LETTERS TO THE EDITOR

Epidemiology of cerebral palsy

EDITOR,—The recent collaborative publication on the epidemiology of cerebral palsy, incorporating data from three cerebral palsy registers, categorises levels of functional disability to reflect difficulties with ambulation, manual dexterity, and learning.¹

We agree that "...severity of disability needs to be recorded..." to facilitate comprehensive monitoring and rational planning, but a measure of how such disability affects the life of a child would further improve our understanding.

The North of England Cerebral Palsy Register contains data on children born between 1960 and 1990 to mothers resident in Newcastle, Northumberland, and North Tyneside. This Register includes a unitary measure of impact of disability, comprising six contributing dimensions.² The functional disabilities described by Pharaoh and colleagues would be captured within the dimensions of mobility, physical independence, and schooling. We reviewed data on children born 1984-9, and identified interesting similarities and differences to the findings of Pharaoh *et al*.

During 1984-9, there were 57 605 live births in Newcastle, Northumberland, and North Tyneside. Among these live births were 316 neonatal deaths and 125 cases of cerebral palsy, giving a neonatal mortality rate of 5.5 per 1000 live births and a cerebral palsy rate of 2.2 per 1000 neonatal survivors. Birthweight and clinical type of cerebral palsy were known for all children. Data on the impact of disability are available for 100/125.

Neonatal mortality and cerebral palsy prevalences are almost identical with those found by

Pharaoh *et al*, as is the observation that the type of cerebral palsy differs among different birthweight groups, with the lightest and heaviest groups showing fewer cases of diplegia and more cases of hemiplegia (table 1).

Table 2 shows the severity of impact of disability for mobility, physical independence, and schooling. After excluding those of unknown severity, like Pharaoh *et al* we found that over 40% of children, irrespective of birthweight, have severe mobility problems. Unlike Pharaoh and his colleagues, however, we found no differences in physical independence among birthweight groups (14/51 children born ≥ 2500 g vs 15/49 of those born < 2500 g had severe problems), and in our cohort, the proportion of children with severe educational problems increased with decreasing birthweight, corresponding to some of the findings of follow up studies of children with low birthweight.^{3 4}

We conclude that a measure of the impact of disability on the lives of children permits greater precision in describing the epidemiology of cerebral palsy.

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- 1 Pharaoh POD, Cooke T, Johnson MA, King R, Mutch L. Epidemiology of cerebral palsy in England and Scotland, 1984-9. *Arch Dis Child* 1998;79:F21-5.
- 2 Mackie PC, Jessen EC, Jarvis SN. The lifestyle assessment questionnaire: an instrument to measure the impact of disability on the lives of children with cerebral palsy and their families. *Child Care, Health and Development* 1998;24:473-86.
- 3 The Scottish Low Birthweight Study Group. The Scottish low birthweight study: II. Language

attainment, cognitive status, and behavioural problems. *Arch Dis Child* 1992;67:682-6.

- 4 Hall A, McLeod A, Counsell C, Thomson L, Mutch L. School attainment, cognitive ability and motor function in a total Scottish very-low-birthweight population at eight years: a controlled study. *Dev Med Child Neurol* 1995;37:1037-50.

Maternal hypertension and its association with cerebral palsy in very preterm infants

EDITOR,—Gray *et al*¹ recently reported an apparently new observation that "maternal hypertension has a protective effect against cerebral palsy in very preterm infants." Do their data support this conclusion, which is different from the conclusion reached by two other case control studies^{2 3} on this topic?

In the same issue, Tin *et al*⁴ remind us that those infants who are difficult to follow up have different (worse) outcomes than those infants who could be followed up without great difficulty. They provide a key message that "studies where it is not possible to see some children for assessment might usefully include a calculation of what the total prevalence would be if there was a fivefold difference in the proportion with the condition in question among the children who were not seen."

Gray *et al*'s study comprised 107 in the study group, of whom there were 101 survivors. At 2 years of age, four in the study group were lost to follow up as were two in the control group. Using the recalculation suggested by Tin *et al*, there is no longer a significant difference between the estimated incidence of cerebral palsy in the two groups.

Spinillo *et al* reported cerebral palsy in 2/92 (2.1%) cases and 4/184 (2.1%) controls. However, their two year follow up was 92 of 97 cases. Ascertainment of the outcomes of the remainder of the group, and applying Tin *et al*'s "correction" would not have changed their conclusion of no difference in the incidence of cerebral palsy between infants born to hypertensive mothers and controls.

The case control study by Szymonowicz and Yu³ reported 27 cases and 26 controls and came to exactly the same conclusion as Gray *et al*. All had a two year follow up, but it is not stated in their paper whether complete follow up was achieved or whether the sample was selected retrospectively on the basis of the availability of two year follow up data.

A prospective study designed to have 80% power to show a protective effect of pre-eclampsia of 25% against cerebral palsy, assuming a 5% cerebral palsy rate in the control group, would require more than 4000 babies in each study arm. Even to detect a 50% reduction from a 10% rate of cerebral palsy in the controls would require about 500 babies in each arm. The combined number of babies of hypertensive mothers in the three case control studies is 216.

In view of Tin *et al*'s timely demonstration of the importance of the effects of incomplete follow up and the above considerations, it is prudent to await further prospective studies before accepting Gray *et al*'s conclusion that "maternal hypertension has a protective effect against cerebral palsy in very preterm infants."

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Table 1 Clinical type of cerebral palsy by birthweight group

Type of cerebral palsy	<1000 g	1000-1499 g	1500-2499 g	≥ 2500 g	All birthweights
Hemiplegia	3 (42.9%)	3 (18.8%)	5 (15.2%)	28 (40.6%)	39 (31.2%)
Diplegia	1 (14.3%)	8 (50.8%)	14 (42.4%)	16 (23.2%)	39 (31.2%)
Quadriplegia	3 (42.9%)	5 (31.3%)	11 (33.3%)	15 (21.7%)	34 (27.2%)
Other			3 (9.1%)	10 (14.5%)	13 (10.4%)
All CP	7 (100%)	16 (100%)	33 (100%)	69 (100%)	125 (100%)

Table 2 Severity of impact of disability by birthweight group

	<1000 g	1000-1499 g	1500-2499 g	≥ 2500 g	All birthweights
Mobility:					
None	1 (14.3%)			2 (2.9%)	3 (2.4%)
Mild	2 (28.6%)	5 (31.3%)	5 (15.2%)	12 (17.4%)	24 (19.2%)
Moderate		6 (37.5%)	10 (30.3%)	15 (21.7%)	31 (24.8%)
Severe	2 (28.6%)	5 (31.3%)	13 (39.4%)	22 (31.9%)	42 (33.6%)
Unknown	2 (28.6%)		5 (15.2%)	18 (26.1%)	25 (20.0%)
Total	7 (100%)	16 (100%)	33 (100%)	69 (100%)	125 (100%)
Physical independence:					
None	1 (14.3%)	1 (6.3%)	1 (3.0%)		3 (2.4%)
Mild	2 (28.6%)	6 (37.5%)	9 (27.3%)	21 (30.4%)	38 (30.4%)
Moderate	1 (14.3%)	6 (37.5%)	7 (21.2%)	16 (23.2%)	30 (24.0%)
Severe	1 (14.3%)	3 (18.8%)	11 (33.3%)	14 (20.3%)	29 (23.2%)
Unknown	2 (28.6%)		5 (15.2%)	18 (26.1%)	25 (20.0%)
Total	7 (100%)	16 (100%)	33 (100%)	69 (100%)	125 (100%)
Schooling:					
None	2 (28.6%)	4 (25.0%)	7 (21.2%)	18 (26.1%)	31 (24.8%)
Mild	1 (14.3%)	5 (31.3%)	4 (12.1%)	16 (23.2%)	26 (20.8%)
Moderate		3 (18.8%)	9 (27.3%)	13 (18.8%)	25 (20.0%)
Severe	2 (28.6%)	4 (25.0%)	8 (24.2%)	4 (5.8%)	18 (14.4%)
Unknown	2 (28.6%)		5 (15.2%)	18 (26.1%)	25 (20.0%)
Total	7 (100%)	16 (100%)	33 (100%)	69 (100%)	125 (100%)

- 1 Gray PH, O'Callaghan MJ, Mohay HA, Burns YR, King JF. Maternal hypertension and neurodevelopmental outcome in very preterm infants. *Arch Dis Child* 1998;79:F88-F93.
- 2 Spinillo A, Iasci A, Capuzzo E, Egbe TO, Colona L, Fuzzi E. Two-year infant neurodevelopmental outcome after expectant management and indicated preterm delivery in hypertensive pregnancies. *Acta Obstet Gynecol Scand* 1994;73:625-9.
- 3 Szymonowicz W, Yu VYH. Severe pre-eclampsia and infants of very low birth weight. *Arch Dis Child* 1987;62:712-16.
- 4 Tin W, Fritz S, Wariyar U, Hey E. Outcome of very preterm birth: children reviewed with ease at 2 years differ from those followed up with difficulty. *Arch Dis Child* 1998;79:F83-F7.

Dr Gray responds:

Professor Colditz cited the report of Tin *et al*⁴ and concluded that a recalculation of our data (on the basis of those infants lost follow up) would reveal that there would no longer be a statistical difference in the estimated incidence of cerebral palsy between study and control groups.

While we reported neurodevelopmental outcome of the infants at 2 years, in general, cerebral palsy of functional significance can be reliably diagnosed by the age of 12 months. One of our four study infants not seen at 2 years was assessed at 1 year, while both control infants not seen at 2 years had follow up data at 1 year of age. None of these three infants had cerebral palsy. Thus cerebral palsy occurred in 0/98 (0%) study infants compared with 5/104 (4.8%) controls.

Tin *et al* suggested that one might include in results "a calculation of what the total prevalence would be if there was a fivefold difference in the proportion with the condition in question among children who are not seen." As the incidence of cerebral palsy in the study children was 0%, a fivefold increase would remain 0%. If, however, one calculated the incidence of cerebral palsy in the total population (5/202, 2.5%) and made a fivefold increase, the incidence of cerebral palsy would be 12.5% in those infants lost to follow up. Thus in both scenarios, of our three infants, less than one would be expected to have cerebral palsy and the significance between the groups would remain.

We acknowledge that our results are at variance with two previous cohort studies,^{5,6} but they agree with the recent case control study of cerebral palsy in preterm infants. Murphy *et al*⁷ found a decreased risk (relative risk 0.4; 95% confidence intervals 0.2-0.9) of cerebral palsy when maternal hypertension/pre-eclampsia was present. Accordingly, while a large multicentred cohort study would be useful, we believe that the current evidence does suggest that maternal hypertension protects against cerebral palsy in preterm infants. We therefore agree with Collins and Paneth,⁸ who concluded in their annotation that preterm infants born to mothers with pre-eclampsia have a lower risk of cerebral palsy than other preterm infants.

- 5 Spinillo A, Iasci A, Capuzzo E, Egbe TO, Colona L, Fuzzi E. Two-year infant neurodevelopmental outcome after expectant management and indicated preterm delivery in hypertensive pregnancies. *Acta Obstet Gynecol Scand* 1994;73:625-9.
- 6 Szymonowicz W, Yu VYH. Severe pre-eclampsia and infants of very low birth weight. *Arch Dis Child* 1987;62:712-16.
- 7 Murphy DJ, Sellers S, Mackenzie IZ, Yudkin PL, Johnson AM. Case-control study of antenatal and intrapartum risk factors for cerebral palsy in very preterm singleton babies. *Lancet* 1995;346:1449-45.

- 8 Collins M, Paneth N. Preeclampsia and cerebral palsy: are they related? *Dev Med Child Neurol* 1998;40:207-11.

Neurological adverse effects of early postnatal dexamethasone in very preterm infants

EDITOR,—Administration of dexamethasone very early after birth has been explored as a prophylactic treatment of bronchopulmonary dysplasia (BPD). The results have been conflicting. Saunders *et al*¹ and the recent meta-analysis by Tushar Bhuta and Arne Ohlsson² concluded a reduction in the odds of BPD. However, Tapia *et al*³ recently failed to show a reduction in its incidence. None of these studies has considered the impact of the treatment on the rate of periventricular leucomalacia (PVL).

We used a protocol similar to Saunderson's study design (0.25 mg/kg intravenously twice before 24 hours of life) in neonates born before 29 completed weeks of gestation with respiratory distress syndrome. This open study conducted over 20 months was interrupted after an important increase in cystic PVL rate had been observed. Indeed, the incidence of PVL during this period (15%) was significantly higher than that observed during both the preceding 20 months (7%) and the following 20 months (7%) ($p < 0.02$). Moreover, during the same period (73 treated and 99 untreated infants), PVL rate was higher in group treated with dexamethasone (23% vs 9%; $p < 0.05$, χ^2 test after controlling for gestational age). Perinatal morbidity in the treated group was greater, but did not account for the higher PVL rate observed during the treatment period. Indeed, early neonatal mortality (< 7 days), the rates of respiratory distress syndrome, haemodynamic failure and congenital sepsis, as well as the circumstances of delivery known to be associated with high rate of PVL (premature rupture of the membranes, intrauterine infection, vaginal bleeding) were not statistically different before, during, and after the treatment period.

Adverse effects on neuromotor functions have already been reported by Yeh *et al* in an early prolonged trial of dexamethasone.⁴ As far as the conflicting data of controlled trials on its benefits are concerned, early postnatal administration of dexamethasone should be considered with caution, as long as follow up results of other randomised studies are not yet available.

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- 1 Sanders RJ, Cox C, Phelps D, Sinkin RA. Two doses of early intravenous dexamethasone for the prevention of bronchopulmonary dysplasia in babies with respiratory distress syndrome. *Pediatr Res* 1994;36:122-8.
- 2 Bhuta T, Ohlsson A. Systematic review and meta-analysis of early postnatal dexamethasone for prevention of chronic lung disease. *Arch Dis Child* 1998;79:F26-F33.
- 3 Tapia JL, Ramirez R, Cifuentes J, *et al*. The effect of early dexamethasone administration on bronchopulmonary dysplasia in preterm infants with respiratory distress syndrome. *J Pediatr* 1998;132:48-52.
- 4 Yeh TF, Lin YJ, Huang CC, *et al*. Early dexamethasone therapy in preterm infants: a follow-up study. *Pediatrics* 1998;101:e7.

Is caffeine treatment given to preterm babies a risk factor for SIDS?

EDITOR,—Ford *et al*¹ examined the association between maternal caffeine intake during pregnancy and the risk of sudden infant death and found a higher risk for babies whose mothers consumed more than 400 mg/day of caffeine during the first and/or the third trimester of pregnancy (with increased risk especially for the third trimester group).

We are concerned because preterm babies, especially those of low and very low birth-weight, are routinely treated with caffeine or theophylline to prevent apnoea and bradycardia at a gestational time which is equivalent to the "third trimester of pregnancy." The question as to whether we can compare the dose given to the neonates with the 400 mg/day taken by pregnant women, the amount found to increase the risk of SIDS.

When we look at the common dose of caffeine citrate (between 3 mg/kg/day and 5 mg/kg/day, after a rather high loading dose) it seems to be somewhat lower than the amounts postulated in Ford's study (assuming that the pregnant woman weighs about 75 kg on average, 400 mg/day would be equivalent to 5.33 mg/kg/day in preterm infants, for example). However, even considering the higher distribution volumes, the pharmacokinetic studies with premature neonates^{2,3} show a markedly lower clearance than the values reported for adults.

We have not been able to find any data for fetal serum concentrations of caffeine, but fetal values would be expected to decrease faster in utero than after delivery, owing to maternal excretion.

The possible explanation suggested for an increased risk of SIDS is the effect of caffeine on the brainstem, which may cause increased vulnerability of the respiratory centre.³ If this theory is right, we cannot find any basic difference in the situation of fetal and neonatal "treatment."

So, the question remains: is the higher incidence of SIDS in premature babies the result of neonatal caffeine treatment?

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- 1 Ford RPK, Schluter PJ, Mitchell EA, *et al*. Heavy caffeine intake in pregnancy and sudden infant death syndrome. *Arch Dis Child* 1998;78:F9-13.
- 2 Lee TC, Charles B, Steer P, *et al*. Population pharmacokinetics of intravenous caffeine in neonates with apnoea of prematurity. *Clin Pharmacol Ther* 1997;61:628-40.
- 3 Thomson AH, Kerr S, Wright S. Population pharmacokinetics of caffeine in neonates and young infants. *Therapeutics Drug Monitor* 1996;18:245-53.

Dr Ford *et al* respond:

Caffeine treatment for apnoea in prematurity is current standard neonatal practice.⁴ Very premature infants have about a fivefold increased risk of SIDS compared with their full term counterparts.^{5,6} Bock *et al* therefore speculate whether this higher incidence of SIDS in premature infants might be related to caffeine treatment. To our knowledge, there is no satisfactory answer to this question. However, as in all treatments, a balance needs

to be struck between the benefit of the treatment and any downstream adverse effects. Their question is important and needs careful study.

- 4 Scanlon J, Chin K, Morgan M, Durbin G, Hale K, Brown S. Caffeine or theophylline for neonatal apnoea? *Arch Dis Child* 1992;67:425-8.
- 5 Malloy M, Hoffman HJ. Prematurity, sudden infant death syndrome, and age of death. *Pediatrics* 1995;96:464-71.
- 6 Darlow B, Horwood L, Mogridge N, Clemett R. Prospective study of New Zealand very low birthweight infants. outcome at 7-8 years. *J Paediatr Child Health* 1997;33:47-51.

Impaired phagocytosis and opsonisation towards group B streptococci in preterm infants

EDITOR.—We were interested to see the article by Kallman *et al.*¹ who have elegantly demonstrated the role that defective polymorphonuclear leucocyte (PMNL) function and reduced opsonic capacity have, in sepsis caused by group B streptococcus in preterm infants. They advocate the need for a vaccine or passive transfer of opsonic antibody. One vaccination strategy has recently been tried in an animal model.²

There are, however, other potential therapeutic strategies. One of us has previously shown that PMNL respiratory burst activity is reduced in preterm infants³ compared with term infants and adults, but can be increased ("primed") by prior exposure to cytokines (rhGM-CSF). Therefore, an alternative approach in treatment is to enhance defective PMNL function with the administration of growth factors or cytokines, and we understand trials of this nature are currently in progress.

These observations highlight the need for further investigation of the mechanisms underlying the relative immunodeficiency of preterm infants as a basis for rational treatment. Even if a vaccine proves to be the most efficient treatment it can only work against the background of the child's own immunological responsiveness.

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- 1 Kallman J, Schollin J, Schalen C, Erlandsson A. Impaired phagocytosis and opsonisation towards group B streptococci in preterm neonates. *Arch Dis Child* 1998;78:F46-50.
- 2 Magliani W, *et al.* Neonatal mouse immunity against group B streptococcal infection by maternal vaccination with recombinant anti-idiotypes. *Nature Med* 1998;4:705-9.
- 3 Jaswon M S, Jones H M, Linch D C. The effects of rhGM-CSF on the neutrophil respiratory burst in the term and preterm infant when

studied in whole blood. *Pediatr Res* 1994;36:623-7.

BOOK REVIEWS

A Neonatal Vade-Mecum. 3rd Edn. B Speidel *et al.* [Pp 481; 17.99 paperback] Arnold, 1998. ISBN 0-340-69140-9.

This is the third edition of a well recognised neonatal handbook. The authors declare their intention to provide a book of a practical nature as a ward guide for medical and nursing staff caring for newborn infants. Much revision has occurred since the previous edition and the depth and breadth of contributions is reflected in the lengthy list of editors and contributors, all of whom are recognised as experienced practitioners.

Have the editors succeeded in their aim? Essentially, yes. The book is of a size and price to be readily accessible. It is very clear in its layout and provides essential neonatal information a shopfloor neonatologist needs. Each section has a useful bibliography as a source for more extensive information.

My main criticism is questionable information. A brief introductory sentence pointing out that local practices may be at variance with those detailed, and should be respected, would be helpful to junior and nursing staff. Some of the information is set out didactically with no hint that there is a wide body of practice. Instances would be the roles of ultrasound and serum screening in antenatal practice, the use of Ribavarin for RSV bronchiolitis, and the choice of anticonvulsants for seizures. There is little evidence that outcome in perinatal asphyxia is helped by the use of therapies to reduce raised intracranial pressure, so mannitol is not used in many centres. The value of cerebral ultrasound in determining cerebral oedema is very questionable and it is now recognised that antenatally diagnosed cystic adenomatous malformations of the lung can regress, obviating the need for lobectomy. The infusion dose of tolazoline is given as 0.1 mg/kg/hour; do they mean this or is this a printing error? These are minor quibbles as most of the management decisions relating to these points will be conducted at a senior level, but for juniors who use this book it would be helpful to know that not all questions have only one answer.

The one area in which it is important to state the opinion given is contentious, is the use of 40%, rather than 100% oxygen for

resuscitation. It is important that all personnel called on to resuscitate newborns are aware of the local policy.

The sections on caring for the family and the dying baby are extremely well written, particularly when considering the size and scope of the book. I recommend anyone working in this area to read them. The ethical and personal issues which have to be faced are clearly, succinctly and compassionately addressed.

The editorial team should be congratulated on producing such a compact yet useful book which, I am sure, will find its way onto many neonatal units.

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Critical Care of the Surgical Newborn.

Edited by Don Nakayama, Carl L Bose, Nancy C Chescher and Robert D Valley. [Pp 610 hardback \$150]. Futura Publishing Co, Inc. ISBN 0-87993-653-3.

"Much study is a weariness of the flesh" stated the writer from Ecclesiastes. The acquisition of medical knowledge requires the consumption of many large, indigestible tomes. This compact textbook on critical care of the surgical newborn provides a suitable antidote. It is small, concise, light in weight, but packs a quality punch. It is a good balance of relevant embryology, antenatal diagnosis, appropriate investigations, and operative management. From a surgical perspective I found the chapters on prenatal diagnosis and ultrasound particularly useful, teaching me many things I probably ought to have known already.

It covers the usual range of child topics on neonatal care well and succinctly and in a sufficiently different way to be interesting. It also discusses ethics and anaesthetics and analgesia. The chapter on anaesthetics finally answered a question I have asked every anaesthetist but to which I have never received a satisfactory reply—namely, what is the intraoperative/anaesthetic death rate in babies? The intraoperative death rate quoted of 8.3/1000 for infants under one month seemed more realistic than the optimistic replies from colleagues. The intraoperative death rate of children between one to 12 months of 0.8/1000 seemed higher than I imagined, but will influence what I say to parents when seeking informed consent in the future.

Unusually for a textbook, it held my interest and attention and was readable and will influence my clinical practice in the future.

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