

## The contribution of airway development to paediatric and adult lung disease

Stephen Stick

Airway development is only one of the factors that is important in the pathogenesis of complex respiratory disorders such as asthma and chronic airflow limitation. For example, knowledge of the interactions between the developing lung, genetic, environmental, and immunological factors is essential if progress is to be made in early diagnosis and the development of new interventions aimed at reducing the long term morbidity from chronic lung diseases. However, such a review is beyond the scope of this article which is limited to the role of airway development during childhood in determining adult lung function and the outcome of chronic airway disease. Some childhood respiratory diseases such as cystic fibrosis and various congenital lung disorders have obvious sequelae or adverse outcomes in adults. However, these conditions are relatively rare compared with chronic airflow limitation and asthma, the major symptomatic manifestations in adults of airway abnormalities. Most studies that have examined the aetiology of chronic airflow limitation and asthma have focused on airway calibre and bronchial responsiveness as possible pathophysiological factors and also as outcome measures with regard to the long term effects of chronic airway disease. This review will therefore focus on studies that have measured airway function including, in some studies, assessment of bronchial responsiveness.

### Normal development

The important factors that determine normal airway development have recently been reviewed<sup>1</sup> and are summarised here. Airway development commences with a ventral diverticulum from the foregut at approximately 24 days after fertilisation. The pre-acinar airway branching pattern is completed by the end of the pseudoglandular phase (5–17 weeks gestation) and requires normal mesenchymal and epithelial tissue.<sup>2</sup> During this phase multiplication of epithelial lining cells results in tube elongation while complex local interactions between epithelial and mesenchymal cells produce branching. For normal branching and growth to occur a balance is achieved between factors that cause multiplication of epithelial cells—for example, insulin-like growth factor, epidermal growth factor—and others that inhibit epithelial cell multiplication but

increase protein synthesis—for example, transforming growth factor  $\beta$ . Physical factors also influence airway development, which is adversely affected by conditions such as oligohydramnios and reduced fetal breathing movements. Between 16 and 26 weeks (canalicular phase) there is vascularisation of the peripheral mesenchyme and capillaries come into close contact with the surface epithelium of the developing airways. The airway lumen enlarges and walls thin as connective tissue components are reduced. During the next phase (terminal sac or saccular) from 24 to 36 weeks gestation the pre-acinar airways grow, additional respiratory bronchioles develop, and acini are formed. Airway growth continues after birth with diameter and length doubling or tripling until adulthood. Evidence from family studies of arterial branching patterns suggests a genetic influence on airway development. Whereas airway development is largely complete by term, alveolar development is predominantly a postnatal process. The alveoli develop, multiply, and increase in volume during the alveolar phase from 36 weeks gestation to at least three years after birth and continue to increase in volume until lung growth ceases in early adult life. Given this pattern of lung development, it is not surprising that prenatal and early postnatal factors have important effects on airway function that can be detected throughout childhood and into adult life. Furthermore, any factor that impacts significantly on the normal airway growth that occurs throughout childhood is likely to adversely affect adult lung function. Thus, it is possible that ultimate adult lung function is influenced by a number of abnormal patterns of airway growth including:

- normal childhood growth but accelerated adult decline;
- failure to attain maximum growth during childhood followed by a normal rate of decline in adulthood;
- failure to attain maximum growth followed by early onset or accelerated decline.

Not all factors that operate during childhood result in abnormal growth and/or development. Some have functional effects such as increasing bronchial responsiveness. However, the physiological consequences of adverse factors are generally detected by measurements that reflect airway calibre.

Department of  
Respiratory Medicine,  
Princess Margaret  
Hospital for Children  
and TVW Institute for  
Child Health  
Research, Perth,  
Western Australia  
S Stick

Correspondence to:  
Dr S Stick  
email: stephen.stick@  
health.wa.gov.au

#### AIRWAY DEVELOPMENT VERSUS AIRWAY REMODELLING

At any stage of development the consequences of the response to injury by airways must be considered since there is the potential for the normal pattern of development to be modified. The processes involved in the repair of damaged airways are referred to collectively as remodelling. Not a lot is known about whether these processes are similar at different ages or how normal development is affected. However, it seems clear that remodelling can affect a number of important structural and functional elements of the airways including epithelium, smooth muscle, extracellular matrix, and mucus secretion.<sup>3</sup> A number of studies have suggested that remodelling is an important factor in the development and persistence of increased bronchial responsiveness; however, some infants appear to be predisposed to increased bronchial responsiveness prior to any insult.<sup>4,5</sup> Future studies should therefore examine the interactions between inherited and congenital risk factors and postnatal injury that causes airway remodelling.

#### Measuring airway function in infants and young children

Various techniques are available to measure aspects of lung function in infants including measures of forced expiration, lung volume, tidal flow-volume variables, and mechanics (resistance and compliance). The appropriate use and interpretation of these techniques are summarised in a joint statement published in 1993 by the American Thoracic Society and European Respiratory Society.<sup>6</sup> Studies published since 1993 using these techniques have shaped our current understanding of early wheezing conditions and longitudinal studies from soon after birth have shed light upon relations between early lung function and lung function later in childhood. Since the 1993 statement there have also been some important advances, particularly in regard to the assessment of airway function. A more complete and detailed description of the techniques used in infants has recently been published.<sup>7</sup> As well as providing important information about lung function and disease status, some tests of lung function have also been used as end points for bronchial challenge tests to assess airway responsiveness. Although a number of tests have been argued to provide information related to airway calibre in infants, at the present time only forced expiratory flow manoeuvres that achieve flow limitation can be seriously considered as providing any useful direct information about airway function. This situation might change as experience is gained in alternative techniques such as low frequency forced oscillation, a technique that has the potential to separate airway and parenchymal components that determine lung behaviour.<sup>8</sup>

#### FORCED EXPIRATORY FLOW MEASUREMENTS

For the past 20 years considerable advances in our ability to assess airway function have been made, in particular the ability to measure variables during forced expiration that reflect

airway calibre. Early attempts at achieving flow limitation during expiration used external compression of the chest wall<sup>9</sup> or application of a negative pressure to the airway via an endotracheal tube.<sup>10</sup> External compression using an inflatable jacket wrapped around the thorax and abdomen of the infant is now the most widely used method.

$\dot{V}_{\text{maxFRC}}$  is the most commonly measured variable obtained from forced expiratory manoeuvres in infants and has been a useful outcome measure in a number of important longitudinal studies. At end inspiration during tidal breathing a forced expiration is obtained by rapidly inflating the jacket. Flow is measured at a lung volume corresponding to the functional residual capacity of the preceding tidal breath. The jacket pressure is increased during successive trials until there is no further increase in  $\dot{V}_{\text{maxFRC}}$  and flow limitation is therefore assumed to have been reached.<sup>7</sup> The major limitation of this technique is that the volume landmark (FRC) is not fixed, resulting in relatively high variability.<sup>6</sup> More recently forced expiratory techniques from raised volume have been developed that emulate forced expiratory volume (FEV) techniques in cooperative subjects and allow the determination of FEVt variables that are less variable than  $\dot{V}_{\text{maxFRC}}$ .<sup>11,12</sup> The raised volume techniques have not yet been used in any longitudinal studies.

#### Factors in childhood that might influence adult respiratory morbidity

The most important factors that have emerged as childhood predictors of later morbidity are lower respiratory illnesses in early life and airway function including bronchial responsiveness.

#### CHILDHOOD RESPIRATORY ILLNESSES AND RESPIRATORY MORBIDITY IN ADULTS

Burrows *et al*<sup>13</sup> in 1977 suggested two main factors associated with accelerated decline in adult lung function: (1) smoking and (2) respiratory trouble dating from infancy (childhood respiratory trouble; CRT). In another study Barker and Osmond examined death rates from chronic bronchitis and emphysema in England and Wales between 1959 and 1978.<sup>14</sup> They found a strong positive correlation between adult mortality during that period and infant mortality due to bronchitis and pneumonia during 1921–5 in the same locations. Their analyses suggested that early childhood infection had a greater influence than cigarette smoking in determining the geographical distribution of chronic bronchitis. In a separate study Barker *et al* measured lung function and collected questionnaire data from over 5000 adult men.<sup>15</sup> Lower birth weight was associated with worse adult lung function. Bronchitis, pneumonia, or whooping cough in infancy further reduced adult lung function. They speculated that factors that reduced weight gain in utero acted to constrain fetal lung growth. However, in the absence of respiratory function measurements during infancy before any respiratory insults have occurred, these observations are difficult to interpret. In these retrospective

studies early CRT was broadly defined. At the other extreme of life, asthma and chronic airflow limitation are difficult to differentiate, particularly in elderly smokers.<sup>16</sup> One of the main limiting factors with regard to cross sectional studies of this type is the lack of diagnostic precision for defining CRT in childhood and chronic airflow limitation in adults.

In recent studies examining relations between childhood and adult respiratory disease attempts have been made to define CRT more precisely. Gold *et al*<sup>17</sup> followed a cohort of Boston school children aged 4–10 years for up to 13 years. Pneumonia or admission to hospital for respiratory illness occurring prior to the commencement of the study were associated with lower pulmonary function at entry. The same risk factors occurring after entry to the study were associated with subsequently slower increases in lung function, even after adjustment for asthma. However, these authors were unable to determine with any specificity the nature of respiratory illnesses prior to entry into the study. This is an important point to consider if inferences about effects on lung function over time are made based upon cases selected according to the presence of early respiratory disease. There are data to suggest that some infants have abnormal airway development that predisposes to respiratory symptoms with common early childhood respiratory infections. For example, Young *et al* found that infants with a clinical diagnosis of bronchiolitis have lower pre-morbid pulmonary function ( $\dot{V}_{maxFRC}$ ) than matched controls,<sup>18</sup> and a recent study by Castro-Rodriguez *et al* has observed similar reductions in  $\dot{V}_{maxFRC}$  at two months of age in infants who subsequently developed pneumonia.<sup>19</sup> These studies suggest the importance of early airway function as a risk factor for later childhood respiratory disease. The study reported by Castro-Rodriguez and colleagues also raises the possibility, based upon observations later in childhood, that airway reactivity might be an important mechanism of persistent airway obstruction from early infancy, predisposing children to more severe responses to lower respiratory infections and later symptoms of recurrent wheeze. However, bronchial responsiveness was not measured during infancy and the role of bronchial responsiveness in determining respiratory outcomes is currently being examined in cohorts, some studied from birth.

#### EARLY LUNG FUNCTION AND LATER RESPIRATORY MORBIDITY

There have been a number of influential longitudinal studies. Information from early studies that measured lung function starting at school age has been supplemented by data from birth cohorts who are now teenagers.

Longitudinal studies that commenced at school age have examined factors associated with persistence of symptoms beyond childhood and the physiological effects of asthma on lung development. One of the most well known is the study started in Melbourne by Williams and McNicol.<sup>20</sup> Children were selected for the original cohort because of recurrent wheeze

and have been studied at ages 7, 10, 14, 21, 28, and 35 years. At the 10 year old follow up the original cohort was supplemented with a group of more severe asthmatics. The wheezy children were compared with a group of non-wheezy children as controls. Findings from these surveys indicate that the persistence of asthma beyond childhood is associated with onset before the age of three years, more frequent or persistent symptoms, and persistent abnormalities of lung function.<sup>21 22</sup>

Unfortunately, the Melbourne data do not help to distinguish whether airway abnormalities predate early respiratory symptoms and whether the persistent airway abnormalities observed in symptomatic adults are a cause of, or result from, persistent disease.

In a study of 11 497 Sydney schoolchildren, lung function was measured regularly over a 10 year period.<sup>23</sup> Small but persisting changes in lung function were found in those who had wheezed before the age of two years. Subsequent bronchitis had an additional effect on lung function in those children with early respiratory illness. Asthma following enrollment had the greatest effect on lung function and the deficit increased through adolescence. Deficits in lung function attributable to smoking were found in some children by the age of 14 years and were most severe in children with asthma. These data suggest that, whereas early respiratory disease might be associated with decrements in lung function, the onset of asthma, independent of early respiratory disease, is a more significant factor affecting lung function later in life.

Recent reports from Tucson are interesting in the light of the Sydney data. In 1988 Martinez *et al* reported data that suggested that early infantile wheeze was determined in part by airway size or geometry.<sup>24</sup> This hypothesis is supported by case-control studies showing that bronchial reactivity is not a significant feature in wheezy infants.<sup>25</sup> The first report of the Tucson cohort used tidal flow and volume profiles as an indirect measure of airway function, but subsequent studies from the Tucson group have reported outcomes in relation to  $\dot{V}_{maxFRC}$  at two months corrected age.<sup>26 27</sup>

In the 1988 study by Martinez *et al* diminished respiratory function was observed in infants who subsequently developed wheezing lower respiratory illnesses (LRI).<sup>24</sup> They measured the time to peak expiratory flow (TPEF) as a fraction of expiratory time (TE) during tidal breathing before any respiratory illness and observed that male infants in the lowest tercile for TPEF/TE were four times more likely than children in the upper terciles to subsequently develop wheezing LRI. Although not reported by the authors, the probability that low TPEF/TE in girls was associated with subsequent wheeze—that is, an odds ratio greater than 1—was 95%. Overall, infants in the lowest tercile for TPEF/TE were 3.5 times more likely to wheeze.

The same group has reported findings when the cohort was studied six years later.<sup>27</sup> By the age of six years 51.5% had never wheezed, 19.9% had only wheezed before the age of

three years (transient wheezers), 15.0% had only wheezed since the age of three years (late wheezers), and 13.7% wheezed both before and after three years (persistent wheezers). The transient wheezers had diminished airway function ( $\dot{V}_{maxFRC}$ ) both before the age of one year and at the age of six years, were more likely than the other children to have mothers who smoked but not mothers with asthma, and were not atopic. Compared with the children who never wheezed, persistent wheezers were more likely to have mothers with a history of asthma, raised serum IgE levels and normal lung function in the first year of life, and to have raised serum IgE levels and diminished lung function at six years of age. These data indicate that early wheezing is a transient phenomenon in the majority of children and is associated with reduced airway function rather than atopy, but that atopy is a risk factor for persistence of wheezing. In this cohort the most significant factor determining lung function at six years of age was lung function in infancy. These data imply that, whilst the reduction in lung function seen in the early wheezers is not an important factor between three and six years of age, the deficit appears to be persistent and could contribute to adult morbidity if present beyond childhood. This notion is supported by data from the same cohort studied at 11 years of age.<sup>28</sup> The persistent wheezers had the largest decrement in lung function but the transient wheezers still had a lower FEV<sub>1</sub> than infants who had never wheezed and there was no increase following salbutamol. An important conclusion from these data is that the reduction in airway function in the persistent wheezers is acquired since it was not a factor that was significant at two months of age, prior to the onset of symptoms. One of the major risk factors for persistent wheeze in the Tucson population is atopy. In other population studies associations have been observed between atopy and asthma, the severity of which appears to be associated with increased bronchial responsiveness to a number of challenge agents and reduced lung function. One plausible explanation for the patterns of lung function seen in the Tucson study is therefore the development or presence of bronchial reactivity.

#### ROLE OF BRONCHIAL RESPONSIVENESS

The observations from the Tucson population and the apparent high prevalence of wheezing illnesses in children have led to speculation that airway responsiveness might be increased in children compared with adults. Some studies appear to support that argument.<sup>29</sup> However, methodological factors with most challenges that are related to the relatively high dose of challenge agent inhaled by small children compared with older subjects make direct cross sectional comparisons almost impossible to interpret.<sup>30</sup> Although the same dose issues apply to longitudinal studies from infancy, it is possible to determine how bronchial responsiveness tracks within a cohort by rank using non-parametric statistics. Such studies also allow bronchial responsiveness in early infancy to be examined in relation to outcomes such as

the development of respiratory illness and lung function. One such study is in progress in Perth, Western Australia. An early report suggested that bronchial responsiveness to histamine at one month of age was associated with a family history of asthma and maternal smoking.<sup>4</sup> When studied at six years of age the major determinant of lung function (FEV<sub>1</sub>) in this cohort was bronchial responsiveness to histamine at one month.<sup>5</sup>

Although the data from Tucson and Perth suggest that atopy and bronchial responsiveness have important influences on lung function during childhood, the observations in infants two months old and younger also demonstrate that in utero or genetic factors might contribute significantly. There are data from family studies that indicate a high degree of heritability for spirometric indices. However, even these observations might be explained in part by genetic determinants of bronchial responsiveness that appear to be independent of any genetic risk for atopy. Interestingly, an association has been described between a polymorphism for the clara cell protein, CC16, and histamine responsiveness at one month. The same polymorphism has been linked with asthma and reduced serum levels of CC16, an anti-inflammatory protein in the airways. Despite these observations it still seems likely that some factors, whether genetic or related to the in utero environment, affect airway development resulting in airways that are relatively small in diameter or with increased compliance and which are thus susceptible to obstruction.

#### Perinatal factors with long term sequelae

These are best considered in terms of prenatal factors that are more likely to impair airway development and postnatal factors that tend to have an impact on airway growth, as well as alveolisation and the microvasculature.<sup>31</sup> Functional effects such as increased airway responsiveness might result from factors operating prenatally or postnatally that may or may not be associated with deviation from the normal pattern of development.

#### PRENATAL FACTORS

The two major pregnancy related determinants of lung development are fetal growth and duration of gestation. Many secondary factors can impact on pregnancy, affecting either or both of these primary factors. Importantly, there appear to be significant relations between in utero pulmonary development, respiratory symptoms, and lung function in later life.

#### *In utero growth*

In the 1970 British cohort study lower birth weight was associated with lower adult lung function.<sup>15</sup> Similarly, in an Indian cohort, adult lung function appeared to be significantly affected by in utero growth. In another historical British cohort no such relationship between birth weight and adult lung function was observed. However, data obtained from a cohort of 5–11 year old children indicate that lung function is significantly affected by in utero growth whereas symptoms of wheeze are

more related to duration of gestation. One possible explanation for this observation is that the in utero environment is an important determinant of bronchial responsiveness; however, other explanations need consideration. For example, small for dates infants might have lung growth that is appropriate for body weight whereas the normal pattern of airway development is disturbed following preterm birth. This results in relative airway obstruction compared with the airway calibre that would have arisen had the pregnancy gone to term.<sup>32</sup> In this situation, because prematurity is a relatively uncommon event, the effect might not be evident from lung function data because the lung function data are so strongly associated with birth weight. Furthermore, there might be a threshold effect where airway development is less likely to be affected after a certain post-conceptual age. The difficulty here is knowing what is an appropriate control since, with increasing prematurity, there is an increased risk of respiratory morbidity and use of therapeutic interventions that have the capacity to affect the normal pattern of development. An illustration of this difficulty comes from a study reported by Doyle *et al*<sup>33</sup> who found lower FEV<sub>1</sub> in survivors of bronchopulmonary dysplasia (BPD) at eight years of age compared with other very low birth weight infants who did not develop BPD. By using birth weight to define the population, some mature growth retarded infants will be included who are less likely to develop neonatal lung disease and more likely to have lung function at eight years that is appropriate for size than infants of shorter gestational age with similar birth weights. Finally, some factors that have a detrimental effect on fetal growth also appear to have factor-specific effects on lung growth—for example, hypoxia, placental insufficiency, antenatal corticosteroids, and cigarette smoke exposure all cause growth retardation. However, airway growth appears appropriate for size in infants exposed to antenatal hypoxia but is abnormal in infants exposed to cigarette smoke. Animal models suggest that placental insufficiency causes increased cortisol secretion that might theoretically advance lung maturation, but there are concerns that exogenous antenatal steroids might adversely affect alveolar development. In future studies in utero growth must be considered as an independent risk factor for airway and lung growth, but may not be the only causative pathway for factors that have diverse effects on the fetus during in utero development.

#### *Gestational age*

The effects of prematurity alone are difficult to separate from the effects of neonatal respiratory disease because the latter is more likely to develop with increasing prematurity. Despite this, a number of studies point to an independent effect of prematurity on pulmonary function and early respiratory morbidity.

#### *Prematurity*

Adverse respiratory health outcomes, especially wheezing illnesses in the early years of

life, have been reported in infants of very low birth weight.<sup>34–35</sup> Prematurity alone appears to have effects on lung function and therefore, by implication, lung development independent of any adverse effects due to the development of chronic neonatal lung disease (CNLD). Studies have demonstrated long term evidence of relative airway obstruction in preterm infants that is not directly related to the occurrence or severity of early neonatal disease, although CNLD does appear to be associated with greater morbidity and larger deficits in lung function in school age children. Remarkably, very few childhood survivors of CNLD have clinically significant abnormal lung function in late childhood. The presence or acquisition of increased bronchial responsiveness appears to be an important additional determinant of long term respiratory morbidity and lung function.

#### *Neonatal lung disease*

A number of follow up studies have examined lung function in survivors of preterm birth at school age and older. In 1981 Smyth *et al* reported reversible airway obstruction in nine children at eight years who had severe CNLD as infants.<sup>36</sup> Since then, a number of studies have demonstrated fixed<sup>37</sup> and reactive airway obstruction<sup>37–40</sup> in long term survivors. Despite the evidence of airway obstruction from group data, few children with a history of preterm birth and CNLD appear to have severe or at least clinically significant airway obstruction.<sup>33</sup> However, recent studies have indicated that lung function abnormalities, apart from those due to airway obstruction, can have significant functional effects, particularly in relation to exercise.<sup>41</sup> Survivors of CNLD appear to use a greater proportion of ventilatory reserve during exercise<sup>42</sup> than other children born preterm, suggesting that underlying abnormalities are likely to be more severe in the survivors of BPD. Pulmonary immaturity is the major consequence of preterm birth that threatens life in the neonatal period and a number of strategies are used to ameliorate its impact. Antenatal steroids are commonly used to reduce respiratory distress in infants of preterm labour, but there have been concerns expressed about their possible adverse effects including effects on pulmonary maturation. However, airway division is usually complete at the time steroids are administered and most of the physiological and histological data suggest that the major effects are on the alveoli rather than on the airways. Alveolar septation seems to be particularly affected, resulting in smaller numbers of larger alveoli. However, more studies are needed, including long term follow up of infants who receive prenatal and postnatal steroids before it can be confidently concluded that there are no adverse effects on airway growth.

#### *Interactions between preterm birth and asthma*

In a study of infants born at less than 33 weeks gestation, in addition to the effect of CNLD, having one parent with bronchial responsiveness increased the risk of wheeze to 1.7 while having both parents with bronchial responsiveness increased the risk to 17.8.<sup>43</sup> A more recent

report showed that a family history of asthma was associated with CNLD as well as the development of asthma in preterm infants.<sup>44</sup> How these effects are mediated is not known. One intriguing possibility is that there is a genetic predisposition to develop BPD that is also a risk factor for asthma.

#### *In utero and environmental tobacco smoke exposure*

An important preventable factor that seems to be important in relation to early pulmonary function is exposure to the constituents of cigarette smoke. Taylor and Wadsworth observed a direct relation in infants between the level of maternal smoking and the risks of bronchitis and admission to hospital due to LRI.<sup>45</sup> However, the risk was determined by the extent of direct in utero exposure to cigarette smoke rather than postnatal passive exposure. Others have examined the effect of maternal smoking on infant lung function. Hanrahan *et al* measured  $\dot{V}_{\text{maxFRC}}$  at one month using the rapid thoracoabdominal compression technique<sup>46</sup> and found reduced forced expiratory flows in infants of mothers who smoked during pregnancy compared with those infants only exposed passively to cigarette smoke postnatally or whose mothers did not smoke. Stick *et al* observed a dose dependent adverse effect of in utero cigarette smoke exposure on tidal flow patterns ( $t_{\text{PEF/TE}}$ ) measured during the first three days of life before any passive exposure was possible.<sup>47</sup> The effect on respiratory function was independent of effects of cigarette smoke exposure on birth weight. These studies suggest that the respiratory system is affected directly by cigarette constituents during in utero development. Observations in preterm infants seem to indicate that this effect is likely to occur early during fetal development at a time when airway development dominates. Hoo *et al* reported lower values of  $t_{\text{PEF/TE}}$  in preterm infants exposed in utero to cigarette smoke.<sup>48</sup> Because  $t_{\text{PEF/TE}}$  appears to reflect airway calibre and maternal cigarette smoking early in pregnancy can affect  $t_{\text{PEF/TE}}$ , it has been argued that the effect of cigarette exposure is likely to be on airway development. However,  $t_{\text{PEF/TE}}$  can be affected by complex interactions between mechanical and neurological control mechanisms and there are at present only limited data available in humans to support such an argument. Furthermore, since in utero exposure to cigarette smoke can affect the control of breathing, it must be assumed that it is at least possible that the observations with regard to  $t_{\text{PEF/TE}}$  might simply reflect alterations in the control of breathing rather than any mechanical changes in the lung.<sup>49</sup> On the other hand, the observations that resistance is higher<sup>50</sup> and  $\dot{V}_{\text{maxFRC}}$  is lower<sup>46</sup> in infants exposed in utero to cigarette smoke support the contention that airways are smaller in infants of smoking mothers. There are histopathological data that also support this hypothesis. In studies carried out in Melbourne Elliot *et al* described increased inner airway wall thickness<sup>51</sup> and increased smooth muscle in victims of sudden infant death syndrome (SIDS)

whose mothers smoked compared with non-exposed controls.<sup>52</sup>

#### POSTNATAL FACTORS

As already alluded to, the effect of exposures, infections, and other potential factors that could affect airway growth and/or function are difficult to assess without knowledge about airway development prior to any postnatal exposure. Furthermore, a crucial element in the airway response to postnatal insults is the development of the immune system and, in particular, the local responses in the airway to allergens, irritants, and infective agents. Despite these problems with interpretation, a number of factors appear to have important effects on airway function as the lungs develop and grow.

#### *Environmental tobacco smoke*

Although there are many difficulties quantifying the extent to which infants are exposed to environmental tobacco smoke, the data are generally consistent and suggest a dose response between chronic wheezing and environmental tobacco smoke exposure.<sup>53</sup> Objective markers of exposure to environmental tobacco smoke have been used in some studies. For example, Reese *et al* measured urinary cotinine levels in children admitted to hospital and found significantly higher levels in infants with bronchiolitis than those in age matched controls admitted with other diagnoses.<sup>54</sup> These data suggest a causal association between exposure to environmental cigarette smoke and severity of lung disease due to bronchiolitis. However, the known effects of in utero exposure on lung development and the possibility of increased risk for more severe sequelae to infection also have to be considered.

#### *Lower respiratory infections*

Most early childhood lower respiratory infections have a viral aetiology. There are problems interpreting cross sectional studies and retrospective studies that examine the relationships between lower respiratory infection during infancy and outcomes such as lung function and adult respiratory morbidity. The most significant of these is lack of information concerning premorbid lung function—that is, do individuals with lower lung function have a predisposition to more severe lower respiratory infection? The data from the Tucson birth cohort suggest that low premorbid airway function might predispose to pneumonia before the age of three years, and that airway responsiveness to bronchodilator is more prevalent in children aged 11 years who suffered early pneumonia than controls. Whether airway tone is a predisposing factor for pneumonia or a consequence of infection cannot be determined because there are no measures of airway responsiveness prior to the episode of pneumonia. However, data from prospective studies do suggest that viral infections can have significant effects on bronchial responsiveness. Although there are numerous putative mechanisms whereby viral

infection can affect airway function and bronchial responsiveness, except in severe infection, changes appear to be transient. The relationships between viral infections, asthma, and bronchial responsiveness have recently been reviewed.<sup>55</sup> Another important consideration is whether early viral infections reduce the risk of developing asthma and whether, paradoxically, early infection might result in better lung function and reduced bronchial responsiveness. This is a complex issue with a number of conflicting studies, mostly retrospective in nature.<sup>56</sup> However, data from the Tucson longitudinal study do support the notion that infants predisposed to persistent wheeze have different IgE and eosinophil responses to infections from infants who do not continue to wheeze.<sup>57</sup> In addition, a recent study from Germany observed a subgroup of asthmatic patients who had frequent early infections, were less atopic, and had a better prognosis than children with asthma and atopy.<sup>58</sup> In this study bronchial responsiveness did not appear to be significantly associated with early infection in either the atopic or non-atopic asthmatic subjects.

#### Allergic sensitisation

Asthma is characterised by increased bronchial responsiveness and the data from longitudinal studies suggest that long term respiratory morbidity is associated with the development and persistence of increased bronchial responsiveness. Atopy is a major risk factor for asthma and persistence of symptoms<sup>57 58</sup> and therefore there has been much interest in the relationship between allergic sensitisation and bronchial responsiveness. In a recent study symptomatic bronchial responsiveness was associated with skin reactivity independent of blood eosinophil numbers and IgE levels.<sup>59</sup> Furthermore, recent analyses of the Perth birth cohort when aged six years suggest that atopy and bronchial responsiveness are independent risk factors for asthma<sup>60</sup> and each appears to be, at least in part, genetically determined.

#### Summary

In summary, factors that affect airway growth early in development appear to cause physiological effects that can be persistent. Reduced airway function early in life does not necessarily result in persistent symptoms, but the long term effects and impact on the development of chronic airflow limitation in adults are yet to be determined. Generally, long term sequelae seem to be related to the severity of the initial insult, but the development of persistent increased bronchial responsiveness is an independent risk factor for symptoms and abnormal lung function in later life. In addition, there appear to be separate genetic factors that influence atopy, airway development, and bronchial responsiveness.

- 1 Jeffery P. The development of the large and small airways. *Am J Respir Crit Care Med* 1998;157:s174-80.
- 2 Masters J. Epithelial-mesenchymal interaction during lung development: the effect of mesenchymal mass. *Dev Biol* 1976;51:98-108.

- 3 Busse W, Elias J, Sheppard D, et al. Airway remodeling and repair. NHLBI workshop summary. *Am J Respir Crit Care Med* 1999;160:1035-42.
- 4 Young S, Le SP, Geelhoed GC, et al. The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *N Engl J Med* 1991;324:1168-73 (published erratum appears in *N Engl J Med* 1991;325:747).
- 5 Palmer L, Gibson N, Rye P, et al. Airway responsiveness (AR) and lung function at 1 month of age predict airway responsiveness and atopy at 6 years of age. *Eur Respir J* 1995;8(Suppl 19):A1001.
- 6 ATS/ERS. Respiratory mechanics in infants: physiologic evaluation in health and disease. *Am Rev Respir Dis* 1993;147:474-96.
- 7 Stocks J, Sly P, Tepper R, Morgan W, eds. *Infant respiratory function testing*. New York: Wiley-Liss, 1996.
- 8 Hayden MJ, Petak F, Hantos Z, et al. Using low-frequency oscillation to detect bronchodilator responsiveness in infants. *Am J Respir Crit Care Med* 1998;157:574-9.
- 9 Adler S, Wohl M. Flow-volume relations at low lung volumes in healthy infants. *Pediatrics* 1978;61:636.
- 10 Motoyama E, Fort M, Klesh K, et al. Early onset of airway reactivity in premature infants with bronchopulmonary dysplasia. *Am Rev Respir Dis* 1987;136:50-7.
- 11 Turner DJ, Lanteri CJ, LeSouef PN, et al. Improved detection of abnormal respiratory function using forced expiration from raised lung volume in infants with cystic fibrosis. *Eur Respir J* 1994;7:1995-9.
- 12 Turner DJ, Stick SM, LeSouef KL, et al. A new technique to generate and assess forced expiration from raised lung volume in infants. *Am J Respir Crit Care Med* 1995;151:1441-50.
- 13 Burrows B, Knudson R, Lebowitz M. The relationship of childhood respiratory illness to adult obstructive airway disease. *Am Rev Respir Dis* 1977;115:51-60.
- 14 Barker D, Osmond C. Childhood respiratory infection and adult chronic bronchitis in England and Wales. *BMJ* 1986;293:1271-5.
- 15 Barker DJ, Godfrey KM, Fall C, et al. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *BMJ* 1991;303:671-5.
- 16 Buist A, Vollmer W. Prospective investigations in asthma. What have we learned from longitudinal studies about lung growth and senescence in asthma? *Chest* 1987;91(Suppl 6):1195-265.
- 17 Gold D, Tager I, Weiss S, et al. Acute lower respiratory illness in childhood as a predictor of lung function and chronic respiratory symptoms. *Am Rev Respir Dis* 1989;140:877-84.
- 18 Young S, O'Keefe PT, Arnott J, et al. Lung function, airway responsiveness, and respiratory symptoms before and after bronchiolitis. *Arch Dis Child* 1995;72:16-24.
- 19 Castro-Rodriguez J, Holberg C, Wright A, et al. Association of radiologically ascertained pneumonia before age 3 years with asthmatic symptoms and pulmonary function during childhood: a prospective study. *Am J Respir Crit Care Med* 1999;159:1891-7.
- 20 Williams H, McNicol K. Prevalence, natural history, and relationship of wheezy bronchitis and asthma in children. An epidemiological study. *BMJ* 1969;321-5.
- 21 Kelly M, Hudson I, Phelan P, et al. Childhood asthma in adult life: a further study at 28 years of age. *BMJ* 1987;294:1059-62.
- 22 Oswald H, Phelan PD, Lanigan A, et al. Childhood asthma and lung function in mid-adult life. *Pediatr Pulmonol* 1997;23:14-20.
- 23 Anonymous. The development of lung function in Sydney children: effects of respiratory illness and smoking. A 10 year study. *Eur J Respir Dis* 1984;132:1-137.
- 24 Martinez F, Morgan W, Wright A, et al. GHMA Pediatricians. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med* 1988;319:1112-7.
- 25 Stick S, Arnott J, Turner D, et al. Bronchial responsiveness and lung function in recurrently wheezy infants. *Am Rev Respir Dis* 1991;144:1012-5.
- 26 Martinez FD, Morgan WJ, Wright AL, et al. Initial airway function is a risk factor for recurrent wheezing respiratory illnesses during the first three years of life. Group Health Medical Associates. *Am Rev Respir Dis* 1991;143:312-6.
- 27 Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133-8.
- 28 Stern D, Morgan W, Taussig L, et al. Lung function at age 11 in relation to early wheezing. *Am J Respir Crit Care Med* 1999;155(Suppl):A44.
- 29 Hopp RJ, Bewtra AK, Nair NM, et al. The effect of age on methacholine response. *J Clin Allergy* 1985;76:609-13.
- 30 Stick SM, Turnbull S, Chua HL, et al. Bronchial responsiveness to histamine in infants and older children (see comments). *Am Rev Respir Dis* 1990;142:1143-6.
- 31 Burri PH, Hislop AA. Structural considerations. Early intervention in childhood asthma. *Eur Respir J Suppl* 1998;27:59-65.
- 32 Hislop AA, Haworth SG. Airway size and structure in the normal fetal and infant lung and the effect of premature delivery and artificial ventilation. *Am Rev Respir Dis* 1989;140:1717-26.
- 33 Doyle LW, Ford GW, Olinsky A, et al. Bronchopulmonary dysplasia and very low birthweight: lung function at 11 years of age. *J Paediatr Child Health* 1996;32:339-43.

- 34 Kitchen WH, Olinsky A, Doyle LW, *et al.* Respiratory health and lung function in 8-year-old children of very low birth weight: a cohort study. *Pediatrics* 1992;**89**:1151-8.
- 35 McLeod A, Ross P, Mitchell S, *et al.* Respiratory health in a total very low birthweight cohort and their classroom controls. *Arch Dis Child* 1996;**74**:188-94.
- 36 Smyth JA, Tabachnik E, Duncan WJ, *et al.* Pulmonary function and bronchial hyperreactivity in long-term survivors of bronchopulmonary dysplasia. *Pediatrics* 1981;**68**:336-40.
- 37 Northway WJ, Moss RB, Carlisle KB, *et al.* Late pulmonary sequelae of bronchopulmonary dysplasia (see comments). *N Engl J Med* 1990;**323**:1793-9.
- 38 Duiverman EJ, Den BJ, Roorda RJ, *et al.* Lung function and bronchial responsiveness measured by forced oscillometry after bronchopulmonary dysplasia. *Arch Dis Child* 1988;**63**(Special No):727-32.
- 39 Hakulinen AL, Heinonen K, Lansimies E, *et al.* Pulmonary function and respiratory morbidity in school-age children born prematurely and ventilated for neonatal respiratory insufficiency. *Pediatr Pulmonol* 1990;**8**:226-32.
- 40 Gross SJ, Iannuzzi DM, Kveselis DA, *et al.* Effect of preterm birth on pulmonary function at school age: a prospective controlled study (see comments). *J Pediatr* 1998;**133**:188-92.
- 41 Santuz P, Baraldi E, Zaramella P, *et al.* Factors limiting exercise performance in long-term survivors of bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 1995;**152**:1284-9.
- 42 Jacob SV, Lands LC, Coates AL, *et al.* Exercise ability in survivors of severe bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 1997;**155**:1925-9.
- 43 Elder D, Hagan R, Evans S, *et al.* Recurrent wheezing in very preterm infants. *Arch Dis Child* 1996;**74**:F165-171.
- 44 Evans M, Palta M, Sadek M, *et al.* Associations between family history of asthma, bronchopulmonary dysplasia, and childhood asthma in very low birth weight children. *Am J Epidemiol* 1998;**148**:460-6.
- 45 Taylor B, Wadsworth J. Maternal smoking during pregnancy and lower respiratory tract illness in early life. *Arch Dis Child* 1987;**62**:786-91.
- 46 Hanrahan JP, Tager IB, Segal MR, *et al.* The effect of maternal smoking during pregnancy on early infant lung function. *Am Rev Respir Dis* 1992;**145**:1129-35.
- 47 Stick S, Burton P, Gurrin L, *et al.* Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. *Lancet* 1996;**348**:1060-4.
- 48 Hoo AF, Henschen M, Dezateux C, *et al.* Respiratory function among preterm infants whose mothers smoked during pregnancy (see comments). *Am J Respir Crit Care Med* 1998;**158**:700-5.
- 49 Ueda Y, Stick SM, Hall G, *et al.* Control of breathing in infants born to smoking mothers. *J Pediatr* 1999;**135**:226-32.
- 50 Brown RW, Hanrahan JP, Castile RG, *et al.* Effect of maternal smoking during pregnancy on passive respiratory mechanics in early infancy. *Pediatr Pulmonol* 1995;**19**:23-8.
- 51 Elliot J, Vullermin P, Robinson P. Maternal cigarette smoking is associated with increased inner airway wall thickness in children who die from sudden infant death syndrome. *Am J Respir Crit Care Med* 1998;**158**:802-6.
- 52 Elliot J, Vullermin P, Carroll N, *et al.* Increased airway smooth muscle in sudden infant death syndrome. *Am J Respir Crit Care Med* 1999;**160**:313-6.
- 53 National Health and Medical Research Council. *The health effects of passive smoking*. A scientific information paper. Commonwealth Department of Health and Family Services, 1997.
- 54 Reese AC, James IR, Landau LI, *et al.* Relationship between urinary cotinine level and diagnosis in children admitted to hospital. *Am Rev Respir Dis* 1992;**146**:66-70.
- 55 Folkerts G, Busse W, Nijkamp F, *et al.* Virus-induced airway hyperresponsiveness and asthma. *Am J Respir Crit Care Med* 1998;**157**:1708-20.
- 56 de Jongste J, Brunekreef B. On eggs and chicken. *Eur Respir J* 1999;**14**:2-3.
- 57 Martinez FD, Stern DA, Wright AL, *et al.* Differential immune responses to acute lower respiratory illness in early life and subsequent development of persistent wheezing and asthma. *J Allergy Clin Immunol* 1998;**102**:915-20.
- 58 von Mutius E, Illi S, Hirsch T, *et al.* Frequency of infections and risk of asthma, atopy and airway hyperresponsiveness in children. *Eur Respir J* 1999;**14**:4-11.
- 59 Jansen D, Rijcken B, Schouten J, *et al.* The relationship of skin test positivity, high serum total IgE levels, and peripheral blood eosinophilia to symptomatic and asymptomatic airway hyperresponsiveness. *Am J Respir Crit Care Med* 1999;**159**:924-31.
- 60 Palmer L, Rye PJ, Gibson NA, *et al.* Airway responsiveness (AR) and lung function at 1 month of age predict airway responsiveness, lung function, asthma and atopy at 6 years of age. *Am J Respir Crit Care Med* 1999;**159**(Suppl):A44.