

Long term sequelae of bronchopulmonary dysplasia (chronic lung disease of infancy)

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Bronchopulmonary dysplasia (BPD) is the most common form of chronic lung disease in infancy. The clinical, radiological, and pathological features of BPD were first described a little more than three decades ago.¹ The disease was then seen in large preterm infants with severe respiratory distress syndrome who had been treated with high inspired oxygen concentrations and prolonged mechanical ventilation with high positive airway pressures resulting in inflammation, fibrosis, and smooth muscle hypertrophy in the airways.² Despite advances in the prevention and management of respiratory distress syndrome (including the widespread use of antenatal steroids and surfactant treatment), neonatal chronic lung disease is still one of the major complications in mechanically ventilated premature infants. Acceptance of modest hypercapnia with less aggressive application of positive pressure ventilation and reduction of the use of high oxygen concentrations led to a decrease in the incidence of BPD in newborn infants with a birth weight above 1500 g. However, with increased survival of extremely premature infants (24–26 weeks gestation, birth weight <1000 g), who are most likely to develop BPD, the overall incidence has remained high or has even increased, albeit with wide variations between institutions.^{3–10} Clearly, the risk of developing BPD increases with decreasing birth weight and gestational age, ranging from 50% in neonates with birth weights of 700–900 g to 5% in those with birth weights >1250 g.³ Apart from differences in patient populations and management, the reported variation in the incidence of BPD might also be due to the use of different criteria to define it.^{1 11 12}

“Classic” BPD, as described by Northway and colleagues, is a severe form of chronic lung disease that has become less common and has been replaced by less severe forms which are observed in very small premature infants who survive after prolonged mechanical ventilation.^{8 13} As a result of these changes in epidemiology, the terms “neonatal chronic lung disease” or “chronic lung disease of prematurity” have been coined to describe either the less severe forms or the complete spectrum of BPD.^{14 15} Thus, the term “chronic lung disease” remains vague and implies a wide

spectrum of disorders and severity ranging from marginally significant to fatal. The milder forms of chronic lung disease are frequently seen in very low birth weight infants with mild or no initial respiratory distress syndrome; in this population a patent ductus arteriosus and nosocomial infection have been found to play an important role in the development of chronic lung disease.¹³ Thus, the two major forms of BPD—“classic” or severe and “new” or mild—appear to have different pathogenic mechanisms within the widely varying clinical presentation of chronic lung disease.

Classic BPD

At present the severe form of chronic lung disease—with radiographic progression through a sequence of four stages, usually seen after severe respiratory distress syndrome before the introduction of surfactant therapy and concomitant advances in ventilator management—is infrequent. Respiratory failure requiring treatment with supplemental oxygen and mechanical ventilation is the most important pathogenetic factor; other causes include neonatal pneumonia, lung hypoplasia, and meconium aspiration syndrome. As mentioned above, the factors that contribute to injury to a relatively immature and surfactant deficient lung are high inspired oxygen concentrations (acting through production of free radicals and lipid peroxidation products) and high positive airway pressures (causing pulmonary barotrauma); there is an ongoing debate concerning the relative roles of oxygen and positive pressure ventilation.¹⁶

Generally accepted pathological findings in infants with severe BPD who died weeks to months after birth include an altered inflation pattern (overdistended alternating with atelectatic lung zones), squamous metaplasia of the airway epithelium, obliterative bronchiolitis, peribronchial fibrosis, airway smooth muscle hypertrophy, and hypertensive vascular lesions.¹⁷

Severe respiratory distress syndrome and severe chronic lung disease have almost uniformly been shown to be more common in boys and in white subjects and to be inversely related to gestational age and birth weight.^{3 5 6 18} Chronic lung disease is characterised by increased airway resistance resulting

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from airway inflammation, and to bronchial hyperresponsiveness.¹⁹⁻²¹ Infants with severe chronic lung disease may also develop tracheomalacia and/or bronchomalacia, resulting in atelectasis and/or hyperinflation due to dynamic airway obstruction.²²⁻²⁴ The course of the disease is frequently complicated by acute pulmonary infections; in some infants with severe chronic lung disease bacterial or viral infections result in respiratory failure.²⁵⁻²⁶ Recurrent respiratory infections may cause further damage to the lungs, thus effecting or perpetuating long term pulmonary morbidity.

New BPD

In contrast to infants who develop severe chronic lung disease, those with the new or mild form initially require only low or moderate concentrations of oxygen and mechanical ventilation with low pressures, and usually respond favourably to the administration of surfactant¹³⁻²⁷; exogenous surfactant results in a rapid normalisation of lung function.²⁸⁻²⁹ However, infections or heart failure secondary to a patent ductus arteriosus, or a combination of both, may trigger a deterioration in lung function which, in turn, may lead to an increase in ventilatory and oxygen requirements.¹³⁻²⁷⁻³⁰

As infants who develop the new BPD are more immature than those with the classic form of previous years, and the most important pathogenetic factors are probably not oxidant injury and mechanical ventilation, a different pathology may be expected. At 24–28 weeks of gestation (the canalicular stage of human lung development extends to 26–28 weeks gestation) the lung is just beginning to develop into a gas exchanging organ. In the saccular (primitive alveolar) stage the distal sacculi are alveolarised with parallel development of the alveolar capillary bed; alveoli are present at approximately 32 weeks.³¹⁻³² Thus, premature birth with initiation of pulmonary gas exchange interrupts normal alveolar development. Whereas this interruption per se, as seen in preterm infants without respiratory problems, may have little adverse influence on lung development, conditions necessitating mechanical ventilation may lead to permanent impairment in alveolar development.³³ Recently, the amount of alveolar septal fibrosis was reported to be substantially less in surfactant treated than in untreated infants with BPD; however, there was an arrest in acinar development of comparable severity in both surfactant treated and untreated patients, resulting in fewer and larger alveoli.³⁴ The total number of arteries was also reduced, maintaining a normal alveolar to arterial ratio in infants with chronic lung disease.³⁵ Such an arrest of lung development has also been shown in animal models.³⁶⁻³⁷ These findings came from necropsy studies and may represent the severe end of chronic lung disease. Thus, the pathology seen in biopsy specimens from infants with milder chronic lung disease is of great interest. Open lung biopsy specimens from infants of low birth weight on ventilatory support (postnatal age 2 weeks to 7 months) were reported to show a simplified distal lung acinus, consistent

lack of significant alveolarisation, abnormal capillary configuration, and an adaptive dysmorphic pattern of vascular organisation.¹⁷ Decreased alveolarisation is not only confined to extremely immature infants with BPD but has also been reported in gestationally older infants treated with supplemental oxygen and mechanical ventilation.³³⁻³⁸

In summary, the features and patterns of chronic lung disease have changed considerably in the last decades, reflecting not only modifications in the management of premature infants but also changes in the degree of lung immaturity. The lungs of infants with new BPD are characterised by minimal alveolarisation, less airway epithelial disease, less severe vascular disease, and less interstitial fibrosis compared with lungs with alternating zones of overdistention and atelectasis in infants with severe BPD. Thus, the new BPD is understood to reflect extreme lung immaturity with an arrest of alveolar growth and development and an inflammatory response to treatment induced injury that leads to cycles of lung injury and repair.¹⁷⁻³⁹

Normal alveolar multiplication is thought to be complete by 2–4 years of age.⁴⁰ It is therefore unlikely that infants with chronic lung disease with alveolar hypoplasia in the first and second year of life will increase their alveolar numbers to normal values. Studies in an animal model showed that chronic lung disease results in a significant and permanent loss of alveoli.³⁶ Infants of very low birth weight with an earlier interruption of lung development might be expected to end up with a greater degree of alveolar hypoplasia than those who are injured later in gestation; these very immature babies could therefore have even more severe lung dysfunction in adolescence and adulthood than those infants who acquired classic BPD. As yet, the long term effects of extreme prematurity and early lung injury on pulmonary function are not known.

Infants with mild forms of chronic lung disease usually show only mild radiographic changes and their oxygen dependence is moderate. Increases in airway resistance are usually not as pronounced as in infants with classic BPD, and acute pulmonary infections are better tolerated.¹⁵

Long term sequelae

It has been pointed out that BPD and chronic lung disease are not clearly definable entities; during the course of chronic lung disease dynamic processes such as continuing injury, inflammation, healing, repair, growth, and maturation occur concurrently or sequentially in the lung.⁴¹ Consequently, it is difficult, if not impossible, to separate the interacting effects of prematurity, low birth weight, neonatal respiratory diseases, treatment, and subsequent respiratory illnesses. Moreover, as the diagnosis of BPD is not based on specific lung function abnormalities and the epidemiology of BPD is affected by a treatment that has been evolving over decades, the spectrum of pulmonary abnormalities and outcomes has to be hetero-

geneous. The neurodevelopmental outcome of children with BPD will not be discussed in this review.

GROWTH FAILURE

In some short term follow up studies infants and young children with BPD were found to be smaller than controls with greater deficits observed in weight than in height.⁴²⁻⁴³ Growth retardation was reported to be associated with severe and prolonged respiratory dysfunction and growth occurred at an accelerated rate with improvement in respiratory symptoms.⁴² Another study showed that growth abnormalities might persist into adolescence and adulthood.⁴⁴ More recently, however, in children aged 8–10 years no consistent differences⁴⁵ or, after controlling for confounding variables, no significant differences⁴⁶ were found between those with and without BPD. In addition, schoolchildren who had been infants of very low birth weight were found to be significantly shorter than normal controls.⁴⁷ Thus, the previously reported poor growth in children with BPD may be related to factors such as birth weight and gestational age rather than to BPD.

RESPIRATORY MORBIDITY

Respiratory morbidity is common in infants and young children born prematurely, particularly when the infant has developed chronic lung disease.⁴⁸⁻⁵² Lower respiratory tract infections contribute to a high rate of readmission to hospital; in the first year of life up to 50% of infants with BPD were reported to require readmission to hospital because of acute respiratory distress associated with a lower respiratory tract illness.⁴²⁻⁵³⁻⁵⁴ Thereafter, wheezing illnesses and hospital readmissions for respiratory problems decline in frequency.²⁰⁻⁴⁹⁻⁵⁵ In symptomatic patients lung function abnormalities are more marked and, in older children, these abnormalities do not seem to be related to neonatal events.⁵⁰ While one group found that respiratory illness in childhood, especially troublesome cough, was related to low birth weight,⁵⁶ others found an association between wheezing and prematurity but not birth weight.⁵⁷ However, as birth weight depends on gestational age, it may be difficult to separate the effects of these two factors on respiratory outcome. One group found increased respiratory morbidity in schoolchildren who were former infants of very low birth weight.⁴⁷ In older children and adolescents respiratory symptoms were reported to be similar in patients with respiratory distress syndrome who had been ventilated (with or without BPD) and in those who had not been ventilated.⁵⁸ In the longest follow up study to date, about 25% of adolescents and young adults with former BPD had current respiratory symptoms; this cohort had had more wheezing, episodes of pneumonia, and long term medication use than controls.⁴⁴

RADIOGRAPHIC FINDINGS

The typical findings on the chest radiograph include interstitial thickening, focal or general

hyperexpansion, and atelectasis.⁵⁹ Radiographic abnormalities tend to improve with age; in most patients, major abnormalities gradually resolve by early childhood but minor abnormalities may persist into childhood and even adulthood.⁴⁴⁻⁴⁸⁻⁵⁹⁻⁶² In general, chest radiographs are not satisfactory for identifying the sequelae of BPD. In patients with chronic pulmonary dysfunction lesions are better visualised on computed tomographic scans.⁶² Recently, abnormal findings on inspiratory and expiratory high resolution computed tomographic scans were described for more than 90% of children and adolescents with a history of BPD; these findings significantly correlated with pulmonary function abnormalities.⁶³

LUNG FUNCTION

Lower birth weight was reported to be associated with reduced lung function in mid life⁶⁴; the authors speculated that intrauterine influences which retard fetal weight gain may irreversibly hamper airway growth. Matthes *et al*,⁶⁵ however, found no evidence that low birth weight *at term* was associated with reduced lung function in adolescence. In infants born prematurely, low birth weight was repeatedly found to be closely associated with reduced lung function in schoolchildren, independent of neonatal respiratory illness.⁴⁷⁻⁴⁹⁻⁵⁷⁻⁶⁶ In addition, lung function was reported to be unrelated to oxygen treatment and mechanical ventilation in two of these studies.⁴⁹⁻⁶⁶ This is somewhat surprising as one might expect that lung function in childhood is related to the severity of the neonatal respiratory illness and/or its treatment in preterm infants. Several workers have tried to confirm or reject this hypothesis. While some authors concluded that neonatal lung disease and its treatment (oxygen and/or mechanical ventilation) are important determinants of abnormal pulmonary function in infancy and childhood,⁴⁷⁻⁴⁸⁻⁵⁸⁻⁶⁷⁻⁷³ others disagreed and have suggested that prematurity *per se* or other undetermined factors affect long term pulmonary abnormalities.⁷⁴⁻⁷⁷ Additional factors that may influence childhood lung function include sex and exposure to smoke.⁶⁶⁻⁷⁸

When considering lung function abnormalities in children who developed BPD compared with those who did not, one has to keep in mind that BPD is not an “all or nothing” condition but rather a continuum where, with the application of different definitions of BPD, infants have to be assigned to one of two groups. Children who developed BPD clearly represent the worse end of the spectrum. Thus, it is not surprising that an unfavourable outcome, not only in terms of lung function and airway responsiveness but also in respiratory morbidity and weight gain, was consistently reported for survivors with BPD compared with prematurely born children without chronic lung disease.²⁰⁻⁴⁸⁻⁵⁵⁻⁵⁸⁻⁶¹⁻⁷⁹⁻⁸⁰

Infants with BPD improve clinically during the first year of life; with lung repair and somatic growth considerable improvements in pulmonary function can also occur.²¹ One group reported that pulmonary mechanics

improved with age in infants with severe BPD, but this conclusion was based on a comparison of pulmonary function tests in two different groups of infants and young children with BPD at different ages.⁸¹ Later, tidal breathing was shown to approach expiratory flow limitation in infants with BPD; as these infants also showed significantly lower absolute and size corrected flow rates than age and size matched controls in their first year of life, airway growth was suggested to be poor.⁵³ In a two year follow up study infants with BPD were compared with a group of premature infants who had had only moderate respiratory distress syndrome; severe peripheral pulmonary obstruction was found in 80% of the BPD infants at 1 year and in approximately 40% at 2 years of age.⁵² In another study children who had developed BPD were compared with healthy controls in a follow up study extending to 36 months of age and were found to have decreased airway conductance during the first 6 months which had reached 85% of normal at 3 years. Lung compliance, which was only 50% of normal at 1 month, also increased with growth.²¹ Infants with BPD were reported to have a significantly lower functional residual capacity than controls during the first 6 months of life, but not later.^{21 53} In a more recent study children up to 3 years of age were investigated by means of the forced deflation technique which allows for registration of maximal expiratory flow volume curves.⁸³ In patients with moderate to severe BPD the authors found that forced vital capacity was decreased in infancy but caught up to the normal range by 3 years of age. In contrast, although a gradual improvement in maximal expiratory flow at 25% of the forced vital capacity was seen in infants with moderate BPD, severe lower airway obstruction persisted in all infants. In summary, lung volume increases normally in the first years of life but obstruction of the smaller intrathoracic airways does not seem to resolve so readily.

A number of cross sectional studies have produced pulmonary function data in older children with a history of BPD. In schoolchildren spirometric values were reported to be significantly lower than in control groups born at term.^{51 58 79 84} Some authors also found evidence of hyperinflation in children who had had BPD.⁸⁴ Hakulinen *et al*,⁴⁸ while not finding significant differences in spirometric measurements, observed a larger residual volume in young schoolchildren with a history of BPD than in a control group born at term. Similarly, compared with control groups of preterm children, subjects with BPD presented with significantly lower values of lung function parameters reflecting airflow and, in addition, a significant degree of gas trapping was found.^{58 80 85 86} Several authors reported that most children and adolescents with a history of BPD tend to show abnormal spirometric measurements^{61 63} with evidence of hyperinflation in half the patients in this age group.⁶³ Reduced inspiratory and expiratory flows, suggesting both upper and lower respiratory tract disease, were recently demonstrated in young schoolchildren with BPD who were still symp-

tomatic after 5 years of age.⁸⁷ Possible reasons for inspiratory flow limitation in children with BPD include subglottic stenosis secondary to mechanical ventilation and dynamic airway obstruction—that is, tracheomalacia of the extrathoracic part of the trachea. Finally, one study investigated adolescents and young adults who had had BPD in infancy and compared them with a group of age matched subjects of similar birth weight and gestational age who had not undergone mechanical ventilation, and with a group of age matched normal subjects.⁴⁴ Most subjects with a history of BPD had pulmonary function abnormalities that indicated airway obstruction, airway hyperresponsiveness, and hyperinflation; most of these abnormalities were mild to moderate but about 25% were severe. This pulmonary dysfunction in adolescents and young adults may not only reflect the effects of BPD alone, but also those of recurrent lower respiratory illnesses in the first years of life.⁸⁸

There are only a limited number of longitudinal studies on pulmonary function in patients with a history of BPD. Blayney *et al*⁶⁹ investigated children with BPD at mean ages of 7 and 10 years and found an improvement in the forced expiratory volume in one second over time for the subgroup with abnormal values at 7 years which suggested that there is continuing lung growth and/or repair in school aged children. On the other hand, consistently decreased spirometric values and significant air trapping were seen in the entire group. Koumbourlis *et al*⁹⁰ followed patients with chronic lung disease with annual measurements of pulmonary function from a mean age of 8 to a mean age of 15 years. For this group with relatively mild chronic lung disease they found gradual normalisation of air trapping although half of the patients had abnormal spirometric values indicating obstruction of the small airways. This airflow obstruction appeared to be associated with airway hyperresponsiveness and did not change over time.⁹⁰ As yet, it is unclear how lung function will track during adolescence and adulthood because relevant longitudinal studies are lacking.

In summary, lung volume improves with age but expiratory flows appear to improve much more slowly, if at all, in the most severely affected patients. Airway obstruction with normal lung volume suggests dysanaptic lung growth—that is, normal growth of lung volume but not of airway size. Bronchial obstruction, hyperinflation, and increased bronchial responsiveness are common in childhood and adolescence; the presence of major pulmonary abnormalities in these age groups implies that pulmonary dysfunction may persist. Hyperinflation may either be the result of obstructive airway disease or of a loss in elastic recoil as a consequence of alveolar underdevelopment which is followed by overenlargement and remodelling of the lungs. The more severe lung function abnormalities seen in children with BPD are likely to be superimposed on abnormal lung growth and development related to prematurity.

AIRWAY RESPONSIVENESS

As airway obstruction may occur very early in the course of BPD, it has been suggested that increased airway responsiveness might play an important role in the development and severity of BPD.^{19 91} In addition, an association between BPD and a family history of asthma has been reported by Nickerson and Taussig⁹² who speculated that genetically predisposed patients might develop airway hyperresponsiveness following neonatal lung diseases and their treatment, and this again might contribute to the development of BPD. Others, however, have suggested that bronchial hyperresponsiveness is a consequence of airway damage in infancy—that is, a non-specific response.^{60 93} Several authors found no evidence of an association between a family history of allergy or asthma and BPD.^{44 61 84} A more recent study concluded that a family history of asthma may worsen chronic lung disease in the neonate but should not be considered as a causal factor.⁹⁴ In addition, a family history of asthma may predispose premature infants to more severe neonatal disease.⁷⁸

Whether or not there is an increased prevalence of bronchial hyperresponsiveness or asthma in the mothers of prematurely born children has not been unequivocally answered to date. Two groups reported a higher incidence of bronchial hyperresponsiveness in mothers of infants with unexplained prematurity compared with control groups.^{67 95} It was suggested that maternal smooth muscle irritability causes premature labour as well as bronchial hyperresponsiveness. Kelly *et al*⁹⁶ recently suggested that maternal asthma is a risk factor for preterm delivery but Chan *et al*⁹⁷ found no increase in the prevalence of maternal asthma, a family history of asthma, or airway responsiveness in the mothers of low birth weight children.

Airway hyperresponsiveness has repeatedly been reported to occur in long term survivors of BPD.^{44 58 60 79 84 89 90 98} Whether this increased responsiveness is due to a genetic predisposition, neonatal lung injury, or anatomically smaller airways is unclear. Whatever the causes, it may be a predisposing factor for the development of chronic obstructive airway disease in later life. Bronchial hyperresponsiveness was reported to be unrelated to atopic status⁶⁰ and no increased prevalence of atopy was found in BPD.⁴⁴ Asthma, as diagnosed from clinical symptoms, was also not reported to be more common in older children and adolescents who had developed BPD.^{58 89}

An increased prevalence of airway hyperresponsiveness was almost consistently found in schoolchildren who were born prematurely, both with and without respiratory distress syndrome not complicated by the development of BPD.^{67 75 97 99} One recent study, however, found no differences between prematurely born children and children born at term for both bronchial hyperresponsiveness and atopic sensitisation.⁷⁸ Many authors were unable to find a relationship between increased airway responsiveness and neonatal respiratory illness or its treatment, or any other perinatal risk factors

other than prematurity itself.^{75 99 100} Chan *et al*¹⁰⁰ found airway hyperresponsiveness to be related to airway calibre and suggested that it is a consequence rather than the cause of airway dysfunction. Preterm birth was reported to predispose to the development of subsequent asthma.⁹⁶ In another study, performed in children aged 9–11 years, prematurely born girls, but not boys, were found to have significantly more asthma than children born at term, especially if they had required mechanical ventilation after birth.⁷⁸ In summary, however, it is doubtful if there is any clinically significant association between prematurity and classical atopic asthma.

EXERCISE TESTING

Only a few studies have investigated the response of the cardiorespiratory system to exercise in children who had survived respiratory distress syndrome, with and without BPD. In two studies^{101 102} in which schoolchildren who had had respiratory distress syndrome were compared with control groups, no significant differences in exercise tolerance or in the cardiorespiratory response to exercise were observed between the groups; individual analysis revealed persistent but subtle abnormalities of pulmonary function and decreased exercise tolerance only in some survivors of respiratory distress syndrome.^{101 102} Some groups reported no differences in terms of exercise capacity between schoolchildren with a history of BPD, those who had had respiratory distress syndrome but did not develop BPD, and children born at term.^{61 84 103} The patients with a history of BPD, however, used a greater percentage of their ventilatory reserve and/or exhibited an exercise induced fall in arterial oxygen saturation and rise in transcutaneously measured carbon dioxide tension.^{84 103} In contrast, studies comparing schoolchildren who developed BPD with preterm children without significant neonatal lung disease and healthy children born at term, respectively, reported reduced exercise tolerance,⁸⁵ disturbed ventilatory response, and reduced aerobic capacity,¹⁰⁴ as well as reduced gas transfer at rest and during exercise.¹⁰⁵ Mitchell and Teague¹⁰⁵ suggested either derangements in lung structure or right ventricular dysfunction as an explanation of these findings.

CARDIOVASCULAR FUNCTION

Pulmonary hypertension and cor pulmonale frequently complicate the course of infants with severe BPD. Cardiovascular complications of BPD include systemic hypertension, left or biventricular hypertrophy, and hypertrophy of systemic-to-pulmonary collateral vessels.^{106–109} Electrocardiographic evidence of right ventricular hypertrophy was reported in about 50% of schoolchildren with BPD.⁶⁰ Cardiac catheterisation in preschool children with BPD has demonstrated structural abnormalities of the pulmonary vascular bed in a number of patients.¹⁰⁸ However, in a group of adolescents and young adults with a history of BPD in infancy, none of the subjects was found to have hypertension and only one presented with right ventricular hypertrophy.⁴⁴

Conclusions

Infants with severe BPD survive with significant pulmonary sequelae. As young adults they have abnormal lung function and thus a reduced respiratory reserve. Most subjects with a history of BPD lead normal lives, but the long term consequences of their pulmonary dysfunction are not yet known. As there is evidence that even relatively mild pulmonary insults in childhood may be the precursors of chronic pulmonary disease in adults, concern exists about the susceptibility of survivors of BPD to develop progressive obstructive pulmonary disease in adulthood. Clearly, this risk will increase with further pulmonary insults so cigarette smoking should be strongly discouraged. The rate of lung function loss with age is as yet unknown in these subjects. As infants with chronic lung disease are much more immature today than those studied in the past, the prognosis for the present population of patients with chronic lung disease may not be comparable to that reported in the literature—that is, these very immature babies could show even more severe lung dysfunction in adolescence and adulthood than those infants who previously acquired classic BPD and have now reached adulthood. As the population of surviving infants keeps changing, follow up studies are and will continue to be difficult to interpret. The effect of extreme prematurity on subsequent lung growth, independent of chronic lung disease, also deserves further investigation. From the perspective of the adult pulmonologist, survivors of BPD who reach adolescence and adulthood might increasingly become a new patient population calling for special preventive and therapeutic measures.

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