LETTERS TO THE EDITOR

Antibiotic treatment of suspected neonatal meningitis

SIR,—The editorial by Drs Gandy and Rennie on antibiotic treatment of suspected neonatal meningitis has provided a timely review of an important neonatal problem.¹ We were surprised to see the use of intraventricular aminoglycosides being advocated for the treatment of Gram negative meningitis, as there is now considerable evidence to suggest that intraventricular treatment is not only ineffective, but may, in addition, be hazardous. We were further disappointed to read the authors' rebuttal of the important arguments made by Drs Short² and Tarlow³ in their subsequent letters to the editor.

The argument put forward by Gandy and Rennie rests on the observation that the aminoglycosides do not penetrate well into the cerebrospinal fluid, and adequate cerebrospinal fluid concentrations to treat Gram negative bacillary meningitis are not achieved when aminoglycosides are administered intravenously. In the past, intrathecal aminoglycosides seemed a logical form of treatment. Since the introduction of the third generation cephalosporins, however, the position has changed. These agents are highly active against *Escherichia coli* and other coliforms, and when administered intravenously, achieved cerebrospinal fluid concentrations several times the minimal inhibitory concentration for these organisms.⁴ It is therefore difficult to justify the use of intraventricular treatment.

The authors seem unconvinced by two multicentre trials of intrathecal aminoglycosides in neonatal meningitis.⁵ Not only was no benefit derived from aminoglycosides given by either the lumbar or the intraventricular route, but the mortality was higher in the patients receiving intraventricular treatment. The authors also avoid the worrying evidence that suggests that the administration of intraventricular aminoglycosides results in higher cerebrospinal fluid concentrations of endotoxin and cytokines than seen after systemic treatment alone.⁶ In view of the increasing evidence that bacterial toxins and host inflammatory mediators are responsible for the damage to the central nervous system associated with bacterial meningitis,³ treatment that increases cerebrospinal fluid concentrations of these substances should be avoided.

The arguments that have developed subsequent to the annotation on the antibiotic treatment of suspected neonatal meningitis highlight the different philosophical approaches to what makes good paediatric practice. We believe that practice should be guided by the results of published therapeutic trials rather than personal belief. As the only trials to date have demonstrated a poorer outcome in patients receiving intraventricular aminoglycosides, this form of treatment should not be advocated.

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- 1 Gandy G, Rennie J. Antibiotic treatment of suspected neonatal meningitis. *Arch Dis Child* 1990;65:1-2.
- 2 Short A. Antibiotic treatment of suspected neonatal meningitis. *Arch Dis Child* 1990;65:810.
- 3 Tarlow MJ. Antibiotic treatment of suspected neonatal meningitis. *Arch Dis Child* 1990;65:810.
- 4 Kaplan SL. Recent advances in bacterial meningitis. *Advances in Pediatric Infectious Diseases* 1989;4:83-110.
- 5 McCracken GH, Mize SG, Threlkeld N. Intraventricular gentamicin therapy in gram negative bacillary meningitis of infancy. *Lancet* 1980;i:787-91.
- 6 Mustafa MM, Mertsola J, Ramilo P, Saez-Llorens X, Risher RC, McCracken GH. Increased endotoxin and interleukin-1-beta concentrations in cerebrospinal fluid of infants with coliform meningitis and ventriculitis associated with intraventricular gentamicin therapy. *J Infect Dis* 1989;160:891-5.

Drs Gandy and Rennie comment:

The correspondence generated by our editorial has highlighted the difficulties experienced by those attempting to manage this condition. We endorse the use of cefotaxime but, as stated in the original annotation, the published results with this agent contain only small numbers of babies (less than 50) and there has not been the improvement in mortality or morbidity which was expected. This could be because of the frequency of ventricular enlargement in neonatal cases which may require drainage or make the cerebrospinal fluid minimal inhibitory concentration inadequate, and it is for these babies and for those who fail to respond to systemic treatment alone that we continue to recommend consideration of intraventricular treatment. The use of intraventricular reservoirs will naturally decline if cephalosporins have the success which is predicted for them.

Drs Heyderman and Levin are correct in their assumption that we remain unconvinced by results regarding 20 neonates with *Escherichia coli* meningitis contained in the only study using intraventricular treatment which was carried out before the introduction of cephalosporins, ultrasound, or intraventricular reservoirs.¹ We agree that ones clinical practice should be guided by the results of well conducted therapeutic trials of adequate size but for neonatal Gram negative meningitis we consider that such studies are yet to be published, and urgently need to be planned.

- 1 McCracken GH, Mize SG, Threlkeld N. Intraventricular gentamicin therapy in gram negative bacillary meningitis of infancy. *Lancet* 1980;i:787-91.

Categories of preventable unexpected infant deaths

SIR,—As members of the Avon Infant Mortality Study Group we were surprised and disturbed by the recent paper from Sheffield by Taylor and Emery.¹ They came to the conclusion that in 43% of sudden unexpected infant deaths there was 'treatable disease' and, by implication, these deaths could have been prevented by appropriate health care intervention. This finding is at variance with our own observations.² We were also concerned to read that eight of 115 (7%) deaths in the Sheffield study were attributed to filicide, a finding which is at variance with our own experience of only one case of proved filicide in over 200 sudden unexpected death victims during a seven year period in Avon.

We see the parents of all infants who die

unexpectedly in Avon within 72 hours of the death (most of them within 24) with the general practitioner and health visitor and collect detailed information from the parents, primary health care team, and hospitals. This contact includes a 'death scene' examination and a structured questionnaire on medical and social history.² All infants undergo a detailed standardised postmortem examination by a paediatric pathologist or a pathologist with special expertise in this field.³

For the past three years all sudden unexpected deaths of infants in Avon have been the subject of a formal multidisciplinary confidential discussion involving two pathologists, a microbiologist, a biochemist, an epidemiologist, and three paediatricians with extensive experience of infant care.

We have drawn up a classification of death using microbiological, gross pathological, and histological criteria. The results of the 95 infant deaths included in the first two years of our study (May 1987 to April 1989) are given below.

In seven (8%) of the total deaths we were able to identify a sufficient explanation for the death, while in 39 (41%) we identified evidence of a potentially significant illness at the time of death, but insufficient to account for the death. In the remaining 49 (51%) no significant abnormalities were identified. None of these deaths was thought to be due to filicide. These results are similar to those previously published by Arneil *et al* in the Scottish National Study.⁴

Taylor and Emery state that minor non-lethal defects may lower the threshold for the onset of severe illness and thus contribute to death. We are not aware of any evidence to support this contention. Signs of illness in infancy are very common,² and interpretation of their significance as contributory factors in infants who die requires carefully matched controls, which are lacking in the Sheffield study.

Workers in the field of sudden unexpected death in infancy have a great responsibility to the children of this country and to the parents of children who have died suddenly and unexpectedly. The paper by Taylor and Emery raises many questions about the interpretation of clinical, psychosocial, and pathological findings after the death of an infant but contains insufficient data to allow the reader to assess the validity of their conclusions.

We are well aware of the confidential nature of inquiries that have to be made where filicide is considered to be a possibility, but we call upon the authors of this work to make available the information that they have for confidential re-examination by an independent group of paediatricians and pathologists. The outcome of this fresh inquiry could then be submitted for publication in this journal.

These questions are too important to be left open by the lack of data in the paper by Taylor and Emery.

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- 1 Taylor EM, Emery JL. Categories of preventable unexpected infant deaths. *Arch Dis Child* 1990;65:535-9.
- 2 Gilbert RE, Fleming PJ, Azaz Y, Rudd PT. Signs of illness preceding sudden unexpected deaths in infants. *BMJ* 1990;300:1237-9.
- 3 Wigglesworth JS, Keeling JW, Rushton DI, Berry PJ. Pathological investigations in cases of sudden infant death. *J Clin Pathol* 1987;40:1481-3.
- 4 Arneil GC, Gibson AAM, McIntosh H, Brooke H, Harvie A, Patrick WJA. National post-perinatal infant mortality and cot death study, Scotland 1981-82. *Lancet* 1985;i:740-3.

Drs Taylor and Emery comment:

The main differences between the Bristol and Sheffield views on unexpected infant death are firstly, that the Bristol group do not accept the concept that several contributory factors may result in a lethal situation, and secondly that they are unable to accept that filicide is the probable cause of a small percentage of cot deaths.

Our view is that many unexpected infant deaths are due to a combination of factors in the sense that but for the presence of all of these factors death might not have occurred.¹ The concept of contributory factors is one which is generally accepted—for example, the increased severity of infections in children who also have nutritional deficiencies or reduced pulmonary reserve due to residual lesions in the lung after perinatal damage. Dr Fleming and his group have themselves postulated that overheating and overwrapping may be a contributory factor in some cot deaths.²

The confidential inquiries undertaken by Dr Fleming and his group with case conferences being hospital based and hospital orientated are very similar to those undertaken in Sheffield in the 1970s, and their results are very similar to our own at that time.

In 1979 we started to hold our case discussions on all 'non-hospital' deaths in the family doctor's surgery. These case discussions are held when data collection, including a home visit by a doctor not concerned with the paediatric care of the family, is complete and the results of a full paediatric necropsy are available and at a time when the initial emotional impact of the death is lessening and more dispassionate views may prevail. These discussions, at which the general practitioner and health visitor are invariably present, are as much concerned with planning for the future health care of the family and of any subsequent child as with the cause of the baby's death. It is these confidential discussions with the general practitioner and health visitor that have revolutionised our views on the aetiology of unexpected infant death and have shown us the importance of family and background factors, and it is at these discussions that the possibility of filicide is occasionally raised. Deaths are only placed in this category if at the conclusion of the case discussion it is a unanimous decision that this was the *most probable* mechanism of death. The prime reason for identifying this small group (less than 10%) is so that an appropriate level of care—paediatric, psychiatric, and health visiting—can be provided for the family. Although the identification of possible filicide only forms a relatively small part of our inquiries, the denial of the possibility of this mechanism of death would also deny some families the extra care that they need.

Fleming *et al* state that our data should be 'inspected by an independent group of paediatricians and pathologists'. As we collect more than 50 pages of data after each death this would be a major undertaking. However, we have no secrets other than the confidential-

ity of information relating to individual families and would welcome a visit from Dr Fleming or one of his colleagues to look at our records, discuss our methods, and attend a case discussion.

- 1 Emery JL. A way of looking at the causes of crib death. In: Tyson Tildon J, Roeder LM, Steinschneider A, eds. *Sudden infant death syndrome*. London: Academic Press, 1983:123-32.
- 2 Fleming PJ, Gilbert R, Azaz Y, *et al*. Interaction between bedding and sleeping position in the sudden infant death syndrome: a population based case-control study. *BMJ* 1990;301:85-9.

Effective bronchodilator treatment by a simple spacer device for wheezy premature infants

STR.—Yuksel and colleagues describe a cheap and easy solution to a common and difficult problem.¹ One cannot help but be impressed by the size of the improvement seen during active treatment.

There are, however, certain aspects of the study which concern me. Firstly, the study was not randomised and all the children were given active treatment after placebo. Although this is disputed by the authors, in this group of children where symptoms are likely to have been exacerbated by viral infections, one would have expected some improvement with time, irrespective of treatment. This possibility is borne out to some extent, as on active treatment there was a 27% reduction in the score for 'runny nose/unwell'; these are symptoms which are suggestive of a viral infection. These symptoms could not have been expected to respond to a bronchodilator and therefore should not have been added to cough and wheeze (their table 1). Also adding together scores for cough and wheeze (their table 1) could double the score for a single event. Admittedly the percentage fall in each symptom category, with active treatment, is remarkable.

Secondly, the authors state 'Administration of the bronchodilator resulted in an increase in functional residual capacity both immediately and during the two week active period'. This is patently not borne out by the results in their table 3, where there is no significant difference in functional residual capacity before and after terbutaline using a paired *t* test (mean (SD) before and after terbutaline: 252 (75) and 269 (58) in the placebo period and 322 (83) and 325 (95) in the active period). Indeed two and three subjects, respectively, showed a 'clinically significant' decrease in functional residual capacity after terbutaline compared with four and two with a 'clinically significant' increase. If we are to believe, as the authors suggest, that an increase in functional residual capacity reflects an improvement in lung function, then the long term improvement in functional residual capacity on active treatment occurred without any evidence of an immediate response. The authors do not address this discrepancy between the long and the short term benefit but misleadingly suggest that an immediate increase in functional residual capacity had occurred.

One is left with a sneaking suspicion that at least part of the improvement on active treatment, in symptoms and lung function, could be related to changes with time. Before accepting the alternative conclusion, that in this group of children twice daily terbutaline has a dramatic effect on symptoms, which is largely

independent of its immediate bronchodilator properties, it would be wise to confirm the results with a better designed study.

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- 1 Yuksel B, Greenough A, Maconochie I. Effective bronchodilator treatment by a simple spacer device for wheezy premature infants. *Arch Dis Child* 1990;65:782-5.

Drs Greenough and Yuksel comment:

We thank Dr Wilson for her interest in our paper. In that preliminary study, as no previous data was available, we set out to assess if bronchodilator given by a simple spacer had any effect on symptomatic preterm infants in the first year of life. We found over the two week period in which bronchodilator was administered a significant improvement in lung function and reduction in symptom score.

We are surprised Dr Wilson felt it necessary to reanalyse the acute lung function data as we did not claim that the change in functional residual capacity 10 minutes after terbutaline was significant. We recognised and stressed in our discussion that the results could in part be explained by an improvement in symptoms with time and felt our results should be confirmed in a randomised trial—which, as a consequence we have subsequently completed (unpublished observations). In a randomised placebo controlled trial inhaled ipratropium bromide administered via a coffee cup, resulted in similar improvements in functional residual capacity and a reduction in symptom score. Unfortunately many infants are symptomatic in the first year of life, the coffee cup technique is cheap and easy; we therefore, like Dr Wilson, are impressed and we are also pleased with the size of improvement seen during active treatment.¹

Gender and the progression of *Escherichia coli* 0157:H7 enteritis to haemolytic uraemic syndrome

STR.—The epidemiologic studies of Milford *et al* continue to advance our understanding of Verocytotoxin producing *Escherichia coli* and the associated haemolytic uraemic syndrome.¹ Notable among their findings is the excess of females in the probable prototypic haemolytic uraemic syndrome subgroup and the observation that such excess has been observed previously in other studies. Our own studies have also previously suggested an excess of females among patients with *E coli* 0157:H7 associated haemolytic uraemic syndrome.² Although in a univariate analysis this excess was not significantly different from a control group of patients who suffered from *E coli* 0157:H7 enteritis only, a multivariate analysis disclosed that female gender was possibly an important predictor variable for progression to haemolytic uraemic syndrome.

In order to determine whether the latter association was coincidental, we continued our study to include 37 patients with haemolytic uraemic syndrome and 95 patients with only enteritis. The sex ratios (M/F) in the two groups were 17/20 and 53/42 respectively. In univariate analysis, gender was not associated