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Early lung growth and chronic airflow obstruction

Over the last 30 years the hypothesis that chronic airflow obstruction has its origins in early life has stimulated much interest.[1–5] Studies have generally focused on lower respiratory tract infection and other influences which act in infancy and early childhood.[6–9] Recent findings, however, suggest that the foundations of chronic airflow obstruction may be laid in utero. A study in Hertfordshire, UK, of men over 60 years of age showed that those who weighed less at birth had a lower FEV_1, after adjusting for current height. It was suggested that this association reflected suboptimal development of the lungs as a result of fetal undernutrition.[10]

Animal experiments have shown that the structure and physiology of organs and tissues may be permanently altered by undernutrition or other influences which affect development during sensitive periods in early life. This phenomenon is known as "programming." One of the best examples is the lifelong effect on sexual physiology of transient early exposure to sex hormones.[11] Tissues are sensitive to programming during periods of rapid cell replication in early development. This occurs at different times in different tissues. The consequences of undernutrition during fetal and early postnatal life therefore depend upon its timing as well as its nature.[12,13] Humans complete relatively more growth in utero than many other mammals, and hence are more vulnerable to prenatal undernutrition.[14]

This discussion will focus on the long term consequences of altered lung structure during early growth as a result of influences such as undernutrition in fetal life. Relations between the early life environment and immunological and physiological pathways involving, for example, IgE and bronchial hyperreactivity, may also be important in the development of chronic airflow obstruction, but will not be discussed here.

Lung growth in animals

In experimental animals, including the rat and guinea pig, the fetal environment can be manipulated in different ways to cause pulmonary hypoplasia, as defined by a reduction in the lung weight/body weight ratio and in total lung DNA. Manipulations include maternal calorie deprivation,[15–17] hypoxia,[18] and exposure to cigarette smoke.[19,20] In the rat interference with lung growth may permanently alter alveolar morphology and parenchymal recoil. Deprivation of calories, protein, or copper leads to a reduction in elastin and collagen in the lung, enlargement of air spaces, and a reduction in elastic recoil in a way that resembles human emphysema.[21–25] Similar changes can be induced by administration of β-aminopropionitrile which, like copper deficiency, inhibits the enzyme lysyl oxidase. This enzyme is essential for normal crosslinking of collagen and elastin and hence normal formation of alveoli.[26]

Animal studies have shown that the timing of adverse influences determines whether effects on lung growth are permanent. In guinea pigs, prenatal starvation alters alveolar morphology permanently, but the changes induced by postnatal starvation are reversible.[27,28] In rats, alveolar changes are more likely to be permanent if protein or calorie restriction occurs in early postnatal life during a critical period of elastin synthesis,[23] but changes induced after weaning may be reversible.[22,28] There are major differences between these two species in the maturity of the lung at birth.[28] Alveolar development is largely completed prenatally in the guinea pig.[29] In the rat, however, alveolar growth is mainly postnatal,[30] with a critical period of rapid cell replication between days 4 and 13.[31]

Lung growth in humans

In humans, airway division down to the level of the terminal bronchioles is completed by the 16th week of gestation.[32] Wigglesworth and Desai[33] have shown that this is followed by a period of rapid lung growth; between 17 and 20 weeks the lung cell population doubles and at 20 weeks the lungs are twice as large relative to body weight as at term. Alveoli can be detected as early as 30 weeks in the fetus.[34,35] Initial studies of small numbers of infants suggested that about 10% of the adult number of alveoli are present at birth.[36,37] More recent studies of larger numbers of infants have suggested that, although there is a wide range in the number of alveoli present at birth, the average number is much higher than previously thought, and possibly as high as 50% of the adult number.[34,38] Postnatally, multiplication slows and is nearly completed by two years of age,[38] but during this period there is a rapid increase in alveolar size and complexity. Of the adult alveolar surface area, 95% is formed postnatally.[34]

How commonly is lung growth impaired in utero? At postmortem examination lung hypoplasia is defined using threshold values for a reduction in the ratio of lung to body weight, the total lung DNA content, or the radial alveolar count, based on series of "normal" values.[33,39] In one survey hypoplasia defined in this way was found in 14% of perinatal postmortem examinations and 27% of cases of late spontaneous abortion, usually in association with other anomalies such as renal agenesis, diaphragmatic hernia, and oligohydramnios.[40]

What are the functional consequences of lung hypoplasia? Airflow obstruction may develop in children who survive repair of a congenital diaphragmatic hernia.[41] Helms has recently drawn attention to the increasing evidence for long term consequences of less severe growth retardation in utero.[42] Epidemiological studies have examined the association between birth weight, as a marker of prenatal lung growth, and lung function in children and adults. Within a group of children who weighed less than 2000 g at birth, lower birth weight was associated with a lower FEV_1, adjusted for height, at the age of 7 years.[43] Most of the children in that study were premature at birth. A larger study of children aged 5–11 years recently showed that the association between birth weight and FEV_1, adjusted for age and height, was independent of gestational age.[44] Among men born 60–70 years ago in Hertfordshire, lower birth weight was associated with a reduced FEV_1, adjusted for age and height, with mean FEV_1 falling by 60 ml with every pound decrease in birth weight. This relation was independent of social class and smoking habits. Furthermore, death rates from chronic airflow obstruction rose with decreasing birth weight and weight at one year of age. There was an approximately fourfold difference in the standardised mortality ratio for chronic airflow obstruction between men with the lowest and the highest weights at birth and one year.[10]

The graded nature of the findings in the Hertfordshire

study across the entire distribution of early weights suggests that even slight impairment of lung growth may impair lung function in later life. What are likely to be the most important influences affecting fetal lung growth? Expiratory flows are reduced in infants born to mothers who smoke during pregnancy,[45] but the relation between birth weight and FEV_1 in children persists after adjustment for maternal smoking.[44] Similarly, the findings in the Hertfordshire study are unlikely to be explained by maternal smoking as the men were born at a time when few women smoked. Fetal undernutrition may therefore be a major determinant of impaired lung growth in utero, and the main explanation for the association found between birth weight and FEV_1 in children and adults.

Control of lung growth

Physical influences appear to be important in the regulation of lung growth.[46] One requirement for normal growth is adequate intrathoracic space. When abdominal contents encroach upon this space through an experimental diaphragmatic hernia, it leads to pulmonary hypoplasia.[47] In humans, congenital diaphragmatic hernia is associated with a reduction in the number of airway branches indicating retardation of lung growth which begins in early gestation.[48,49] Intrathoracic space can also be restricted by abnormal chest wall growth. This can occur as a result of chest compression in association with oligohydramnios[50,51] or as a result of skeletal deformity as in kyphoscoliosis.[52,53] Thurlbeck has suggested that the growing chest wall provides a "stretch" stimulus for growth of the underlying lung.[51]

Distensive forces from within the lung also appear to be important and are provided by fetal breathing movement and lung fluid. Fetal breathing depends on normal diaphragmatic function. If this is abolished by spinal cord or phrenic nerve section, lung growth is impaired.[54,55] Pulmonary hypoplasia has been linked to an absence of fetal breathing in humans.[56]

In animals reducing the volume of amniotic fluid[50,57,58] or draining lung fluid from the airways[59,60] leads to pulmonary hypoplasia. Similarly, in humans oligohydramnios is associated with lung hypoplasia and narrow airways.[40,61] The earlier the onset of the reduction in amniotic fluid volume, the more severe the degree of lung hypoplasia.[62,63] Hence, an adequate amount of lung fluid within the airways appears to be necessary for optimal airway growth. A recent study showed that growth factors are involved in human airway growth[64] and these may be transported by lung fluid.[40]

Hypoplastic lungs may also be immature[51] and physical influences such as fetal breathing[55] and amniotic fluid volume[61] may be important in lung maturation. However, hormones appear to play the major part.[65] The most studied aspect of maturity is type 2 cell surfactant production.[51] Surfactant production is stimulated by glucocorticoids and thyroid hormone and inhibited by testosterone. Hence, male human fetuses lag behind females by 1–2 weeks with respect to lung maturation and are more at risk of respiratory distress syndrome.[65]

Disproportionate lung growth

We know from the animal studies by McCance and Widdowson[66] that the timing of undernutrition determines the pattern of growth retardation. Early undernutrition produces small but normally proportioned animals. Later undernutrition leads to selective organ damage and, as a result, lung growth is diminished more than somatic growth. Babies who have experienced undernutrition in later gestation therefore have small lungs for their body size. Failure of airway growth to catch up with somatic growth would lead to airways which were small for adult height. This pattern of disproportionate growth could explain the association between birth weight and height adjusted FEV_1 found in children and adults.[10,44]

Green proposed that disproportionate or "dysanaptic" growth may occur between the airways and parenchyma and that this may explain the substantial variability in maximum expiratory flows between individuals.[67]

Certain environmental influences may impair airway growth or enhance alveolar growth, depending on their nature and timing, and this could lead to airflow obstruction as indicated by a reduction in FEV_1/FVC. For example, in animals alveolar growth may be stimulated by hypoxia leading to an increase in vital capacity; this also appears to occur in humans born at altitude.[68] Mid gestation is likely to be a particularly vulnerable time for airway growth in humans. Although there are no morphological data, the doubling in lung DNA between 17 and 20 weeks,[33] which occurs before the first alveoli are apparent,[35] suggests that airway growth is rapid at this time. Undernutrition and hypoxia in mid and late gestation may therefore lead to a disproportionate pattern of lung growth resulting in airways which are narrow in relation to parenchymal size. Subsequent failure of airway growth to catch up with respect to parenchymal growth in childhood would result in a lower FEV_1/FVC ratio as an adult.

What is the evidence to suggest that small airways at birth remain small through to adulthood? There are no anatomical data on airway growth in humans but airway size may be inferred from physiological measures of flow.[69,70] Longitudinal studies of lung function suggest that "tracking" of airway growth, without catch-up, does occur through childhood.[71] Furthermore, the trajectory of growth appears to be determined by one year of age.[72]

Lower respiratory tract infection, lung growth, and chronic airflow obstruction

A geographical study found that infant mortality from bronchitis and pneumonia 50 years ago was strongly correlated with current adult mortality from chronic airflow obstruction. This finding was consistent with the hypothesis that lower respiratory tract infection in infancy may be important in the aetiology of chronic airflow obstruction.[6] Studies which have addressed the hypothesis in individuals have been difficult to interpret. A major limitation is that subjects have not been followed from infancy to an age when clinical chronic airflow obstruction develops,[3] and adult recall of childhood illness is likely to be inaccurate and biased.[73] Nevertheless, retrospective follow up studies of infants with bronchiolitis[7,8] and a prospective study of a national sample of men and women in the UK[9] have found an association between lower respiratory tract infection in the first few years of life and a reduction in subsequent lung function.

Two recent studies have provided further evidence for a link between symptomatic lower respiratory tract infection in early childhood and chronic airflow obstruction in late adult life. In these studies information about symptomatic lower respiratory tract infection in early childhood, recorded at the time, was related to the lung function of men aged 59–74 years living in Hertfordshire and Derbyshire. The Hertfordshire study showed that bronchitis and pneumonia in infancy, but not in later childhood, was associated with a lower mean FEV_1, adjusted for age and height, in men aged 59–67 years.[10] In the Derbyshire study pneumonia under two years of age was associated with a large reduction in mean FEV_1, adjusted for age and height,

in men aged 67–74 years. The deficit in FEV_1 of 0·65 l was approximately twice the reduction associated with lifelong smoking.[74] In both studies the findings were independent of smoking and social class.

The findings in the Hertfordshire and Derbyshire studies are consistent with a causal link between lower respiratory tract infection in early childhood and chronic airflow obstruction in adult life. Taussig has proposed an alternative explanation, namely that lower respiratory tract infection plays no part in aetiology but merely identifies individuals in whom airway size is reduced in early life and who are therefore more likely to exhibit clinical symptoms if infection occurs.[75] Thus symptomatic lower respiratory tract infection may simply identify the individual with small airways who is more prone to continuing problems throughout life. Prospective studies in which lung function has been measured soon after birth[76] may help to disentangle the relations between airway growth in utero, lower respiratory tract infection in infancy, and lung function in adult life. It may be the case that respiratory viruses are only capable of causing permanent structural damage if there is pre-existing impairment of local lung defences or systemic immunity, or if the infection is severe.[77]

Sex differences in early lung growth

In recent years it has been recognised that there are differences in the pattern of early lung growth between boys and girls. Airway growth tends to lag behind parenchymal growth in boys in early life.[70] Boys have a larger lung volume than girls of a similar age and stature,[38] but girls appear to have shorter wider airways for their lung volume.[78] In the Hertfordshire study the associations between birth weight and FEV_1 and between weight at one year and chronic airflow obstruction mortality found in men were weaker in women (unpublished). Differences in early growth patterns may explain this.

Similarly, the associations between lower respiratory tract infection in early childhood and FEV_1 in men were weaker in women in Hertfordshire (unpublished) and in Derbyshire.[74] This is consistent with a study of children in which pneumonia in early childhood was related to impaired lung function in boys but not in girls.[79] It is recognised that boys suffer more severe lower respiratory tract infection than girls in infancy and are more likely to be hospitalised with bronchiolitis.[80,81] This has been partly attributed to the smaller airway size in boys in early life.[69]

Conclusions and future agenda

In the past, discussion of the natural history of chronic airflow obstruction has tended to focus on the rate of decline of adult lung function.[82] The Hertfordshire findings, however, show that clinical chronic airflow obstruction may also develop through impaired lung growth in early life.[10] Influences which determine the rate of functional decline, of which smoking is the most important, add to the effects of poor early growth. A moderate smoker who failed to attain maximal lung function potential as a young adult may develop chronic airflow obstruction at the same age as a heavy smoker who achieved maximal lung growth.[3] Green proposed that the susceptibility to smoking damage may be determined by the pattern of lung growth and structure.[67] The Hertfordshire findings suggest that the effects of poor growth and smoking on lung function are additive and not synergistic, although measures of early weight may be poor indicators of lung growth. To test this more rigorously it will be necessary to relate early growth to the longitudinal rate of decline in FEV_1 in smokers.

There is clear evidence from animals that undernutrition during critical periods of lung growth has permanent effects on lung structure. This may be the most likely explanation for the association between poor growth in utero and in infancy and impaired adult lung function,[10] but at present there are no data on undernutrition and lung growth in humans.[28] It would be of interest to investigate this in developing countries where severe restriction of calories and protein in early life is common.

Could undernutrition affect different pulmonary structures depending on its nature and timing, and hence lead to different clinical patterns of chronic airflow obstruction? We have little insight into why some subjects with chronic airflow obstruction are "pink puffers" and others are "blue bloaters." Previous thinking about the pathogenesis of emphysema in humans has been dominated by a destructive model involving protease–antiprotease balance,[83] but it has been suggested that a "developmental" model of emphysema, as produced in animals, may be relevant in humans.[25] If so, it may be useful in future epidemiological studies to go beyond measurement of FEV_1 and to subclassify subjects with chronic airflow obstruction who have emphysema.

It is 20 years since Green proposed that the pattern of fetal lung growth may influence the development of chronic airflow obstruction.[67] Recent epidemiological findings support this and indicate the importance of learning more about early lung growth.

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