In humans, the lung develops during prenatal life and infancy, after which it increases in size but not complexity. Exposure to sub-optimal environmental conditions during these early life stages can alter lung development, leading to reduced lung function and an increased risk of respiratory illness later in life. Environmental factors prevailing during early life that have been linked to long-term changes in lung structure, lung function and respiratory health include undernutrition, preterm birth, reduced intrathoracic space, respiratory infections, maternal tobacco smoking and exposure to allergens. In this chapter, we briefly review the impact of some of the major factors.

**Fetal Growth and Lung Development**

Intrauterine growth restriction (IUGR) affects 8–10% of all births. A major cause is reduced oxygen or nutrient supply to the fetus resulting from maternal vascular diseases, placental pathology, maternal undernutrition or drug use. IUGR is an established risk factor for respiratory complications in both term and preterm neonates [1]. These neonatal problems are not likely to be a result of surfactant deficiency [2, 3], but are more likely a result of delayed clearance of lung liquid or structural immaturity of lung tissue. IUGR has also been associated with reduced lung function in infants [4], children [5], and adults [6], indicating that it can program the lung for altered function throughout life.

Experimental studies have shown that IUGR alters the development of lung parenchyma and airways, and that these effects can persist to maturity. Such studies show that the degree and type of nutrient restriction, as well as its gestational timing, affect the final structure of the lungs. In sheep, the effects of IUGR on lung structure have been studied at 3 stages of life: near-term fetuses, 8-week-old lambs and young adults.
At 8 weeks after birth, IUGR animals had fewer, larger alveoli, with thicker septa and blood-gas barriers [9], resulting in impaired lung function [3]. The reduced number of alveoli and thicker blood-gas barriers were still evident in adult IUGR sheep [8]; fenestrations in the alveolar walls of the adult IUGR sheep suggest accelerated aging of the lungs. These studies show that adequate nutrition during early life is necessary for normal alveolar development and that the deleterious effects of impaired fetal nutrition can persist into adulthood.

IUGR can also affect the conducting airways. In fetal sheep, IUGR led to thinner airway walls and fewer submucosal glands [7]. In adult sheep exposed to IUGR as fetuses, the structure of the airway walls was not different to that in adult control sheep; however, the number of alveolar attachments to bronchioles (per mm of basement membrane) in airways whose circumference ranged from 500–2,000 μm was significantly reduced by about 10% (fig. 1). This reduction in bronchiolar tethering in adults exposed to IUGR, likely a result of a reduced number of alveoli [10], could contribute to the reduced lung function (i.e. reduced FEV1) reported in adults born with a low birthweight [6].

There are likely to be a number of factors underlying the effects of IUGR on lung development, including fetal hypoxia, reduced nutrient availability and endocrine factors such as elevated plasma levels of glucocorticoids. Fetal lung development is also affected by the physical environment, notably the degree of expansion of the fetal lung and fetal breathing movements [11]. IUGR is associated with diminished fetal breathing, which could contribute to impaired fetal lung development.
Postnatal Nutrition, Growth and Lung Development

After birth, the lung continues to mature both structurally and functionally, with the development of new alveoli continuing for 1.5–3 years after birth. Nutrition during this early postnatal period is likely to influence lung development. The importance of early nutrition is supported by the finding that size at 1 year is a significant predictor of later deaths from respiratory cause [12]. Lung development in preterm infants may be especially vulnerable to impaired nutrition, which can arise as a result of limited fat deposits, parenteral feeding, poor suckling ability or gut immaturity. As the lungs are still at an early stage of development in preterm infants, undernutrition or a lack of necessary micronutrients, could have detrimental long-term effects on lung antioxidant and defence mechanisms and alveolar formation. Undernutrition may also affect the innate immunity of the lung. Human and animal studies have shown that malnutrition causes impaired macrophage function, mucociliary clearance, and specific B and T cell responses to infection [13]. Such effects could underlie the increased incidence of respiratory infections in undernourished infants and children.

Animal studies have shown that early postnatal undernutrition can exert persistent effects of alveolarization. In rats, intermittent postnatal starvation coinciding with saccular and alveolar phases of lung development resulted in enlarged alveoli, thicker septa and reduced elastin deposition [14]. Even in long gestation species such as primates and sheep, it is likely that postnatal nutrition can have persistent effects on lung development; this is because the distal regions of the lung continue to develop after birth. A recent study in mature sheep has shown that slow postnatal growth can result in reduced numbers of alveoli and a reduced surface area for gas exchange in relation to lung or body weight [15]. In this study, postnatal growth rate was significantly correlated with the adult number of alveoli and alveolar surface area (fig. 2).
The conducting airways may also be affected by undernutrition. Children who were undernourished in infancy and early childhood are reported to show impaired lung function [16]. A recent study in adult sheep showed that airway wall structure was altered in sheep that grew more slowly than normal sheep after birth [17]. Such changes could contribute to the long-term programming effects of early postnatal undernutrition on lung function.

The Effects of Maternal Smoking on Lung Development

Numerous studies have shown that maternal smoking during pregnancy results in a persistent deficit in lung function of children, most commonly due to reduced flow in the small airways [18]. It is likely that nicotine, which readily crosses the placenta, plays a major role in causing these effects [10]. Altered alveolarization and abnormalities in airway development have been found after gestational exposure to nicotine [19, 20].

Alveolarization

Exposure to tobacco smoke and nicotine are thought to adversely alter lung parenchymal development largely via effects on pulmonary fibroblasts. Fibroblasts play a critical role in alveolarization, during which there is substantial proliferation of interstitial fibroblasts. The formation of elastin by fibroblasts is thought to be critically involved in alveolarization by providing structural support for new secondary septa. Cigarette smoke inhibits fibroblast proliferation and migration by increasing cell cycle transit time; consequently alveolarization is reduced. Smoke exposure also compromises fibroblast-induced repair responses which may contribute to lung disease [21]. In vivo studies also show that nicotine exposure during development can permanently suppress energy metabolism in the lung [22]. It is therefore plausible that nicotine adversely affects the long-term maintenance of lung structure. The type I alveolar epithelial cell (AEC), for example, depends on glycolysis for the supply of ATP required for the membrane-linked Na⁺-K⁺ ATPase pump [23] that plays a vital role in maintaining cell volume; reducing its activity by inhibition of glycolysis results in cell swelling and the formation of membrane blebs [24]. Inhibition of glycolysis by nicotine will therefore interfere with the ability of type I AECs to maintain cell volume; this is characterized by cell membrane blebbing and rupture (fig. 3). Type II AECs are more numerous in the lungs of nicotine-exposed animals, which is thought to be a response to the loss of type I AECs [25].

It appears that the negative impact of maternal nicotine exposure during gestation and lactation on the growth, development and repair processes of the lungs of offspring is such that lung structure ages more rapidly than in nonexposed animals. One possible reason is the permanent decrease in the glycolytic activity in the lungs.