Lung growth: implications for the development of disease

The high prevalence of respiratory illness in the very young and the very old is a clinical challenge to paediatricians and chest physicians while presenting a number of questions to epidemiologists and respiratory physiologists. This remarkable similarity in the impact of respiratory illness in the young and the elderly has been explained, in the first instance, by immaturity of the lung and respiratory system, and, in the second, by the effects of ageing and environmental damage on the lung.

Growth and maturation
In the young it is the immaturity of the chest wall and the resultant poor support to the underlying lung that is a major factor, while in the elderly the loss of lung recoil with ageing results in an increased tendency to airway closure and symptomatic airflow obstruction. Airway closure occurs close to or within the tidal volume range in infants and young children and results in reversal of the “adult” distribution of ventilation with a decrease in ventilation towards the lung bases. This reversal of ventilation distribution is associated with only a modest reduction in perfusion gradient, which explains the larger fixed intrapulmonary shunt found in infants and their relatively low arterial oxygen tension.

Lung function, as assessed by spirometric testing and arterial oxygenation, rises to its peak in early adult life with a subsequent decline with age. This rise and fall in lung function with growth and ageing not only explains, in large measure, the observed fall in respiratory morbidity during growth and subsequent rise during ageing, but also points to important developmental and environmental influences on lifelong respiratory health. For example, smoking accelerates the natural decline in lung function with age and is further accentuated by the presence of a history of “chronic respiratory trouble” in childhood.

Not only is wheezing illness remarkably common in early childhood, but the associated chronic airway inflammation may have long term consequences in itself. As with the suggested link between significant childhood respiratory illness and chronic respiratory illness in adulthood, this recent observation for wheezing illness and asthma may point to a common intrauterine origin.

FETAL INFLUENCES ON STRUCTURE AND FUNCTION
Many adverse intrauterine influences, for example, congenital diaphragmatic hernia, renal agenesis, and oligohydramnios are known to have devastating effects on lung growth and development. The earlier the insult the more profound the effects. This is not surprising when the ordered sequence of lung development and maturation in utero is considered. Airway development is known to be complete by 16 weeks of gestational age and alveolar development, which begins at around 20 weeks of gestational age, is largely complete by the age of 2–3 years. Early studies of lung growth and development suggested a 10-fold increase in the number of alveoli from birth to adulthood with the achievement of the full adult number by 8 years of age. It is now accepted that the major part of structural lung growth is complete by the age of 2–3 years and that the number of alveoli is only likely to double from birth to adulthood.

In an elegant series of experiments in laboratory animals it has been shown that adequate amounts of lung liquid and “respirable” amounts of amniotic fluid are required for normal lung development. In human infants fetal breathing movements have been shown to be a necessary stimulus for normal lung growth and development. Surviving infants with congenital diaphragmatic hernia and in those with reduced fetal breathing movements due to spinal muscular atrophy physiological evidence for a decrease in airway development has also been found. Follow up studies have also shown the extent of pulmonary perfusion abnormalities after successful repair of diaphragmatic hernia, despite a normal radiological appearance and minimal lung function abnormalities. The more significant effects of intrauterine disturbance over and above the well known lung restriction associated with scoliosis have also been shown by the greater reduction of vital capacity in children with intrauterine onset scoliosis than in those with a postnatal onset. A growing body of evidence now points to the conclusion that the main determinants for growth and development of the lung are decided in utero, and that the degree and nature of the disturbance will depend on the timing of the adverse influence. The earlier the disturbance the more likely that airway branching will be disturbed, and the later the disturbance the more likely that airway development will be normal and alveolar development impaired. As alveoli develop at the periphery of the conducting airways it is likely that late disturbances can be compensated for while early disturbances cannot, since a significantly reduced number of airways will limit the subsequent numbers of alveoli.

The effects of interference with normal intrauterine lung growth can be dramatic and are easy to understand with an elementary knowledge of embryogenesis and early lung development. However, recent studies have pointed to more subtle but important early influences on subsequent respiratory health. Careful long term follow up studies of adult men born in the Edwardian era in Hertfordshire have shown a clear linkage between birth weight (a crude index of the quality of intrauterine nutrition) and death from chronic obstructive lung disease. Similar linkages between growth in the first year of life and subsequent development of a number of common degenerative diseases in old age have also been shown. These findings are obviously relevant to a much larger population than the rare anomalies described above, and will require further studies for confirmation and more precise identification of the relations between fetal nutrition and lung growth and development.

Early environment and sex differences
A causal link between the high prevalence of respiratory illness in the young and old has been suggested, but this hypothesis is falling out of favour as more and more evidence points to an earlier common origin of chronic respiratory symptoms that are subsequently expressed in the early and later years of life. Studies in early infancy have shown that functional abnormalities suggestive of airway obstruction are evident soon after birth and predate the subsequent development of respiratory symptoms. The increased risk of male infants and elderly men-
veloping chronic respiratory symptoms is well known. This sex difference is marked in early childhood, disappearing in one survey soon after puberty, while increasing during puberty in another study with a reversal of the male dominance in early adulthood. During the prepubertal years boys appear to have a disadvantage in terms of airway development, with lower flow rates at all comparable lung volumes than those found in girls. This difference disappears in late puberty when all lung function measures in boys accelerate to adult values, establishing the adult male to female functional advantage.

**EFFECTS OF SMOKING**

The discussion so far has focused on the natural evolution of lung growth and development and its modification by a number of sporadic and largely unavoidable influences. However, the major and avoidable detrimental influence on the respiratory health of the whole population is active and passive smoking. Although it has been noted that postnatal passive smoking has a significant influence on respiratory morbidity, as judged by hospital admissions during the first few years of life, and reported lower respiratory infections, most of these effects can be attributed to maternal smoking with a less consistent effect for paternal smoking. Studies which have examined infants soon after birth, when the effects of postnatal passive smoke exposure would be expected to be small, have reported diminished lung function and increased airway response to histamine. In the fetal rat maternal smoking significantly reduces lung weight/body weight ratios, total lung DNA and alveolar number, and the amount of parenchymal elastic tissue compared with controls.

Other studies have shown reductions in elastin and decreased parenchymal tissue with a slower rate of secondary septal growth. While the prevalence of smoking is decreasing in the population as a whole, it appears that an increasing number of girls and young women are taking up the habit with the result that the risk of intratracheal exposure to subsequent generations is increasing. Maternal smoking has also been associated with elevated levels of IgE in cord blood and with a higher incidence of subsequent atopic symptoms in infants which, if expressed as chronic wheezy illness, may adversely influence subsequent lung development.

**Conclusion**

Any disturbance to the ordered sequence of lung growth and development before birth can significantly reduce the ability of the lung to reach full structural and functional maturity. Although such effects are easily understood for conditions such as congenital diaphragmatic hernia, there is an ever increasing body of evidence for more subtle but important consequences for the population as a whole. The future respiratory health of the whole population may be determined, to a significant extent, by adverse influences on lung growth and maturation in utero and in very early childhood.

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