LETTERS TO THE EDITOR

Double blind trial of recombinant human erythropoietin in preterm infants

EDITOR,—A recent paper demonstrates very clearly the dangers of allowing those who may benefit financially from the results of a study to be involved in reporting that study. The double blind trial of recombinant human erythropoietin (r-HuEpo) in preterm infants reported by Emmerson, *et al* was supported by Cilag Ltd.¹ The r-HuEpo used was supplied by Cilag Ltd and one of the authors is employed by Cilag Ltd.

The abstract of the paper outlines the form of the double blind study. It reports a significant rise in the reticulocyte count in the r-HuEpo group, and a reduction in the number of transfusions needed compared with the placebo group, and some differences in haematological indices. The abstract concludes: 'The study provides strong evidence for the efficacy of r-Hu-Epo in stimulating erythropoiesis and reducing the requirement for transfusions for anaemia of prematurity'.

I suspect I was not alone in at first accepting that abstract at face value. It was only on reading the whole paper that I discovered that the abstract is dangerously misleading. In fact there was no significant difference in the proportions of each group requiring transfusion, there was no significant difference in the mean volume of blood transfused in each group, and at no time during the study or three months' follow up was there any significant difference in mean haemoglobin concentration between the two groups.

By far the most misleading aspect of the abstract, however, was the failure to mention that 20% of the r-Hu-Epo group died within a month of the end of the trial, while no infant in the placebo group died. Three out of 15 infants receiving r-HuEpo while in hospital died within four weeks of being discharged home, one from volvulus and gut infarction, and two from sudden infant death syndrome (SIDS). Whether one looks at the incidence of SIDS, or more general figures of mortality in preterm infants, the odds against three such deaths happening by chance in a group of 15 infants are several thousands to one.

Such deaths should surely have resulted in very obvious warnings, in the abstract and elsewhere, about an as yet unexplained potential danger of r-HuEpo. Instead the authors are dismissive of the danger, and conclude that: 'further studies with larger numbers of infants are required to clarify the optimal dose, frequency, and starting time for the prevention of this anaemia'.

Your publication of this paper raises several questions that require answers:

- (1) Do the authors have any better reasons than those so far presented for believing that the deaths were not linked to r-HuEpo, when statistically it is highly likely that they were?
- (2) Why have the deaths not been reported to the Committee on Safety of Medicines?
- (3) Can the authors rebut the inevitable suspicion that the abstract was framed in such a way as to protect Cilag Ltd's commercial interests?

(4) How did the paper and its abstract manage to pass the peer review and editorial processes?

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- 1 Emmerson AJB, Coles HJ, Stern CMM, Pearson TC. Double blind trial of recombinant human erythropoietin in preterm infants. *Arch Dis Child* 1993; 68: 291-6.

Dr Emmerson comments:

The deaths of the infants in the clinical trial of r-HuEpo in preterm infants are a concern shared by many, not least by the authors of the paper, however that this should lead to very obvious warnings in the abstract is strongly refuted.

It is inappropriate to group the three deaths together. One of the deaths was an infant who developed an acute volvulus of the gut after cessation of treatment, and this was a clear cause of death. Of more concern are the two infants who died from SIDS, four weeks after stopping treatment, both having received different r-HuEpo doses. Statistically the chance of two infants dying of SIDS within one group of 15 infants is small, but this does not confirm a causal relationship.

No attempt was made to mislead the reader. Throughout the paper there is open discussion of these deaths, including in the subjects and methods section where the premature termination of the study was reported. This demonstrates that the authors took these deaths extremely seriously, feeling it inappropriate to continue the double blind trial without breaking the code and analysing the data. In addition to very careful scrutiny of the data for the whole group and for the two SIDS infants, an extensive search of the world experience (published and unpublished) was made for other cases. No other cases of SIDS have occurred with the use of r-HuEpo. The doses employed in some other studies have been several times higher, and taking this and the numbers treated in all studies the significance of the possible association of SIDS and r-HuEpo is reduced.¹⁻³ These points are made clearly in the paper. Theoretical mechanisms whereby r-HuEpo may have resulted in SIDS are given in the discussion, and the whole approach of the paper cannot be considered to be dismissive of the danger.

The authors did not feel that a warning of the dangers of using r-HuEpo in preterm infants was appropriate, for the reasons stated above, and in that respect it was not recorded in the abstract which, being a brief summary, should in no way replace reading the full paper.

The authors take strong exception to the suggestion that Cilag's commercial interests influenced the publication. The inclusion of the author from Cilag Ltd, a senior clinical research associate, acknowledged her contribution to the monitoring and conductance of this study ensuring adherence to good clinical practice.

Dr Nicholson's question relating to the reporting of the deaths to the Committee on Safety of Medicines is unfounded as all the deaths were promptly reported (as is the legal requirement) between two and 10 days after death.

All the authors agree that it is essential to have proper reporting of adverse events, but to have over interpreted the possible association of SIDS and the use of r-HuEpo in the absence of any other evidence to support it

would have been incorrect and irresponsible.

The authors maintain the view that there was appropriate consideration and reporting of the data and that the correct balance between the data in the abstract and the whole paper was made.

- 1 Carnielli V, Montini G, Da Riò R, Dall'Amico R, Cantarutti F. Effect of high doses of human recombinant erythropoietin on the need for blood transfusions in preterm infants. *J Pediatr* 1992; 121: 98-102.
- 2 Shannon KM, Mentzer WC, Abels RI, *et al*. Enhancement of erythropoiesis by recombinant human erythropoietin in low birth weight infants: a pilot study. *J Pediatr* 1992; 120: 586-92.
- 3 Ohls RK, Christensen RD. Recombinant erythropoietin compared with erythrocyte transfusion in the treatment of anaemia of prematurity. *J Pediatr* 1991; 119: 781-8.

Antenatal assessment of neurological impairment

EDITOR,—We write to criticise the management of a 23 year old primigravida with a varicella infected fetus reported by Taylor *et al*.¹ Their stated purpose is to illustrate that antenatal assessment can offer insight into the ultimate prognosis of the infant. However, it is possible that the authors miss the point.

The mother presented at 27 weeks for decreased fetal movements. The fetus exhibited a markedly fixed fetal heart rate pattern. The primary care centre appropriately referred her to a maternal fetal centre.

The consultants gathered every piece of data to reach the exact diagnosis. Varicella IgM was present in fetal blood. Fetal blood showed normoxia and normal acid base balance. The occurrence of a fixed fetal heart rate pattern with normoxia and normal pH has been well described in the literature as being consistent with fetal brain death.²⁻⁴ The differential diagnosis of a fixed fetal heart rate is limited, including: fetal quiet sleep (fetal behavioural state IF), maternal drug ingestion (diazepam, pethidine), and anencephaly. Fetal quiet sleep is excluded simply by extending the fetal heart recording to at least 60 minutes. Fetal drug ingestion is confirmed by history and anencephaly is, of course, diagnosed by ultrasound.

This fetus never had sustained breathing movements, and polyhydramnios developed.

After this elegant evaluation one would expect state of the art management. What follows is most surprising: (1) conservative management 'in the absence of evidence of hypoxaemia'; (2) 'elective caesarean section at 39 weeks because of the difficulty of monitoring a fetus with an unvarying heart rate'; and (3) extremely aggressive paediatric management of a severely damaged child. Therefore, in spite of a correct diagnosis of congenital varicella zoster infection with hepatic and brain stem involvement the fetus and subsequently the infant were managed aggressively. The child lived for 10 months with a tracheostomy, fundal plication, gastrostomy, and ligation of the patent ductus arteriosus.

The discussion reviews the elements necessary to assess fetal distress, yet never mentions 'fetal brain death'.

There are excellent data in the European obstetric literature showing that a non-variable fetal heart rate accompanied by normoxia and normal acid base balance is consistent with fetal brain death; in such cases caesarean section must be avoided. If the consultants had made the diagnosis of fetal brain death, the unnecessary caesarean

section and costly (financial and emotional) care of this infant could have been avoided.

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- 1 Taylor WG, Walkinshaw SA, Thomson MA. Antenatal assessment of neurological impairment. *Arch Dis Child* 1993; 68: 604-5.
- 2 van der Moer PE, Gerretsen G, Visser GHA. Fixed fetal heart rate pattern after intrauterine accidental decerebration. *Obstet Gynecol* 1985; 65: 125-7.
- 3 Nijhuis JG, Kruyt N, Van Wijck JAM. Fetal brain death. Two case reports. *Br J Obstet Gynaecol* 1988; 95: 197-200.
- 4 Nijhuis JG, Crevels AJ, Van Dongen PWJ. Fetal brain death: the definition of a fetal heart rate pattern and its clinical consequences. *Obstet Gynecol Surv* 1990; 45: 229-32.

Mr Taylor and Mr Walkinshaw comment:

We are aware of the case report literature on fetal brain death, almost all of which is secondary to known severe hypoxia.¹ In our case we aimed to illustrate cranial nerve defects, and our dynamic ultrasound findings evolved over several weeks. There was no evidence from the history or later postmortem examination to suggest an anoxic insult. The confirmation of fetal varicella IgM antibodies was delayed for several weeks. Local laboratory testing was negative, but referral to the Manchester PHSL Reference Laboratory gave the reported result. The cardiotocograph (our fig 1) does not fulfil all of the criteria for fetal brain death. The baseline was appropriate for the gestation and close scrutiny of the illustration reveals shallow decelerations.¹ We accept, however, that this should have been elaborated on in our discussion.

Lessons are being learned from anatomical prenatal diagnosis and false positive diagnoses illustrate its lack of precision. We would urge caution in the new field of functional diagnosis rather than to take a didactic approach.

We are not aware of any reported literature on how often a potential false positive diagnosis of fetal brain death is made. Even a biophysical profile score of 2 before delivery is not always associated with a poor neonatal outcome.² We felt after discussion with the parents that the baby should be given the benefit of these doubts.

The paediatric management was aggressive and reflected the reluctance of the paediatricians to accept the reliability of a functional diagnosis. The obstetric authors (WGT, SAW) agree with Sheila Gahagan and Claudine Amiel-Tison that some of the paediatric investigations and management was unnecessary.

- 1 Nijhuis JG, Crevels AJ, Van Dongen PWJ. Fetal brain death. The definition of a fetal heart rate pattern and its clinical consequences. *Obstet Gynecol Survey* 1990; 45: 229-32.
- 2 Manning FA, Morrison I, Harman CR, Menticoglou SM. The abnormal biophysical profile score. Predictive accuracy according to score composition. *Am J Obstet Gynecol* 1990; 162: 918-24.

Should we look after babies less than 800 g?

EDITOR,—Dr Robertson writes that 'babies between 500 g and 800 g ... clearly have an

excellent chance of neurologically intact survival' (p 329) and yet provides us with scant data to support this.¹

The results quoted (based on the survival rate of all babies born in the state of Victoria, Australia and weighing under 1000 g) show no survivors under 600 g and a neurologically intact survival rate of 8% for babies weighing 600-699 g.^{2,3} This is a very commendable achievement but surely not 'clearly an excellent chance'.

Dr Robertson tells us that 'the cost of looking after these babies is not prohibitive, about £10 000-£15 000 per survivor'. This figure comes from the estimated cost per survivor of £13 720 in a trial of 19 babies in Belfast Royal Maternity Hospital in 1985-7. The mean birth weight was 1287 g and the cost per day in special care £77.⁴ I suggest that the cost of caring for a 500-800 g baby in 1993 is considerably more than this. (Dr Robertson says earlier in the article that '8-10 year old data apply to a standard of neonatal care that is obsolete' (p 327)). He describes the above cost as 'phenomenally cheap compared with ... hormone treatment for the menopausal middle aged' (p 328). The March 1993 edition of the *British National Formulary* gives the cost of one year's treatment with ethinyloestradiol as £11.31.

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- 1 Robertson NRC. Should we look after babies less than 800 g? *Arch Dis Child* 1993; 68: 326-9.
- 2 Kitchen WH, Doyle LW, Ford GW, et al. Changing 2 year outcome of infants weighing 500-999 g at birth. A hospital study. *J Pediatr* 1991; 118: 938-43.
- 3 Victoria Infant Collaborative Group. Improvement of outcome for infants of birth weight under 1000 g. *Arch Dis Child* 1991; 66: 765-9.
- 4 Tubman TRT, Halliday HL, Norman C. Cost of surfactant treatment for severe neonatal respiratory distress syndrome. A randomised controlled trial. *BMJ* 1990; 301: 842-5.

When will my baby go home?

EDITOR,—Powell *et al* report that parents of preterm babies frequently ask: 'when will my baby go home?'.¹ This question is being asked in the Netherlands as well. In the study cited by Powell *et al* as reporting mortality and morbidity only,² we asked exactly that

question. The results have been published in a Dutch language medical journal.³ Of the nationwide cohort of very preterm (gestational age less than 32 completed weeks) and (or) very low birthweight (less than 1500 g) infants the 992 surviving infants were discharged home after a mean hospital stay of 68 days (range 6-380 days).

For all infants, the difference was calculated between the expected date of delivery and the date of discharge. The figure shows the number of infants discharged per category of days before and after term. The distribution shows that, as in the study of Powell *et al*, many of these infants were discharged around 36 to 37 weeks' postconceptional age (term minus 25 to minus 15 days). A total of 60% of all infants went home at or before 42 weeks' postconceptional age. However, 10% of these very preterm infants were still in the hospital at five weeks after the expected date of birth. We concluded that for this category of preterm babies, the answer to the parents' question should be: half of these babies can go home at or before the expected date of delivery, 70% are home two weeks after that, and 90% are home at five weeks after term.

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- 1 Powell PJ, Powell CVE, Hollis S, Robinson MJ. When will my baby go home? *Arch Dis Child* 1992; 67: 1214-6.
- 2 Verloove-Vanhorick SP, Verwey RA, Brand R, Bennebroek Gravenhorst J, Keirse MJNC, Ruys JH. Neonatal mortality risk in relation to gestational age and birthweight. Results of a national survey of preterm and very-low-birthweight infants in the Netherlands. *Lancet* 1986; i: 55-7.
- 3 Pel M, Verloove-Vanhorick SP. Wanneer gaat een couveuse-kind naar huis? (When does a special-care-baby go home?) *Ned Tijdschr Geneesk* 1988; 132: 1687-8.

Bilateral congenital diaphragmatic hernia - delayed presentation of the contralateral defect

EDITOR,—Approximately 3% of congenital diaphragmatic defects are bilateral.¹ Historically this condition has been almost uniformly fatal, with the first UK survivor reported in 1990.² We have successfully treated two patients in whom diagnosis of the contralateral hernia was delayed.

Number of infants discharged at various ages in relation to term date (expected date of delivery) (n=992). (Figure adapted from *Het Nederlands Tijdschrift voor Geneeskunde* (1988; 132: 1687-8³) and reproduced with permission.)