LETTERS TO THE EDITOR

Fatal familial surfactant protein B deficiency

EDITOR,—In 1993 a sibship of three infants who died of hyaline membrane disease had had an absence of surfactant protein B (SP-B) and its mRNA in lung tissue.¹ The gene coding for SP-B has been located and a frameshift mutation in this gene has been identified in the reported sibship and in two other families.² A further six cases of SP-B deficiency with varying clinical and genetic findings have been described.³ We describe the first British cases in two siblings.

Case 1

This first girl of healthy, non-consanguineous, caucasian parents was born in 1991, at term, weighing 3.5 kg. Apgar scores were nine and 10 at one and five minutes, respectively. At 5 hours of age she developed respiratory distress and was mechanically ventilated. She received maximal ventilation and failed to respond to artificial surfactant, Tolazoline, or prostacyclin. She died at 53 hours of age. The clinical diagnosis at death was persistent fetal circulation. Postmortem examination found extensive hyaline membrane with no evidence of pulmonary artery hyperplasia. Occasional alveoli contained granular eosinophilic material.

Case 2

This boy, the index case, was born at term, weighing 3.2 kg after a normal pregnancy, labour, and delivery. Apgar scores were nine and 10 at one and five minutes, respectively. Respiratory distress was evident from 1 hour of age and mechanical ventilation was started at 16 hours. He remained ventilator dependent until death. Chest x ray pictures showed severe hyaline membrane disease and remained unchanged throughout the course of his illness. There was only a transient response to artificial surfactant, Dexamethasone, and high frequency oscillation.

No microbial pathogens were identified and echocardiography was normal. Open lung biopsy on day 21 showed alveoli filled with granular eosinophilic material staining positive with periodic acid Schiff. Degenerating foamy and granular macrophages were present. Immunohistochemistry showed undetectable concentrations of SP-B in lung tissues. SP-B was undetectable by enzyme linked immunosorbent assay (ELISA) in tracheal aspirates, and accumulation of a pro-SP-C fragment, typical of SP-B deficiency disease, was present (personal communication, J Whitsett, Cincinnati). DNA studies identified the known mutation in one allele (personal communication, L Nogee, Baltimore). Following informed consent from both parents, ventilation was electively discontinued on day 32.

Comment

These two infants illustrate the clinical presentation of this newly diagnosable condition. The histological findings are identical with those seen in pulmonary alveolar proteinosis, a rare alveolar disease described in older children and adults. The aetiology of this con-

dition is unknown but in babies presenting from birth it is likely to be due to surfactant B protein deficiency. This diagnosis should be considered in all term babies dying of respiratory distress. As further mutations are identified antenatal diagnosis will be possible and in the future gene therapy may be effective. We have subsequently identified two further cases in Asian babies. We urgently need data on the prevalence of this condition in Britain and we have contacted the British Paediatric Surveillance Unit with a view to establishing this.

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- 1 Nogee L, DeMello D, Dehner L, Colten H. Brief report: Deficiency of pulmonary surfactant protein B in congenital alveolar proteinosis. *N Engl J Med* 1993; 328: 406-10.
- 2 DeMello D, Nogee L, Heyman S, Krous H, Hussain M, Merritt A. Molecular and phenotypic variability in the congenital alveolar proteinosis syndrome associated with inherited surfactant protein B deficiency. *J Pediatr* 1994; 125: 43-50.
- 3 Nogee L, Garnier G, Dietz H, Singer L, Murphy A, DeMello D, et al. A mutation in the surfactant protein B gene responsible for fatal neonatal respiratory disease in multiple kindreds. *J Clin Invest* 1994; 93: 1860-3.

Application of measured spontaneous inspiratory and expiratory times to improve infant ventilation

EDITOR,—We read with interest the two papers from Addenbrooke's Hospital.^{1,2} These two studies measured spontaneous inspiratory times (Ti) by a method unaffected by ventilator settings, and confirm our impressions based on endotracheal flow information in practice. However, the obvious application of the method remains to facilitate true synchronised ventilation to spontaneous inspiratory and expiratory efforts.

We have attempted to synchronise both phases of respiration using VIP Bird Infant Ventilators. These systems can utilise proximal endotracheal tube flow as a sensitive signal to cycle into inspiration. However, infants display a wide variation in spontaneous respiratory rate related to the level of arousal. When the infant triggers ventilator breaths with preset inspiratory times during periods of high respiratory rate, there is a danger of 'reversed ratios', and the inspiratory time exceeds the expiratory time (Te). Moreover, using a graphical interface, which displays breath to breath measurements of endotracheal flow and pressure and volume in real time, we have also demonstrated that endotracheal inspiratory flow may decay to zero or to minimum flow (generated by continuous gas leak around the tube) well before the elapse of a preset inspiratory time. Thus alveolar ventilation does not occur throughout the fixed inspiratory cycle.

In weaning babies not dependent on a high mean airways pressure for oxygenation, fixed inspiratory time can be reduced without adverse effects on blood gases. On the VIP Bird ventilator there is an algorithm to reduce the delivered inspiratory time during fast breathing and increase it during slower breathing, known as 'termination sensitivity'. This uses the detection of inspiratory flow decay to signal termination of ventilator

inspiration. Thus ventilation becomes pressure limited, and flow cycled into both inspiration and expiration, allowing the infant to select its own inspiratory time. We use the 'termination sensitivity', to modulate the delivered inspiratory time in weaning infants to 0.2 to 0.25 seconds. We have confirmed previously reported observed improvements in patient blood gases and comfort.³ Inspiratory flow decay is subject to lung volume and time constant, and may be confounded by altered peak ventilator pressure and changes in pulmonary dynamics.

The use of the graphical display of pressure-volume loops in real time allows us to optimise ventilator pressure to minimise these effects. In addition, as with all ventilator settings, termination sensitivity is subject to rigorous review and adjustment on a frequent basis, which minimises variation induced by the compliance of changing lung pathology.

The Graseby capsule used in the method described¹ has been shown to be less effective as a sensor for inspiration synchronised ventilator systems, because of difficulties with placement of the transducer and a long trigger delay time.⁴ However, the response time is short,¹ and improved electronic processing could reduce the total trigger delay time and permit incorporation into a system allowing true infant inspiratory and expiratory synchronisation. This would be a true partnership of infant and ventilator.

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- 1 Mockridge JNA, Ahluwalia JS, Morley CJ. Computerised determination of spontaneous inspiratory and expiratory times in premature neonates during intermittent positive pressure ventilation. I: a new technique. *Arch Dis Child* 1994; 71: F156-60.
- 2 Ahluwalia JS, Morley CJ, Mockridge JNA. Computerised determination of spontaneous inspiratory and expiratory times in premature neonates during intermittent positive pressure ventilation. II: a new technique. *Arch Dis Child* 1994; 71: F161-4.
- 3 Servant GM, Nicks JJ, Donn SM, Bandy KP, Lathrop C, Dechert RE. Feasibility of flow-synchronised ventilation to very low birth weight infants. *Respiratory Care* 1992; 37: 249-53.
- 4 Hird MF, Greenough A. Comparison of triggering systems for neonatal patient triggered ventilation. *Arch Dis Child* 1991; 66: 426-8.

Drs Mockridge and Morley comment:

Drs Derrick and Sinha point out that given a means for continuous measurement of spontaneous inspiratory and expiratory times in the ventilated neonate, as we have described, the obvious application is to facilitate synchronisation of the ventilator and baby. This is exactly our intention, allowing the baby to control ventilator inspiratory and expiratory time without triggering. However, we would like to address some points arising from their letter.

We believe triggering has inherent problems. Neonatologists assume that trigger ventilators achieve synchrony. With our apparatus we have shown that all the trigger ventilators we tested can trigger during expiration, often miss spontaneous breaths, and may not deliver regular ventilator inflations. Trigger ventilators cannot reliably terminate inflation to coincide with the end of spontaneous inspiration: the inflation time is either set to a fixed value, or some arbitrary cutoff point indicates end inspiration. For instance, in the Bird VIP this cutoff