

Chronic Obstructive Pulmonary Disease and Bronchopulmonary Dysplasia: Common Mechanisms But Distinct Manifestations?

Enid R. Neptune, M.D.

The complex disorders of chronic obstructive pulmonary disease (COPD) and bronchopulmonary dysplasia (BPD) are common, costly, and clinically burdensome. Both lung disorders develop after complex injurious triggers and can result in significant lung disease and disability. Similarities in their lung pathology and injury measures suggest common pathogenetic mechanisms. Evidence exists for both common molecular triggers and for injury-by-age interactions that may confer distinct end pathology. An emerging concept is that BPD may be a predisposing pathology for COPD development in late life. Future studies focusing on this provocative connection between BPD and COPD may translate into novel ameliorative and regenerative therapies for both disorders.

Why Compare Chronic Obstructive Pulmonary Disease and Bronchopulmonary Dysplasia?

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) and bronchopulmonary dysplasia (BPD) are common pulmonary disorders of complex origin that are associated with significant morbidity, mortality, and medical costs.^{1,2} COPD, a chronic inflammatory lung disorder usually caused by heavy cigarette smoke exposure (>20 pack-year), is the fourth leading cause of death in the United States affecting >12 million persons.³ BPD, the most common chronic lung disease in infancy, is a disease of prematurity, affecting 10–15,000 neonates per year in the United States, frequently leading to acute and chronic respiratory morbidity and overall disability.^{4,5} In the postsurfactant era, BPD is punctuated by airspace enlargement with inflammation but minimal fibrosis, the latter feature distinguishing the new BPD from the old BPD. Although much research into COPD and BPD utilizes animal models, we largely restrict our discussion here to human studies. Further details about the pathogenetic mechanisms involved in BPD development are elegantly presented in the accompanying Aucott review.⁶

This review will focus on 2 issues:

1. Could the commonalities between the diseases reflect a common molecular trigger(s) or common defect in repair?
2. Could the phenotypic differences reflect the timing of the injury: neonatal versus adult contexts?

Evidence for Common Molecular Triggers or Defects in Repair

Both COPD and BPD are disorders of the distal lung compartments. COPD affects 2 major lung compartments, the

bronchioles (distal airways) and the alveoli (airspace) culminating in the dual pathologies of small airway obstruction and alveolar septal loss. A prominent inflammatory component accompanies the injury likely escalating and perpetuating the damage. Although chronic exposure to cigarette smoke is the most common trigger, inflammation and oxidative stress continue despite cessation of smoking, suggesting a self-perpetuating pathogenic mechanism.^{7,8} BPD results from the combined insults of prematurity, manifest in an underdeveloped lung, and a second hit, which can range from infection (amnionitis, pneumonia, and bronchiolitis) to ventilator-induced lung injury (reviewed in Ref.⁴). The classic lung pathology of BPD in the postsurfactant era is a defect in alveolar formation with a reduction in internal surface area, vascular dysmorphology, and mild inflammation.⁹ Thus, the triad of complex inciting injury, airspace enlargement, and distal lung inflammation is evident in both diseases.

Mechanism 1: Oxidant injury

A unifying pathogenetic scheme for both COPD and BPD is oxidant injury.¹⁰ Oxidative stress occurs when oxygen free radical production exceeds the ability of an organ or tissue to mount a sufficient antioxidant response. In the case of COPD, cigarette smoke contains active oxidants that directly injure the distal airway and airspace. The consequent inflammation further enhances the oxidative burden. Several studies show evidence of increased oxidative stress in smokers and/or persons with COPD.^{11–13} However, the multiple antioxidant trials in COPD patients, although plagued by methodological problems, have not shown consistent evidence of benefit with respect to lung function.^{14,15} There is a suggestion of reduced exacerbations with the use

of N-acetyl cysteine, an antioxidant and mucolytic. However, without the advantage of a large randomized, controlled trial of one or more antioxidants, the true value of targeting oxidant injury cannot be determined. Another concern is whether systemically administered antioxidants have sufficiently high levels in the lung parenchyma to attenuate the oxidant injury.

Compelling clinical data suggest that oxidant injury is a critical initiator and/or mediator of BPD.^{16,17} Because premature birth effects an early transition from the relatively hypoxic *in utero* environment to the normoxic postnatal milieu, an attendant induction of significant oxidative stress occurs.¹⁸ Several factors contribute to the oxidant burden, including a relative underproduction of local antioxidants and active inflammation.^{19,20} Samples from lungs of premature infants who develop BPD display elevated levels of biomarkers of oxidative stress.²¹ Supplemental oxygen treatment in the perinatal setting contributes to further enhancement of oxidative stress. We found that early postnatal oxidative stress in a murine model of BPD, the TSK mouse, induced both cell death and airspace enlargement.²² Further, antioxidant treatment markedly attenuated airspace enlargement, suggesting that early antioxidant treatment might have therapeutic effects. A randomized trial of recombinant copper/zinc superoxide dismutase, an antioxidant highly expressed in the lung, in ~300 premature infants showed no reduction in the incidence of BPD but did demonstrate a reduction in wheezing, emergency room visits, and respiratory hospitalizations at 1 year.²³ Smaller trials of N-acetylcysteine and allopurinol (xanthine oxidase inhibitor) similarly showed no effect on predischARGE lung function or incidence of BPD, respectively.^{24,25} Although these trials yielded negative results, concerns about suboptimal antioxidant effects in the distal lung, as noted above, and the relatively short follow-up periods in the published studies serve to maintain interest in devising more effective strategies for targeting oxidative stress in BPD.

An important difference in the oxidant stress of COPD and BPD is the timing of the insult. Most studies in premature infants suggest that the maximal stress is early, within the first week of postnatal life, and then resolves secondary to a responsive increase in the local antioxidant milieu.^{26,27} In COPD, by contrast, the oxidative stress seems to be chronic and low level. Whether this reflects a suboptimal antioxidant response or chronic stress conferred by cigarette smoke (CS) and inflammation is unknown. Of note is that despite the general presumption that oxidative stress accompanies COPD and BPD, no standardized diagnostic assay to measure this stress has been developed. Therefore, the ability to subphenotype patients into those with high versus low oxidant stress for targeted interventions remains a therapeutic obstacle.

Mechanism 2: Accelerated cell death

Impaired formation or destruction of alveolar septae can result from resident epithelial or endothelial cell death. Several groups report evidence of enhanced cell death in the airspaces of patients with COPD.^{28–30} Inhibition of an endothelial survival pathway, vascular endothelial growth factor (VEGF) signaling, induces both endothelial cell death and airspace enlargement in an adult murine model, suggesting a causative role of cell death in emphysema patho-

genesis.³¹ Intratracheal administration of other inducers of cell death similarly causes airspace enlargement.^{32–34} Despite these data, whether cell death in human COPD is a critical element of disease development or an ancillary effect of cigarette smoke exposure is unknown. To complicate matters, phagocytosis of apoptosing cells in the alveolus may be impaired by chronic cigarette smoke exposure, creating misleading evidence of enhanced cell death.³⁵ Less is known about cell death in BPD. May et al. found increased numbers of both apoptotic and proliferating cells in autopsy specimens from BPD lungs compared with stillborn controls.³⁶ Another study showed a reduction in epithelial apoptosis commensurate with lessened inflammation and injury in lung tissue from BPD patients treated with antenatal steroids compared with untreated controls.³⁷ Neonatal hyperoxia in mice, a model of BPD, can also produce modest levels of alveolar cell death.³⁸ Common mechanisms of cell death have been proposed in COPD and BPD. As stated above, inhibition of VEGF signaling impairs airspace formation (eg, BPD pathology) and homeostasis (eg, COPD pathology) in animal models presumably via the loss of the endothelial survival effects of VEGF signaling. Similarly, the enhanced transforming growth factor beta (TGF β) signaling reported in human BPD and in some studies of COPD can have proapoptotic and antiproliferative effects in the airspace epithelium and may contribute to epithelial apoptosis.^{39,40} Despite such suggestive data, the role of apoptosis in the development of airspace enlargement in either disorder remains unresolved. Moreover, as there are no studies correlating differences in cell death with clinical outcomes, whether increased cellular turnover is an important pathogenic mechanism or a manifestation of generic tissue injury is unknown.

Mechanism 3: Inflammation

Inflammation assumes a critical though complex role in the progression of both BPD and COPD. Chronic inflammation comprised of innate immune cells, macrophages, dendritic cells, and lymphocytes is a well-described element of COPD pathogenesis. Cigarette smoke induced cell death, oxidative stress, and cytokine induction culminate in the influx and expansion of these cells in the distal lung creating a self-sustaining cycle of inflammation and tissue injury. Antiinflammatory treatments such as inhaled and parenteral steroids are foundational components of the COPD treatment armamentarium. These agents not only reduce breathlessness and frequency of infectious exacerbations, but may in selective circumstances slow lung function decline.⁴¹ Pulmonary inflammation can accompany BPD but is usually seen in the setting of triggering infections such as prenatal chorioamnionitis or nosocomial infection or mechanical ventilation.⁴² Some have postulated that the inflammatory component, by enhancing oxidative stress and promoting tissue injury, is critical to the pathogenesis of BPD.⁴³ Both Merritt and Groneck found that premature infants at highest risk of BPD showed elevated chemokine levels and neutrophil elastase activity, both markers of inflammation, in tracheal aspirate fluid.^{44,45} Steroids are frequently used in the perinatal setting to accelerate lung maturation for impending preterm delivery. In the postnatal setting, however, the anti-inflammatory effects of steroids are pursued but not consistently demonstrated. In fact, while

enhancing the differentiation of alveolar epithelial cells, steroid treatment inhibits alveolar septation, culminating in a reduced surface area for gas exchange.⁴⁶ These complex effects of steroids confound clear evidence of clinical benefit in the BPD patient. Therefore, whether the anti-inflammatory effects of steroids contribute to protective or restorative effects on lung architecture and function in the premature infant is not well established.

Mechanism 4: Defect in lung repair

The constant exposure to environmental toxins and ambient oxygen virtually insures chronic low level oxidant stress in the lung. Also, despite generalized pulmonary inflammatory insults such as multilobar pneumonias and severe acute lung injury, lung architecture is frequently restored. Thus, the lung must harbor robust mechanisms for tissue maintenance and regeneration despite injury. Why are not these strategies insufficiently operative in the setting of COPD and BPD? The delicacy of airspace structure may make alveolar injuries that affect the matrix scaffold refractory to full regeneration. Alternatively, the cytokine milieu, specifically the trophic growth factors that mediate the multicellular survival agenda in the airspace, may be sub-optimal in COPD and severe BPD. A trenchant concept is that the ability of BPD lung to recover, fully or partially, differs from the COPD lung because of intrinsic age-related prosurvival mechanisms. This idea is discussed below in the Injury-by-Age Interactions section. Here, we consider whether severe BPD, which results in chronic lung disease, is similar to COPD in manifesting a global impairment in lung repair. Ligands for receptor tyrosine kinases, such as hepatocyte growth factor (HGF), keratinocyte growth factor (KGF), and epidermal growth factor (EGF), participate in tissue repair after a variety of injuries by inducing cell survival cascades and morphogenic programs that serve to maintain structural integrity. Abundant data in animal models show that defects in these pathways contribute to abnormal lung formation and increased susceptibility to lung injury.^{47,48} HGF is locally induced during acute lung injury in patients, plausibly initiating a repair program.⁴⁹ Neonatal rats deficient in HGF signaling display enhanced susceptibility to hyperoxia and HGF treatment protects rats subjected to neonatal hyperoxia from severe alveolar defects and lung function abnormalities.^{50,51} The expression of EGF, HGF, and its receptor cmet is maintained in the postnatal rodent and human lung.^{52–54} Higher concentrations of HGF or KGF in tracheal aspirate fluid from premature infants is associated with less severe lung disease and reduced progression to BPD.^{55,56} Similarly, lower levels of EGF were observed in the lung lavage fluid from infants with BPD compared with controls.⁵² Thus, the ability to induce EGF and HGF may confer a critical protective milieu to the developing lung and thereby be candidate biomarkers for BPD. Confirmation of these data in larger studies is not as yet available. Although a defect in lung repair is often invoked to explain the inability of airspaces to regenerate in the adult COPD lung, the examination of growth factor pathways as possible molecular culprits is lacking. A small study of HGF and KGF levels in lung lavage fluid from COPD patients compared with controls showed a significant increase in HGF levels in the COPD lungs but no change in KGF levels.⁵⁷ A recent examination of tissue repair genes in COPD found that HGF

was downregulated in the airways of patients with severe COPD compared with controls.⁵⁸ Thus, whereas data suggest that a defect in growth factor activity contributes to BPD, the role of growth factors in COPD development or progression remains to be determined.

Mechanism 5: Enhanced matrix turnover

One of the critical mechanistic links between cigarette smoke and airspace destruction in COPD is the activation of enzymes that digest the structural elements of the airspace such as elastin (metalloproteases and elastases) and arguably collagen (collagenases) (reviewed in Ref.⁵⁹). This mechanism, termed protease-antiprotease imbalance, is well validated in animal models in which the instillation of elastase into the lung results in delayed airspace injury with destruction of septae and in the rare genetic disease alpha-1 antitrypsin (A1AT) deficiency in which the loss of an inhibitor of neutrophil elastase confers increased risk of COPD. Much human and animal model data suggest exaggerated matrix turnover in BPD.^{60–62} Such a mechanism plausibly operates in the perpetuation of inflammation-associated lung injury and resistance to repair. Evidence that low antitrypsin activity might be reliable risk factor for BPD prompted the consideration that A1AT supplementation might have a protective role for BPD.²³ Two trials of A1AT augmentation in premature infants did not show any meaningful protection from BPD although one demonstrated a reduced incidence of pulmonary hemorrhage in treated patients.⁶³

From a pathologic standpoint, both COPD and BPD share evidence of elastin fragmentation coupled with exaggerated elastin deposition.⁶⁴ This latter finding likely reflects a failed reparative response with quantitative restoration of elastin abundance but poor structural reconstitution or maintenance of alveolar septae. Pathways that promote matrix synthesis, such as TGF β signaling, are frequently dysregulated in COPD and BPD.^{59,65–67} Conversely, proteins that induce matrix turnover, such as metalloproteases/collagenases, are often activated in these disorders.^{61,68,69} This conflation of increased matrix breakdown and enhanced matrix production in these disorders without a clear temporal sequence creates a therapeutic targeting dilemma. In fact, inhibitors of metalloproteases, which ostensibly reduce elastin turnover, show variable efficacy in animal models.^{70,71} However, there have been no published clinical studies showing therapeutic value in COPD or BPD. Similarly pharmacologic inhibitors of TGF β signaling, which reduce elastin production and promote epithelial cell survival, attenuate the altered lung histology that results from neonatal hyperoxia, a model of BPD.⁷² No trials of TGF β inhibition in COPD or BPD have been pursued.

Genetic and genomic analyses of COPD and BPD

Genome-wide surveys can identify genetic and genomic signatures that associate with complex diseases. Do these signatures overlap in COPD and BPD, diseases known to have a significant heritable component?^{73,74} Establishment of heritability for both disorders is a challenging exercise. BPD typically occurs in the setting of prematurity and a direct pulmonary insult. Thus, twin studies with implicit shared *in utero* environments complicate the distinction between common environments and common genetics (discussed in

Ref.⁷⁵). Further, genes that impact on lung development may appear to confer susceptibility to BPD. COPD studies are similarly confounded by whether tobacco addiction or impaired lung development can be uncoupled from the risk for COPD development.^{76,77} Many candidate gene association studies have been performed for both disorders showing statistically significant associations but minimal validation. We have elected not to include such studies here. Further, ongoing genome-wide association studies with large and diverse validating populations may provide more persuasive genetic information about BPD and COPD.

Whereas several genome-wide analyses of COPD have been performed focusing on either transcriptional signatures in lung samples or genetic polymorphisms, only small exploration studies targeting certain pathways or candidate genes have been pursued for BPD. Small studies show evidence of association of surfactant protein gene polymorphisms (surfactant protein A and surfactant protein B) with respiratory distress syndrome and BPD.^{78,79} Since surfactant deficiency is an attractive contributing mechanism for BPD, these results are especially intriguing. However, these studies do not establish whether the identified polymorphisms associate with reduced surfactant levels and whether they are linked to prematurity rather than BPD. Examination of surfactant protein polymorphisms in COPD have yielded conflicting data showing no association with surfactant protein B, a canonical surfactant protein, but a possible association with surfactant protein D, a member of the collectin family of anti-inflammatory molecules.^{76,80} Recently, a prospective observational study of premature infants to find genes associated with incident BPD identified polymorphisms in the gene metalloprotease 16, an endopeptidase that activates a metalloprotease with elastase function highly abundant in the lung, metalloprotease 2.⁸¹ Importantly, this study validated expression using rodent models of neonatal lung injury. Regarding COPD, animal models of emphysema invoke a critical contribution of metalloprotease activation to disease pathogenesis. The first demonstration that these genes contribute to human COPD came from a large study of pediatric and adult populations which showed that polymorphisms in metalloprotease 12, a protease highly implicated in COPD pathogenesis, were linked to both COPD and childhood asthma.⁸² Thus, matrix turnover, a known consequence of oxidative stress and inflammation in the lung, appears to be a genetic point of convergence for COPD and BPD.

Injury-by-Age Interactions

If COPD and BPD result from common mechanisms of lung injury, what accounts for the differences in manifestations? We invoke the concept of injury-by-age interactions. The neonatal lung is advantaged by an active milieu for tissue formation and plausibly regeneration. However, the innate and adaptive immune systems are immature, which could compromise responses to infection or exaggerate triggers for inflammation. By contrast, the adult lung has a questionable capacity for regeneration but is advantaged by a mature immune system. How could these factors impact on the presentation of BPD and COPD?

The major difference between BPD and COPD is the natural history of the disorders. Children with BPD tend to improve with age, whereas adults with COPD inevitably demonstrate progressive deterioration in lung function. The

few longitudinal studies of infants with BPD in the post-surfactant era are small with surveillance typically through the first 3–5 years of life. Infants with BPD frequently have mild residual lung disease by early childhood that is manifest as mild chronic airflow obstruction without hypoxemia or significant reduced exercise capacity.^{83–85} Thus, the lungs are able to undergo at least partial repair with the airway obstruction possibly reflecting dysanaptic growth of the airways relative to the airspace compartment conferred by the transient insult. Of note, a small subset of patients with BPD demonstrates progressive loss of lung function, similar to the natural history of COPD.⁸⁶ Patients with COPD, by contrast, show chronic lung function deterioration that can be slowed by smoking cessation and arguably by pharmacologic treatments. This difference in long-term outcome is consonant with the fact that lung growth normally occurs through the first 2–3 years of postnatal life, whereas no active lung growth is likely occurring in the adult lung, regardless of concurrent disease.⁸⁷ Thus, if the BPD insult is transient, then the infant or toddler lung has the capacity for restorative growth after the severe injury has resolved. This reparative process is inferred from longitudinal studies of lung function as no confirming histologic data is available.

A histologic and possibly mechanistic difference between the disorders is the prominence of vascular dysmorphology in BPD but not in COPD. Again, this may reflect a higher susceptibility of the lung microvasculature to oxidative injury within the developing rather than adult lung. An intriguing notion, however, is whether the dysmorphology is a protective lesion. Several investigators advance the concept that BPD is a disorder of vascular injury, hypothesizing that the alveolar phenotype is secondary to an inadequate microvascular contribution to normal alveolar maturation/septation.⁸⁸ Pathologic examination of human BPD specimens and large animal models of BPD consistently demonstrates evidence of vascular dysmorphology and, arguably, reduced vascular surface area.^{89,90} Despite the fact that human specimens are often obtained from infants who die from the most severe complications of BPD that are frequently punctuated with pulmonary hypertension, careful histologic analysis of BPD lungs from humans and large animal models shows evidence of vascular immaturity but a maintenance of the microvascular supply to the airspace and preserved proliferative activity.^{91,92} The classic features of pulmonary hypertension, intimal hyperplasia with medial muscularization, are not consistently observed. Compelling data from rodent models show that whereas inhibition of angiogenic pathways in neonatal life results in transient airspace enlargement and microvascular remodeling, hyperoxia exposure causes permanent airspace enlargement with variable, species-dependent evidence of vascular remodeling.^{93,94} Treatment with angiogenic agents, such as VEGF, can improve or worsen alveolar formation in these models.^{95,96} These data suggest that the vascular injury in BPD is that of impaired development and, while common, may be neither necessary nor sufficient for durable airspace changes in the neonatal lung. The vascular contribution to COPD is similarly complicated. Histologic analyses of COPD lungs have not shown a characteristic vascular lesion apart from findings of intimal hyperplasia and microvascular muscularization that are thought to result from truncation of the vascular bed secondary to airspace destruction and hypoxemia.⁹⁷ Pulmonary hypertension in COPD occurs in 2 clinical

settings: (1) a subset of patients with severe COPD and is attributed to a truncation of the microvascular bed with emphysema and systemic hypoxemia and (2) a much smaller subset of patients with mild COPD attributable to primary vascular dysfunction.⁹⁸ In neither of these circumstances has a lesion replicating the dysmorphic immature vasculature evident in BPD been reported. By contrast, inhibition of angiogenic pathways in the adult lung also confers airspace enlargement similar to that observed with neonatal rodents, potentially reflecting a limitation of rodent model systems.³¹ Taken together, it remains unclear how the vascular lesion observed in BPD contributes to the clinical course and whether its presence underscores a protective response utilized in the neonatal (BPD) but not adult (COPD) airspace. Further, whether severe BPD punctuated by pulmonary hypertension represents a subset of premature neonates who are unable to mount a protective vascular response is unclear. Further studies of this subset of BPD patients should prove elucidating.

Could BPD Be the Predisposing Pathology for COPD?

Certain early life pulmonary insults such as interstitial lung disease, cystic fibrosis, and bronchiectasis result in histologic and functional defects that persist into adulthood. Since only 20% of heavy cigarette smokers develop COPD, an emerging idea is that neonatal lung injury, in the premature or full term lung, confers increased risk for apparently acquired adult lung disorders such as COPD. BPD is an attractive predisposing disorder as it is caused by alveolar injury conferring airspace enlargement and may indicate a systemic susceptibility to oxidant injury. Further, as the vast majority of patients with BPD have minimal pulmonary symptoms into adulthood, the possibility that a large cohort of mild BPD patients could be predisposed to develop late life apparently acquired lung diseases such as COPD is an intriguing possibility. Another provocative notion recently advanced by Shi and Warburton is that the critical early life predisposition is the inability to attain a maximal lung function during by early adulthood. It is well established that lung function decline develops after middle age in all persons.⁹⁹ An early life disorder that reduced the maximal achieved lung function, evident in BPD, would reasonably result in a greater susceptibility to late life insults that accelerate the decline in lung function. The major limitation to examining these possibilities is the lack of longitudinal data from the BPD population to show that cigarette smoke exposure results in a higher prevalence of COPD and pulmonary symptoms compared to controls without perinatal BPD or even prematurity. One potentially productive strategy would be to include queries about perinatal morbidity in large cross-sectional and longitudinal studies of smokers with COPD (eg, COPD-Gene, Spiromics). As molecular phenotyping of both pediatric and adult lung disorders becomes more refined, these types of mutually informative datasets will be of great translational interest.

Directions for Future Investigation

A challenge in any comparison of complex inflammatory lung disorders such as COPD and BPD is the issue of subphenotyping. Both disorders represent a spectrum of disease

with common primary insults but distinct functional manifestations and natural histories. Large longitudinal and cross-sectional studies of COPD patients are currently in active enrollment and will hopefully describe the variety of COPD subphenotypes that are relevant to prognosis. Longitudinal observational studies of infants with BPD should also be pursued as these would avail important information about the natural history of the disease, various courses of progression or resolution, and long-term responses to neonatal interventions. Such studies will provide the clinical detail that could inform both molecular subphenotyping and targeted drug development for these very challenging disorders.

Author Disclosure Statement

No competing financial interests exist.

References

1. Bancalari E, Claure N, Sosenko IR. Bronchopulmonary dysplasia: changes in pathogenesis, epidemiology and definition. *Semin Neonatol* 2003; 8:63–71.
2. Eisner MD, et al. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010; 182:693–718.
3. Rabe KF, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007; 176:532–555.
4. Baraldi E, Filippone M. Chronic lung disease after premature birth. *N Engl J Med* 2007; 357:1946–1955.
5. Behrman RE, Butler AS, eds. *Preterm Birth: Causes, Consequences, and Prevention*. Washington, DC: National Academies Press, 2007, pp 31–52.
6. Aucott S. Bronchopulmonary dysplasia: development and progression in the NICU. *Pediatr Allergy Immunol Pulmonol* 2011; 24:00–00.
7. Willemse BW, et al. Effect of 1-year smoking cessation on airway inflammation in COPD and asymptomatic smokers. *Eur Respir J* 2005; 26:835–845.
8. Louhelainen N, et al. Persistence of oxidant and protease burden in the airways after smoking cessation. *BMC Pulm Med* 2009; 9:25.
9. Husain AN, Siddiqui NH, Stocker JT. Pathology of arrested acinar development in postsurfactant bronchopulmonary dysplasia. *Hum Pathol* 1998; 29:710–717.
10. Rahman I, Adcock IM. Oxidative stress and redox regulation of lung inflammation in COPD. *Eur Respir J* 2006; 28:219–242.
11. Kanazawa H, et al. Imbalance between levels of nitrogen oxides and peroxynitrite inhibitory activity in chronic obstructive pulmonary disease. *Thorax* 2003; 58:106–109.
12. Petruzzelli S, et al. Plasma 3-nitrotyrosine in cigarette smokers. *Am J Respir Crit Care Med* 1997; 156:1902–1907.
13. Pinamonti S, et al. Detection of xanthine oxidase activity products by EPR and HPLC in bronchoalveolar lavage fluid from patients with chronic obstructive pulmonary disease. *Free Radic Biol Med* 1998; 25:771–779.
14. Decramer M, et al. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet* 2005; 365:1552–1560.
15. Poole P, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006; 3:CD001287.
16. Didrik Saugstad O. Oxygen and oxidative stress in bronchopulmonary dysplasia. *J Perinat Med* 2010; 38:571–577.
17. Collard KJ, et al. Pulmonary antioxidant concentrations and oxidative damage in ventilated premature babies. *Arch Dis Child Fetal Neonatal Ed* 2004; 89:F412–F416.

18. Haddad JJ. Oxygen-sensitive pro-inflammatory cytokines, apoptosis signaling and redox-responsive transcription factors in development and pathophysiology. *Cytokines Cell Mol Ther* 2002; 7:1–14.
19. Frank L, Sosenko IR. Prenatal development of lung antioxidant enzymes in four species. *J Pediatr* 1987; 110:106–110.
20. Autor AP, Frank L, Roberts RJ. Developmental characteristics of pulmonary superoxide dismutase: relationship to idiopathic respiratory distress syndrome. *Pediatr Res* 1976; 10:154–158.
21. Banks BA, et al. Plasma 3-nitrotyrosine is elevated in premature infants who develop bronchopulmonary dysplasia. *Pediatrics* 1998; 101:870–874.
22. Podowski M, et al. Complex integration of matrix, oxidative stress, and apoptosis in genetic emphysema. *Am J Pathol* 2009; 175:84–96.
23. Davis JM, et al. Pulmonary outcome at 1 year corrected age in premature infants treated at birth with recombinant human CuZn superoxide dismutase. *Pediatrics* 2003; 111:469–476.
24. Sandberg K, et al. N-acetylcysteine administration during the first week of life does not improve lung function in extremely low birth weight infants. *Biol Neonate* 2004; 86:275–279.
25. Russell GA, Cooke RW. Randomised controlled trial of allopurinol prophylaxis in very preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1995; 73:F27–F31.
26. Pitkanen OM, Hallman M, Andersson SM. Correlation of free oxygen radical-induced lipid peroxidation with outcome in very low birth weight infants. *J Pediatr* 1990; 116:760–764.
27. Gladstone IM, Jr., Levine RL. Oxidation of proteins in neonatal lungs. *Pediatrics* 1994; 93:764–768.
28. Yokohori N, Aoshiba K, Nagai A. Increased levels of cell death and proliferation in alveolar wall cells in patients with pulmonary emphysema. *Chest* 2004; 125:626–632.
29. Demedts IK, et al. Role of apoptosis in the pathogenesis of COPD and pulmonary emphysema. *Respir Res* 2006; 7:53.
30. Calabrese F, et al. Marked alveolar apoptosis/proliferation imbalance in end-stage emphysema. *Respir Res* 2005; 6:14.
31. Kasahara Y, et al. Inhibition of VEGF receptors causes lung cell apoptosis and emphysema. *J Clin Invest* 2000; 106:1311–1319.
32. Giordano RJ, et al. Targeted induction of lung endothelial cell apoptosis causes emphysema-like changes in the mouse. *J Biol Chem* 2008; 283:29447–29460.
33. Petrache I, et al. A novel antiapoptotic role for alpha1-antitrypsin in the prevention of pulmonary emphysema. *Am J Respir Crit Care Med* 2006; 173:1222–1228.
34. Aoshiba K, Yokohori N, Nagai A. Alveolar wall apoptosis causes lung destruction and emphysematous changes. *Am J Respir Cell Mol Biol* 2003; 28:555–562.
35. Henson PM, Cosgrove GP, Vandivier RW. State of the art. Apoptosis and cell homeostasis in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2006; 3:512–516.
36. May M, et al. Apoptosis and proliferation in lungs of ventilated and oxygen-treated preterm infants. *Eur Respir J* 2004; 23:113–121.
37. Lukkarinen HP, Laine J, Kaapa PO. Lung epithelial cells undergo apoptosis in neonatal respiratory distress syndrome. *Pediatr Res* 2003; 53:254–259.
38. McGrath-Morrow SA, Stahl J. Apoptosis in neonatal murine lung exposed to hyperoxia. *Am J Respir Cell Mol Biol* 2001; 25:150–155.
39. Lecart C, et al. Bioactive transforming growth factor-beta in the lungs of extremely low birthweight neonates predicts the need for home oxygen supplementation. *Biol Neonate* 2000; 77:217–223.
40. Takizawa H, et al. Increased expression of transforming growth factor-beta1 in small airway epithelium from tobacco smokers and patients with chronic obstructive pulmonary disease (COPD). *Am J Respir Crit Care Med* 2001; 163:1476–1483.
41. Suissa S, et al. Inhaled corticosteroids in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2007; 4:535–542.
42. Speer CP. Pulmonary inflammation and bronchopulmonary dysplasia. *J Perinatol* 2006; 26 Suppl 1:S57–S62; discussion S63–S64.
43. Kallapur SG, Jobe AH. Contribution of inflammation to lung injury and development. *Arch Dis Child Fetal Neonatal Ed* 2006; 91:F132–F135.
44. Groneck P, et al. Association of pulmonary inflammation and increased microvascular permeability during the development of bronchopulmonary dysplasia: a sequential analysis of inflammatory mediators in respiratory fluids of high-risk preterm neonates. *Pediatrics* 1994; 93:712–718.
45. Merritt TA, et al. Elastase and alpha 1-proteinase inhibitor activity in tracheal aspirates during respiratory distress syndrome. Role of inflammation in the pathogenesis of bronchopulmonary dysplasia. *J Clin Invest* 1983; 72:656–666.
46. Vyas J, Kotecha S. Effects of antenatal and postnatal corticosteroids on the preterm lung. *Arch Dis Child Fetal Neonatal Ed* 1997; 77:F147–F150.
47. Franco-Montoya ML, et al. Pulmonary effects of keratinocyte growth factor in newborn rats exposed to hyperoxia. *Am J Physiol Lung Cell Mol Physiol* 2009; 297:L965–L976.
48. Yanagita K, et al. Hepatocyte growth factor may act as a pulmonary factor on lung regeneration after acute lung injury. *J Biol Chem* 1993; 268:21212–21217.
49. Verghese GM, et al. Hepatocyte growth factor and keratinocyte growth factor in the pulmonary edema fluid of patients with acute lung injury. Biologic and clinical significance. *Am J Respir Crit Care Med* 1998; 158:386–394.
50. Padela S, et al. Hepatocyte growth factor is required for alveologenesis in the neonatal rat. *Am J Respir Crit Care Med* 2005; 172:907–914.
51. Ohki Y, et al. Hepatocyte growth factor treatment improves alveolarization in a newborn murine model of bronchopulmonary dysplasia. *Neonatology* 2009; 95:332–338.
52. Currie AE, et al. Epidermal growth factor in the lungs of infants developing chronic lung disease. *Eur Respir J* 2001; 18:796–800.
53. Kagoshima M, et al. Developmental changes in hepatocyte growth factor mRNA and its receptor in rat liver, kidney and lung. *Eur J Biochem* 1992; 210:375–380.
54. Lassus P, et al. Consistent expression of HGF and c-met in the perinatal lung. *Biol Neonate* 2006; 90:28–33.
55. Danan C, et al. High concentrations of keratinocyte growth factor in airways of premature infants predicted absence of bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2002; 165:1384–1387.
56. Lassus P, et al. Lower concentration of pulmonary hepatocyte growth factor is associated with more severe lung disease in preterm infants. *J Pediatr* 2003; 143:199–202.
57. Saulea J, et al. Pulmonary and systemic hepatocyte and keratinocyte growth factors in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2008; 3:719–725.
58. Gosselink JV, et al. Differential expression of tissue repair genes in the pathogenesis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010; 181:1329–1335.
59. Turino GM. The origins of a concept: the protease-antiprotease imbalance hypothesis. *Chest* 2002; 122:1058–1060.
60. Margraf LR, et al. Morphometric analysis of the lung in bronchopulmonary dysplasia. *Am Rev Respir Dis* 1991; 143:391–400.
61. Thibeault DW, et al. Collagen scaffolding during development and its deformation with chronic lung disease. *Pediatrics* 2003; 111(4 Pt 1):766–776.
62. Bruce MC, Pawlowski R, Tomashefski JF, Jr. Changes in lung elastic fiber structure and concentration associated with hyperoxic exposure in the developing rat lung. *Am Rev Respir Dis* 1989; 140:1067–1074.
63. Shah P, Ohlsson A. Alpha-1 proteinase inhibitor (a1PI) for preventing chronic lung disease in preterm infants. *Cochrane Database Syst Rev* 2001; 3:CD002775.
64. Thibeault DW, et al. Lung elastic tissue maturation and perturbations during the evolution of chronic lung disease. *Pediatrics* 2000; 106:1452–1459.

65. Ichiba H, Saito M, Yamano T. Amniotic fluid transforming growth factor-beta1 and the risk for the development of neonatal bronchopulmonary dysplasia. *Neonatology* 2009; 96:156–161.
66. Kompass KS, et al. Highly conserved transcriptional responses to mechanical ventilation of the lung. *Physiol Genomics* 2010; 42:384–396.
67. Kunzmann S, et al. Antenatal inflammation induced TGF-beta1 but suppressed CTGF in preterm lungs. *Am J Physiol Lung Cell Mol Physiol* 2007; 292:L223–L231.
68. Bruce MC, et al. Risk factors for the degradation of lung elastic fibers in the ventilated neonate. Implications for impaired lung development in bronchopulmonary dysplasia. *Am Rev Respir Dis* 1992; 146:204–212.
69. Fukunaga S, et al. MMP-9 and TIMP-1 in the cord blood of premature infants developing BPD. *Pediatr Pulmonol* 2009; 44:267–272.
70. Morris A, et al. Comparison of cigarette smoke-induced acute inflammation in multiple strains of mice and the effect of a matrix metalloproteinase inhibitor on these responses. *J Pharmacol Exp Ther* 2008; 327:851–862.
71. Le Quement C, et al. The selective MMP-12 inhibitor, AS111793 reduces airway inflammation in mice exposed to cigarette smoke. *Br J Pharmacol* 2008; 154:1206–1215.
72. Nakanishi H, et al. TGF-beta-neutralizing antibodies improve pulmonary alveologenesis and vasculogenesis in the injured newborn lung. *Am J Physiol Lung Cell Mol Physiol* 2007; 293:L151–L161.
73. Wan ES, Silverman EK. Genetics of COPD and emphysema. *Chest* 2009; 136:859–866.
74. Lavoie PM, Pham C, Jang KL. Heritability of bronchopulmonary dysplasia, defined according to the consensus statement of the national institutes of health. *Pediatrics* 2008; 122:479–485.
75. Abman SH, Mourani PM, Sontag M. Bronchopulmonary dysplasia: a genetic disease. *Pediatrics* 2008; 122:658–659.
76. Foreman MG, et al. Polymorphisms in surfactant protein D are associated with COPD. *Am J Respir Cell Mol Biol* 2011; 44:316–322.
77. Wilk JB, et al. A genome-wide association study of pulmonary function measures in the Framingham Heart Study. *PLoS Genet* 2009; 5:e1000429.
78. Hallman M, Haataja R, Marttila R. Surfactant proteins and genetic predisposition to respiratory distress syndrome. *Semin Perinatol* 2002; 26:450–460.
79. Marttila R, et al. Surfactant protein A and B genetic variants in respiratory distress syndrome in singletons and twins. *Am J Respir Crit Care Med* 2003; 168:1216–1222.
80. Baekvad-Hansen M, Nordestgaard BG, Dahl M. Surfactant protein-B polymorphisms, pulmonary function and COPD in 10,231 individuals. *Eur Respir J* 2011; 37:791–799.
81. Hadchouel A, et al. Matrix metalloproteinase gene polymorphisms and bronchopulmonary dysplasia: identification of MMP16 as a new player in lung development. *PLoS One* 2008; 3:e3188.
82. Hunninghake GM, et al. MMP12, lung function, and COPD in high-risk populations. *N Engl J Med* 2009; 361:2599–2608.
83. Fakhoury KF, et al. Serial measurements of lung function in a cohort of young children with bronchopulmonary dysplasia. *Pediatrics* 2010; 125:e1441–e1447.
84. Baraldi E, et al. Pulmonary function until two years of life in infants with bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 1997; 155:149–155.
85. Robin B, et al. Pulmonary function in bronchopulmonary dysplasia. *Pediatr Pulmonol* 2004; 37:236–242.
86. Doyle LW, et al. Bronchopulmonary dysplasia in very low birth weight subjects and lung function in late adolescence. *Pediatrics* 2006; 118:108–113.
87. Thurlbeck WM. Postnatal human lung growth. *Thorax* 1982; 37:564–571.
88. Thebaud B, Abman SH. Bronchopulmonary dysplasia: where have all the vessels gone? Roles of angiogenic growth factors in chronic lung disease. *Am J Respir Crit Care Med* 2007; 175:978–985.
89. Bhatt AJ, et al. Disrupted pulmonary vasculature and decreased vascular endothelial growth factor, Flt-1, and Tie-2 in human infants dying with bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001; 164(10 Pt 1):1971–1980.
90. Coalson JJ. Pathology of bronchopulmonary dysplasia. *Semin Perinatol* 2006; 30:179–184.
91. De Paep ME, et al. Growth of pulmonary microvasculature in ventilated preterm infants. *Am J Respir Crit Care Med* 2006; 173:204–211.
92. Coalson JJ, et al. Neonatal chronic lung disease in extremely immature baboons. *Am J Respir Crit Care Med* 1999; 160:1333–1346.
93. McGrath-Morrow SA, et al. Vascular endothelial growth factor receptor 2 blockade disrupts postnatal lung development. *Am J Respir Cell Mol Biol* 2005; 32:420–427.
94. Le Cras TD, et al. Treatment of newborn rats with a VEGF receptor inhibitor causes pulmonary hypertension and abnormal lung structure. *Am J Physiol Lung Cell Mol Physiol* 2002; 283:L555–L562.
95. Le Cras TD, et al. VEGF causes pulmonary hemorrhage, hemosiderosis, and air space enlargement in neonatal mice. *Am J Physiol Lung Cell Mol Physiol* 2004; 287:L134–L142.
96. Kunig AM, et al. Recombinant human VEGF treatment enhances alveolarization after hyperoxic lung injury in neonatal rats. *Am J Physiol Lung Cell Mol Physiol* 2005; 289:L529–L535.
97. Peinado VI, Pizarro S, Barbera JA. Pulmonary vascular involvement in COPD. *Chest* 2008; 134:808–814.
98. Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. *Eur Respir J* 2008; 32:1371–1385.
99. Shi W, Warburton D. Is COPD in adulthood really so far removed from early development? *Eur Respir J* 2010; 35:12–13.

Address correspondence to:

Enid R. Neptune, M.D.

Division of Pulmonary and Critical Care Medicine

Johns Hopkins University School of Medicine

1830 East Monument St., Room 547

Baltimore, MD 21205

E-mail: eneptune@jhmi.edu

Received for publication January 11, 2011; accepted after revision March 30, 2011.

