LETTERS TO THE EDITOR

Infant mortality rate in Sheffield

EDITOR,—In 1994 Sheffield had the highest infant mortality rate in England and Wales.¹ The impact of neonatal care in Sheffield immediately came under the spotlight. An investigation led by the Public Health Department of Sheffield Health took place to establish the reasons for the high infant mortality rate.²

It is well known that factors affecting infant mortality and morbidity may operate in the antenatal, as well as the postnatal period.³ The Sheffield Health led investigation consequently included the antenatal period. Similar to Spencer *et al*, the investigation found that increased social deprivation as indicated by the Townsend Deprivation Index was related to a higher proportion of very low birth weight (less than 1500 g) infants.⁴ Furthermore, a higher proportion of very low birth weight (less than 1500 g) infants was related to a higher infant mortality rate. The investigation found that the infant mortality rate in Sheffield was not significantly different to other areas of England and Wales with a similar level of social deprivation. Neonatal care in Sheffield was not found to be substandard.

The investigation highlights the hazards of interpreting annual mortality rates as league tables of clinical performance.⁵ In the Sheffield Health investigation, the most important factor on infant mortality was the level of social deprivation.

Spencer *et al* conclude that the differences in birth weight in their study may have major implications for later life. The investigation carried out in Sheffield, shows that differences in birthweight will certainly have major implications for later life.

The Government's commitment to reducing inequalities is to be welcomed, and we wait with interest to see what impact new policy initiatives in maternal and child health will have on the health of the most disadvantaged children in our society. The issue for Sheffield, and indeed the rest of the United Kingdom, is that if we are to be serious about reducing health inequalities, we must be serious in reducing social deprivation.

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- 3 Pharoah POD, Cooke T, Cooke RWI, Rosenbloom L. Birthweight specific trends in cerebral palsy. *Arch Dis Child* 1990;65: 602-6.
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Absence of written guidelines in neonatal units for ECMO referral may delay referral

EDITOR,—Extracorporeal membrane oxygenation (ECMO) is a complex technique for providing life support in respiratory failure. ECMO support has been shown to be both clinically¹ and economically² justifiable for mature newborn infants with severe respiratory failure. As a result of the UK trial, the Department of Health (England and Wales) has decided to fund centrally three centres to provide an ECMO service for these children. Prompt and appropriate referral is essential to maximise the potential benefits from ECMO. Recent data have shown that the success of ECMO is inversely associated with the number of days pre-ECMO ventilation.³ It is vital that information regarding eligibility for ECMO referral, and contact numbers for referral should be readily available.

In the past, guidelines in the form of a brief pamphlet giving information about the service have been circulated to regional neonatal units and special care baby units. We decided to ascertain what was known about the service we offered.

We undertook a simple postal questionnaire survey of all 238 neonatal intensive care units and special care baby units in England, Northern Ireland, and Wales. This asked whether written guidelines for ECMO referral were available on their unit. If these were, then the respondents were asked to send a photocopy of these with the reply in the accompanying stamped addressed envelope.

We had a high response rate, with 162 completed replies (71% response rate) within six weeks of posting. However, only 20 units had guidelines for ECMO referral (12.3% of responders). The potential delay that this may cause has obvious clinical implications. It is estimated that 100 to 200 neonates per year will benefit from ECMO. The neonatal ECMO trial established the following criteria for referral:

- Oxygenation index >40
- Gestational age >34 weeks
- Weight >2 kg
- Reversible lung disease (<10 days high pressure ventilation)
- No major (> grade 1) intracranial haemorrhage
- No lethal congenital abnormalities
- If in doubt discuss with your nearest ECMO centre.

$$\text{Oxygenation index} = \frac{\text{Mean airway pressure} \times \text{FiO}_2 \times 100}{\text{Postductal PaO}_2 \text{ (mmHg)}}$$

Contact telephone numbers:

Glenfield Hospital, Leicester: 0116 287 1471 and ask for the ECMO coordinator.
Great Ormond Street, London: 0171 405 9200 and ask for Cardiac ICU.
Freeman Hospital, Newcastle-upon-Tyne: 0191 284 3111 and ask for Paediatric ICU.

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- 1 UK Collaborative ECMO Trial Group. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. *Lancet* 1996;348:75-82.
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Evaluating urinary flow and solute excretion from urinary creatinine in the first week of life

EDITOR,—Matos *et al*¹ have used indirect measurements in their recent paper to conclude that the urinary excretion of solutes cannot be evaluated by factoring them against urinary creatinine in the first week of life. They say they "would have preferred to compare the reported spot urine results with normal data obtained by complete, timed urine collection" because this would have given them "the ultimate proof of [their] assertion", but seem unaware that such data already exist and that they contradict their conclusions.²⁻⁴

In the 1980s, we independently quantified creatinine excretion in 101 infants of 26-42 weeks gestation (and 640 to 4200 g birth weight) when 1.5-63 days old. In Newcastle, we used a constant inulin infusion technique⁵ to measure urine flow in 41 babies, some of whom required ventilatory support.³ In London, 24 hour urine collections were obtained from 60 stable babies using a continuously drained adhesive urine bag.⁴ Our measurements of daily urinary creatinine excretion were virtually identical. In Newcastle, we reported mean values of 104 $\mu\text{mol/kg}$ in the first week of life and 95 $\mu\text{mol/kg}$ in weeks 2 to 4, and in London we recorded an arithmetic mean of 96 $\mu\text{mol/kg}$ throughout. In each case, the values were unaffected by gestational or postnatal age, or by the baby's weight centile.

Because urinary creatinine excretion per kilogram is constant from two days to two months, it follows that ratios of the concentrations of substances to creatinine can be used to estimate urinary excretion during that time. Similarly, urine flow can be estimated from the reciprocal of the creatinine concentration. Indeed, the coefficient of determination (r^2) of the measured sodium excretion rate was 0.94 when correlated with the urinary sodium to creatinine ratio, compared with 0.14 when correlated with the urinary sodium concentration alone.³ In other words, whereas the raw sodium concentration only predicted 14% of the differences in sodium excretion rates, the sodium to creatinine ratio predicted 94% of the variation seen. Although such estimates are inevitably imprecise (the sodium excretion and urine flow estimates each having 95% confidence intervals of 62 to 161%),

1 Office for National Statistics. 1994 key population and vital statistics. Local and health authority areas. Series VS no. 21 PP1 No. 17. Office for National Statistics, 1997.

2 Billingham K, Gibson A, Parry G. Infant and perinatal mortality in Sheffield. The report of the working group. Sheffield Health, May 1998.

Figure 1 Serial daily urine excretion rates of creatinine, water (volume), and osmoles in 16 babies studied using inulin infusion during the first week of life.

they are better than estimates based on a knowledge of urinary sodium concentration or osmolality alone, as suggested by Matos *et al.*¹

Matos *et al.*¹ concluded that urinary creatinine excretion was very variable because their urinary creatinine concentrations and urinary sodium to creatinine ratios varied widely, but this deduction does not necessarily follow. We present longitudinal data on 16 babies (mean of five data points each) obtained during the first week of life at the time of our earlier study,³ but not previously published, which undermine this conclusion. Creatinine excretion was very stable from day to day (despite some slight suggestion of a downward trend) particularly in individual babies, although urine flow and osmolar excretion varied widely. Creatinine excretion varied threefold, urine flow varied ninefold, and osmolar excretion tenfold (fig 1).

We would contend that it is possible to obtain a clinically useful estimate of the excretion of a substance, *x*, in units/kg per day from an untimed ("spot") urine sample using the simplified, but easily memorable, formula $0.1U_x/U_c$, while urine volume in ml/kg per day can be approximated from $100/U_c$, where U_x is the urine concentration of any substance in units/l, and U_c is the creatinine concentration in mmol/l. Such estimates, although imprecise, are of practical value in babies of any age.

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- 1 Matos V, Drukker A, Guignard JP. Spot urine samples for evaluating solute excretion in the first week of life. *Arch Dis Child Fetal Neonatal Ed* 1999;80:F240-2.
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- 4 Al-Dahman J, Stimmler L, Chantler C, Haycock GB. Urinary creatinine excretion in the newborn. *Arch Dis Child* 1988;63:398-402.
- 5 Coulthard MG. A comparison of methods of measuring renal function in preterm babies using inulin. *J Pediatr* 1983;102:923-30.

Dr Guignard and Dr Drukker respond:

Dr Coulthard and colleagues start their letter saying that we have used indirect measure-

ments . . . to conclude that "the urinary excretion of solutes cannot be evaluated by factoring them against urinary creatinine in the first week of life". This is clearly not the case. We drew our conclusion from simple direct (!) measurement of the urinary creatinine concentration and osmolality in fresh spot urine samples. Therefore the data are what they are: the urinary creatinine concentrations show a wide scatter that is somewhat corrected but not explained by different states of urine concentration, as shown when the data were factored by urine osmolality. We did not quote the paper of Al-Dahman *et al.*¹ or that of Coulthard *et al.*² precisely because they did not provide simple data such as the urinary creatinine concentration in spot urine samples. Actually, the same wide dispersion of urinary creatinine excretion rates can be found in the paper by Al-Dahman *et al.*¹ During the first 10 days of life, we see (figs 5 and 6) that 24 hour creatinine excretion rates vary from about 40 to 450 $\mu\text{mol/l}$ per day. The variation is still substantial (30-180 $\mu\text{mol/l}$ per day) when the excretion rate is expressed per kg body weight. The findings by Al-Dahman *et al.* therefore support our contention, rather than that they disagree with our results.³

Why there is such a scatter in the urinary creatinine excretion rates is not really known and was not addressed in our paper nor by Al-Dahman *et al.* It certainly is a rather amazing finding, taking into account that newborn babies have about the same birth weight, receive similar nutrition, and have the same kind of bodily activity. This finding probably reflects, at least in part, the special situation of the neonate, who has to cope with the significant creatinine load transmitted from the mother, at a time when its glomerular filtration rate is very low and there is net creatinine reabsorption by the renal tubules which are presumably leaky.⁴

Some of the data of Coulthard *et al.*² also confirm our recent work. We refer to their observation that the clearance of creatinine underestimates inulin clearance. This supports our thesis that the neonatal tubule reabsorbs creatinine.⁴ The other findings by Coulthard *et al.* are more difficult to interpret. The daily excretion of creatinine indeed shows less variation (50-150 $\mu\text{mol/kg}$ per day) than found by Al-Dahman *et al.*¹ and us.³ One has, however, to take into account that these data were actually calculated without urine collection! Their data are indeed indirect measurements, not ours! Instead of collecting urine, the authors extrapolated urine flow rates from inulin

concentrations in spot urine samples taken in the course of a constant (± 24 hours) infusion of inulin. It is clear that such values cannot provide reference data on absolute rates of urinary excretion of solutes! Precisely because of this significant drawback, we also do not find much use for the proposed formula $0.1U_x/U_c$. For this formula, the urine flow rate (ml/kg per day) has to be "approximated" by another formula ($100/U_c$), again drawn from studies without urine collections. Estimating such values appears to us a little risky, even if the formula is "easily memorable".

- 1 Al-Dahman J, Stimmler L, Chantler C, Haycock. Urinary creatinine excretion in the newborn. *Arch Dis Child* 1988;63:398-402.
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- 4 Guignard J-P, Drukker A. Why do newborn infants have a high plasma creatinine? *Pediatrics* 1999;103:e49.

Use of inhaled nitric oxide to improve oxygenation in the neonate

EDITOR.—We read with interest the recent annotation by Rennie and Bokhari¹ on the subject of recent advances in neonatology. The piece was introduced by a foreword indicating that the article was aimed at the non-specialist. It seems particularly important therefore that the information contained should have been clear and well balanced; we feel that this was not the case with regard to inhaled nitric oxide (NO).

In relation to mature infants, a number of studies have shown that short term improvements in oxygenation can be achieved in some babies. What is more important, however, is to assess what this means in terms of more substantive clinical outcomes. One large trial conducted in North America did show that a significant number of infants with persistent pulmonary hypertension of the newborn can avoid extracorporeal membrane oxygenation if treated with NO, although no benefit in terms of preventing death was detected.² Later outcome data for that study have recently been presented showing no significant difference between the groups at 18-24 months.³ The Bayley scores of the NO treated group were, however, some 8 points lower. This could have been due to chance,

as the trial was not sized on this outcome. It is also plausible, however, that a poorer long term outcome may result from NO treatment as if there is no response referral for extracorporeal membrane oxygenation and the establishment of physiological stability is delayed.

The situation with regard to preterm babies is even less clear, and there is very little evidence either for or against NO use. Again short term improvements in oxygenation have been noted, but there are no studies reporting substantive longer term outcomes. It is in this group that concerns about intraventricular haemorrhage and toxicity are most acute. There are, as yet, no studies that adequately address the risks to the developing lung of NO exposure in terms of its ability to influence local inflammation and disrupt cell signalling pathways. The annotation simply refers to current recommendations on the environmental exposure of adults.

To state that NO "... has already proved to be effective treatment" seems to distort the current picture. It is our view that sufficient uncertainty remains in relation to NO that its current use should remain part of a randomised trial such as INNOVO, funded by the MRC. New centres are still being recruited, and clinicians may choose to enter either term or preterm infants or both, depending on their position of equipoise. Currently, clinical uncertainty has mainly led to the recruitment of severely ill infants. In time, continued recruitment into INNOVO will allow more knowledgeable statements about the role of NO in this vulnerable population.

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- 1 Rennie JM, Bokhari SA. Recent advances in neonatology. *Arch Dis Child Fetal Neonatal Ed* 1999;**81**:F1-4.
- 2 Neonatal inhaled nitric oxide study group. Inhaled nitric oxide in full term and nearly full term infants with hypoxic respiratory failure. *N Engl J Med* 1997;**336**:597-604.
- 3 Finer N, Vohr B, Robertson C, Verter J, Wright L, Ehrenkrantz R. Neonatal inhaled nitric oxide study group (NINOS) and the NICHD neonatal network. Inhaled nitric oxide and hypoxic respiratory failure in term infants: neurodevelopmental outcome. Annual Meeting of the Paediatric Academic Societies, 1999, San Francisco. Poster session I.

Rationing in child health services

EDITOR,—Aidan MacFarlane argues that further funding for neonatal and paediatric intensive care should not be provided unless funding for the long term needs of severely handicapped children is guaranteed.¹ His comments imply that neonatal intensive care produces more neurologically impaired survivors, which in turn leads to greater cost in the long term.

In fact, improved survival in very low birthweight (VLBW) infants has been accompanied by a fall in intracranial haemorrhage and cerebral palsy, probably

owing to a combination of antenatal steroids and postnatal surfactant replacement treatment. Cooke studied 1722 VLBW infants born between 1982 and 1993 and showed an increase in survival rates (from 69.2% to 79.7%) with a decrease in intracranial haemorrhage (from 14.9% to 10.5%) and cerebral palsy (from 10.9% to 7.3%).²

Although some technological advances, such as surfactant, high frequency oscillation ventilation, and extracorporeal membrane oxygenation are expensive, their impact on mortality has been shown in well conducted randomised controlled trials with either a decrease or no increase in neurological morbidity.³⁻⁵

Dr MacFarlane's view is an oversimplified one. A baby born at 28 weeks' gestation who is denied intensive care may well still survive but is then more likely to be neurologically damaged. Survival rates may be lower and disability rates higher with diminishing maturity, but a considerable number of infants born at 24 weeks' gestation survive neurologically intact. We note that Dr MacFarlane avoids specifying a gestational age below which resuscitation should not be offered.

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- 1 MacFarlane A. Rationing in child health services: a personal view. *Arch Dis Child* 1999;**81**: 1-4.
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- 3 Enhorn G, Shennan A, Possmaier F, et al. Prevention of neonatal respiratory distress syndrome by tracheal instillation of surfactant. A randomized clinical trial. *Pediatrics* 1985; **76**:145-53.
- 4 Gerstmann DR, Minton SD, Stoddard RA, et al. The Provo multicentre early high-frequency oscillatory ventilation trial: improved pulmonary and clinical outcome in respiratory distress syndrome. *Pediatrics* 1996; **98**:1044-57.
- 5 UK Collaborative ECMO Trial Group. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. *Lancet* 1996;**348**:75-82.

Dr MacFarlane responds:

Louise Grant and Peter MacDonald quite rightly point out the improvements that can be obtained in neurological outcomes by intensive care and I would not have expected them to do less. Yes, I over simplified to make my point, but most severely handicapped children do not survive as a result of neonatal intensive care but rather from other causes. However, these children (as well as those who do survive as a result of neonatal intensive care) and their families desperately need full support over a lifetime (and I doubt whether Louise Grant or Peter MacDonald would disagree). Given that there is and always will be limited funding for health services as a whole, my argument is that it is time to readress the balance as to what is provided for severely handicapped children and their families and what is provided for highly technological and expensive medical innovations. This is the reality and needs to be debated publicly (as the subject is far too important to leave to doctors) as well as the gestational age below which resuscitation should not be offered.

Missed opportunities for preventing perinatal hepatitis B infection

EDITOR,—Hepatitis B continues to be a public health problem despite the existence, for the past decade, of a safe and effective vaccine. Particular concern exists for infants at risk of vertical transmission. The Department of Health recommends that all babies born to mothers who are hepatitis B carriers receive hepatitis B immunisation at birth, 1 month, 6 months, and 12 months of age. Universal screening of pregnant mothers for hepatitis B has been in place in Cardiff since 1995. We were concerned that, although babies received immunisation at birth, second and third doses were being missed. An audit was therefore undertaken to assess the coverage of hepatitis B immunisation in infants at risk born between 1 January 1994 and 31 December 1996.¹

All hepatitis B carriers identified by antenatal screening at Llandough Hospital were included. Data on the hepatitis B status were obtained from the virology laboratory records. The mother's antenatal notes and the baby's neonatal notes were reviewed. Immunisation details on the infants were obtained from hospital notes, general practitioner records, and the computerised child health system.

Seventeen women were identified by antenatal screening as hepatitis B carriers. One woman moved out of the area antenatally, two postnatally, and one woman had an intrauterine death. Thirteen mothers and infants were included in the study. Twelve of the 13 women (92%) belonged to ethnic minorities and six (46%) had poor English comprehension, as reported by their general practitioner and health visitor. In only two cases was there evidence in the antenatal notes that the implications of the hepatitis B carrier state had been discussed. In none of the neonatal notes was there documentation of parental counselling on the need for follow up of the baby and further hepatitis B immunisation.

All 13 babies were immunised within 48 hours of birth and received immunoglobulin. Eleven (85%) received a second dose, including five babies who received their second dose from one to six months late. Only five (38%) babies received their third dose, and three of them received it later than scheduled.

Our study highlights the difficulties of achieving adequate hepatitis B immunisation coverage in high risk infants. Most women belong to ethnic minorities, with a considerable number having poor English comprehension. Also, communication between health professionals and patients, and between the various health professionals is poor. The Department of Health recently issued a directive to all health authorities to ensure that arrangements for universal antenatal screening are in place by April 2000, and that all babies born to infected mothers receive a complete course of immunisation.² Our study shows that even when universal antenatal screening is established, full protection of babies at risk does not necessarily follow. Since this audit, a public health nurse with specific responsibility for these families has been appointed. The consultant in communicable disease control now oversees the follow up and hepatitis B immunisation of these babies. Unless health authorities ensure that there is

an effective system in place for vaccine delivery, low prevalence countries like the United Kingdom may have to consider universal immunisation.³

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- 1 United Kingdom Health Departments. *Immunisation against infectious disease*. London: HMSO, 1996:95–111.
- 2 Department of Health. Screening of pregnant mothers for hepatitis B and immunisation of babies at risk. *Health Service Circular HSC* 1998:127.
- 3 Van Damme P, Kane M, Meheus A. Integration of hepatitis B vaccine into national immunisation programmes. *BMJ* 1997;**314**:1033–5.

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