LETTERS TO THE EDITOR

Low soluble FcRIII receptor demonstrates reduced neutrophil reserves in preterm neonates

EDITOR,—Studies of human neonate granulopoiesis have been hampered by the lack of a marker of overall neutrophil cell mass. Assumptions about neonate granulopoiesis have therefore largely been extrapolated from rat data. Direct measurement of total neutrophil cell mass (in terms of neutrophils per g body weight) in newborn rats has shown that they have about one quarter the neutrophil mass of adult animals and that their neutrophil mass increases to adult levels by the time they are 4 weeks old.[1] In addition, newborn rodents do not have the reserve pool of quiescent granulocyte progenitors, as found in adults, to recruit into production during sepsis. Circumstantial evidence for a similar immaturity of neutrophil production in human neonates comes from the low proportion of quiescent progenitors in cord blood[2] and the frequent occurrence of postnatal neutropenia in preterm infants. Some additional insight comes from a study of mid-trimester abortuses,[3] which showed minimal numbers of neutrophils in haemopoietic tissue before 24 weeks gestation. Until now, direct quantification of total body neutrophil cell mass in human neonates between 24 weeks and term has remained elusive.

In 1992 we reported[4] that preterm neonates born before 32 weeks gestation have very low plasma concentrations of the soluble FcRIII receptor (sFcRIII). sFcRIII is the plasma form of the neutrophil membrane receptor FcγRIII which, together with other membrane receptors, is responsible for binding opsonised particles and initiating phagocytosis. We observed that, between 24 and 32 weeks gestation, sFcRIII concentrations are about 15% of normal adult values (mean (SE) 15.3 (1.3)%), while sFcRIII concentrations in fetal samples collected between 19 and 23 weeks are even lower (mean (SE) 8.3 (1.4)%). Between 33 and 36 weeks in utero, sFcRIII increases rapidly so that babies born at term have concentrations similar to adults. In babies born before 32 weeks, sFcRIII increases gradually after birth to achieve adult concentrations by the fourth week of postnatal life. At the time, we interpreted these data to indicate reduced FcRIII production by individual cells and thus immaturity of neonate neutrophil function.

Since we published these data, further work has clarified the origins and significance of plasma sFcRIII. These studies have shown that sFcRIII is derived from apoptotic neutrophils, and its concentration in plasma reflects the total body neutrophil cell mass as well as the overall production of neutrophils in the bone marrow.[5 6]

This new understanding of sFcRIII alters the interpretation of our original observation. It is now apparent that our data confirm what was previously only suspected: preterm human infants of less than 32 weeks gestation have reduced neutrophil production and a reduced total neutrophil cell mass at birth. Our data also show that neutrophil reserves remain low for about three weeks after preterm birth. Term infants, by contrast, have neutrophil production and stores that are similar to those of adults.

The reduced neutrophil mass of preterm neonates explains the common occurrence of postnatal and sepsis induced neutropenia. The relevance of this finding to the high sepsis incidence associated with prematurity is emphasised by a recent study of patients with idiopathic neutropenia, which has shown that a low sFcRIII concentration is a more accurate predictor of infection risk than the peripheral blood neutrophil count.[7] Furthermore, this new insight into neonatal immune development suggests that stimulation of neutrophil production by colony stimulating factors early in postnatal life could reduce the incidence and severity of sepsis in preterm neonates by accelerating expansion of their deficient neutrophil reserves.

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Chasing hyponatraemia in preterm infants

EDITOR,—In a recent issue, Hartnoll *et al*[1 2] described the effect of postnatal sodium supplementation on oxygen dependency, body weight, and body composition of preterm infants. According to them, an overzealous approach to correcting hyponatraemia in preterm infants is not scientific. In the same context, I would like to describe a case of a preterm infant who developed symptomatic patent ductus arteriosus after supplementation with sodium.

The infant was a 1060 g baby boy born at 29 weeks of gestation with no significant antenatal history. The first five days were unremarkable. On day 6 of life, he was noted to have hyperglycaemia, which persisted, requiring an insulin drip. At the same time, his hyponatraemia was corrected with extra sodium supplementation. On day 11, he was noted to have a murmur, which later was confirmed by echocardiography as patent ductus arteriosus. Table 1 summarises the events.

The case clearly indicates a need for a conservative approach to hyponatraemia in preterm infants, as "chasing" it may lead to fluid retention and development of patent ductus arteriosus.

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Suxamethonium is safe in safe hands; mivacurium should also be considered

EDITOR,—We thank Whyte *et al*[1] for detailing the premedication policies for intubation in United Kingdom neonatal units. There is a wide disparity in both the type and dosage of drugs.

Whyte *et al*[1] mention that, as a muscle relaxant, suxamethonium, has important safety benefits. It has a very rapid onset and offset of action, and therefore there is a "get out clause" for the difficult intubation or intubation by an inexperienced operator. However, other considerations need to be taken into account when suxamethonium is used.

Firstly, intravenous premedication is contraindicated in conditions known to be associated with difficult intubations, such as the Pierre Robin sequence. Further, suxamethonium is a depolarising muscle relaxant and can therefore cause sinus bradycardia. Atropine can be given in an attempt to avoid this.

Suxamethonium causes depolarisation at the neuromuscular junction, rarely leading to hyperkalaemic induced cardiac arrest.[2] Undiagnosed myopathic conditions were found in a number of affected children, and paediatric licensing for this drug was therefore removed in the United States. However, no other very rapidly acting drug has been manufactured, and, because of its popularity, suxamethonium was reinstated. Before its use, a detailed family history for myopathic conditions must be taken.

In our neonatal unit, we have started to use fentanyl, an opioid, with mivacurium as the muscle relaxant.[3] The disadvantage of mivacurium is that it is only a rapidly acting muscle relaxant.[4] Its major advantage is that it is a non-depolarising muscle relaxant and therefore carries no risk of life threatening arrythmias. The routine use of atropine is not necessary.

Table 1 Summary of the events

Day no	*Total fluids (ml/kg)*	*Urinary output (ml/kg/h)*	*Sodium input (mmol/day)*	*Serum sodium (mmol/l)*	*Weight (g)*
6	217	7	3	124	860
7	248	7.8	7	120	860
8	213	7	10	128	870
9	214	4.9	14	134	890
10	203	5.3	15	131	900
11	206	6.1	15	136	940 (PDA)

PDA, patent ductus arteriosus.

We agree that a randomised trial needs to be undertaken to prove that premedication has the desirable end point of reducing neonatal morbidity, particularly intraventricular haemorrhage.

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Premedication for intubation in neonates

EDITOR,—We were very interested in the recent papers by Bhutada *et al*[1] and Whyte *et al*[2] on the use of premedication for semielective intubation in neonates. It is now well accepted that term and preterm neonates tolerate awake intubation poorly, often exhibiting hypoxia, bradycardia, and systemic and intracranial hypertension during nasotracheal or orotracheal intubation.[3 4] Analgesia and sedation are still used infrequently in nurseries for intubation and other "routine", but invasive, therapeutic or diagnostic procedures.[5]

We recently performed a randomised, double blind, placebo controlled trial to assess whether sedation with midazolam in premature infants would improve physiological stability and the success rate of endotracheal intubation. Eight premature infants underwent 16 intubation procedures after being randomly assigned to one of three groups: I (n = 3), the control group, received placebo only; II (n = 6) received atropine and placebo; III (n = 7) received atropine and midazolam. Infants could be randomised again to a different group after completion of each intubation procedure. Heart rate, blood pressure, and oxyhaemoglobin saturation were recorded at 10 minute intervals for each infant. The study was terminated and the data reviewed early because of concerns over adverse events. The number of episodes of oxyhaemoglobin desaturation around the time of intubation was significantly greater in group III (86%) than in group I (0%; p = 0.01). Cardiopulmonary resuscitation was required in 29% of group III compared with 0% of group II (p = 0.16).

In our trial, premature infants who received midazolam were at increased risk of oxyhaemoglobin desaturation during tracheal intubation. There was also a trend toward an increased need for cardiopulmonary resuscitation in these infants. Although regrettably underpowered because of early termination, our study indicates caution in the use of midazolam as routine premedication for tracheal intubation in premature infants. Further investigation with a larger number of infants is needed to clarify its safety and efficacy profile.

Although we agree that an important goal in neonatal medicine is to minimise pain and stress, more information is needed on the effects of intravenous anaesthetic agents, such as thiopental and methohexital,[6] in both stable and unstable preterm neonates before these medications can be recommended for routine use. Further randomised controlled trials are needed to help formulate specific premedication guidelines for the variety of noxious procedures that infants undergo in neonatal intensive care units.

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Incidence of severe retinopathy of prematurity

EDITOR,—We were interested to read the article of Vyas *et al*[1] on the incidence of severe retinopathy of prematurity (ROP) in 11 neonatal units in five cities in England in 1994. We have published similar data from eight neonatal units in New South Wales (NSW) Australia in 1993 and 1994.[2] These data were prospectively collected in the NSW Neonatal Intensive Care Unit's data collection and is stored and maintained in the NSW Centre for Perinatal Health Services Research, University of Sydney, NSW.

For infants of < 29 weeks gestation, there was no significant difference in severe ROP (≥ stage 3) between the five cities in England and NSW (table 1).

Unlike Vyas *et al*,[1] we could not find an association between improved survival and the development of severe ROP. In six of the neonatal units in our study (two have been excluded from this analysis as they are children's hospitals and have very few small premature infants), survival in infants of < 27 weeks gestation ranged from 51.3% to 68.8%. The percentage with severe ROP for the two units with the lowest and highest survival was 15 (3/20) and 24 (5/21) respectively, while the range of severe ROP in the six neonatal units was 15% (3/20) to 36% (9/25). In infants of 27–28 weeks gestation, survival ranged from 85.1% to 96.7% and the percentage with severe ROP for the two units with the lowest and highest survival was 7 (4/56) and 3 (2/58) respectively, while the range of severe ROP in this group of infants was 2% (1/50) to 7% (4/56) (unpublished observations). We have also shown that, despite an increase in survival of preterm infants following the introduction of surfactant, there was no significant impact on the incidence or severity of ROP.[3]

Table 1 Incidence of severe retinopathy of prematurity (ROP) in five cities in England and in New South Wales (NSW), Australia

Gestation	*Five cities in England*	*NSW Australia*
<27 weeks	20/95 (21.0)	44/157 (28.0)
27–28 weeks	5/162 (2.6)	15/269 (5.6)

Data are expressed as number with severe ROP/number examined with the percentage in parentheses. The differences are not statistically significant.

In infants of 29–31 weeks gestation, six of 443 infants (1.4%) developed severe ROP and one required Cryo/Laser treatment.[2] This infant was 30 weeks gestation with a birth weight of 1305 g. We therefore agree with Vyas *et al*[1] that there should be no reduction in the upper limit of gestation or birth weight for screening for ROP.

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Blood pressure standards for very low birthweight infants

EDITOR,—Based on careful invasive blood pressure measurements in a cohort of 61 very low birthweight (VLBW) infants during the first 24 hours of life, Lee *et al*[1] report on blood pressure standards in this population. The quality of the blood pressure readings was assessed using continuous video recordings of real time wave forms. The inclusion of a relatively large number (n = 28) of extremely low birthweight infants is another strength of this study.

In an attempt to define normal blood pressure values in a population that by definition is not "normal", the authors have excluded very ill infants and infants requiring inotropic support. They have also excluded infants who developed intraventricular haemorrhage (IVH) grades III and IV during the first week of life. They suggest that the lower limits of mean arterial blood pressure (MAP) for infants between 26 and 32 weeks of gestation are numerically similar to the gestational ages.

With the exclusion of infants who developed severe IVH, it became impossible to detect any association between blood pressure and IVH. Decreases in cerebral blood flow may play an important role in the pathogenesis of IVH, and, although blood pressure is not a reliable parameter to assess cerebral blood flow,[2] at least two published studies[3 4] have shown that the incidence of IVH was higher in infants with lower MAP. Perhaps the authors could indicate how many infants

with IVH grades III and IV were excluded and what blood pressures were recorded in these infants. For similar reasons, it remains uncertain whether the proposed blood pressure standards are applicable to very ill infants or infants who require inotropic support. It is conceivable that cerebral vascular resistance in sick preterm infants differs from that in the study patients, and consequently the application of the suggested blood pressure standards to sick preterm infants would result in different—and possibly inadequate—cerebral blood flows.

The data presented add to our knowledge on blood pressure in VLBW infants, but do not allow the conclusion that the suggested blood pressure standards are safe for all VLBW infants.

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Drs Juin, Rajadurai, and Wee respond:

We would like to thank Dr Berger for his comments. Our objective was to define the normal range of blood pressures for very small infants and this would logically exclude those with IVH and those on inotropes, both of which could affect blood pressure.

We did not compare infants with and without IVH because that was not our aim. There may very well be a correlation between hypotension and IVH, but studies looking at this association were not optimal because there is controversy as to what constitutes hypotension. We hope that our standards will provide norms for such studies. Blood pressure is the practical surrogate for cerebral blood flow because with present technology we cannot continuously monitor the latter by the bedside. Tyszczuk *et al*[1] determined that cerebral blood flow was independent of blood pressure in preterm infants, but again the selection of a mean arterial pressure of 30 mm Hg as the cut off is open to debate. We think that choosing such an arbitrary number was not appropriate and more such studies are needed with particular attention being paid to the very different normal blood pressures among preterm infants with various birth weights and gestational ages.

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Patient triggered ventilation in neonatal respiratory distress syndrome

EDITOR,—Baumer reports the results of a large multicentre study comparing the effects of patient triggered ventilation (PTV) with conventional ventilation (IMV).[1] There appears to be no benefit from PTV compared with IMV in death rate, development of chronic lung disease, pneumothorax rates, and cerebral ultrasound abnormality. In addition, because of an increased trend toward a higher pneumothorax rate, Baumer concludes that, at present, PTV delivered with either the SLE 2000 or the Dräger babylog 8000 ventilators cannot be recommended for infants of less than 28 weeks gestation with respiratory distress syndrome (RDS).

However, we are concerned that this may be a premature conclusion given the significant difference in PTV delivered by the two main ventilators used and the potential heterogeneity of clinical practice within the different centres involved, despite agreed ventilation protocols. Dimitriou *et al*[2] showed that neonates and infants trigger a significantly lower proportion of breaths using the SLE 2000, an airway pressure triggered ventilator, compared with the Dräger babylog 8000, an airflow triggered ventilator that provides synchronised intermittent positive pressure ventilation (SIPPV). Attempts to optimise the trigger rate of the SLE 2000 ventilator by increasing pressure sensitivity often results in autotriggering as discussed by Baumer. Therefore the PTV modes of the two ventilators are substantially different. This prompts us to ask whether the findings of this multicentre study are only applicable to PTV provided by the SLE 2000? Would there have been a different outcome if all the triggered babies had received SIPPV?

It is not known how many of the 40/213 babies of less than 28 weeks gestation who had pneumothoraces were receiving SIPPV. As only 11% (52/465) of all triggered babies ever received SIPPV, we surmise that very few of the 40 were ventilated in this way. Is it fair to conclude that the Dräger babylog 8000 has a trend to pneumothorax on SIPPV?

In a separate smaller study, Baumer also reports 120 patients in three centres randomly assigned to either the Dräger babylog 8000 or the SLE 2000 ventilator, and found a non-significant trend to higher pneumothorax rate, chronic lung disease, and death for the former group. But we are not told how many of the babies were actually on trigger mode (PTV or SIPPV). They could all have been receiving IMV on the Dräger babylog 8000. Therefore is it possible that SIPPV is not being tested?

A further finding was a significantly higher rate (124/463) of triggered babies that departed from their assigned mode of ventilation, 45 of these failing to trigger their ventilator. Were they all on the SLE 2000 ventilator, as Dimitriou *et al*[2] would predict?

Finally, we note that 10 of the 22 neonatal units each recruited less than 20 patients over the four year period, one contributing only one patient. Could the technique of PTV ventilation in units contributing so few be different from those enrolling 60–136 neonates over the same period, despite prior visits from the trial coordinator? Would a logistic regression for morbidity against number of patients contributed from each unit show that the greatest morbidity occurred in units that contributed fewer patients, rather than those using PTV or SIPPV modes?

Given the heterogeneity of the units involved and the significant difference in ventilators used, we think that it is premature to dismiss SIPPV on the Dräger babylog 8000 in neonates less than 28 weeks gestation with RDS. We agree with Baumer that further studies are required, and extend his conclusion by saying that PTV with the SLE 2000 (n = 411) rather than SIPPV from the Dräger babylog 8000 ventilator (n = 52) cannot be recommended in this group.

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1 Baumer JH. International randomised controlled trial of patient triggered ventilation in neonatal respiratory distress syndrome. *Arch Dis Child Fetal Neonatal Ed* 2000;**82**:F5–10.
2 Dimitriou G, Greenough A, Laubscher B, Yamaguchi N. Comparison of airway pressure triggered and airflow triggered ventilation in very immature infants. *Acta Paediatr* 1998;**87**:1256–60.

Dr Baumer responds on behalf of the trial collaborators:

The interest displayed in the trigger ventilation trial by Burmester and Petros is welcome. Their letter raises questions about the interpretation of the performance of the Dräger babylog 8000, which was used in a minority of infants in the study.

The trigger sensor device is different, and I agree with their implied statement that, as each trigger ventilator performs differently, results obtained using one ventilator cannot be extrapolated to another. However, both ventilators were used in PTV mode (sometimes referred to as synchronised intermittent positive pressure ventilation, assist control, or synchronised assisted ventilation in infants), with the ventilator set to trigger at each inspiratory effort. No infants in this study were ventilated with SIMV (synchronised intermittent mandatory ventilation) where the baby's breaths, selected during a "time window", trigger the ventilator with the preset number of breaths per minute.

The results were reported in the way that they were for a reason. The original study design allowed a four way randomisation between the two makes of ventilator and the two modes of ventilation. As was reported, only three centres had enough of both ventilators to allow this to occur. Other centres ventilating infants with the Dräger babylog had a two way randomisation between PTV and IMV.

Therefore the possibility of confounding by differences in practice between centres needed to be excluded. If the centres using the Dräger as well as the SLE ventilator had different outcomes from those using only one make of ventilator, this may have led to inappropriate conclusions being drawn if all infants being ventilated with one ventilator were simply compared with those being ventilated with another. A logistic regression model was therefore used to allow for possible centre effects (as well as other significant factors such as gestation).

With that caveat, I have extracted the numbers from the database giving details of the crude observed rates of pneumothorax in the infants of less than 28 weeks gestation, separately reported for the two makes of ventilator (table 1).

The observed rate of pneumothorax was substantially (but not significantly, χ^2 2.8, $p > 0.05 < 0.1$) higher in the infants ventilated in PTV mode than in IMV mode using the SLE 2000. Although the numbers are small, the observed pneumothorax rate was higher in infants ventilated with the Dräger babylog 8000 than in those ventilated with the SLE ventilator. It therefore seems somewhat illogical to recommend caution in using

Table 1 Rates of pneumothorax in infants of less than 28 weeks gestation using two different makes of ventilator

	PTV mode	*IMV mode*
Dräger without pneumothorax	19	20
Dräger with pneumothorax	5 (20%)	4 (17%)
SLE without pneumothorax	154	114
SLE with pneumothorax	35 (18.5%)	14 (10.9%)

PTV, patient triggered ventilation; IMV, intermittent mandatory ventilation.

the SLE 2000 in PTV mode in infants less than 28 weeks gestation, but not extend this caution to ventilating infants with the Dräger babylog 8000.

Given that none of these differences were statistically significant, no clear recommendation can be given. This is why the wording used in the publication was "it might be prudent to avoid . . .".

As regards the number of infants departing from their assigned mode of ventilation, several points should be emphasised. The study protocol permitted changing the mode of ventilation at the discretion of the attending clinicians. This was inevitably interpreted differently by each clinical team. Departure from the assigned mode of ventilation was not an intended outcome, and it is evident that this occurred more commonly in the more immature infants and those that subsequently died. High rates of departure from the assigned mode cannot therefore readily be interpreted as evidence of failure of the assigned mode. Table 2 shows the numbers of infants of all gestations departing from the assigned mode of ventilation.

There was therefore a higher crude rate of departure from the assigned mode of ventilation in infants ventilated with the Dräger babylog 8000, with a similar proportion transferred for failure to trigger.

It would be difficult to interpret the pneumothorax rates for infants who were actually being ventilated with their assigned mode of ventilation. Some infants were switched to another mode of ventilation after sustaining their pneumothorax. Most of the pneumothoraces occurred while infants were receiving their assigned mode of ventilation, and this included infants being trigger ventilated using the Dräger ventilator.

Burmester and Petros ask whether centres contributing few patients may have higher morbidity rates, correcting for potential confounding factors by using a logistic regression model. The pneumothorax rate from centres contributing less than 20 patients was the same as the centres contributing more infants.

We have used a model to identify outcome differences in infants randomised within three months of the first infant being entered into the study, correcting for individual centre effects, gestation, birth weight, and mode of ventilation. There was no significant difference in rates of death and chronic lung disease, abnormal cranial ultrasound scan, or duration of ventilation. However, an appreciable and statistically significant difference was found for pneumothorax rates. The 139 infants randomised within three months had a pneumothorax rate of 5% compared with a rate of 13% for those randomised more than three months into the trial (odds ratio 0.30; 95% confidence intervals 0.12 to 0.74; p = 0.009). This was seen equally for both modes of ventilation.

Table 2 Numbers of infants of all gestations departing from the assigned mode of ventilation

	PTV	*IMV*
Dräger not departing	35	40
Dräger departing	16 (31%)	15 (27%)
SLE not departing	303	274
SLE departing	107 (26.1%)	47 (14.6%)

PTV, patient triggered ventilation; IMV, intermittent mandatory ventilation.

This finding suggests that the initial educational visit by the trial coordinator had a beneficial effect on ventilator management which disappeared as infants continued to be enrolled.

In summary, there is no evidence from this study of any trend towards better outcomes with the Dräger babylog 8000 ventilator, although the small numbers enrolled make any conclusions less robust. There is evidence that suggests there may have been a short term reduction in pneumothorax rates from the educational package offered at the start of the trial.

In conclusion, there was no convincing evidence of a beneficial effect of a policy of using PTV in preterm infants with RDS with the ventilators used. Regular attention to staff education on ventilator techniques is recommended.

I would like to use this opportunity to pay tribute to the two trial coordinators (Sue Ellis and Tom Mill), to the trial statistician (David Wright), and to the data monitoring committee (David Field and Diana Elbourne), whose details were inadvertently omitted from the final paper and without whom, together with the trial collaborators, the study would not have been possible.

Pyridoxine dependent epilepsy: a suggestive electroclinical pattern

EDITOR,—There are several problems with describing the electroclinical pattern in pyridoxine dependent seizures.[1] One is defining the electrical features. Until now all published reports (including four of the five cases of Nabbout and colleagues) have described the electroencephalogram (EEG) in neonates who have received other anticonvulsants beforehand. It seems likely that anticonvulsants could affect the EEG, as suggested by the infant with the most pronounced burst suppression pattern in the paper of Nabbout and colleagues. The only other method of assessing the electrical pattern is on withdrawal, when we, like others, found that a continuous or intermittent high volt slow wave pattern with or without spikes was typical.[2] It would be very useful to know the EEG features of the patient who did not receive any other drugs before pyridoxine, as this would be the first description of the true electrical pattern in pyridoxine dependent seizures.

This study raises issues on the use of EEGs in neonatal units. Very few of the neonates reported in the literature or in the UK study[3] had EEGs before receiving pyridoxine. Presumably this reflects difficulties in obtaining EEGs out of hours or when there is no facility attached to the neonatal unit, as well as the desire to treat without delay. As a result, for some neonatal units it may be difficult to detect a specific electroclinical pattern.

A second difficulty is that the clinical features are not very specific. The neonatal presentation can be: as an acute encephalopathy, followed by later seizures; as seizures accompanied by encephalopathy (both of which introduce a wide differential diagnosis); as seizures alone; or, more unusually, as apparent acute abdominal obstruction or respiratory distress, usually accompanied by irritable behaviour, again followed by seizures. In some reports, seizures have been precipitated by sudden sounds or movements, although some of these could be an exaggerated startle response. Although we too found that a variety of seizures, especially generalised tonic and generalised clonic, occurred in most of our cases,[2] some only had one or two seizure types. In the UK study, five of the 20 definite and probable cases with an early onset were reported to have a single seizure type (unpublished data).

The third concern is that Nabbout and colleagues did not include later presenting cases (older than 28 days) in their report. These also appear to be pyridoxine dependent as judged by trials of withdrawal and occurrence in siblings. They accounted for three of the 23 definite and probable cases in the UK population study, although a further five had early seizures that responded to routine anticonvulsants and then remained seizure free for several weeks or months. In all these, both the clinical and electrical features can differ from neonates. For example, the inter-ictal EEG can be normal, or show focal or generalised spikes or sharp waves with or without high voltage slow activity. The clinical features include recurrent episodes of status and less varied seizure types. Concentrating on a possible neonatal pattern risks overlooking such cases.

As Nabbout and colleagues emphasise, there needs to be a high index of suspicion. Clinically it is important that pyridoxine dependency should be considered in all early childhood seizures, because (*a*) other features may be misleading and (*b*) early treatment does appear to be beneficial.

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Parental visiting in neonatal units

EDITOR,—We read with interest the paper by Cuttini *et al*.[1] Although policy on parental visiting is an easier issue to evaluate, parental participation in decision making, particularly in decisions with strong ethical overtones, is much more complex. It is difficult to evaluate with accuracy, and by its nature is much more controversial. The paper does not stress that data collected from each participating unit, through a structured questionnaire completed by the unit coordinator, represent policies—that is, the intention and stance of each unit towards the particular issue for evaluation. Data collected through questionnaires and interviews involving both unit staff and parents would have provided a better understanding of the actual practice of each participating unit.

No unit from Greece took part in the study by Cuttini *et al*,[1] but Greece is briefly mentioned in the Discussion, using results from a previous study,[2] in which, in a sample

of 38 units from 11 European countries, it was shown that the nine units that imposed visiting restrictions were in France, Greece, Italy, and Portugal.

We would like to provide further information on visiting policy in Greek neonatal intensive care units (NICUs). There are 15, two of which are private; 12 are attached to maternity hospitals and the remaining three are in children's hospitals and accept distant referrals. In all but one (Aglaia Kyriakou Children's Hospital), visiting restrictions are imposed. These allow parents only, and the usual practice is 30 minutes to one hour visiting time in the morning and afternoon (except for lactating mothers). The most common reasons given for imposing restrictions are increased danger of infection and a disruptive effect on the unit.

We conducted a survey, through questionnaire and interview, of parents with a baby who had been cared for in another NICU that imposed visiting restrictions before it was transferred to our NICU and/or parents who had had a previous baby in another NICU that imposed restrictions. The overwhelming majority (98.6%) said that they preferred our liberal policy on visiting. One mother of a preterm baby with bronchopulmonary dysplasia said that "if I had delivered at term I would be with my baby; if I had not delivered prematurely I would also be with my baby (in my womb); now that I have delivered prematurely why can't I be with my baby?"

We conclude that in Greece there is a demand for unrestricted parental visiting, but most Greek NICUs do not meet this demand for reasons not based on medical or sociological evidence.

It is worth noting that, in Greece, infants beyond the neonatal period have been admitted to children's wards with their mothers for many years.

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1 Cuttini M, Rebagliato M, Bortoli P, *et al*. Parental visiting, communication, and participation in ethical decisions: a comparison of neonatal unit policies in Europe. *Arch Dis Child Fetal Neonatal Ed* 1999;**81**:F8–91.
2 Reid M, Andersen E, EC Study Group of Parental Involvement in Neonatal Care (Adam H, Cuttini M, *et al*). Variations in family visiting policies in neonatal intensive care units in eleven EC countries. *Pediatr Perinat Epidemiol* 1994;**8**:41–52.

Ureaplasma colonisation and chronic lung disease in neonates

EDITOR,—We read the article by Hannaford *et al*[1] with interest. We would like to point out that in our recent retrospective analysis,[2] our findings of the colonisation rate of genital mycoplasmas (*Ureaplasma urealyticum* and *Mycoplasma hominis*) in the respiratory tract of premature infants of 27% were similar to their study. We also found a higher incidence of chronic lung disease (CLD) in our cohort colonised with genital mycoplasmas.[2]

We are, however, intrigued by the implication of a "protective effect" of *Ureaplasma urealyticum* (Uu) colonisation on respiratory distress syndrome (RDS) in this study. The hypothesis that this may be related to the "stimulatory effect of subacute intrauterine infection on lung maturation . . ." is interesting but unsubstantiated. Current evidence suggests that the sicker infant with RDS has an increased early inflammatory response and a higher rate of CLD.[3 4] In the present study,[1] the incidence of RDS in Uu colonised infants was lower—but their incidence of CLD at 36 weeks was higher. Were there other factors—for example, increased incidence of PDA, more IV fluid use, that predisposed these infants to develop CLD? Another issue is that in the multivariate analyses, Uu colonisation was a significant risk factor for CLD only in singleton infants, but the relationship did not hold true when all infants were analysed. Based on these observations, we wonder if the "protective effect" is real or a statistical aberration? More research needs to be done to study this "protective effect" of Uu colonisation on RDS before any conclusions can be drawn.

The treatment of Uu colonisation was not discussed in this paper. In our experience, erythromycin alone was not effective in clearing the organism from the respiratory tract. We found a short course of postnatal steroids alone or in combination with erythromycin more effective.[2] We wonder if infants receiving postnatal steroids were confounders in the discrepancy between the incidence of RDS and CLD.

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1 Hannaford K, Todd DA, Jeffery H, John E, Blyth K, Gilbert GL. Role of ureaplasma urealyticum in lung disease of prematurity. *Arch Dis Child Fetal Neonatal Ed* 1999;**81**:F162–7.
2 Bhandari V, Hussain N, Rosenkrantz T, Kresch M. Respiratory tract colonization with mycoplasma species increases the severity of bronchopulmonary dysplasia. *J Perinat Med* 1998;**26**:37–42.
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Dr Gilbert *et al* respond:

EDITOR,—We thank Drs Bhanadri and Hussain for their interest in our paper. We too were intrigued by the apparently contradictory effects of ureaplasma colonisation on the lungs of affected infants and acknowledge that our hypothesis is unsubstantiated. The possibility that a subacute intrauterine infection could stimulate endogenous surfactant production is a plausible explanation for the significantly lower incidence of respiratory distress syndrome (RDS) in these infants. The fact that intrauterine infection is low grade, may also mean that delivery is delayed for long enough for exogenous steroids to take effect.

The development of chronic lung disease (CLD) is dependent on many factors, and, in our study, it correlated less closely with ureaplasma infection than did RDS. We assumed that other effects of multiple gestation outweighed those of ureaplasma infection on the development of CLD in twins. Presumably, the lower rate of RDS in ureaplasma infected singleton infants reduced their risk of CLD, directly or indirectly. If so, there must be other respiratory insults severe enough to offset this effect. We were unable to identify factors associated with CLD apart from RDS and ureaplasma infection. In particular, the incidence of PDA did not differ between infants with and without CLD.

We postulate that the low grade inflammatory effect of intrauterine ureaplasma infection could cause significant irreversible lung damage and predispose to CLD, as well as stimulating the production of surfactant. The outcome is unlikely to be affected by erythromycin therapy after birth, except in the minority of infants in whom there is frank pneumonitis, with progression after birth.

We have not studied the effects of postnatal steroids, but this is unlikely to be a significant confounding factor in these infants since, at the time the study was done, steroid therapy was not given until about four weeks of age, when CLD was already established.

Although we agree that further research is needed to confirm our findings, we believe that the inverse relationship between ureaplasma colonisation and RDS was too strong to be dismissed as a statistical aberration.

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Editor's note
References 22–30 of the paper by Hannaford *et al* were incorrect, and each correlate with the number below in the text. Thus reference 22 in the reference list corresponds with reference 21 in the text, and so on. This correction appears online [adc.bmjjournals.com/cgi/content/full/fetalneonatal;81/3/F162/DC1] The journal would like to apologise for this error.

CORRECTION

The authors of the paper "Risk adjusted and population based studies of the outcome for high risk infants in Scotland and Australia" *Arch Dis Child Fetal Neonatal Ed* 2000;**82**:118–123 have asked us to publish the following corrected version of table 6. The authors apologise for the error.

Table 6 Relative risk of neonatal death for very low birthweight infants in Scotland and England and Wales compared with Australia

	500–999 g		*1000–1499 g*		*500–1499 g*	
	Relative risk of neonatal death	*95% confidence interval*	*Relative risk of neonatal death*	*95% confidence interval*	*Relative risk of neonatal death*	*95% confidence interval*
Scotland *vs* Australia 1993–94	1.24	1.09–1.42	1.20	0.90–1.61	1.22	1.08–1.39
Scotland *vs* Australia 1993–96	1.48	1.35–1.63	1.34	1.09–1.65	1.30	1.18–1.42
England and Wales *vs* Australia 1993–94	1.15	1.07–1.24	1.18	1.01–1.39	1.17	1.09–1.25
England and Wales *vs* Australia 1993–96	1.25	1.19–1.32	1.23	1.09–1.39	1.22	1.16–1.28