LETTERS TO THE EDITOR

Neonatal respiratory distress syndrome

EDITOR,—Professor Southall and colleagues¹ question the comments of the working group on the management of neonatal respiratory distress syndrome regarding parameters of oxygenation.² We write in support of the provisional and practical suggestion of an arterial oxygen saturation (SaO₂) range of 85–93% and suggest that much of the data quoted by Southall *et al* is not applicable to this clinical setting.

Professor Southall and colleagues suggest an upper limit for SaO₂ of 96% and quote four studies in support of this choice. In two of these papers,^{3,4} the majority of the patients were not preterm and were receiving treatment for other conditions, mainly congenital heart disease. These infants constitute a very different population from those suffering from respiratory distress syndrome. Our own study of 477 measurements made in clinical practice using Ohmeda Biox oximeters on a population under 33 weeks' gestation found that if the saturation value was 93% or below the arterial oxygen tension (PaO₂) was never greater than 12 kPa.⁵ To maintain the PaO₂ below 10 kPa, which is the upper limit suggested by the working party, requires a saturation of 92% or less. Certainly, when using an Ohmeda oximeter, an upper limit of 93% seems very reasonable.

When discussing a lower limit for SaO₂, Professor Southall recommends 95%, based on a study of well preterm infants.⁶ These infants bear little relation to the sick, low birthweight infants who, until very recently had experienced a physiological, umbilical venous oxygen tension (PO₂) of approximately 4.5–6.0 kPa.

With regard to the adverse effects of hypoxia, there is no firm evidence which defines the optimal range for any of the indices of oxygenation. There are almost no modern data relating levels of oxygenation to outcome; the papers quoted by Professor Southall regarding hypoxia describe physiological responses to lower levels of oxygenation and not outcome.

Limited by the lack of scientific data, the working party have had to make reasonable and, equally important, practical recommendations. We feel that there is little evidence to support a range of 94 to 96% and in addition would be surprised to find any neonatal unit able to maintain the SaO₂ within such narrow limits. With the marked fluctuations in oxygenation seen in preterm infants receiving intensive care, it would be difficult to make sufficiently frequent adjustments in ventilator settings to comply with these limits. Based on our own data we currently employ the range 86 to 94%, similar to that mentioned in the working party report and look forward to further studies to give us more guidance on this difficult question.

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- 1 Southall DP, Samuels MP, Poets CF. Neonatal respiratory distress syndrome [letter]. *Arch Dis Child* 1993; 69: 330.
- 2 Joint Working Group of the British Association of Perinatal Medicine and the Research Unit of the Royal College of Physicians. Development of audit measures and guidelines for good practice in the management of neonatal respiratory distress syndrome. *Arch Dis Child* 1992; 67: 1221–7.
- 3 Southall DP, Bignall S, Stebbens VA, Alexander JR, Rivers RPA, Lissauer T. Pulse oximeter and transcutaneous arterial oxygen measurements in neonatal and paediatric intensive care. *Arch Dis Child* 1987; 62: 882–8.
- 4 Poets CF, Wilken M, Seidenberg J, Southall DP, von der Hardt H. Reliability of the pulse oximeter in the detection of hyperoxemia. *J Pediatr* 1993; 122: 87–90.
- 5 Cochran DP, Shaw NJ. The use of pulse oximetry in the prevention of hyperoxia in preterm infants. *Pediatric Reviews and Communications* (in press).
- 6 Poets CF, Stebbens VA, Alexander JR, Arrowsmith WA, Salfeld SAW, Southall DP. Arterial oxygen saturation in preterm infants at discharge from the hospital and six weeks later. *J Pediatr* 1992; 120: 447–54.

Professor Southall and colleagues comment:

The upper limit for SaO₂ that we recommend is based on several studies correlating PaO₂ and saturation levels.^{1–3} Although the two papers mentioned by Cochran and Shaw did include older infants,^{1,2} the potential bias would result in an underestimation of the pulse oximeter's sensitivity to hyperoxia – the higher proportion of fetal haemoglobin in preterm infants would result in a higher SaO₂ at any given PaO₂. With regard to avoidance of hyperoxia (PaO₂>13 kPa), the Nellcor N100 has been found to identify hyperoxia with a 95% sensitivity at saturations of 96% and above; the Ohmeda Biox 3700 had a similar sensitivity, but at saturations of 89%.³

The different sensitivity, averaging times, and algorithms of available pulse oximeters must be taken into account when discussing acceptable ranges of SaO₂ in the neonatal population. Until manufacturers standardise their technology, it would be safer to (a) use oximeters that have been validated for use in the neonatal population, with demonstrated sensitivity for the detection of hyperoxia but allowing a range that avoids the risk of hypoxaemia, (b) ensure that when defining acceptable ranges for SaO₂, the range is model specific to avoid inadvertent hypoxia or hyperoxia by using inappropriate limits.

Our recommended lower limit for saturation was originally based on a study of 'well' preterm infants at discharge from hospital. It has now been confirmed in a study of non-distressed preterm neonates investigated during their first week of life.⁴ It does not seem unreasonable to aim to achieve the same range of SaO₂ in 'sick' preterm infants. The argument that the latter group had recently experienced a physiological *intrauterine* PaO₂ of 4.5–6.0 kPa is untenable in the light of the very different stresses of extrauterine life, not least of which are the opening of the pulmonary vascular bed and a significant increase in oxygen consumption.

Finally, larger swings in SaO₂ will be seen in an infant if lower SaO₂ values are maintained. This is because of the shape of the dissociation curve, and the resultant effects of hypoxaemia and airway hypoxia on pulmonary vascular and bronchomotor reactivity time.

- 1 Southall DP, Bignall S, Stebbens VA, Alexander JR, Rivers RPA, Lissauer T. Pulse oximeter and transcutaneous arterial oxygen measurements in neonatal and paediatric intensive care. *Arch Dis Child* 1987; 62: 882–8.
- 2 Poets CF, Wilken M, Seidenberg J, Southall DP, von der Hardt H. Reliability of the pulse

- oximeter in the detection of hyperoxemia. *J Pediatr* 1993; 122: 87–90.
- 3 Bucher HU, Fanconi S, Baekert P, Duc G. Hyperoxemia in newborn infants: detection by pulse oximetry. *Pediatrics* 1989; 84: 226–30.
- 4 Richard D, Poets CF, Neale S, Stebbens VA, Alexander JR, Southall DP. Arterial oxygen saturation in preterm neonates without respiratory failure. *J Pediatr* 1993; 123: 963–8.

Blood pressure and blood volume in preterm infants

EDITOR,—We read with interest the article by Bauer *et al* on blood volume and blood pressure in preterm infants.¹ We have looked at a very similar group of infants and assessed the blood volume but with different results.

In 31 infants the mean arterial blood pressure (MABP) was measured by invasive arterial methods. Blood volume was assessed using an indocyanine green dye dilution method described previously in this age group.² The infants had a median gestational age of 26 weeks (range 25–31 weeks) and a median birth weight of 900 g (range 580–1380 g). Readings were all obtained in the first three days of life.

The median blood volume observed in our infants was 85 ml/kg (range 46–131 ml/kg), very similar to both the 83 ml/kg of Bauer *et al* and to previously published data. We found a median MABP of 36 mm Hg (range 18–47). We found no significant relationship, on regression analysis, between observed blood volume and MABP, $p=0.42$ (figure).

Relationship between MABP and blood volume.

Thus, we have not confirmed the third order polynomial relationship described by Bauer *et al*. This may be for a number of reasons, but it may be of note that the majority of the recordings of blood pressure from Bauer's group were by a non-invasive method, that has been previously criticised in the sick very low birthweight infant.³

We would agree with the conclusion of Bauer *et al* that blood pressure assessment alone is a poor measure of absolute hypovolaemia in very low birthweight infants. It is important that more than one cardiovascular parameter is considered in the assessment of the hypotensive infant so that volume expansion and inotropes are used appropriately in this age group.

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- 1 Bauer K, Linderkamp O, Versmold HT. Systolic blood pressure and blood volume in preterm infants. *Arch Dis Child* 1993; 69: 521–2.
- 2 Anthony MY, Goodall SR, Papouli M, Levene MI. Measurement of plasma volume in neonates. *Arch Dis Child* 1992; 67: 36–40.
- 3 Weindling AM. Blood pressure monitoring in the newborn. *Arch Dis Child* 1989; 64: 444–7.

Dr Bauer, Professor Linderkamp, and Professor Versmold comment:

Drs Wright and Goodall present blood volume and mean arterial blood pressure (MABP) measured in 31 very low birthweight infants. No relationship was found between blood volume and MABP over a blood volume range of 46–131 ml/kg. The authors measured MABP by an invasive method, whereas we determined systolic blood pressure (SBP) by an invasive method in 14 infants and by oscillometry in 29 infants.¹ We observed a significant overall third order polynomial function between SBP and blood volume ($r=0.54$; $p<0.001$) due to increased SBP in infants with blood volume >100 ml/kg (59 (9) mm Hg) when compared with infants with blood volume <100 ml/kg (48 (7) mm Hg). Drs Wright and Goodall suggest that the different results of the two studies may be due to the use of oscillometry in the majority of SBP measurements. In our study, only two out of 10 infants with blood volume >100 ml/kg had their SBP measured by an invasive method. Moreover, separate analysis of the relationship between SBP and blood volume showed a significant relationship only for SBP measured by oscillometry. It may, therefore, be argued that SBP was overestimated in the infants with high blood volume.

Problems associated with oscillometry have been summarised by Weindling.² Inflation of the cuff may disturb the infant. Oscillometry tends to overestimate blood pressure when the infant is hypotensive.³ Sonesson and Broberger observed that by using a cuff width to arm circumference ratio of 0.33–0.42, SBP is overestimated by 7 (11) mm Hg, whereas the error is only +1 (5) when a cuff width to arm circumference ratio of 0.44–0.55 is used.⁴ In our study, the cuff width to arm circumference ratio was always between 0.44 and 0.55. In hypotensive infants, oscillometry may give normal instead of low blood pressure readings, but not abnormally high values.³ It appears unlikely that infants with high blood volume were more disturbed by cuff inflation than infants with normal or low blood volume. Thus, we believe that the oscillometric blood pressure recordings were reliable.

It is important to stress that both studies agree that arterial blood pressure alone is a poor indicator of hypovolaemia in very low birthweight infants.

- 1 Bauer K, Linderkamp O, Versmold HT. Systolic blood pressure and blood volume in preterm infants. *Arch Dis Child* 1993; 69: 521–2.
- 2 Weindling AM. Blood pressure monitoring in the newborn. *Arch Dis Child* 1989; 64: 444–7.
- 3 Diprose GK, Evans DH, Archer LNS, Levene MI. Dinamap fails to detect hypotension in very low birthweight babies. *Arch Dis Child* 1986; 61: 771–3.
- 4 Sonesson SE, Broberger U. Arterial blood pressure in the very low birthweight neonate. *Acta Paediatr Scand* 1987; 76: 338–41.

Patent ductus arteriosus in the newborn

EDITOR.—We read Nick Archer's recent paper with interest.¹ We thought that it was a helpful paper but feel that we must comment on some of Dr Archer's recommendations regarding fluid intake in the newborn.

Dr Archer suggests that 'fluid intakes greater than 140 ml/kg/24 hours ... are inadvisable' without distinguishing between sodium and water. The evidence linking fluid volumes with certain neonatal problems is incomplete and does not separate sodium and water. Coulthard and Hey have shown that preterm babies are able to cope with widely

varying water intakes provided that their sodium intake is kept constant.² The recommendation to treat preterm babies who have symptomatic patent ductus arteriosus (PDA) with 'fluid restriction' is based on retrospective studies that failed to take into account sodium input and as far as we are aware there have been no prospective randomised trials to show that it is an effective treatment.

Advice to limit fluid intake without further qualification may be harmful in certain circumstances. Nutritional intake is reduced to a significant degree and prolonged restriction of fluid volumes is a serious cause of suboptimal nutrition in neonatal intensive care units. Many extremely immature babies have high insensible water losses, and failure to keep up with water loss will lead to hypernatraemic dehydration. Further, when treating a PDA, dehydration will exacerbate indomethacin toxicity.

The age of the baby at the time of discovery of the PDA is also important. There is a post-natal maturation in the ability to handle a sodium load³ and clinical management should take account of this.

Dr Archer suggests that a symptomatic PDA would rarely be missed if clinical signs are looked for regularly. However, evidence suggests that clinical assessment is insensitive.⁴ The profession is indebted to Dr Archer for having done so much to introduce echocardiography into the neonatal intensive care unit but we suggest that we should look to see echocardiography progress into an essential tool for all competent neonatologists in much the same way that cranial ultrasound scanning has progressed from a specialised to a generalised skill.

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- 1 Archer N. Patent ductus arteriosus in the newborn. *Arch Dis Child* 1993; 69: 529–32.
- 2 Coulthard MG, Hey EN. Effect of varying water intake on renal function in healthy preterm babies. *Arch Dis Child* 1985; 60: 614–20.
- 3 Modi N. Sodium intake and preterm babies. *Arch Dis Child* 1993; 69: 87–91.
- 4 Walther FJ, Kim DH, Ebrahimi M, Siassi B. Pulsed Doppler measurements of left ventricular output as early predictor of symptomatic patent ductus arteriosus in very preterm infants. *Biol Neonate* 1989; 56: 121–8.

Dr Archer comments:

Some enlargement of the statement with respect to limiting fluid intake to not more than 140 ml/kg/24 hours is certainly helpful. That figure came from a paper in which the smallest baby was 751 g. Now, babies much smaller than this receive successful intensive care and fluid and sodium requirements, of course, have to be individualised and will, among other things, be determined by the environment in which the infant is nursed. The comments by the Hammersmith group are, therefore, relevant. However, I should point out that I was referring to prevention of symptomatic PDA in the first week of life and not treatment of the condition, nor was I recommending prolonged restriction.

Hartnoll and colleagues refer to the paper by Walther *et al*¹ as proof that clinical assessment is insensitive in detecting symptomatic PDA. What Walther *et al* actually demonstrated was that Doppler echocardiography can be used as a predictor for the development of symptomatic patent ductus which is a different matter.

The brief for the paper I wrote was a practical approach to PDA in the newborn nursery of the district general hospital where echocardiography would not normally be available. Even if it were available, the assessment used by Walther *et al* is quite a difficult one for occasional users to master, although I do agree with Hartnoll and colleagues that neonatologists should be developing echocardiographic skills.

- 1 Walther FJ, Kim DH, Ebrahimi M, Siassi B. Pulsed Doppler measurements of left ventricular output as early predictor of symptomatic patent ductus arteriosus in very preterm infants. *Biol Neonate* 1989; 56: 121–8.

Clinical trials and neonatal intensive care

EDITOR.—The Department of Health now acknowledges that randomised clinical trials are an essential part of routine practice and will lead to improved medical care for patients.¹ The observation has also been made that participants in a clinical trial have better outcomes than non-participants, regardless of the arm of the trial to which they are assigned.² Randomised clinical trials therefore confer benefit upon both populations and individuals. It follows that there is a moral obligation upon clinicians to advise their patients to enter randomised trials.

In neonatal intensive care, consent to enter a baby into a trial is sought from the parents. They have just had a baby and their baby is critically ill. They are asked to listen to complex medical arguments which spell out the uncertainties of treatment and they are asked to make a positive decision to consent that their baby is entered into a trial. In addition, in academic units, it is likely that, given the relatively small numbers of babies receiving intensive care, each infant may be suitable for entry into more than one trial, for each of which consent must be sought. Many parents in this situation find it easier to make no decision and so their baby is not entered.

There are a number of issues here that deserve further scrutiny. Parents clearly have a right to know about their baby's care, but it is cruel to present them with a mass of complex medical information at a time when they are already frightened and confused. The neonatal paediatrician also has an obligation to act in the best interests of his or her patient and so it must be unethical to reduce the chances of a baby's entry into a randomised trial, given the advantages it is accepted that this will bring. Is there a way out of these dilemmas?

Education of the public in the concept and importance of randomised clinical trials has been advocated.³ Other options might also be considered. If a trial sets out to compare two treatment strategies, each of which is regarded as acceptable clinical practice and each of which individually might be implemented without parental consent, then it should be legitimate to randomise a baby without parental consent. An example might be a trial comparing antibiotic policies, each of which might be used as treatment without parental consent. Such an approach would clearly be inappropriate in, for example, a trial comparing conventional versus operative treatment, as operative treatment may only be given with parental consent. This approach would avoid having to force parents to grapple with issues that would not normally be presented to them and the equally morally questionable practice of forcing parents to