his', and I'm sure he doesn't like me having to shower him and I certainly don't like doing it. I suppose it was embarrassment. You know—it takes up so much time, it takes about an hour from start to finish, you know, get him in the shower and get him out and dressed."

Children carers have little power or status and families assume that what has begun voluntarily will become embedded in their habits, even though the young person would rather relinquish the role.

School attendance and performance is poor among young care givers; one study found that one in four were missing school. It is a poor reflection on school health services that support has not been provided to help these children back into school.

I found that the authors take a long time to make a few simple points. Having learned that caring is common and not beneficial for children, I wanted to know what I should do but there are no clear messages. The UN Convention on the Rights of the Child should

underpin policy, but its impact in the UK has been limited. Only 11 of 71 local authorities defined these children as in need under the Children's Act. The Carers Act 1996 ensures that children may request to have their needs assessed but in a typical British Catch 22, the Act does not oblige departments to provide any services.

A useful type of support are the Young Carers' Projects with now over 100 in the UK. These raise awareness, develop supportive services, act on behalf of young carers to ensure that they receive appropriate benefits, and arrange leisure activities.

The authors identify the need to inform young carers on medical conditions, pointing out that this is woefully inadequate and that many children know so little about their parents' medical condition that they had invented their own version of diagnosis, prognosis, and consequences.

It saddened me that in the section on the role of professionals in identifying and assisting young carers, there is no mention of paediatricians. Is this because they are seen as purely medical, or because they have little contact with young carers? I suspect that it is the former, and that we need to be more outspoken about our wish to work across disciplines on behalf of children's health. We also need to look out for child carers in the families whom we see.

What I searched for was a child or young person's perspective, to try and understand some of the positive aspects of caring. I found little, perhaps because little has been done. Usually children have pretty good answers to difficult questions. Searching hard, I found a reference to a national survey of young people in which they thought that children of 10 should make their own bed and help with the washing up, children of 14 could take a part time job, young people at 16 could baby sit a child of 5, and 18 year olds could marry and vote. Caring for a parent was not mentioned.

So what might paediatricians take away from this book? First, an understanding that children who are carers are around and are being harmed; second, that they are often invisible to the agencies who should be helping; and third, that we have a role in highlighting this type of exploitation, as well as looking out for young carers among our patients. We would do well to network with the agencies locally who have young carers' projects. Only when I was writing this did I discover who they are in my district.

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