Editorial

Early lung development

The early development of the lung, and indeed of much of the contents of the thorax apart from the heart and aorta, is intimately associated with the development of the foregut. This review therefore inevitably includes oesophageal and other foregut congenital abnormalities. Gerle et al1 introduced the term congenital bronchopulmonary-foregut malformation, which covers the subject matter of this review; and although it is a rather cumbersome term it embodies a unifying concept. Spencer has listed a large number of these developmental errors and summarised the various theories of their embryogenesis.2

In a Tudor Edwards memorial lecture Lynne Reid talked of the laws of lung development.1 “The bronchial tree is developed by the 16th week of intrauterine life” was presented as the first law; the other two are “The alveoli develop after birth” and “The preacinar vessels follow the development of the airways, the intra-acinar that of the alveoli”. The crucial period between the third and the 16th weeks of fetal development will be considered here.

During the third week there is contiguity between the ectoderm and the endoderm and the formation of a transient neurenteric canal.4 Failure to obliterate this structure completely results in a range of posterior enteric cysts with or without spinal malformations and with or without neural deformities.5 As this group of congenital abnormalities arises before there is any development of the primitive respiratory tract it is unlikely to affect the later development of the lungs. If, however, there is serious neural maldevelopment then there may be secondary pulmonary hypoplasia associated with oligohydramnios. The importance of lung and amniotic fluid and of neural integrity to the developing lung has been discussed by Wigglesworth et al6 and Reid,7 while Liggins7 has emphasised the part played by phasic and tonic forces acting on the lung and encouraging its proper formation. These forces, however, do not exert their effect until after the 16th week.

Abnormalities associated with structural links between the liver, pancreas, and lung probably occur during the middle of the third week. At this time the primordia of these organs derived from the foregut are in close proximity.8 The septum transversum begins to form during the fourth week and this structure separates the future thoracic oesophagus from the abdominal stomach, duodenum, liver, and pancreas. The septum is complete by the fifth week, so it is unlikely that such anomalies as bronchobiliary fistula9 and sequestrations containing pancreas10,11 or connected to the stomach12 are initiated after this date. The pancreatic sequestration described by Tilson and Touloukian10 was supradiaphragmatic and had no respiratory tissue component, while the anomaly of Morris11 was subdiaphragmatic, adjacent to the pancreas, and contained lung tissue and, although amylase was found in the lung cyst fluid, no pancreatic tissue was seen histologically.

If this supposition is correct it may help to date the time of origin of thoracoabdominal foregut duplications to the period before the completion of the septum transversus. Pokorney and Goldstein did not consider the embryology of these malformations in their clinical review of this condition.12

Embryology is a subject that does not seem to have lent itself to assessment of interobserver concordance. In 1982, however, Zaw-Tun8 re-examined the Carnegie embryo collection that formed the basis of Smith’s 1957 study of the early development of the trachea and oesophagus.11 By using wax reconstruction of the serial sections Zaw-Tun concluded that Smith was in error in describing lateral folds that by their ingrowth separated the trachea from the oesophagus. These folds were the sides of the primitive pharyngeal floor, whose mesodermal component is the major factor in separating the developing respiratory primordium from the oesophagus. The cephalic end of the primitive pharyngeal floor forms the supraglottic region of the larynx.

Another interesting point that Zaw-Tun makes is that soon after the respiratory primordial pouch forms it produces the two bronchial rudiments, so that at this stage the trachea has not really begun to be formed. This is at the beginning of the fourth week. Towards the end of the fourth week the trachea and the oesophagus are elongating at the time when the heart is beginning to enlarge and develop. The formation of oesophagotracheal fistulas must occur during this period. The range of oesophagotracheal malformations has been fully documented by Kluth,14 some 54 variants having been recorded. Gruenwald15 reported a 9 mm fetus and reviewed other examples of 8–9 mm fetuses

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with oesophagotracheal fistulas. He postulated that, as the trachea might be elongating faster than the oesophagus, any connection between the two structures would stretch the oesophagus more than the trachea and thus account for the much more frequent occurrence of oesophageal than tracheal atresia.

The occasional occurrence of bronchogenic cysts in the lower oesophagus indicates that there is also considerable growth of the subcarinal oesophagus, some early respiratory epithelial cells being drawn out with some respiratory mesenchyme in a caudal direction. This abnormality must occur at the time of initiation of the primitive respiratory primordium. During the fourth week the lower oesophagus is stretched and attenuated by the rapidly growing heart. The developing oesophagus would seem to be relatively fixed at each end and at the level of the carina.

Reports of familial tracheo-oesophageal fistula suggest a genetic basis. But a careful study produced the conclusion that apart from cases occurring as part of a known chromosomal abnormality (various trisomies and monogenic abnormalities) these cases are multifactorial despite being familial. In the mouse, however, Essien and Maderious have bred a strain (lec) that possesses an autosomal recessive gene for development of a laryngo-oesophageal cleft without any other morphological congenital abnormalities. Further studies of the pedigree of probands with all grades of tracheo-oesophageal fistula could therefore be rewarding. While laryngo-oesophageal cleft in the mouse results in gaseous distension of the stomach, in man this deformity may easily be overlooked unless accompanied by other tracheo-oesophageal abnormalities.

The development of the bronchial tree depends on an interaction between the budding epithelium and the investing mesenchyme. Hutchins et al observed that the basement membrane in the immediate vicinity of the growing tip of the bronchus is poorly formed and that the investing mesenchyme is condensed as the bronchial bud extends. As a result the advancing tip becomes splayed out and is forced to separate into two or three daughter branches. Besides providing a mechanical moulding mechanism, the mesenchyme probably produces an epithelial growth stimulating factor. By the fifth week the lobar bronchi are formed and during the following week the process has progressed to the formation of all the subsegmental bronchi.

The site of sequestrations and the bronchial or enteric connections depend on the interaction of embryonic tissues and structures. Clearly the amount of respiratory tissue in sequestrations will depend on the amount of primitive respiratory mesenchyme carried along with the bronchial tissue that has lost its connection with the rest of the bronchial tree. Because of the frequency of mixed types of sequestration Gerle et al suggested that there is little point in distinguishing developmentally between intralobar and extralobar forms, even if there are differences between these in the frequency of other associated congenital abnormalities. This apparent anomaly may reflect a difference in the severity or timing of whatever may be the inducing agent or agents. Rarely the vascular anomalies associated with sequestration may cause heart failure in the neonatal period. More usually the presence of heart failure is related to a concomitant cardiac malformation.

The systemic arterial supply to most sequestrations may be accompanied by systemic venous drainage. The various combinations of vascular supply encountered in sequestrations has been reviewed by Thilenius et al. It is generally agreed that the vessels develop after the epithelium has formed the anlage. So could the systemic vessels leading to sequestrations be the result and indicator of an early embryonic connection between the respiratory primordium and the enteric primordium that would normally be supplied by vessels developing at the latter's somite level? Normally the bronchial vessels develop after the pulmonary vessels, so that the presence of large anomalous systemic arteries is most unlikely to be due to failure to develop a pulmonary arterial supply.

I have found no information about what influences the primitive respiratory mesenchyme to develop bronchial cartilage and muscle on the one hand and alveolar connective tissue on the other. Tracheal and bronchial cartilages make their appearance at about the end of the second month. The development of the alveolar tissue must be related to the division of the bronchial buds and cannot take place normally until the main bronchi appear. The formation of the trachea after the appearance of the bronchial buds ensures that peritracheal alveolar tissue does not develop. Tracheal accessory segments or lobes probably arise at this time. Their situation close to the carinal end of the trachea indicates that they arise at the time of the initial formation of the trachea.

A lung does not develop in the absence of the appropriate bronchial bud, even though primitive respiratory mesenchyme may be present. In a case studied by Reid there was agenesis of one lung, while the other lung had fewer than normal airways but was polyalveolar, suggesting a defect in primitive respiratory epithelium with a normally functional respiratory mesenchyme. Primary mesenchymal deficiency may be the main factor in pulmo-
nary aplasia where there is a main bronchial bud but no respiratory or vascular tissue.

The formation of bronchogenic cysts could occur by one of two mechanisms. Either a bronchial bud forms after the pulmonary mesenchyme in its vicinity has completed its commitment to alveolar development, or some intra-uterine event produces a proximal and distal obliteration of the epithelium in a bronchial segment. In either case this defect is likely to develop later than a tracheal accessory lobe.

The last congenital abnormality of the lung to be considered is the congenital cystic adenomatoid malformation. The appearance of this lesion suggests that there has been an arrest of development in the canalicular phase\(^{20,24}\)—that is, some time during the 10–16th weeks. Whether this is an epithelial or mesodermal dysfunction or even an acquired, possibly virus induced, lesion is uncertain. The rare occurrence of striped muscle in such malformations,\(^{24,25}\) however, suggests that there may be a translocation of laryngopharyngeal mesenchyme with the developing bronchial bud. With the development of ultrasound fetal examination the cystic form can be detected as early as the 36th week.\(^{26}\) To what extent the solid or cystic forms reflect early or later times of origin, or secondary changes such as secretory accumulation or activity, is as yet undetermined. Many cases have a bronchial connection, but it has not been established that this is so in all.\(^ {25}\) Occasionally this malformation is found in association with a sequestration.\(^ {27}\) In such cases the cystic adenomatoid malformation may be a secondary phenomenon, because sequestrations probably occur earlier in fetal development. The association of these two conditions, however, and the occasional finding of striped muscle suggest that cystic malformation may be a mesenchymal form of the more usual type of sequestration.

The general thesis is that many developmental anomalies can be explained on the basis that there is a crucial time and set of intercellular relations that allow a sequence of developmental changes to occur. If, for reasons of increased cellular cohesion, translocations occur at a critical time for a particular organisational stage then a malformation is produced. If this translocation is complete a localised cystic lesion results; while if the translocation is incomplete a trail of competent embryonal cells is left to mark this translocation, as in the bronchobiliary fistula mentioned above.\(^ {9}\)

There are many unanswered questions in the early development of the oesophagus and lung. Elucidating the part played by the development of cell surface antigenic markers in differentiation is an important, newly developing area of research.\(^ {28}\) In the fetal mouse an alveolar cell marker appears in the terminal part of the developing lung before the bronchial branching pattern is completed.\(^ {29}\) Reid\(^ {1}\) indicated that the fetal lung in rhesus isoimmunisation might be affected at about the 12th week. Contact between cells appears to be important\(^ {21}\) but the underlying mechanism is not understood. But with an increasing knowledge of the times at which the developmental aberrations are initiated detailed investigation of the relevant periods of the pregnancy should become possible, in the hope of throwing more light on causal factors.

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