Annotation**Bronchopulmonary dysplasia**

All those working in intensive neonatal care will have had first-hand experience of bronchopulmonary dysplasia (BPD).¹ Yet reading the extensive reports on the subject it is difficult to find any agreement on the incidence, aetiology, or indeed, on the most appropriate management. A timely attempt to pool our knowledge of this condition was made by the National Heart, Lung, and Blood Institute, who set up a workshop on BPD, the proceedings of which have recently been published.²

Definition

The first problem is one of definition. It is not difficult to diagnose the condition in a preterm baby who has required prolonged intermittent positive pressure ventilation (IPPV) for hyaline membrane disease, and who subsequently has a chronic respiratory disease lasting for months, associated with hyperinflation, dense linear opacities, and scattered translucent cysts on chest x-ray, equivalent to stage IV, as defined by Northway and Rosan.³ At the other extreme⁴ some would include all babies who had any x-ray abnormality at age 30 days associated with hypoxia, carbon dioxide retention, or oxygen dependence. This definition will inevitably include babies with the Wilson-Mikity syndrome, a condition which probably represents a functional and anatomical immaturity of the small airways,⁵⁻⁶ and repeated aspiration. The picture is further complicated by histological evidence that the changes of BPD are more often present in babies surviving hyaline membrane disease than would be expected from the incidence of the condition clinically.⁷ Abnormalities of lung function can be detected in the ensuing months in a high proportion of preterm babies requiring IPPV.⁸⁻⁹ These findings suggest that there is a continuous spectrum of disease, and provide some explanation for the wide variety in the incidence of the disorder, ranging from less than 3% to as high as 38%⁴ of all preterm babies. The problem of precise definition also makes retrospective studies of incidence difficult to assess but the evidence suggests that in the last few years improvements in ventilatory techniques have not only resulted in higher survival rates but have also led to a fall in the incidence of BPD,¹⁰ or at any rate not an increase.¹¹ However,

most authorities would agree that the diagnosis can be established if there is a history of IPPV or prolonged high oxygen administration, clinical evidence of lung damage persisting for at least one month, and x-rays showing translucent cystic areas and dense bands of fibrosis. In one of the early papers³ Northway and Rosan described radiological values from a generalised ground glass appearance (stage I), through dense areas of parenchymatous opacification with intervening normal lung (stage II), to the striking x-ray seen in stage IV. Others have been unable to support these findings, and it is likely that stages I and II represent the acute and resolution phases of hyaline membrane disease.

Aetiology

The aetiology of BPD has generated more discussion than any other aspect. Northway and his colleagues considered that most of the damage was due to oxygen toxicity.¹⁻³ Certainly similar lung lesions can be produced by exposing newborn mice and other animals to 100% oxygen for 6 weeks,¹¹ although the brunt of the disease tends to fall on the alveoli whereas in BPD more of the damage is at the level of the airways. Further evidence implicating oxygen has been provided by the occasional reports of BPD in babies with respiratory distress syndrome who have not been ventilated.¹²⁻¹³ It has also been claimed that BPD represents a delayed recovery stage of hyaline membrane disease. This is unlikely as the condition has also been reported after IPPV for a wide variety of neonatal cardiorespiratory disorders.¹⁴ The single most important factor is almost certainly artificial ventilation, as this not uncommonly causes the picture of BPD even when oxygen concentrations of 60% have not been exceeded.^{9 15-16}

The presence of interstitial air and also of patent ductus has also been incriminated and indeed does appear to be associated with the development of BPD.¹⁷⁻¹⁸ Whether this merely reflects the severity of the initial lung lesion has not yet been defined. The presence of an endotracheal tube with secretion retention and local infection provides yet a further mechanism for lung damage.

The evidence suggests that this is a disorder

resulting from a number of insults, but that the most important single factor is high pressure ventilation producing changes that can be exacerbated by exposure¹ to high oxygen concentration.

Prognosis

Much has been written about the long-term prognosis. This is inevitably related to the severity of the disease but, of those with stage IV BPD, up to 40% are likely to die, often at about 3½ months of age,¹⁹ generally with secondary bacterial or viral infection and cor pulmonale. Those surviving show progressive improvement during the succeeding months although x-ray changes tend to persist for at least 2 years. Lung function abnormalities and disordered lung growth are likely to persist throughout childhood and may sow the seeds of respiratory problems in adult life.

Prevention and treatment

From what has been learnt about important pathological factors, exposure to high inflation pressures and high oxygen concentrations should be kept to a minimum compatible with adequate oxygenation. BPD rarely if ever occurs in babies ventilated using external negative pressures²⁰ but, as this is a relatively ineffective method of respiratory support, the babies surviving are unlikely to have had severe hyaline membrane disease. Corticosteroids are contra-indicated in the acute phase as there is evidence that the newborn lung is relatively resistant to oxygen toxicity, perhaps due to immaturity of the hypophyseal adrenocortical response to stress. Certainly hypophysectomy and adrenalectomy are known to protect against oxygen toxicity.²¹ Generous doses of vitamin E have been recommended in the acute phase on the assumption that oxygen toxicity is of major importance. It is known that vitamin E acts as an antioxidant in the lungs and that vitamin E-deficient rats have an increased susceptibility to lung oxygen toxicity which can be reversed by the administration of vitamin E.²² Preterm babies tend to have a relative vitamin E deficiency. So far, controlled trials on this form of treatment, using daily doses of up to 20 mg/kg intramuscularly are encouraging but not conclusive.²³ Fluid restriction during the first few days of life has been advocated by some workers in an attempt to reduce the frequency of patent ductus.²⁴ Others recommend the early use of indomethacin or, failing that, surgical closure of the duct in any baby requiring IPPV for hyaline membrane disease who has a significant shunt.²⁵ Closure of a large shunt undoubtedly produces a

more compliant lung, so that lower inflation pressures can be used to achieve acceptable blood-gases.

In the ensuing months babies with BPD are susceptible to repeated respiratory tract infections which can be viral or bacterial. As these babies inevitably have poor lung drainage it would seem reasonable to teach their parents to give regular physiotherapy and to treat infections generously with a broad spectrum of antibiotics.

References

- Northway W H, Jr, Rosan R C, Porter D Y. Pulmonary disease following respirator therapy of hyaline membrane disease; bronchopulmonary dysplasia. *N Engl J Med* 1967; **276**: 357-68.
- Workshop on bronchopulmonary dysplasia. *J Pediatr* 1979; **95**: 815-920.
- Northway W H, Jr, Rosan R C. Radiographic features of pulmonary oxygen toxicity in the newborn: bronchopulmonary dysplasia. *Radiology* 1968; **91**: 49-58.
- Tooley W H. Epidemiology of bronchopulmonary dysplasia. *J Pediatr* 1979; **95**: 851-5.
- Burnard E D, Grattan-Smith P, Picton Warlow C G, Grauaug A. Pulmonary insufficiency in prematurity. *Aust Paediatr J* 1965; **1**: 12-38.
- Saunders R A, Milner A D, Hopkin I E. Longitudinal studies of infants with the Wilson-Mikity syndrome. *Biol Neonate* 1978; **33**: 90-9.
- Thurlbeck W M. Morphologic aspects of bronchopulmonary dysplasia. *J Pediatr* 1979; **9**: 842-3.
- Bryan M H, Hardie M J, Reilly B J, Swyer P R. Pulmonary function studies during the first year of life in infants suffering from the respiratory distress syndrome. *Pediatrics* 1973; **52**: 169-78.
- Stocks J, Godfrey S, Reynolds E O R. Airway resistance in infants after various treatments for hyaline membrane disease. Special emphasis on prolonged high levels of inspired oxygen. *Pediatrics* 1978; **61**: 178-83.
- Wung J T, Koons A H, Discoll J M, Jr, James L S. Changing incidence of bronchopulmonary dysplasia. *J Pediatr* 1979; **95**: 845-7.
- Bonikos D S, Bensch K G, Northway W H, Jr. Oxygen toxicity in the newborn: the effect of chronic continuous 100 per cent oxygen exposure on the lungs of newborn mice. *Am J Pathol* 1976; **85**: 623-50.
- Lamarre A, Linsao L, Reilly B J, Swyer P R, Levison H. Residual pulmonary abnormalities in survivors of idiopathic respiratory distress syndrome. *Am Rev Respir Dis* 1973; **108**: 56-61.
- Banerjee C K, Girling D J, Wigglesworth J S. Pulmonary fibroplasia in newborn babies treated with oxygen and artificial ventilation. *Arch Dis Child* 1972; **47**: 509-18.
- Edwards D K. Radiographic aspects of bronchopulmonary dysplasia. *J Pediatr* 1979; **95**: 823-9.
- Barnes N D, Glover W J, Hull D, Milner A D. Effects of prolonged positive pressure ventilation in infancy. *Lancet* 1969; **ii**: 1096-9.
- Reynolds E O R, Taghizadeh A. Improved prognosis of infants mechanically ventilated for hyaline membrane disease. *Arch Dis Child* 1974; **49**: 505-15.
- Watts J L, Ariagno R L, Brady P J P. Chronic pulmonary disease in neonates after artificial ventilation: distribution of ventilation and pulmonary interstitial emphysema. *Pediatrics* 1979; **60**: 273-81.

- ¹⁸ Brown E R, Stark A, Sosenko I, Lawson E E, Avery M E. Bronchopulmonary dysplasia: possible relationship to pulmonary edema. *J Pediatr* 1978; **92**: 982-4.
- ¹⁹ Hodson W A, Truog W E, Mayock D E, Lyrene R, Woodrum D E. Bronchopulmonary dysplasia: the need for epidemiologic studies. *J Pediatr* 1979; **95**: 848-51.
- ²⁰ Stern L, Ramos A D, Outerbridge E W, Beaudry P H. Negative pressure artificial respiration: use in treatment of respiratory failure of the newborn. *Can Med Assoc J* 1970; **102**: 595-60.
- ²¹ Northway W H, Jr, Petriceks R, Canty E, Bensch K G. Maturation as a factor in pulmonary oxygen toxicity: a preliminary report. *J Pediatr* 1979; **95**: 859-64.
- ²² Taylor D W. The effects of vitamin E and of methylene blue on the manifestations of oxygen poisoning in the rat. *J Physiol* 1956; **131**: 200-6.
- ²³ Ehrenkranz R A, Bonta B W, Ablow R C, Warshaw J B. Amelioration of bronchopulmonary dysplasia following vitamin E administration: a preliminary report. *N Engl J Med* 1978; **299**: 564-9.
- ²⁴ Bell E F, Warburton D, Stonestreet B S, Oh W. Randomized trial comparing high and low volume maintenance fluid administration in low weight infants (abstract). *Pediatr Res* 1979; **13**: 489.
- ²⁵ Jacob J, Gluck L, DiSessa T, *et al.* The contribution of PDA in the neonate with severe RDS. *J Pediatr* 1980; **96**: 79-87.

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