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Good News for Lung Repair in Preterm Infants

In this issue of the *Journal*, Narayanan and colleagues (pp. 1104–1109) demonstrated with hyperpolarized helium nuclear magnetic resonance (NMR) (^3He NMR) that the alveolar number and size in preterm infants who had bronchopulmonary dysplasia (BPD) were normal at 10 to 14 years (1). This good news will change how we think about the growth and repair of the injured preterm lung. There is a developmental context for appreciating this new result. The fetal human airways branch about 17 times by about 18 weeks of gestation. A further six generations of airway branching forms the bronchioles and alveolar ducts to yield 500,000 saccules by about 32 to 34 weeks gestation (2). Amazingly, the saccular preterm human lung at 24 weeks gestation can provide gas exchange, and saccular divisions can continue until alveolarization begins. Very preterm lungs also can have altered development from antenatal exposures such as maternal smoking, fetal growth restriction, and chorioamnionitis. The preterm lung is easily injured by mechanical ventilation, oxygen, infection, and probably nutritional deficits despite the best efforts of caretakers. Although survival of these infants has increased strikingly in recent years from advances such as antenatal corticosteroids, postnatal surfactant, and more gentle approaches to mechanical ventilation, the incidence of BPD remains over 40% for infants born at 22 to 28 weeks gestation who survive to 36 weeks gestation (3).

But what is BPD? The lungs of most very low birth weight infants are not normal at term or over the first several years of life. Physiologic measurements demonstrate primarily airway abnormalities thought to represent abnormal growth (4). These infants also receive more pulmonary medications and have more lung-related hospitalizations over the first years of life than term infants (5). The BPD described by Northway and colleagues in 1967 (6) was a severe lung injury syndrome resulting from prolonged mechanical ventilation and high oxygen exposure in relatively mature infants cared for at the dawn of the use of mechanical ventilation for infants. Today, the diagnosis of BPD in very low birth weight survivors is an arbitrary point on a spectrum of lung abnormalities from mild to severe. The current understanding of the anatomy associated with BPD is based on autopsy descriptions of a delay or arrest of alveolar and pulmonary microvascular development resulting in an emphysematous-appearing lung, but without severe fibrosis (7). This understanding of the anatomy of BPD is supported by the inhibition of alveolarization into adulthood after brief oxygen exposures of the saccular newborn rodent lung. Mechanical ventilation alone can also inhibit alveolar septation in ventilated preterm sheep or baboons (8). Several older infants with severe BPD had deficits in alveolarization on biopsy (7), and Cutz and Chiasson (9) reported an alveolar deficit at 12 years of age in a child with a history of severe BPD. However, the anatomy of the lungs of the great majority of the preterm infants that survive with or without a clinical diagnosis of BPD remains unknown. I suspect that there is a highly variable range of abnormalities.

Very preterm infants must develop their lungs toward normal to survive, despite some inevitable injury. Thus, three complex processes are occurring simultaneously over months—lung development, injury, and repair. The concept has been that these infants must have catch-up alveolarization before alveolarization ceases at 2 to 3 years of age based on earlier anatomic studies reviewed by Narayanan and colleagues (1). Late deaths from progressive BPD are rare, and most children that had BPD do remarkably well as they grow. Therefore, empirically these lungs must repair, grow, and alveolarize. The time interval for that to occur has been greatly increased by the demonstration with ^3He NMR that normal alveolarization continues to at least 20 years of age (10). Although not as satisfying as seeing the anatomy, such noninvasive techniques are essential for studies of alveolarization in at-risk populations. Recently, the technique was used to demonstrate an increase in alveolar number in a 33-year-old woman following a pneumonectomy (11). Narayanan and colleagues (1) now report in the *Journal* that alveolar size as estimated by ^3He NMR is normal for children 10 to 14 years of age with a history of BPD. They measured alveolar size in children born at term, modestly preterm infants, infants with an average gestational age of 30 weeks with no BPD, and 28-week-gestation infants with BPD. The only abnormality was a larger standard deviation for the measurements of average alveolar dimensions for the children with a history of BPD. Although not discussed in the article, this wider standard deviation suggests to me that the infants with BPD have less uniform alveoli, perhaps a subtle abnormality. A weakness of the study is that the preterm infants were born at gestations where severe lung injury and BPD are infrequent. Further, only 9 of 18 infants had a diagnosis of moderate to severe BPD by Consensus Conference criteria (12). A population of 11-year-old children born at less than 25 weeks gestation had more abnormal pulmonary function with impaired cardiovascular performance, and decreased exercise capacity than the children reported by Narayanan and colleagues (13, 14). Populations of higher-risk survivors who had more lung injury should be evaluated for alveolarization using ^3He NMR (13, 14). I predict that abnormalities will be present.

Nevertheless, the really good news for preterm infants is that the lung has the ability to grow and alveolarize throughout childhood. Infants without severe BPD and at mean ages of 28 weeks gestation can catch up if they had an alveolarization delay during early life. Empirically, infants with birth gestations of 25 weeks or less also can grow and alveolarize their lungs, although the completeness of that development remains to be evaluated. The microanatomy of the lungs of older children who survive BPD remains essentially unknown. Caution is warranted in assuming that alveolarization and microvascular development are normal. As the human lung normally ages with a slow loss of alveoli, a theoretical concern is an accelerated loss of alveoli with aging. Hopefully, the answer is no. Technologies such as that used by Narayanan and colleagues (1) will allow us to better understand the remarkable resilience of the lungs of preterm infants across the lifespan.

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ALAN H. JOBE, M.D., PH.D.
*Division of Neonatology/Pulmonary Biology
 Cincinnati Children's Hospital Medical Center
 Cincinnati, Ohio
 and
 University of Cincinnati
 Cincinnati, Ohio*

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Microbes in Bronchiectasis: The Forest or the Trees?

Bronchiectasis is a condition defined by irreversible dilation of the bronchi accompanied by chronic sputum production, decreased lung function, and recurrent exacerbations, that leads to significant morbidity. Known causes of bronchiectasis are diverse and include previous infection or foreign body aspiration, inherited or acquired immunodeficiencies, congenital abnormalities of the airway, and chronic aspiration. Bronchiectasis is also seen commonly in cystic fibrosis, but this is usually considered separately in most studies. A specific etiology of bronchiectasis is apparent only 50% of the time even after extended evaluation (1). Airway infection is prominent in bronchiectasis; however, the relationship between infection and disease progression is not well understood (1–3). Infection of bronchiectatic airways is also associated with an exuberant inflammatory response. Antibiotic treatment, often with broad-spectrum antimicrobials, is a prominent part of management. Improved knowledge of bacteria in the airways of patients with bronchiectasis could lead to better targeted use of antibiotics. In bronchiectasis, antibiotics have been shown to improve lung function and inflammatory markers during acute pulmonary exacerbation, supporting the importance of bacterial infection (4). Traditional culture approaches detect aerobic pathogens including *Haemophilus*, *Pseudomonas*, and *Streptococci*; however, there are many instances where no pathogenic organism is detected (1–3).

In this issue of the *Journal*, Tunney and coworkers (pp. 1118–1126) contribute importantly to our knowledge of airway bacteria in bronchiectasis in several ways (5). First, they performed careful anaerobic cultures in addition to standard aerobic cultures in two clinical cohorts (6). They examined 40 subjects cross-sectionally during clinical stability and 14 patients longitudinally

over the course of a pulmonary exacerbation. They also began exploration of airway bacteria through microbiome analysis in a subgroup of patients. The molecular approach they used is based on identification of bacteria through amplification and sequencing of ribosomal RNA genes present in airway samples. Furthermore, they evaluated systemic markers of inflammation, which can be useful clinically, and are critical in understanding the pathogenicity of particular bacteria and bacterial communities.

Their major finding is the demonstration of polymicrobial infection with mixed aerobic and anaerobic bacteria in sputum from patients with bronchiectasis by culture and sequencing during clinical stability and exacerbation. They also find that total bacterial burden by culture, including aerobic and anaerobic bacteria, and bacterial community structure did not change during treatment of exacerbation. Systemic markers of inflammation (C-reactive protein and white blood cell count) improved with treatment for exacerbation, but lung function did not; inflammatory markers and lung function did not correlate well with bacterial measurements. In clinically stable patients, the only relationships that achieved significance were total and anaerobic cfu versus C-reactive protein. The authors speculate that changes in lung microbiota do not account for onset of exacerbation in bronchiectasis, but acknowledge that strain-level differences may contribute.

There are limitations of this study, a number of which are recognized by the authors. Some limitations are inherent to studying bronchiectasis. The root cause in an individual patient is often not understood, and it is by no means clear that the pathway to airway dilation is the same in all patients. Clinical use of antibiotics cannot be well controlled. The half of stable patients treated with antibiotics had one of three different regimens, and