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Abstract: There is increasing evidence that chronic obstructive pulmonary disease (COPD) is not simply a disease of old age that is largely restricted to heavy smokers, but may be associated with insults to the developing lung during foetal life and the first few years of postnatal life, when lung growth and development are rapid. A better understanding of the long-term effects of early life factors, such as intrauterine growth restriction, prenatal and postnatal exposure to tobacco smoke and other pollutants, preterm delivery and childhood respiratory illnesses, on the subsequent development of chronic respiratory disease is imperative if appropriate preventive and management strategies to reduce the burden of COPD are to be developed. The extent to which insults to the developing lung are associated with increased risk of COPD in later life depends on the underlying cause, timing and severity of such derangements. Suboptimal conditions *in utero* result in aberrations of lung development such that affected individuals are born with reduced lung function, which tends to remain diminished throughout life, thereby increasing the risk both of wheezing disorders during childhood and subsequent COPD in genetically susceptible individuals. If the current trend towards the ever-increasing incidence of COPD is to be reversed, it is essential to minimize risks to the developing lung by improvements in antenatal and neonatal care, and to reduce prenatal and postnatal exposures to environmental pollutants, including passive tobacco smoke. Furthermore, adult physicians need to recognize that lung disease is potentially associated with early life insults and provide better education regarding diet, exercise and avoidance of smoking to preserve precious reserves of lung function in susceptible adults. This review focuses on factors that adversely influence lung development *in utero* and during the first 5 years of life, thereby predisposing to subsequent COPD.

Keywords: adult, foetal origins of lung disease, foetal programming, infant, intrauterine growth restriction, lung function, lung growth and development, pollution, prematurity

Introduction

Chronic obstructive pulmonary disease (COPD) is a serious global health problem, which is increasing in prevalence worldwide, with serious social and economic burdens [GOLD, 2011]. The World Health Organization (WHO) estimates that around 210 million people worldwide have COPD [WHO, 2008]. COPD is the primary contributor to mortality caused by chronic lower respiratory diseases, which became the third leading cause of death in the USA in 2008 [CDC, 2012]. A chronic inflammatory response to inhaled smoke and other noxious particles results in pathological changes in susceptible subjects with subsequent air trapping, progressive airflow limitation and increasing breathlessness characteristic of COPD. A diminished ratio of forced expiratory volume in 1 s to forced vital capacity (FEV_1/FVC) has frequently been used in clinical practice and research to diagnose COPD, with severity based on the level of FEV_1. This can, however, lead to confusion and it is now recommended that the term 'COPD' only be used in the appropriate clinical (diagnostic) context [Agusti and Vestbo, 2011; GOLD, 2011; Postma *et al.* 2012].

Until recently, cigarette smoking was considered the main causal factor for developing COPD. However, evidence from population-based studies now suggests that both indoor and outdoor

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pollution and gene–environment interactions make a greater contribution to the burden of COPD than previously appreciated [Salvi and Barnes, 2009]. In addition, there has been growing awareness that the origins of many chronic adult lung diseases such as COPD may arise very early in life, that is, the 'foetal origins' hypothesis. The concept that chronic respiratory disease in adulthood is not simply due to an accelerated decline in lung function with ageing, but failure to achieve optimal peak function by early adulthood due to prior adverse exposures, was first proposed several decades ago. Subsequent studies showed that both low birth weight (LBW) and respiratory infections in infancy were associated with decreased adult lung function and death from COPD [Barker *et al.* 1991]. Evidence to support the concept of 'foetal programming', whereby insults during critical periods of development produce permanent structural, physiological or epigenetic changes with lifelong consequences [Miller and Marty, 2010; Barker, 2012], has also been provided by experimental animal models [Kallapur and Ikegami, 2006; Kramer *et al.* 2009; Shimoda and Semenza, 2011; Abbott and Winzer-Serhan, 2012; Hilgendorff *et al.* 2012; Magnani *et al.* 2012; Maritz and Mutemwa, 2012; Sutherland *et al.* 2012]. These studies have shown that insults to the developing lung during intrauterine or very early postnatal life lead to increased susceptibility to respiratory disease during both childhood and later life [Gluckman *et al.* 2008; Harding and Maritz, 2012].

Recent adaptations that enable spirometric measures of lung function to be applied from birth and throughout the preschool years [Stocks and Lum, 2012], and the incorporation of such tests into clinical and epidemiological studies commencing from birth have greatly enriched our understanding of the effects of prenatal insults and the early origins of adult lung disease. Subsequent follow up of these cohorts into adult life has also produced clear evidence of 'tracking', whereby an individual's lung function remains on a similar centile over time. Thus, infants born with low lung function due to prenatal insults or those in whom normal lung and airway growth during the first years of life is impeded by postnatal insults, tend to retain this position thereafter [Bisgaard *et al.* 2012]. Since diminished lung function by early school age is a strong predictor of subsequent low lung function in early adulthood [Phelan *et al.* 2002; Sears *et al.* 2003; Stern *et al.* 2007], such individuals will be at increased risk of COPD [James *et al.* 2005].

This review will focus on factors that affect structural and functional maturation of the lung and the impact of alterations in early lung development (i.e. up to 5 years of age) on COPD. Due to the immense literature in this field, citations during the past decade have been prioritized, the bibliographies of which contain pertinent references to the older literature. Since the ultimate result of aberrant lung development depends on the type, severity and duration of the insult and the developmental stage at which it occurs [Kallapur and Ikegami, 2006], the review commences with a brief description of normal lung development.

Normal lung development

Lung development, which is influenced by numerous mechanical and biochemical factors, commences *in utero* and continues through various phases to adolescence and early adulthood [Quanjer *et al.* 2010, 2012], with the most marked structural changes occurring during foetal life and the first few years after birth [Burri, 2006]. In humans, the lung first appears during the fourth week of gestation and the two lungs can be distinguished as separate organs by 6 weeks. By 17 weeks' gestation, all conducting airways have formed by branching morphogenesis [Morrisey and Hogan, 2010], with airway wall structure and epithelium being essentially in adult form by 24 weeks' gestation. Mechanical forces, exerted on lung tissue through alterations in lung expansion, are a major determinant of foetal lung development [Hooper and Wallace, 2006]. Such forces are dependent on appropriate quantities of lung fluid and foetal breathing movements, which are detected from about 10 weeks' gestation. Airway smooth muscle (present from 6 weeks' gestation and innervated from 8 weeks' gestation) is important for fluid movement within the lung. From 16 weeks' to 27 weeks' gestation there is growth and maturation of the peripheral airways to form prospective respiratory airways, differentiation of epithelial cells to form type I and type II alveolar cells and further development of the pulmonary capillary network. By this stage, the blood–gas barrier is as thin as in the adult and of sufficient surface area to sustain life. Alveoli appear from 29 weeks' gestation by a process of alveologenesis [Galambos and Demello, 2008], which depends on the presence of elastin, smooth muscle cells and a capillary network [Burri, 2006], with 100–150 million alveoli present by 40 weeks' gestation, that is, 'full-term' [Stocks and Hislop, 2002]. While some structural studies have suggested that

the variable adult number of alveoli (300–600 million) is reached by 2–4 years, there is no certainty about when alveoli finally cease to multiply. Recent studies using helium^3 magnetic resonance imaging in man [Butler *et al.* 2012; Narayanan *et al.* 2012], as well as experimental animal studies [Schittny *et al.* 2008], suggest that alveoli may continue to increase in number as well as in size and complexity through to adolescence and even adulthood. While this offers exciting possibilities with respect to recovery from earlier injuries, it also widens the potential window of vulnerability of the developing lung, with respect to environmental exposures [ATS, 2004]. Alveoli continue to increase in size and complexity to increase the gas-exchanging surface area until body growth is complete.

After birth, lung size increases with body size, but is also influenced by age, sex and ethnicity [Quanjer *et al.* 2010, 2012]. Maximum lung volumes are attained at around 22 years in males and slightly earlier in females [Kohansal *et al.* 2009; Quanjer *et al.* 2012], representing a 30-fold increase in lung volume and a 20-fold increase in gas-exchanging surface area between birth and maturity, with at least a doubling of airway length and diameter over the same period. Even in health, both FEV_1 and FVC gradually decline after reaching their peak in early adulthood, due to a gradual loss of lung elasticity [Quanjer *et al.* 2012]. Changes in FEV_1/FVC occur with age, being highest in early childhood when the airways are relatively large in relation to lung volume and elastic lung recoil is high [Quanjer *et al.* 2010]. Consequently, the use of fixed thresholds, such as < 0.7 for FEV_1/FVC, to diagnose airway obstruction should be avoided as it results in serious underdiagnosis in younger subjects and overdiagnosis in the elderly [Quanjer *et al.* 2011, 2012; Brusasco, 2012].

Early life influences that may predispose to COPD

The extent to which insults to the developing lung are associated with subsequent increased risk of COPD depends on the underlying cause, timing and severity of such derangements. For clarity, various risk factors are discussed individually below, but in reality it is the interaction between such factors in genetically susceptible individuals that will be important in predisposing to COPD. Whereas prenatal factors are more likely to impair airway development, postnatal factors tend to impact on subsequent airway growth, as well as alveolarization and microvasculature. Diminished airway calibre associated with suboptimal intrauterine conditions may be evident shortly after birth and prior to any postnatal insults. Reduced airway calibre and hence airflow limitation may reflect structural changes to the airway wall and supporting parenchyma as well as bronchial hyperresponsiveness (BHR). The complex relationship between deficits in airway function and BHR in early life, genetic susceptibility and subsequent respiratory morbidity and lung function has been highlighted by longitudinal cohort studies [Turner *et al.* 2004; Le Souef, 2005; Bisgaard *et al.* 2012].

Prenatal risk factors for COPD

Irregularities during the susceptible period of foetal lung development may render the adult lung less effective as a gas-exchanging unit and/or increase susceptibility to disease and the effects of ageing [Hooper and Wallace, 2006; Kallapur and Ikegami, 2006; Miller and Marty, 2010; Thornburg *et al.* 2010; Joss-Moore *et al.* 2011]. Differences in alveolar number due to early insults can influence the rate of disease progression, including accelerating rate of decline in FEV_1 in patients with COPD [Massaro and Massaro, 2004].

Maternal smoking during pregnancy

While the incidence of maternal smoking during pregnancy has decreased during the past decade, it remains the single, most important, potentially preventable insult to the developing lung and a major cause of sudden infant death, LBW, preterm delivery and intrauterine growth restriction (IUGR) [Hayatbakhsh *et al.* 2009]. Experimental studies in various animal models have demonstrated that *in utero* exposure to nicotine leads to smaller lungs with a reduced number of enlarged alveoli, alveolar changes suggestive of premature ageing and a low capillary density [Harding and Maritz, 2012]. There is evidence from animal models that prenatal exposure to nicotine causes abnormalities in airway branching and dimensions and results in increased airway smooth muscle and collagen deposition, with subsequent reductions in airflow limitation, reduced FEV_1 and airway hyperreactivity [Sandberg *et al.* 2011; Wongtrakool *et al.* 2012].

Most evidence regarding postnatal effects of intrauterine smoke exposure in humans on subsequent lung function or respiratory morbidity has been derived from epidemiological and physiological studies [Stocks and Dezateux, 2003; Svanes *et al.*

2004; Moshammer *et al.* 2006; Palmer *et al.* 2006; Goksor *et al.* 2007; Haberg *et al.* 2007; Wang *et al.* 2008; Hayatbakhsh *et al.* 2009; Wenten *et al.* 2009; Henderson *et al.* 2010; Hersoug *et al.* 2010; Schultz *et al.* 2010; Abbott and Winzer-Serhan, 2012; Neuman *et al.* 2012]. Prenatal nicotine exposure may predispose to BHR during infancy, especially in those with a maternal history of asthma, with BHR still evident in early adulthood [Goksor *et al.* 2007]. Prenatal nicotine exposure is also associated with poor lung function at birth, which persists into early adulthood [Svanes *et al.* 2004; Hayatbakhsh *et al.* 2009], regardless of postnatal exposure. Maternal smoking of 10 cigarettes/day was found to increase risk of COPD in offspring by 1.7 (95% confidence interval, 1.2–2.5) after adjustment for potential confounders. Within families, the effect of maternal smoking of 10 cigarettes/day had the same effect on airflow limitation in the offspring as 10 years of personal smoking by the offspring [Upton *et al.* 2004].

Low Birth Weight (LBW)

Most epidemiological studies have shown that LBW is associated with increased cardiovascular and respiratory morbidity in later life. Factors responsible for LBW include both preterm delivery and IUGR. The commonest causes of IUGR, usually defined as birth weight less than tenth centile for gestational age, are impaired transplacental supplies of oxygen and/or nutrients to the foetus, which are often associated with maternal smoking or pregnancy-induced hypertension [Pike *et al.* 2012; Narang and Bush, 2012]. Reductions in nutrients and oxygen supplies have wide-ranging effects on the developing lung, including diminished alveolar surface area, thickened air–blood barriers and a reduction in lung weight. Animal models have indicated that these changes persist into adulthood [Karadag *et al.* 2009; Pike *et al.* 2012].

IUGR has been identified as a risk factor for reduced lung function and respiratory morbidity during infancy [Hoo *et al.* 2004], childhood [Kotecha *et al.* 2010], and adulthood [Barker *et al.* 1991; Lawlor *et al.* 2005; Rona *et al.* 2005; Canoy *et al.* 2007], and has been shown to exacerbate the adverse impact of preterm delivery and postnatal hyperoxia. IUGR in the first and second trimester has been found to be associated with reduced vitamin E and abnormal lung function at 5 years of age, together with increased risk of developing asthma [Turner *et al.* 2011]. The long-term impact of poor maternal nutrition during pregnancy in humans has also been shown by the increased prevalence of COPD amongst those born to mothers exposed to the Dutch famine (1944–1945) [Lopuhaa *et al.* 2000].

Associations have been reported between maternal (prenatal) and postnatal dietary intake of fruit, fish or antioxidant vitamins and asthma [Fogarty and Britton, 2000], or COPD [Tabak *et al.* 2001]. Antioxidant vitamins may protect the lungs from oxidative damage by smoking or air pollution as shown in animal studies [Maritz and Rayise, 2011; Maritz *et al.* 2011]. Vitamin D is known to regulate multiplication of bronchial smooth muscle cells, which may be important in both asthma and COPD [Banerjee and Panettieri, 2012]. Recent studies have attempted to determine whether maternal vitamin D supplementation can prevent the occurrence of chronic respiratory diseases [Weiss and Litonjua, 2011]. A number of studies have shown that maternal diets poor in vitamin D may lead to an increased risk of reactive airways in the offspring [Devereux *et al.* 2007; Erkkola *et al.* 2009; Miyake *et al.* 2010; Camargo *et al.* 2011]. However, other studies have reported that higher serum 25(OH) D concentrations during pregnancy may increase the risk of asthma in offspring by 9 years of age [Gale *et al.* 2008], and that children receiving supplemental vitamin D in the first year of life have a nonsignificant increased risk of developing asthma [Hypponen *et al.* 2004]. Current evidence does not support routine vitamin D supplementation during pregnancy.

Postnatal risk factors for COPD

Chronic lung disease of prematurity

Advances in prenatal and neonatal intensive care have led to marked improvements in survival rates for extremely preterm infants during recent years, but the prevalence of pulmonary sequelae in such infants has not declined [Moore *et al.* 2012; Costeloe *et al.* 2012]. Preterm delivery, that is, that occurring before 37 weeks' gestation, is the most common cause of abnormal lung development, and one with potentially life-long consequences. Although there are currently limited longitudinal studies beyond early adulthood, there is concern that such individuals face increased risk of developing COPD in later life [Silverman and Kuehni, 2007; Bush, 2008].

Infants born before 28 weeks' gestation rarely survive without supplementary oxygen and ventilatory assistance, the iatrogenic effects of which may compound the disruption of lung development caused by preterm delivery *per se*. Exposure to hyperoxia, especially if combined with prenatal inflammation, results in the disruption of alveolar development, reduced surface area for gas exchange, diffuse fibrosis and increased airway resistance in mice [Velten *et al.* 2010]. Even if preterm infants can be managed in room air at birth, this is relatively hyperoxic compared with the foetal environment. Similarly, the switch from foetal to extrauterine breathing movements represents major changes in the mechanical forces imposed on the immature lung, which may adversely impact alveolar multiplication [Hooper and Wallace, 2006], elastin deposition and airway smooth muscle [Stocks and Hislop, 2002]. It is therefore hardly surprising that abnormal postnatal lung function and development have been reported even among preterm infants who require no ventilatory assistance at birth [Hoo *et al.* 2002; Friedrich *et al.* 2007; Colin *et al.* 2010].

Bronchopulmonary dysplasia (BPD) is commonly defined as continuing dependence on supplemental oxygen at 36 weeks' gestation in those born prematurely. BPD develops as the net result of pulmonary inflammation, oxidant stress and mechanical trauma to these extremely fragile and immature lungs, leading to disruption of normal alveolar and vascular development. Morphological studies in infants who died with BPD have reported substantial thickening of airway wall dimensions over the entire size range of airways, compatible with subsequent airflow obstruction in survivors [Tiddens *et al.* 2008]. Animal models suggest that hyperoxic insults to the immature lung may not only result in smooth muscle hyperplasia and airway remodelling [Choi *et al.* 2009], but reprogramming of key innate immunoregulatory pathways in the lung [O'Reilly *et al.* 2008], thereby contributing to both reduced resistance to respiratory viral infections and the long-term risk of COPD.

In addition to increased risk of asthma and other respiratory morbidity, most longitudinal studies of lung function have reported evidence of persistent airflow limitation (reduced FEV_1 and FEV_1/FVC) and/or BHR during childhood, adolescence and adulthood in survivors of preterm birth [Vrijlandt *et al.* 2006; Baraldi and Filippone, 2007; Baraldi *et al.* 2009; Doyle and Anderson, 2010; Fawke *et al.* 2010; Kwinta and Pietrzyk, 2010; Greenough, 2012; Hacking *et al.* 2012; Kotecha *et al.* 2012a, 2012b]. However, the male disadvantage with respect to reduced lung function and increased morbidity that is evident during infancy and childhood [Becklake and Kauffmann, 1999], appears to be reversed in adulthood [Vrijlandt *et al.* 2005; Postma, 2007]. Evidence of persistent respiratory symptoms and abnormal structure and lung function has been reported in young adults with BPD [Wong *et al.* 2008]. The persistent reduction in airway function in those born preterm may be accompanied by an accelerated rate of decline of lung function [Doyle *et al.* 2006; Filippone *et al.* 2009]. Recent studies on young adult survivors of preterm birth have also revealed a worryingly high prevalence of current smoking (about 30% across various studies) [Doyle *et al.* 2006; Vrijlandt *et al.* 2006], which appears to further accelerate decline in lung function in this vulnerable population. Together, these findings suggest that young adult survivors of BPD may be left with residual functional and characteristic structural pulmonary abnormalities, most notably emphysema.

Postnatal growth and nutrition

As alveolar numbers continue to increase after birth, postnatal nutrition and growth also affect the size of the adult lung. Studies show that children who are breastfed have improved lung volumes relative to those who are formula fed in early life [Ogbuanu *et al.* 2009; Dogaru *et al.* 2012; Soto-Ramirez *et al.* 2012]. The impact of postnatal nutrition on lung development is especially pertinent in preterm infants, in whom nutrition and growth are often impaired, contributing to reduced lung function and increased risk of respiratory morbidity in survivors during childhood and adolescence [Pike *et al.* 2012]. Vitamin A, D or E deficiency seems to have greatest effect on alveolar rather than airway development, with evidence that postnatal supplementation may potentially improve lung structure both in animal studies and humans [Checkley *et al.* 2010; Zosky *et al.* 2011; Esteban-Pretel *et al.* 2013]. While evidence from observational studies suggests a role for diet in asthma and COPD, causality of the association is far less conclusive.

Postnatal exposure to environmental tobacco smoke

There are recognized difficulties in separating the effects of pre- and postnatal tobacco smoke

exposure, since virtually all women who smoke during pregnancy continue to do so after child birth [Le Souef, 2000; Stocks and Dezateux, 2003]. Although current evidence suggests that smoking during pregnancy has the most detrimental effects on the developing lung, postnatal nicotine exposure has been shown to increase the risk of lower respiratory illness and reduced lung function in young children. Nevertheless, not all children who are exposed to pre- or postnatal tobacco smoke have diminished lung function or increased respiratory morbidity, reflecting, at least in part, differences in maternal and foetal genetic susceptibility [Tsai *et al.* 2008]. Several, though not all, studies have reported a protective effect of the infant and/or maternal $GSTT_1$ non-null genotype in children of smoking mothers, with respect to lung function, airway reactivity and respiratory morbidity [Gilliland *et al.* 2002; Murdzoska *et al.* 2010; Schultz *et al.* 2010].

Environmental pollution

The developing lung is highly susceptible to damage from exposure to environmental pollutants [Miller and Marty, 2010; Soto-Martinez and Sly, 2010]. The association between acute and chronic exposure to environmental pollutants and respiratory symptoms [Dales *et al.* 2009; da Silva *et al.* 2012], as well as reduced lung function [Gauderman *et al.* 2007; Schindler *et al.* 2009; da Silva *et al.* 2012], is well described in both children and adults. However, during the last decade, there has been growing interest in determining the impact of early life exposures to specific environmental risk factors on the developing respiratory system. In addition to tobacco smoke, environmental pollutants relevant to respiratory tract illnesses include oxidant gases (ozone, nitrogen dioxide and oxygen), traffic-related emissions (carbon monoxide, nitrogen oxides and particulate matter [PM]), PM from biomass fuel combustion (wood, dung or straw) and xenobiotics. Recent WHO reports estimate that up to 35% of those with COPD in low- and middle-income countries developed the disease after exposure to biomass fuel combustion [Lopez *et al.* 2006]. School children in rural India, where use of biomass is common, also have significant reductions in lung function and increased incidence of asthma when compared with nonexposed peers [Padhi and Padhy, 2008].

Ambient ozone is formed by the action of sunlight on nitrogen oxides and reactive hydrocarbons, both of which are emitted by motor vehicles and industrial sources. Studies have demonstrated that foetal exposure to PM, ozone and carbon monoxide can lead to a host of developmental conditions including IUGR, LBW and preterm birth, with subsequent increased respiratory morbidity. Exposure to traffic-related air pollution during infancy affects lung function in children up to 8 years of age, particularly in those sensitized to common inhalant or food allergens [Schultz *et al.* 2012]. A direct link between childhood exposure to PM and increased vulnerability to adult respiratory disease is provided by studies showing an association between life-long biomass smoke exposure and development of COPD in noncigarette-smoking women [Grigg, 2009]. Experimental studies show that mice exposed to traffic-related PM, either pre- or postnatal, develop significant alterations of alveolar structure and lung elastic properties that adversely impact lung growth [Mauad *et al.* 2008]. Results from animal studies also implicate a number of xenobiotics (e.g. nitrofen, naphthalenes, arsenic, tetrachlorodibenzo-p-dioxin, di(2-ethylhexyl) phthalate) in adversely influencing lung maturation and growth [Miller and Marty, 2010].

Childhood respiratory illnesses

The association between respiratory infections during childhood and chronic lung disease in later life has long been recognized. However, whether this is due to a viral infection in early life that affects the normal course of lung development making the individual susceptible to airway obstruction thereafter, or to pre- or perinatal insults to the developing lung that predispose the infant to early wheeze and subsequent airway obstruction has remained the subject of much debate. Until recently, inability to measure routinely lung function in children below 6 years of age made it impossible to determine whether diminished lung function preceded early respiratory infections or *vice versa*, a situation that has now been overcome by advances in the field of infant and preschool lung function testing [Stocks and Lum, 2012]. While it has been reported that lower respiratory tract infections, especially those associated with respiratory syncytial virus (RSV), are associated with abnormal lung function at follow up [Broughton *et al.* 2007], several studies have shown that children hospitalized as a result of RSV tend to have abnormal lung function before as well as after such infections [Turner *et al.* 2002; Drysdale *et al.* 2011]. Considerable evidence now exists that diminished

airway function, associated with a suboptimal intrauterine environment (e.g. maternal smoking, IUGR) may be present from birth and that such children are more likely to wheeze with subsequent viral infections [Pike *et al.* 2011, 2012; Narang and Bush, 2012]. In the follow up of the Tucson study at 22 years of age, those in the lowest quartile for forced expiratory flows during the first year of life prior to any infections had the lowest lung function as adults [Stern *et al.* 2007].

Although lung function was not measured in the Dunedin cohort until school age, subsequent assessments demonstrated that lung function tracked between 9 years of age and 26 years of age, the lowest FEV_1/FVC being observed in those with history of wheeze or asthma. Similarly, tracking of lung function has been clearly demonstrated in the Melbourne asthma cohort, with lower levels by 7 years of age in those with asthma (many of whom subsequently developed COPD) [Phelan *et al.* 2002; Tai *et al.* 2010]. A recent study suggested that childhood disadvantages, which included the additive effect of maternal, paternal or childhood asthma, maternal history of smoking and childhood respiratory infections, were at least as great a risk for subsequent COPD as those related to active smoking in adults [Svanes *et al.* 2010]. It has also been suggested that diagnosis of asthma as a child may confer a similar risk of developing COPD as an increase in age of 22 years or 62 pack years of cigarette smoking [Shirtcliffe *et al.* 2012]. This functional evidence, combined with the structural changes observed in animal models described above, suggest that airway abnormalities are determined during foetal or early postnatal life and will increase the risk both of developing wheezing illnesses during childhood and COPD in later life.

Summary

Normal lung development is essential to attain maximum lung health in adulthood and minimize the risk of COPD. A better understanding of the long-term effects of early life factors on subsequent development of respiratory disease is imperative if appropriate preventive and management strategies to reduce the burden of COPD are to be developed. Research in this field, however, is challenged by the need to separate the independent effects of genetic predisposition, preterm delivery, IUGR, neonatal respiratory disorders and the impact of a wide range of treatment strategies and early environmental insults, including childhood respiratory infections and environmental exposures. Adult chest physicians need to recognize the potential relevance of young adults presenting with airway obstruction and enquire about neonatal history including birth weight and preterm delivery. Investigations should then be directed at establishing the nature of the impairment and whether the airway obstruction is reversible in nature. It should be remembered that while reductions in airway calibre or increased airway wall compliance are usually responsible for symptoms of airway obstruction, reduced pulmonary elastic recoil, such as may result from a disruption of alveolar development in early life, can also contribute to decreased airflows and hence the risk of developing emphysematous changes and COPD.

The onset of well-recognized but benign age-related changes in lung function during early adulthood is of little consequence in health, due to the considerable lung reserves that are available. The outlook, however, is very different for those who fail to reach their full potential due to derangements in lung development or those in whom the rate of lung decline is accelerated due to active smoking/environmental exposures or to structural and functional alterations present since birth. In such individuals, symptoms of COPD and associated restrictions on lifestyle are likely to develop once a critical threshold of lung function is reached. Since a reduced FEV_1 in adult life carries with it a poor prognosis with respect not only to respiratory health but also to cardiovascular disease and overall mortality [Sin *et al.* 2005; Young *et al.* 2007], adult physicians need to recognize that lung disease is potentially associated with prematurity and other early life insults and offer long-term monitoring and advice to susceptible adults regarding the preservation of existing lung reserves. Where appropriate, such advice should include education regarding smoking cessation, physical activity levels and maintaining a healthy diet [GOLD, 2011].

Conclusion

Given the evidence presented above it is no longer plausible to consider COPD as a disease of old age that is largely restricted to heavy smokers. Instead it has been shown that antenatal programming, intra- and extrauterine environmental exposures and gene–environment interactions all play a major role in determining subsequent susceptibility to diseases such as COPD. As a result of such insults, some individuals are born with

low lung function, which then tracks through life, those with the lowest lung function as infants and young children tending to retain this state thereafter. With increasing survival of ever more immature infants, an increasing proportion of the population may be at risk of COPD in the future. If the continuing increase in incidence of COPD is to be reversed, it is essential to not only provide better education regarding diet, exercise and avoidance of smoking to preserve precious reserves of lung function, but to minimize risks to the developing lung by improvements in antenatal and neonatal care and reduction in pre- and postnatal exposures to environmental pollutants.

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