

# Editorial

## The problem of lung growth

Postnatal growth of the lung has excited controversy over many years. Much of the work on this subject has been conducted on small animals<sup>1-4</sup> and it is not certain that results so obtained can be extrapolated to the human situation. Most attention has been centred on alveolar development.

There are two possible modes of growth. Firstly, the animal could be born with its full complement of units (that is, alveoli), further increase in lung size occurring purely by increase in the volume of existing units. Secondly, there could be formation of new units. In rats there is rapid cell multiplication in early postnatal life, as shown by the sharp increase in the DNA content of the lung.<sup>5-7</sup> Histological examination of the newborn animal indicates that there are numerous air sacculles,<sup>4</sup> which differ from adult alveoli in that they are larger and of a different shape. Measurement of alveolar surface area at varying stages during postnatal growth in the rat has shown three phases.<sup>8</sup> During the first day the lung expands but there is little in the way of cell proliferation. The second phase consists of both cell multiplication, with formation of new alveoli, and expansion of air spaces. A plot of alveolar surface area against lung volume at this stage indicates that the surface area increases at a rate of 1.6 to the power of the lung volume, whereas if the increase in surface area were due entirely to expansion of existing air spaces surface area would be expected to increase at a rate of about two-thirds the power of lung volume. The third phase has been described as that of equilibrated growth, during which enlargement of the lung occurs by expansion of existing units and increase in size of existing cells rather than by formation of new alveoli. An interesting feature of the lung in the newborn rat is that much of the surface of the air spaces is lined by recognisable type II pneumocytes, with relatively few type I cells. It is these type II cells that synthesise DNA and thus become labelled with tritiated thymidine,<sup>9</sup> and they are the progenitors of the type I cells that form the major part of the lining surface of adult alveoli.<sup>10</sup>

Experiments have shown that this normal pattern of lung growth can be influenced by hormonal and physical factors. Administration of growth hormone results in increased lung volume,<sup>11</sup> but there is no evidence that this is due to an increase in number of

alveoli and it is likely to be achieved by increase in the size of existing units. Hypophysectomy results in smaller lungs<sup>12</sup> but whether this is due to decrease in number of alveoli or to smaller individual alveoli is not known. In utero, if the pituitary is removed by decapitation the effect on lung development is to retard cell differentiation.<sup>13</sup> Because of its potential practical importance in man much attention has been devoted to the effect of unilateral pneumonectomy in the growing animal.<sup>14</sup> Thurlbeck and his colleagues were able to show quite clearly that unilateral pneumonectomy in 10-week-old rabbits resulted in cellular multiplication and formation of new alveoli in the contralateral lung.<sup>15</sup> Apparently there is a strong physical stimulus to growth and that lung increases in size to fill the extra space available in the thorax. If after pneumonectomy the vacant pleural cavity is filled with wax compensatory growth of the contralateral lung is greatly restricted.

Knowledge of postnatal growth of human lung is of necessity rather more limited. Although at the beginning of the century preacinar airways were thought to increase in number,<sup>16</sup> recent work has established that they are complete at birth.<sup>17</sup> Growth of these airways takes place in a symmetrical manner in both length and diameter, with a constant relation to the rest of the lung.<sup>18</sup> The lungs increase in volume from about 250 ml at birth to 6000 ml in the adult<sup>19</sup> and the weight increases from 60 to about 750 g. The major portion of this growth affects the acinar or respiratory zone. There is some confusion about terminology. It has been contended that sacculles rather than true alveoli are present at birth, yet the spaces seen and illustrated in studies of neonatal lung are essentially similar to alveoli in the adult though less well formed, being more rounded and less angular. The ratio of tissue to air volume is higher at birth than in the adult. The precise number of alveoli at birth is disputed and figures ranging from  $17 \cdot 10^6$  to  $71 \cdot 10^6$  have been given.<sup>19-21</sup> This wide variation is partly due to experimental error associated with intraobserver variation,<sup>5</sup> partly to the counting method used, and partly to the ill-defined shape of the air spaces, which makes estimation of the shape constant needed for use in the Weibel and Gomez method subject to error.<sup>35</sup> Most authors agree that there is an increase in number of

alveoli in the neonatal period and during early childhood. Yet controversy surrounds the point at which alveolar multiplication ceases. It has been claimed<sup>22, 23</sup> that the adult complement of alveoli is present at 1 year but most workers consider that new alveoli are formed up to at least 8 years.<sup>19, 24, 25</sup> The position is further complicated by some uncertainty about normal alveolar number in adults. Weibel's original figure of  $296 \cdot 10^6$  has been accepted for many years; but Thurlbeck and Angus<sup>20</sup> found considerable variation in the number of alveoli in normal adult human lungs, with a range varying from 200 to 600 million. The significance of these observations, if correct, is emphasised by Thurlbeck,<sup>5</sup> who points out that a child of 8 years with 300 million alveoli may in fact have only half its adult complement and alveolar formation may still be in full swing. Probably alveolar multiplication shows a gradual slowing during childhood but does not cease altogether until somatic growth stops.<sup>26</sup> Perhaps alveolar number is related to body size or more precisely height.<sup>27</sup>

Data on factors influencing lung growth and alveolar development in man are scanty and this makes the papers by Thurlbeck and Cooney in this issue (pp 564–83) all the more welcome. The effect of pneumonectomy on contralateral lung growth is ill understood. In adults there does not appear to be any alveolar multiplication after the operation<sup>28</sup> but one functional study suggests that if pulmonary resection is carried out during childhood or adolescence there may be further alveolar growth.<sup>29</sup> In patients in whom there is deformity of the thoracic cage there is evidence that alveolar formation in childhood is impaired. This is particularly true in children with kyphoscoliosis.<sup>28, 30</sup> Enlargement of the thoracic cavity may also influence lung growth. Those born and growing up at high altitudes have much larger chests than subjects living at or near sea level,<sup>31</sup> and some observations imply that these folk have a larger number of alveoli and a larger alveolar surface area than those who spend their life at or near sea level.<sup>32</sup>

Of more practical importance is the effect of respiratory disease during childhood on lung growth. Children with frequent respiratory infections are known to be more liable to develop chronic obstructive airways disease in adult life.<sup>33</sup> Future research is likely to be directed towards the effects of disease in the neonatal period. The advent of intensive care units for premature infants and use of continuous positive-pressure ventilation has lent some urgency to such investigations. The ultimate effect on lung growth of bronchopulmonary dysplasia in those infants who recover needs thorough investigation. Research has to be directed not only

to morphometry of the lungs but also to the biochemical mechanisms influencing growth and maturation of pulmonary tissue. Wigglesworth and his colleagues<sup>34</sup> have found biochemical abnormalities, particularly in relation to phospholipid and DNA content, in hypoplastic lungs in cases of oligohydramnios. Future work, concentrating more on the quantitative relation of collagen and elastin in lung to alveolar development and growth in infancy and childhood, should help to elucidate the effect of neonatal and paediatric pulmonary disorders on chronic lung disease in adult life.

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