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, on average, to twice adult body weight 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 and the frequent occurrence of postnatal neutropenia in preterm infants.2 Some additional insight comes from a study of mid-trimester abortions,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 reported4 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 by 37 weeks gestation concentrations are similar to adults. In babies born before 32 weeks, sFcRIII concentrations gradually increase 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 neonatal 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

This new understanding of sFcRIII alters the interpretation of our original observation. It is now apparent that our data confirm what we 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

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Table 1 Summary of the events

<table>
<thead>
<tr>
<th>Day no</th>
<th>Total fluids (ml/kg)</th>
<th>Urinary output (ml/kg)</th>
<th>Sodium input (mmol/d)</th>
<th>Serum sodium (mmol/l)</th>
<th>Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>217</td>
<td>7</td>
<td>3</td>
<td>124</td>
<td>860</td>
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<tr>
<td>7</td>
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<tr>
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<td>7</td>
<td>10</td>
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<td>870</td>
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<tr>
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<td>214</td>
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<td>900</td>
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<tr>
<td>10</td>
<td>203</td>
<td>5.3</td>
<td>15</td>
<td>131</td>
<td>900</td>
</tr>
<tr>
<td>11</td>
<td>206</td>
<td>6.1</td>
<td>15</td>
<td>136</td>
<td>940 (PDA)</td>
</tr>
</tbody>
</table>

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PDA, patent ductus arteriosus.

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

Editor,—We thank Whyte et al 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 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 therefore can 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.7 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 is 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.8 Its use is that it is a non-depolarising muscle relaxant and therefore carries no risk of life threatening arrhythmias. The routine use of atropine is not necessary.
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. 

ASRAR RASHID
Specialist Paediatric Registrar
Neonatal Unit
Birmingham Heartlands Hospital
Bordesley Green, Birmingham B9 5SS
email: Drasar@iname.com

MICHAEL WATKINSON
Consultant Neonatologist
Neonatal Unit
Birmingham Heartlands Hospital

Premedication for intubation in neonates

EDITOR.—We were very interested in the recent papers by Bhutada et al1 and Whyte et al2 on the use of premedication for sedative 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 naso-tracheal or orotracheal intubation.3 Analgesia and sedation are still used infrequently in nurseries for intubation and other “routine”, but invasive, therapeutic or diagnostic procedures.

We recently performed a randomised, double blind, placebo controlled trial to assess whether sedation with midazolam in premature infants is needed to clarify its safety and efficacy profile.

In our trial, premature infants who required intubation were randomised to receive methohexital for elective 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 naso-tracheal or orotracheal intubation. Analgesia and sedation are still used infrequently in nurseries for intubation and other “routine”, but invasive, therapeutic or diagnostic procedures.

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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.

THOMAS M BERGER
Neonatal and Paediatric Intensive Care Unit
Kinderspital Luzen, CH-6000 Luzen 18
Switzerland


Drs Juin, Rajaaduri, 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 a practical surrogate for cerebral blood flow because with present technology we cannot continuously monitor the latter by the bedside. Tyszkczuk et al 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.


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 should not 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 principles. Dimitriou et al showed that neonates and infants trigger a significantly lower proportion of breaths using the SLE 2000, an airway pressure 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 result in artefacts, as previously 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 Dräger babylog 8000? 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 pneumothorax 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 towards higher pneumothorax rate, chronic lung disease, and death for the former group. But we are not told how many of the 40/213 babies were actually on trigger mode (PTV or SIPPV). They should 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 (124/465) of all triggered babies that departed from their assigned mode of ventilation, 45 of these failed to trigger their ventilator. Were they all on the SLE 2000 ventilator, as Dimitriou et al 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 three patients over the same period, despite prior visits from the trial coordinator? Would a different outcome if all the makes of ventilator were simply compared with those being ventilated with another? Logistic regression models were therefore used to allow for possible centre effects (as well as other significant factors such as gestation). With that caveat, I have calculated 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, χ² 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 2000. It therefore seems somewhat illogical to recommend caution in using...
intermittent mandatory ventilation. 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 in infants ventilated with the Dräger babylog 8000 and 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. One is defining the electroclinical 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 before hand. It seems that the 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 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. 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 investigated use of EEGs in neonatal units. Very few of the neonates reported in the literature or in the UK study had EEGs before receiving pyridoxine. Presumably this reflects difficulties in obtaining EEGs out of hours, or indeed 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 problem 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 exaggerated startle responses. Although we too found that a variety of seizures, especially generalised tonic and generalised clonic, occurred in most of the cases, 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 late 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. In both of 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) their occurrence may be misleading and (b) early treatment does appear to be beneficial.

PETER BAXTER
Sheffield Children’s Hospital Western Bank Sheffield S10 2TH, UK

### Letters, Correction

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

<table>
<thead>
<tr>
<th></th>
<th>PTV mode</th>
<th>IMV mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dräger</td>
<td></td>
<td></td>
</tr>
<tr>
<td>not pneu-</td>
<td>19 (10%)</td>
<td>20 (10%)</td>
</tr>
<tr>
<td>mothorax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>without pneumothorax</td>
<td>154 (14%)</td>
<td>114 (14%)</td>
</tr>
<tr>
<td>SLE with pneumothorax</td>
<td>35 (18.5%)</td>
<td>14 (10.9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>PTV, patient triggered ventilation; IMV, intermittent mandatory ventilation.</th>
</tr>
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<tbody>
<tr>
<td>Dräger</td>
<td></td>
</tr>
<tr>
<td>not pneu-</td>
<td>15 (31%)</td>
</tr>
<tr>
<td>mothorax</td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td></td>
</tr>
<tr>
<td>not pneu-</td>
<td>303</td>
</tr>
<tr>
<td>mothorax</td>
<td>107 (26.1%)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>PTV</th>
<th>IMV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dräger</td>
<td></td>
<td></td>
</tr>
<tr>
<td>not pneu-</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>mothorax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>not pneu-</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>mothorax</td>
<td>303</td>
<td>274</td>
</tr>
<tr>
<td>SLE</td>
<td>107 (26.1%)</td>
<td>47 (14.6%)</td>
</tr>
</tbody>
</table>

No unit from Greece took part in the study 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.1,2 While Greece is briefly mentioned in the Discussion, using results from a previous study, 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. Of the units that imposed restrictions, 13/15 (Agia 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 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.

V H DELLAGRAMMATICAS NICOLLETA IACOVIOU NICU, 2nd Department of Paediatrics, University of Athens, Agia Kyriakou Children’s Hospital, 115 27 Athens, Greece

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.[3]

We are, however, intrigued by the implication of a “protective effect” of Ureaplasma urealyticum 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.[4] In the present study, 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 imposed 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.[5] We wonder if infants receiving postnatal steroids were confounders in the discrepancy between the incidence of RDS and CLD.

VINEET BHANDARI Department of Paediatrics, Albert Einstein Medical Center, Philadelphia, PA 19141, USA

NAVEED HUSSAIN Department of Paediatrics, University of Connecticut Health Center, Mailcode 2203, Farmington, CT 06030–2203, USA


De Gilbert et al respond:

Editor,—We thank Drs Bhanda 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 acknowledged 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 suggested 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 other than 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. We noted, however, that 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.

Center for Infectious Diseases and Microbiology, Institute of Clinical Pathology and Medical Research, Westmead Hospital, Westmead NSW Australia 2145

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 [Arch Dis Child Fetal Neonatal Ed: first published as 10.1136/fn.83.2.F160A on 1 September 2000. Downloaded from http://fn.bmj.com/].