17. The Respiratory System

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Introduction

One of the most critical events of birth is the conversion of the fluid-filled lung, unimportant to fetal intrauterine existence, into a hollow organ distended with air and capable of gaseous exchange sufficient to support life. Indeed, it has been argued that the major determinant of perinatal survival is respiratory function (Wigglesworth and Desai 1982)

The failure to make this conversion adequately may lead, directly or indirectly, to infant death and the pathologist will often need to assess the contribution made by respiratory inadequacy to the sequence of events leading to death. In the preterm infant, problems are mainly related to pulmonary immaturity and associated therapy. In the mature infant, birth asphyxia primarily results in cerebral damage but can engender significant respiratory complication when associated with aspiration of meconium. Even in stillbirths, where primary pulmonary pathology is rarely a cause of death, lung pathology may provide clues to antecedent events. Poor lung growth and maturation may point to the presence of pathology elsewhere.Consequently, adequate pathological investigation of the fetal or infant respiratory system is critical in any perinatal autopsy.

Examination of the Respiratory System

Postmortem radiology may be useful in identifying pneumothoraces, although some caution is needed in interpretation of other pulmonary changes because of postmortem absorption of air. Where radiology is not available, the more conventional approach to diagnosing pneumothorax can be used by releasing pleural air under water. This can often be achieved easily by immersing the whole infant thorax under water.

Choanal patency can be tested by passing a probe through each of the nares in turn and ensuring it reaches the nasopharynx. Inspection of the mouth may reveal palatal clefts and whether they involve the hard or soft portions. The larynx should initially be examined for the presence of clefts and, in conjunction with dissection of the oesophagus, tracheo-oesophageal fistulae. After removal of the oesophagus, the form of the tracheal rings should be checked for either complete rings or rings with large posterior pars membranacea that might accompany tracheomalacia. The major airways can be opened conventionally by a posterior longitudinal incision, but where histology will be important, it is frequently of value to fix the larynx whole, and cut it transversely into three or four blocks for processing and step or serial histological sectioning (Gould and Howard 1985).

Lungs should be removed with the heart to allow inspection of the pulmonary arterial and venous system. The lower borders of the lungs and heart should be approximately at the same level; if they are not it is often an indication of lung hypoplasia. Lung weights followed by calculation of lung body weight ratios are the simplest and most useful guide to the normality of lung growth or otherwise(see below). Inflating one of the lungs with formalin instilled through the airways can be valuable, particularly in assessing maturity. The precise diagnosis of lung pathology macroscopically is difficult and histology is mandatory, with at least one block from each main lobe.

Normal Development

The respiratory system can be divided developmentally into upper and lower tracts. Whilst histoanatomic discussion inevitably dominates the approach to respiratory development, it is

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important to consider the maturation of vital biochemical pathways, the immaturity of which contribute significantly to the postnatal morbidity and mortality of preterm infants.

Upper Respiratory Tract

The nose and mouth commence development at 5 weeks post-conceptional age and are derived from five main facial processes: a fused pair of frontonasal prominences, paired maxillary processes and paired mandibular processes. Migration of these processes, derived from cephalic neural crest, is a precisely orchestrated series of events and failure may lead to a wide variety of facial malformations.

The maxillary processes fuse with the frontonasal processes and their medial point of fusion becomes the philtrum of the upper lip. Caudally the mandibular processes fuse and the intervening space between mandibular and maxillary processes becomes the primative mouth, or stomatodeum. On either side of the midline of the frontonasal process, thickening of the epithelium forms circular nasal discs or placodes, each of which recede from the surface due to a combination of active invagination and proliferation of surrounding mesenchyme. Eventually this burrowing activity forms the anterior nares (Ferguson 1991). The newly developed nasobuccal membrane separating the nose from the mouth breaks down posteriorly at 7 weeks to form the communicating posterior choanal space. Anteriorly the bucconasal membrane ultimately remains as the primary palate, the remainder being replaced by the secondary or definitive palate derived from horizontal palatine processes. Fusion commences at the primary palate and extends rostrally. Normal palatal fusion is dependent on epithelial programmed cell death (Goldman 1992) at the point of fusion and mesenchymally signalled epithelial differentiation (Ferguson et al. 1992).

The larynx develops separately but at the same time from the endodermal lining of the laryngotracheal tube and the mesenchyme of the 4th to 6th branchial arches. A diverticulum forms in the ventromedial aspect of the foregut at day 20, and gives rise to the larynx, trachea and lungs. Separation of the larynx and trachea from the oesophagus occurs by ingrowth of tissue to form the tracheo-oesphageal septum. During development, proliferation of mesenchyme in the lateral wall of the larynx, partially obliterates the lumen for a time. Final recanalization occurs between the 8th and 10th week of gestation (Hamilton et al. 1972; Zaw-Tun 1988).

Lower Respiratory Tract

As described above, the trachea becomes separated from the oesophagus by the tracheo-oesophageal septum. After initial branching, the bronchial tree forms by dichotomous divisions which is completed by 17 weeks' gestation.

Conventionally, fetal lung development is divided into three main phases (Hislop and Reid 1974) although more recent data would argue for a fourth.

Pseudoglandular Phase (7–17 weeks)

Major lung components develop including bronchial glands, cartilage and, towards the end of this period, ciliated epithelium. The bronchial buds divide dichotomously with completion of preacinar branching by 17 weeks, faster in the right than the left lung. Airways terminate in blind ending tubes, and are lined by low columnar or cuboidal epithelium containing glycogen (Fig. 17.1). Mesenchyme is abundant but capillaries are sparse and not closely apposed to epithelium. Respiration is not possible at this stage.

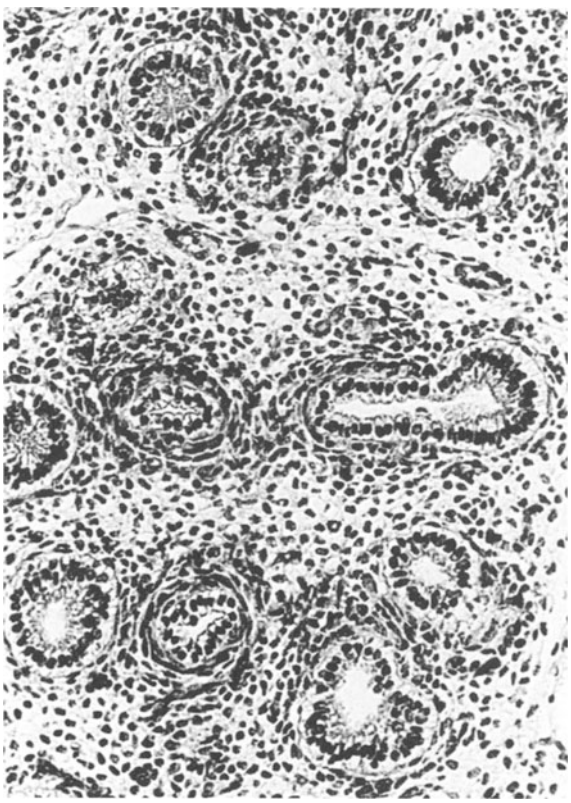


Fig. 17.1. Lung from a 13 week spontaneous abortion showing pseudoglandular development.

Canalicular Phase (17–27 weeks)

Tubules begin to dilate and the mesenchymal tissues become more vascularized. The epithelial cells are characterized by abundant glycogen initially but from about 20 weeks, and associated with differentiation, glycogen diminishes. Type 1 pneumocytes, stretched over capillaries, are identifiable by 22 weeks and type 2 cells shortly afterwards (McDougall and Smith 1975) (Fig. 17.2). Around 23 to 24 weeks' gestation, capillaries are pushing into the airways, the first blood–air barriers are forming and there is sufficient area for respiration to occur (Fig. 17.3).

Terminal Sac Phase (28 weeks–Term)

This phase is characterized by rapid maturation of the acinus. Further septation of the saccule leads to formation of true thin walled alveoli although some retain a double capillary layer. Alveoli start to develop between 28 and 32 weeks and up to 20–30% of the adult number have developed by term gestation (Langston et al. 1984; Hislop et al. 1986). Arguably, therefore, an alveolar or fourth phase of lung development could be considered to start in this third trimester and has been arbitrarily set at approximately 35 to 36 weeks' gestation (Hodson 1992). Alveolarization continues to about 8 years of age.

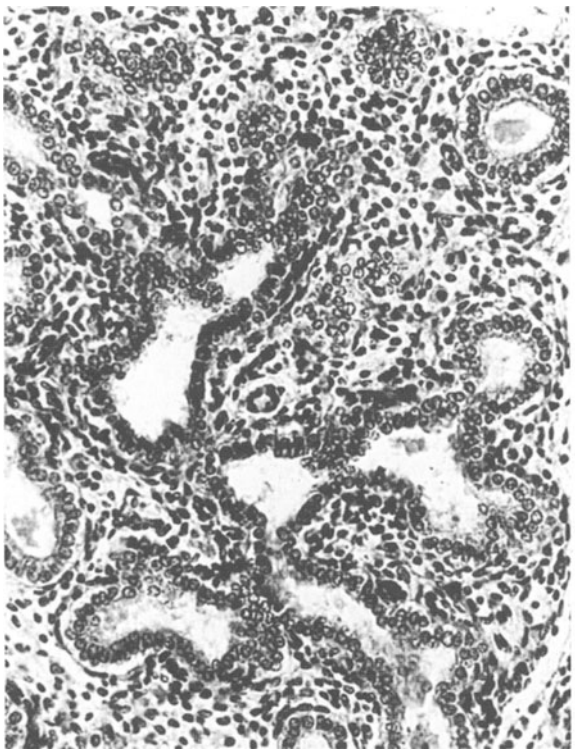


Fig. 17.2. Early canalicular stage of development at 17 weeks' gestation. Vascularity is still poor and there is no blood/air barrier formation.

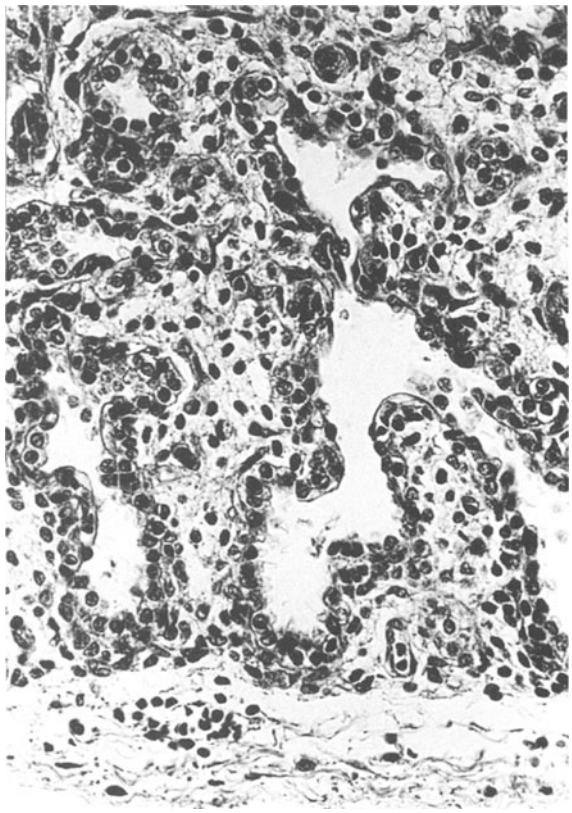


Fig. 17.3. Canalicular stage lung at 23 weeks' gestation. Capillaries are starting to push into the airways, pulmonary epithelium is becoming attenuated and blood–air barriers are recognizable. Epithelium at distal sites, adjacent to the pleura remains cuboidal.

A characteristic of the terminal sac phase is the rapid differentiation of type 1 and type 2 pneumocytes (Fig. 17.4). The development of the former is reflected in the increasing numbers of blood-air barriers and surface area available for gaseous exchange, the latter in production of surfactant, a complex surface active secretion formed of phospholipid and protein. The lung interstitium diminishes and by term, there is little residual mesenchyme between respiratory units.

Lung Development – Control

Normal lung development and function is dependent on a wide variety of factors, many of them extrinsinc to the lung itself. Many of these factors

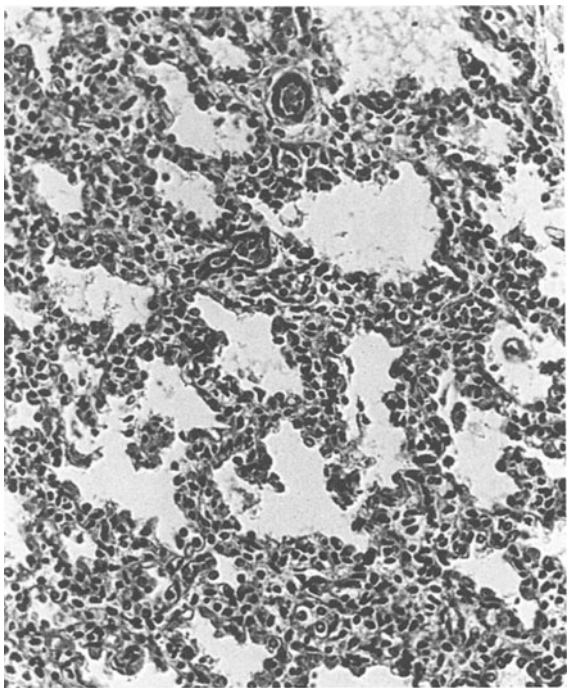


Fig. 17.4. Terminal sac development at 28 weeks' gestation. Mesenchyme is less prominent and vascularization more marked.

are more conveniently discussed in the context of lung pathology, especially pulmonary hypoplasia.

The precise mechanisms that control lung development, particularly in the early part of gestation, are not fully understood although the interaction between mesenchyme and the in-growing epithielial buds is fundemental. The appearance and subsequent disappearance, during the transition from pseudoglandular to canalicular phase, of various laminins and integrin subunits in bronchial bud basement membranes imply a critical role at this stage of normal lung branching. (Virtanen et al. 1996). Further, alterations in concentrations of different sub-units around the time of type 1 and 2 pneumocyte appearance suggest a role in epithelial differentiation (Sigurdson et al. 1994; Durham and Snyder 1995, 1996). Growth factors, such as fibroblast growth factor-2 located in basement membranes, may also influence both the processes of branching and cell differentiation (Gonzalez et al. 1996). Epidermal growth factor with receptor, and transforming growth factor-alpha, have been colocalized in airway epithelium in normal fetal lung (Strandjord et al. 1995). Insulin -like growth factor -2 has been localized in mesenchymal fibroblasts. Some of the mitogenic properties of the growth factors may be via a local paracrine or autocrine action (Harding et al. 1993).

More systemic influences stem from hormones. Glucocorticoids, possibly acting synergistically with thyroid hormones stimulate pulmonary fibroblasts to produce fibroblast-pneumocyte-factor (FPF). FPF causes pulmonary epithelia to differentiate into type 2 pneumocytes, indicated by an increase capacity to produce surfactant (Smith and Post 1989). In vitro, this occurs rapidly (< 60 min), suggesting a post-translational effect. Of interest, androgens appear to block FPF production and this might partly account for the increase risk of respiratory distress in male infants. Glucocorticoids may also stimulate the de novo synthesis of fatty acids, used by type 2 pneumocytes to produce surfactant (Rooney 1989). In contrast, thyrotropin releasing hormone with or without dexamethasone depresses the late gestation surge in anti-oxidants probably at the level of gene transcription rather than post-transcriptionally (Chen and Frank 1993).

Biochemical and Physiological Maturation

It is clear that the simple physical process of blood–air barrier formation that will permit rapid diffusion of gases to and from the pulmonary vasculature, and recognizable microscopically, is an important prerequisite for the transition to extrauterine life. However, successful transition is also dependent on the concurrent maturation of specific biochemical enzyme systems. Whilst not readily assessable by the pathologist, an awareness of them can assist in the understanding of the problems of early neonatal life that produce respiratory difficulties, particularly in the preterm infant. Three main systems have been studied, although only a brief outline will be presented.

Surfactant

Synthesized by type 2 pneumocytes, surfactant is a compound formed mainly of phospholipid (80%; 50% of which is dipalmitoyl-phosphatidylcholine), cholesterol (10%), and at least four surfactant -associated proteins (SP-A to D) (10%).

Type 2 pneumocytes store surfactant in lamellar bodies which are secreted onto the alveolar surface by exocytosis to form a monolayer of surface active material. Production and secretion appears to be further stimulated after birth by mechanical factors such as lung expansion (Wright and Clements 1987)). Once secreted, turnover is rapid and approximately 10–30% is replaced per hour. The means by which surfactant is removed is not clear but there

is evidence that alveolar macrophages are involved and recycling occurs (Mendelson and Boggaram 1989).

Lung Liquid Secretion

The fetal lung is filled by a liquid, the production of which starts early in gestation and normally terminates only in the early stages of labour. Pulmonary epithelium actively secretes chloride ions into the duct lumen and this passage of negative ions is accompanied by sodium and water (Olver and Strang 1974). At birth, lung liquid secretion needs to cease and that already present, absorbed. Adrenaline, to which pulmonary epithelium becomes increasingly sensitive as term approaches, appears to control this latter aspect (Brown et al. 1983). Its action on chloride transport is unclear, but adrenaline may open sodium channels and stimulate active sodium transport from the alveolar lumen (Walters and Ramsden, 1987). Where there is a failure of this process, persistance of lung liquid may cause transient neonatal respiratory distress. Of greater importance to the pathologist is the evidence which indicates that the secretion of lung liquid and its gradual loss into the amniotic fluid is vital to normal lung growth (Nicolini et al. 1989).

Antioxidant Enzymes

Oxygen, even at normal inspired concentrations, is damaging to lung epithelium and endothelium because of the production of toxic radicals. Evolution has provided a number of defence mechanisms including some vitamins (A, C and E), and enzymes such as superoxide dismutase, catalase and glutathione peroxidase. Under normal circumstances, fetal lung is only exposed to low oxygen tensions, and consequently antioxidant enzyme levels are relatively low. In parallel with those of surfactant, antioxidant enzyme systems mature with gestation and reach a peak at term (Frank and Sosenko 1987). Recent evidence suggests that resistance/susceptibility to oxygen is determined less by baseline levels of antioxidant enzymes than the response of those enzymes to hyperoxia. A deficient response has been detected in the prematurely born (Frank and Sosenko 1991).

Pulmonary Vascular Changes at Birth

Only some 10–12% of cardiac output passes through the pulmonary vasculature in utero, most bypassing it via the ductus arteriosus and foramen ovale. Intrapulmonary arteries are thick-walled and endothelial cells are plump and overlap. At birth, the closure of the ductus and foramen ovale is associated with a rapid increase in pulmonary blood flow. To cope with this, and partly under the influence of increased oxygen tensions, pulmonary arteries dilate, vessel walls become thinner and endothelial cells are stretched and appear flatter. In the precapillary arteries, the changes may occur within minutes after birth. In the first 4 days, more muscular arteries are "recruited" to the pulmonary circulation so that the cross-sectional area of the precapillary bed rises. This allows an increase in cardiac output through the pulmonary vasculature, but without a parallel rise in pulmonary vascular resistance. Over a period of weeks, these changes are "fixed" structurally, by smooth muscle hyperplasia, increases in the connective tissue of the media and an increase in the internal elastic lamina (Haworth 1988).

Developmental Anomalies

Upper Respiratory Tract

Anterior and Posterior Nares

Total absence of the nose may result from failure of development of the nasal placodes or occur as part of a wider range of cerebro-cranial abnormalities (Gifford et al. 1972). More often the nose is replaced by a blind-ending proboscis or lies superior to a single fused orbit. Many of these mid-line defects are associated with trisomy 13 (p. 613).

Attempts at passing a probe through the nares into the nasopharynx may reveal the presence of choanal atresia, which may be unilateral. It can be an isolated finding or be part of a wide range of anomalies including those of the ear, eye, cardiac defects such as Fallot's tetralogy and cerebral abnormalities (**C**oloboma, **H**eart disease, **A**tresia choanae, **R**etarded **G**rowth and **E**ar anomalies (CHARGE) association) (Pagon and Graham 1981).

Lips and Palate

Failure of the maxillary process to fuse with the nasal prominence gives rise to a lateral cleft, sometimes with alveolar margin involvement. Clefts of the lip and palate are common abnormalities seen both individually or together. In that absence of other malformations they are commoner in males but the sex incidence is approximately equal in the presence of non-facial malformation.There is a considerable list of potential associations and

syndromes (Winter et al. 1988). The underlying causes are extremely varied from the chromosomal, such as the mid-line clefts frequently associated with trisomy 13, to the physical such as in the Pierre–Robin sequence in which a displaced tongue interferes with normal palatal fusion

Lower Respiratory Tract

Larynx

Laryngeal Atresia This may occur at any level within the larynx, although there always appears to be some involvement of the supraglottic region. Smith and Bain (1965) classified 9 examples into 3 types.

- *Type 1*: the vestibule is a shallow cleft flanked by the apices of the arytenoids. Below this is a mass of muscle with partially fused arytenoid cartilages behind which is a fine pharyngo-tracheal duct < 1 mm in diameter.The cricoid is malformed and conical (Fig. 17.5).
- *Type 2*: The vestibule is normal and the arytenoid cartilages separate. The glottis is a blind cleft between the vocal folds and the cricoid dome-shaped with a pharyngotracheal duct passing posteriorly.
- *Type 3*: The glottis is occluded by a fibrous connective tissue membrane and a fused mass of lateral cricoarytenoid muscles. The vocal processes of the arytenoid are fused and the pharyngotracheal duct passes posteriorly.

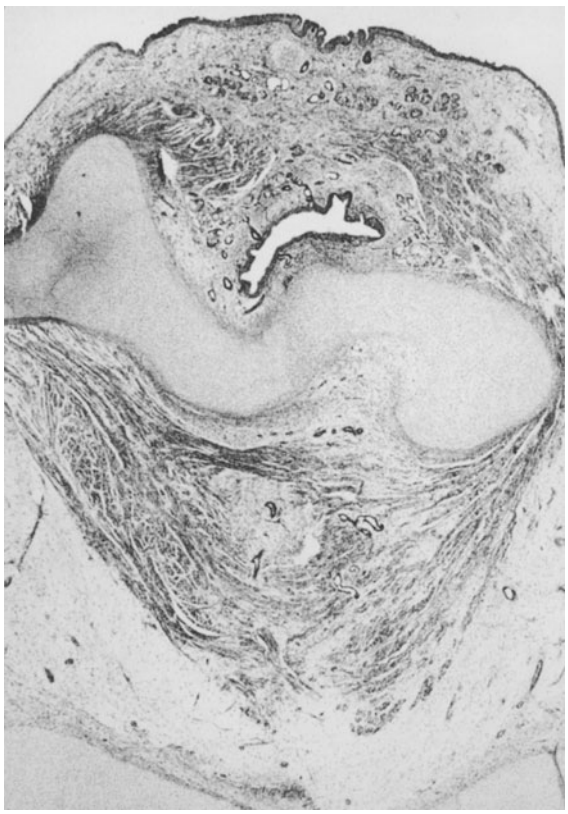


Fig. 17.5. Transverse section across laryngeal atresia with abnormal, fused arytenoid cartilages. The pharyngotracheal duct passes dorsally and a mass of muscle is fused anterior to the cartilage.

Laryngeal atresia represents an arrest of normal development when there is failure of recanalization of the lumen during the 8th to 10th week of gestation, after it has been obliterated by proliferation of pharyngeal mesoderm (Zaw-Tun 1988). Although in the original description there was only one example of type 3, it is the more common and represents a late failure of recanalization. Zaw-Tun regards the type 3 as having been described as a laryngeal web elsewhere and, as such, is less severe and often remediable; types 2 and 3 are rarely other than fatal (Hicks et al. 1996). Types 1 and 2 are more usually associated with malformation elsewhere whereas type 3 is usually an isolated abnormality.

Of interest, the lungs in the severe forms of atresia may be hyperplastic due to failure of lung liquid to eflux normally from the developing alveoli.

Laryngeal Stenosis and Obstruction Excluding laryngeal webs, which for pathogenetic reasons are discussed under atresia, most laryngeal stenoses are below the true vocal cords in the subglottis. Stenosis may be soft, due to fibrous tissue and mucous gland overgrowth, or hard (Fig. 17.6), due to cricoid cartilage overgrowth (McMillen and Duvall 1968), an abnormally shaped cricoid or even a displaced first tracheal ring (Tucker et al. 1979). The laryngeal inlet may appear normal. A combined soft and hard tissue stenosis with posterior cleft has been described (Kaufmann and Kohler 1995).

Laryngeal Clefts Occasionally, clefts are anterior but most laryngeal clefts are in the midline posteriorly and represent a failure of fusion of the tracheo-oesophageal septum. They have been classified into:

- Type 1, involving larynx only;
- Type 2, partial cleft involving larynx and upper trachea;
- Type 3, complete cleft involving trachea as far down as the carina (Lim et al. 1979).

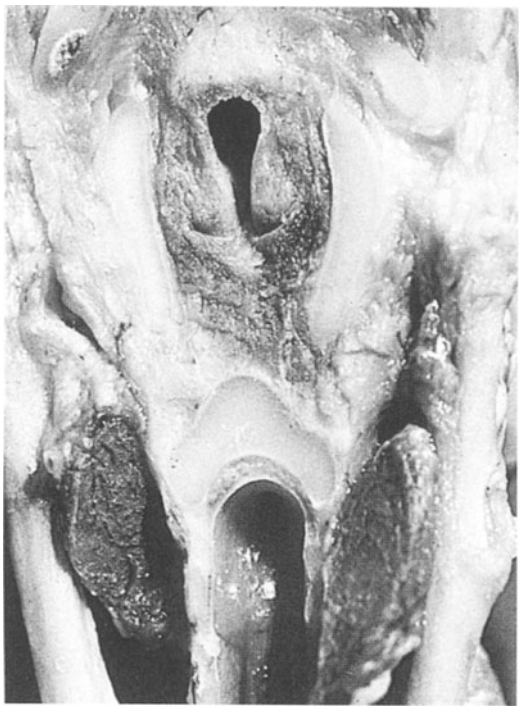


Fig. 17.6. Laryngeal stenosis. Coronal slice through the larynx shows an abnormal bar of cartilage obstructing the lumen (courtesy of Dr S. Knowles).

Neonates often suffer from stridor and/or respiratory distress. Mortality is high and surgery is required for type 2 and 3 clefts for survival (Samuel et al. 1997). Up to 40% of type 1 clefts are associated with a tracheo-oesophageal fistula.

Laryngeal Cysts Laryngeal cysts may present with neonatal stridor (90%) or respiratory distress (55%) usually on the first day of life (Mitchell et al. 1987). They have been classified as either saccular when they are present in the laryngeal saccule or ductal, when they result from distention of obstructed ducts (De Santo et al. 1970). Laryngocoeles that develop in the saccule and contain air and fluid, may cause external compression (Chu et al. 1994). Obstruction by cystic hygroma and a hamartoma has been described (Thompson and Kasperbauer 1994; Fine et al. 1995).

Laryngomalacia A frequent clinical, though rare pathological diagnosis, laryngomalacia is one of the commonest causes of congenital laryngeal stridor (Friedman et al. 1990). Sometimes stated to be due to a soft cartilagenous framework of the larynx (Cotton and Richardson 1981), the pathology is very poorly defined and the histology may be normal. It has been suggested that stridor may result from a mild localized form of hypotonia due to neuromuscular dysfunction (Belmont and Grundfast 1984). Laryngomalacia resolves spontaneously during the second year in 90% of cases.

Trachea

There are about 22 cartilagenous rings between the lower border of the larynx and the carina. Most are simple C-shaped transverse rings, open posteriorly, but a significant number of half-rings or Y-shaped structures are present even in normal infants (Landing and Wells 1973). A reduction in ring numbers may be associated with Klippel–Feil syndrome and a wide variety of other conditions including chromosomal disorders, skeletal dysplasias and neural tube defects (Wells et al. 1990).

Tracheal Agenesis Tracheal agenesis may be total or segmental, usually of the lower part, and is rare with less than 50 cases reported. It results from ventral or dorsal displacement of the tracheo-oesophageal septum. The agenetic segment of trachea may be long or short and sometimes linked by a thin fibrous cord. The distal trachea or bronchi may arise from the oesophagus (Fig. 17.7) (Diaz et al. 1989). It is commonly associated with tracheo-oesophageal fistulae (Floyd et al. 1962; Bray and Lamb, 1988) and other congenital abnormalities, particularly in the cardiac or genito-urinary systems (McNie and Pryse-Davies 1970; Diaz et al. 1989).

Tracheal Stenosis Tracheal stenosis may present as stridor or respiratory distress in the neonate or recurrent pneumonia in the older infant (Loeff et al. 1990). It may be due to an intrinsic abnormality of the trachea or from extrinsic pressure. Intrinsic tracheal stenosis is either diffuse or segmental. Diffuse stenosis may result from a posterior fusion of the tracheal cartilages. In some cases the trachea is funnel shaped, the trachea gradually becoming more stenotic. Common associations include a sling left pulmonary artery or pulmonary agenesis. Diffuse stenosis may also be caused by a solid cartilagenous sleeve usually associated with craniosynostosis syndromes such as Apert's. It probably reflects a generalized mesenchymal defect. The most frequent stenosis is a segmental, napkin-ring type with individual cartilages having a complete tracheal ring.

More frequent than intrinsic tracheal stenosis, is extrinsic compression from a vascular ring encircling the trachea such as a double aortic arch, or an abnormal vessel such as an aberrant left pulmonary artery (Fig. 17.8).

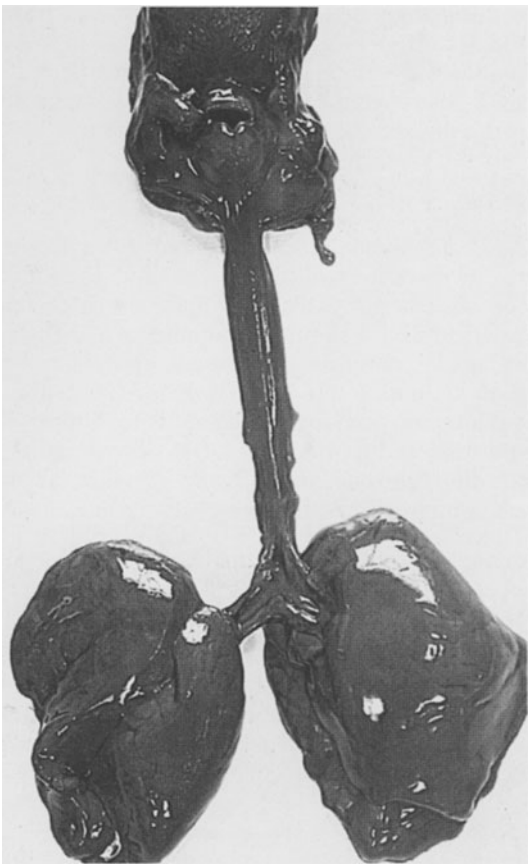


Fig. 17.7 Tracheal agenesis in a 34 week's gestation stillbirth. Laryngeal inlet appears relatively normal despite the absence of airway below the cricoid and the bronchi are arising directly from the oesophagus. Both lungs are of normal size.

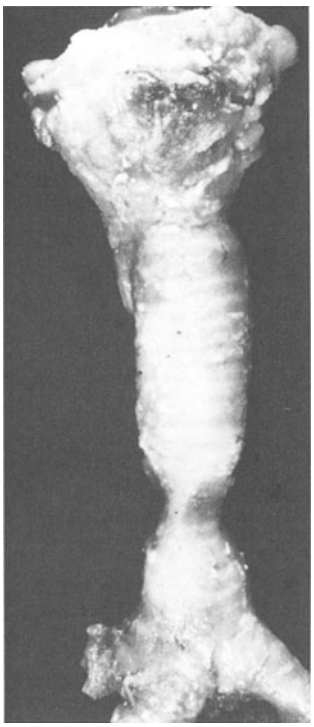


Fig. 17.8. Localized tracheal stenosis in a baby with aortic arch anomalies and congenital heart disease.

Tracheo-oesophageal Fistula A tracheo-oesophageal fistula is the most common congenital abnormality to affect the trachea, which almost invariably demonstrates abnormalities of the tracheal cartilages similar to those found in tracheomalacia. The usual variant of tracheo-oesophageal fistula is a blind-ending, upper oesophageal pouch associated with a fistulous connection between the lower oesophagus and the trachea (Holder and Wooler 1970). Tracheo-oesophageal fistula is discussed more fully in GI tract (p. 383).

Tracheo- and Bronchomalacia Tracheo- and bronchomalacia are due to an inadequacy of the respective cartilagenous frameworks and cause a loss of airway patency at some point in the respiratory cycle. They may present clinically as stridor and/or respiratory distress and diagnosis is made bronchoscopically by visualizing airway collapse, usually during expiration. As the problem can resolve spontaneously, and is more frequent in preterm infants, it has been attributed to "immaturity" of tracheal or bronchial cartilages (Cogbill et al.1983), implying abnormally thin or floppy cartilage. A deficit in the cartilagenous rings may be present (Gupta et al. 1968; Belmont and Grundfast 1984; Benjamin 1984). Describing the normal cartilage to soft tissue ratio as 4.5 : 1, Benjamin states that the C-shaped cartilages in tracheomalacia are smaller and the ratio may fall to 2 : 1. The increase in the soft tissue posteriorly, allows anteroposterior collapse of the airway. Familial malacia is recorded (Agosti et al. 1974) and an association with other congenital abnormalities, particularly congenital heart disease is common.

Secondary tracheomalacia, in this context implying acquired damage to the trachea, is a rare complication of chronically ventilated preterm infants. Damage to the cartilagenous framework is presumed to occur from recurrent tracheal infection or possibly trauma from the endotracheal tube (Sotomayor et al. 1986).

Lungs

Bronchial Abnormalities Abnormalities of bronchial segmentation may be extra- or intrapulmonary.

Many are incidental findings and of little significance, although some abnormalities of bronchial origin may present in later life with pneumonia. The commonest extrapulmonary anomaly is that of isomerism, in which bronchial development is similar on both sides (either left or right). These are associated with abnormalities of "left–right symmetry" elsewhere, especially of the heart (Landing 1984; Stewart et al. 1984; DeVine et al. 1991).

Bronchial atresia is extremely rare and usually apical. The pathology is variable. Some atresias have been associated with bronchogenic cysts and adenomatoid malformation which suggests a malformative basis for the lesions (Kuhn and Kuhn, 1992; Mori et al. 1993) but the presence of fibrotic material in some atresias suggest some are "acquired". Bronchial stenosis is rarely caused by an intrinsic abnormality (Chang et al. 1968) and is usually caused by extrinsic pressure. Enlargement and pressure from pulmonary arteries from pulmonary hypertension is the commonest association.

Pulmonary Agenesis Bilateral pulmonary agenesis is extremely rare (Ostor et al. 1978) but unilateral agenesis is encountered occasionally (Booth and Berry 1967; Engellener et al. 1989; Cunningham and Mann 1997). Agenesis may be complete; associated with a rudimentary bronchus; or associated with a rudimentary bronchus with ill-developed pulmonary tissue. Congenital anomalies of the VACTERL type (**V**ertebral defects, **A**nal atresia, **C**ardiac defects, **T**racheo-**E**sophageal atresia, **R**enal anomalies, **L**imb defects) are common associations and, it has been suggested, unilateral pulmonary agenesis may "replace" tracheo-oesophageal fistula as a component of the syndrome (Knowles et al. 1988). The solitary lung may show the normal bronchial divisions but a compensatory increase in alveolar number may produce mediastinal shift. Chromosomal abnormalties have not been recognized in association with pulmonary agenesis although a recurrence has been reported (Podlech et al 1995).

Other Pulmonary Lobar Anomalies Herniation into the lungs into the neck has been described in iniencephalus and Klippel–Feil syndrome. A part of the right upper lobe may grow medial to the right posterior and common cardinal veins to form an azygos lobe. Fusion of the lung bases behind the pericardial sac forms a horseshoe lung. This is generally asymptomatic except when associated with other anomalies especially pulmonary vascular anomalies such as scimitar syndrome (Figa et al. 1993).

Pulmonary Cystic Disease

A wide variety of pulmonary abnormalities can lead to a clinical diagnosis of a congenital pulmonary cyst or cysts. The timing and nature of their clinical presentation is extremely variable, and some may be an incidental discovery at autopsy. Rarely, congenital pulmonary cystic lesions have been associated with the late development of malignant neoplasia (Ueda et al. 1977; Domitzio et al. 1990; Ribvet et al. 1995; Kaslovsky et al. 1997).

Bronchogenic Cysts Bronchogenic cysts are usually an incidental finding in the perinate. Considered to result from an abnormal "late" budding of the primitive tracheobronchial tree, they may be intrapulmonary, anterior mediastinal or occasionally apposed to the trachea in the neck. Rarely they are found at unusual sites with no respiratory tract connection infra-diaphragmatically or in subcutaneous tissues. Bronchogenic cysts should not be in communication with tracheobronchial tree. The epithelium is ciliated columnar, but squamous metaplasia can be present. Although some searching may be necessary, bronchial glands or cartilage in the cyst wall is the most reliable histological means of distinguishing bronchogenic from oesophageal cysts (Salyer et al. 1977).

Congenital Lobar Emphysema This presents postnatally with respiratory distress due to lobar overexpansion and compression of adjacent tissues. It is usually attributed to a defect in the cartilagenous framework of the local bronchial tree (Warner et al. 1982). Intracardiac defects are a common association (Buntain et al. 1974).

Cystic Adenomatoid Malformation Congenital cystic adenomatoid malformation (CCAM) is increasingly diagnosed antenatally by ultrasound as a cystic, solid or combined mass in the fetal chest. In the fetus it can be a cause of effusions, overt hydrops and mediastinal shift. Venous obstruction may be a major factor in fluid accumulation. Differential diagnosis typically includes diaphragmatic hernia or a sequestration. Increasing experience of ante-natal detection indicates prognosis is not as bad as formerly thought, even in the presence of systemic complications. CCAMs, followed during gestation by ultrasound may gradually become less visible. At birth, imaging may detect the more cystic lesions only with difficulty. Postnatally, CCAM often presents with respiratory distress but it can be an incidental radiographic finding. It is likely many go undetected and adult presentation is recorded (Lackner et al. 1996).

The diagnosis of CCAM is straightforward and CCAM can be simply described as solid and/or cystic. A more detailed and widely used classification has been provided by Stocker et al. (1978), although it is often difficult to apply to fetal lung (Cha et al. 1997), especially in diffentiating types 1 and 2. Some lesions may resemble other pulmonary anomalies (Bale 1979; Fisher et al. 1982). Clinical features associated with in utero diagnosis are often more related to the volume of lung affected by the malformation and factors such as mediastinal shift than subtype (Fig. 17.9). The cyst sizes quoted below relate to lungs removed in the neonatal or infant period and may not be appropriate to preterm infants or fetuses.

It has been suggested that the subtype corresponds to the level of the malformative process from proximally (type 1 = major bronchi) to distal (type 4 = distal acinar origin).

- *Type 1*: Multiple large cysts, or single predominant cyst, usually 3–7 cm in diameter but occasionally up to 10 cm diameter, and affecting one or more lobes of one lung. Smaller cysts may blend with adjacent normal lung and cysts communicate with the bronchial tree but distention and compression of adjacent tissue may cause mediastinal shift. Microscopically, cysts are lined by respiratory type ciliated columnar epithelium, which may be flattened, or a mucigenic epithelium (Fig. 17.10). The wall comprises a thin fibromuscular layer and small islands of cartilage may be present. Cysts with the appearance of enlarged alveoli are interspersed between the larger cysts.
- *Type 2*: Multiple, evenly spaced cysts, usually less than 1.2 cm, which communicate with the bronchial tree and occupy an entire lobe or, rarely, a whole lung. The cyst lining is very similar to bronchiolar epithelium and may be difficult to distinguish from normal structures except they are present to excess (Fig. 17.11). The cyst wall is formed of a thin fibromuscular layer, but cartilage is not seen. Very occasionally striated muscle may be found, randomly distributed throughout the malformation (Fig. 17.12). Of the three main subtypes, type 2 is most commonly associated with malformation elsewhere, especially of the renal tract.
- *Type 3*: This subtype is formed of small cysts less than 0.5 cm in diameter, involving an entire lobe. Cyst lining is ciliated cuboidal epithelium on a very thin fibromuscular layer with no cartilage or mucigenic cells (Fig. 17.13). Due to the overall size of the affected lung, type 3 CCAM invariably produces mediastinal shift and carries a poor prognosis.
- *Type 4*: A newly proposed subtype (Stocker 1994), type 4 has an equal sex incidence, and presents usually with mild respiratory distress, an asymptomatic incidental finding or sudden respiratory distress from a pneumothorax. It comprises large peripheral thin walled cysts up to 7 cm in diameter lined by type 1 alveolar and cuboidal cells. The cyst walls are formed of thin loose mesenchyme often with thick walled arteries.

Fig. 17.9. Cystic adenomatoid malformation affecting most of the left lower lobe in an 18 week gestation fetus. Cysts are of variable size.

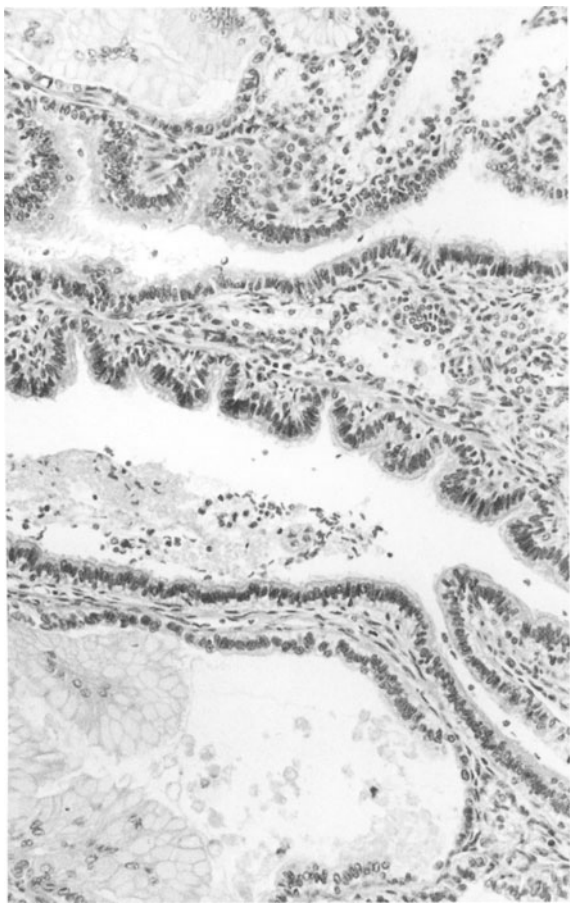


Fig. 17.10. CCAM type 1 showing typical respiratory epithelium with thin layer of fibromuscular tissue. Metaplastic, mucous epithelium is characteristic of type 1 but is not always found.

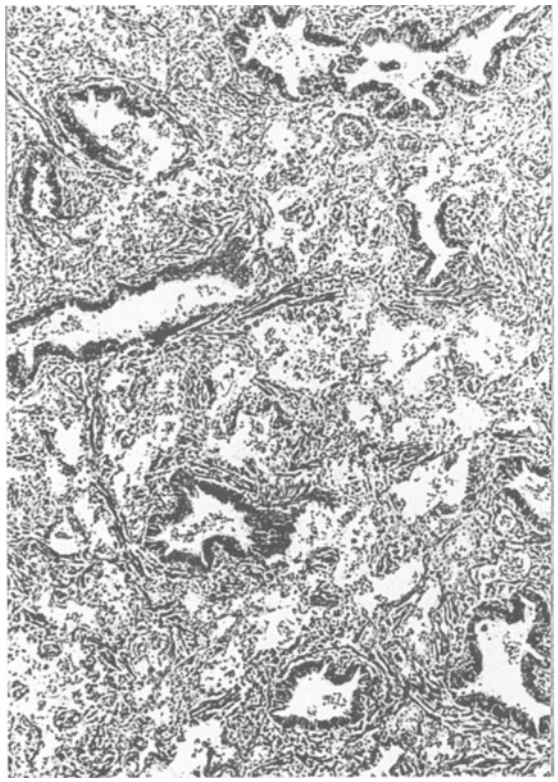


Fig. 17.11. Type 2 CCAM. Under low power, the cysts might be mistaken for a slightly excessive number of bronchioles.

- *Type 0, Acinar dysplasia*: Initially reported as acinar dysplasia (Rutledge and Jensen 1986), this has been proposed as a type 0, adenomatoid malformation. Incompatible with life, the macroscopic appearance is of a hypoplastic lung. Microscopically, acinar development is extremely poor with terminal sacs lined by pseudostratified, bronchial type columnar epithelium with goblet cells (Fig. 17.13b). Some authors have regarded this more as a form of very severe, pulmonary hypoplasia (Chambers 1991).

Pulmonary Sequestration In its classic forms, sequestered lobes are abnormal masses of pulmonary tissue which do not communicate with the main pulmonary bronchial tree and are supplied by an anomalous artery arising from the descending aorta. Sequestration may be intrapulmonary (ILS), or extrapulmonary (ELS), when the sequestered lobe is invested by its own pleura. ILS is usually found within the left lower lobe. Because ILS is rarely found in fetuses or neonates (Ng et al. 1994) and presentation is often late, it is suggested only a few may be true malformations , and most are the result of infection (Stocker and Kagen-Hallet 1979). Macroscopically, the segment of collapsed lung may be cystic and show changes of repeated infection histologically.

ELS may present in the fetus with hydrops, or as an incidental finding by ultrasound or at post-mortem associated with other anomalies. In infancy it may present with respiratory distress. ELS may lie anywhere in the thorax or even sub-diaphragmatically. Histologically, ELS shows bronchi, oddly branching smaller airways and poorly formed alveolar tissue and may be associated with the changes of CCAM.

A wide range of bronchial connection, arterial supply and venous drainage is described and should be allowed for in the dissection of sequestrations (Clements and Warner 1987). The embryological origin of pulmonary sequestration is a matter of debate although there does appear to be a consensus

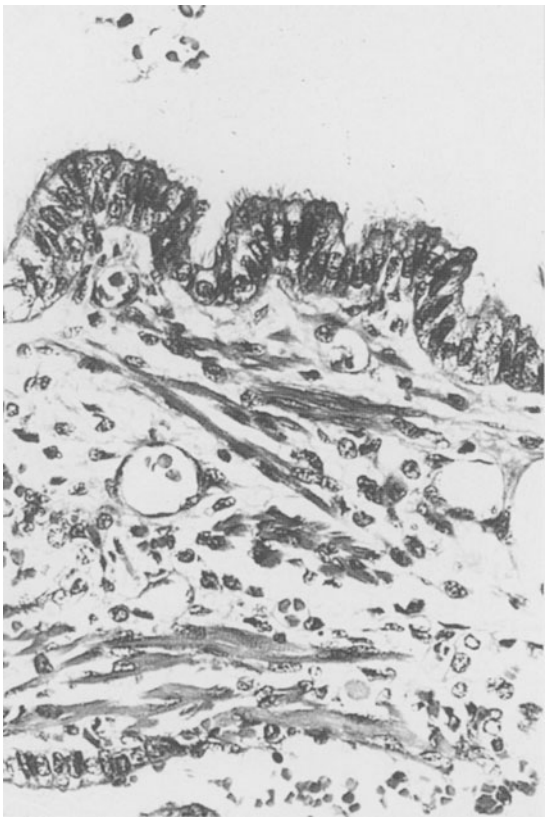


Fig. 17.12. Type 2 CCAM. The wall of this cyst contains a number of large muscle cells, the striations of which are visible.

that other broncho-pulmonary abnormalities may be related (Heithoff et al. 1976; Landing and Dixon 1979; Clements and Warner 1987).

Sequestered lung that communicates with the gut, most commonly the oesophagus or stomach, are generally termed bronchopulmonary foregut malformations. They are generally right sided and present in infancy either as an associated finding with other malformations or symptoms related to infection (Srikanth et al. 1992).

Pulmonary Heterotopias/Hamartomas Solid hamartomas are rare anomalies and may contain cartilage and adrenal (Bozic 1969). Glial and skeletal muscle masses are sometimes seen in anencephaly (Fig. 17.14a). Rhabdomyomatosis or diffuse heteroplasia of skeletal muscle is described and is usually associated with a cardio-vascular malformation (Chi and Shong 1982; Chellam 1988, Chen et al. 1991; Hardisson et al. 1997).

Alveolar Capillary Dysplasia This results from failure of normal alveolar capillarization. It is associated with an abnormality of the vascular bundle such that there is both pulmonary artery and vein together, often in the same adventitial coat; alveolar capillary dysplasia is sometimes known as misalignment of the pulmonary veins (Fig. 17.14b). Babies present with severe ventilatory difficulties and marked pulmonary hypertension (Janney et al. 1981; Wagenvoort 1986; Cater et al. 1989; Langston 1991; Oldenburg et al. 1995; Guttierez et al. 2000).

Lymphangiectasia Lymphangiectasia, or cystic dilatation of pulmonary lymphatics may be primary or secondary. The former is rare and probably results from failure of pulmonary lymphatics to establish connections with the thoracic duct (Laurence 1955; France and Brown 1971). Secondary lymphagiectasia is usually associated with cardiac malformations, particularly anomalous pulmonary venous drainage (Esterly and Oppenheimer 1970). In contrast to interstitial emphysema, which it grossly resembles and in which air is trapped in the interstitial tissues, the lungs are firm, inelastic and heavy. Bilateral pleural effusions are usual and these may be chylous. Histologically, dilated lymphatic spaces are present within interlobular septa, beneath the pleura and between large vessels at the hilus of the lung.

Lung Hypoplasia

Although lung hypoplasia is a congenital condition it is not a malformation, and is almost invariably secondary to pathology outside the respiratory tract. It is considered at some length, firstly because it is one of the most common abnormalities encountered in perinatal pathology, second, because of its varied pathogenesis, and third, because of the impact the study of lung hypoplasia has had on the study of normal lung growth.

Lung hypoplasia is common and has been estimated to occur in up to 14% of perinatal autopsies (Wigglesworth and Desai 1982; Husain and Hessel 1993). In stillbirths, it may be an incidental finding. In neonates, however, it can present within minutes or hours of birth and simulate intractable asphyxia so it is an important pathological diagnosis (Devlieger et al. 1994). Occasionally, a clinical diagnosis of lung hypoplasia is not associated with immediate death and postnatal changes in the lung may make pathological confirmation of the diagnosis difficult or impossible.

In most instances, however, diagnosis is straightforward, with macroscopically small lungs in a small thoracic cage (Fig. 17.15). After removal as a block, the diaphragmatic surfaces of the lungs are not in line with the apex of the heart (Fig. 17.16). Another

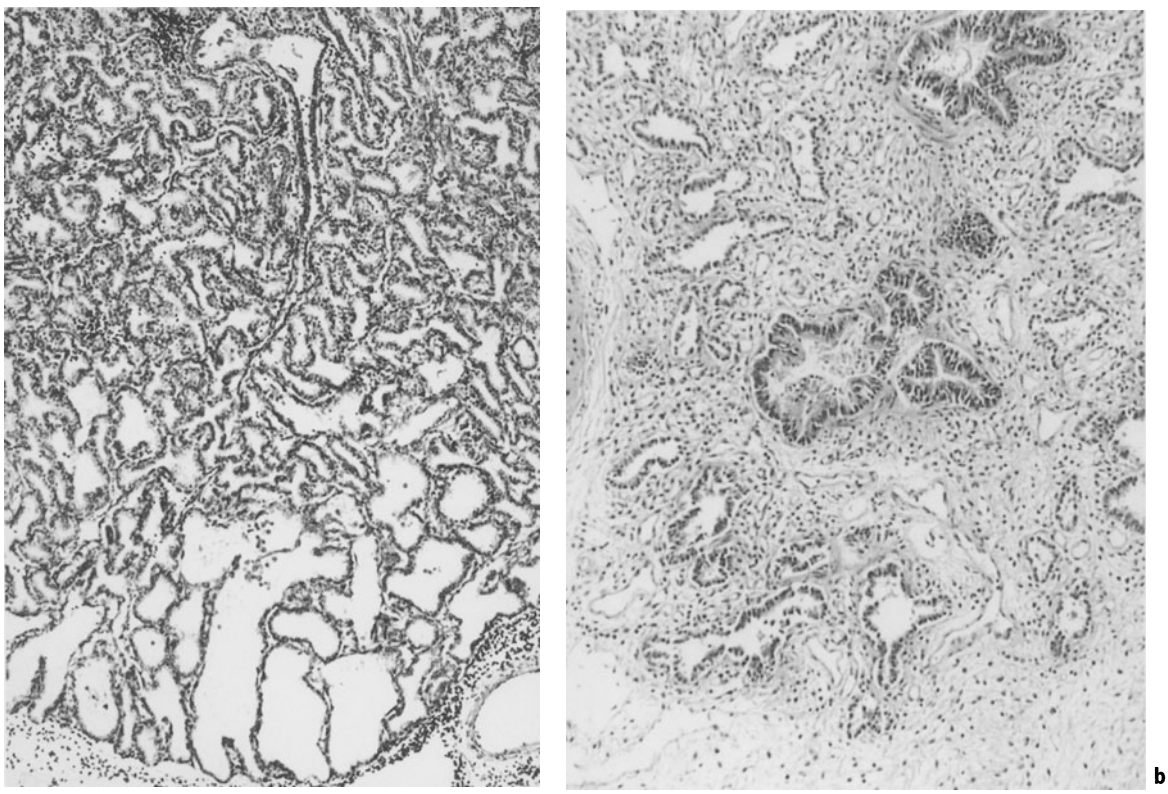


Fig. 17.13. **a** Solid, type 3 CCAM with uniform small cysts lined by cuboidal epithelium which is surrounded by a very thin connective tissue layer. **b** Acinar dysplasia from a term infant dying at 1 day of age. The central bronchiole is essentially normal, but distal to this there is no normal alveolar development (courtesy of Dr C.J.H. Padfield, Nottingham).

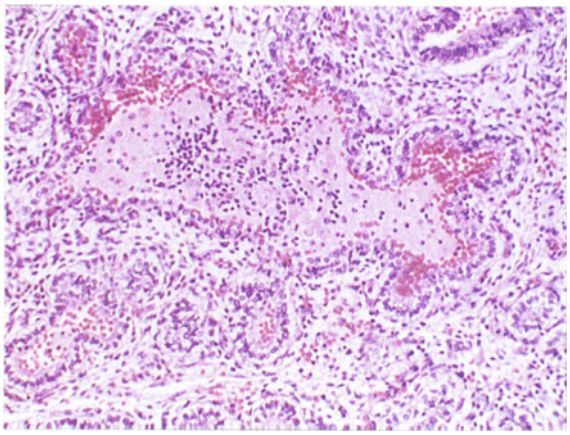
readily available measure is lung/body-weight ratio: below 28 weeks' gestation, a lung/bodyweight ratio of < 0.015 and one of < 0.012 at 28 weeks' of gestation or more, is indicative of hypoplasia The lungs should always be greater than 1.2% of bodyweight (Askenazi and Perlman 1979, Wigglesworth and Desai 1981). However, ratios need to be interpreted cautiously in the presence of pathology such as infection or significant postnatal survival.

Histomorphometrically, hypoplastic lungs demonstrate reduced radial alveolar counts (Emery and Mithal 1960) although this may be a difficult assessment as a "one-off" procedure and normal standards may vary (Cooney and Thurlbeck 1982).

Two patterns of histology in lung hypoplasia have been described (Wigglesworth et al. 1981). In the first pattern, the lungs appear immature as well as poorly grown. This manifests itself as narrow airways, retardation of epithelial differentiation and delay in development of blood–air barriers. Evidence suggests that this is due to failure of differentiation of undifferentiated cells into type 1 pneumocytes. In the second pattern, the lungs are poorly grown but maturation is appropriate for the gestation of the infant.

The poor maturation with poor growth pattern is especially associated with oligohydramnios-related hypoplasia. However, this simple division at the structural level may not always reflect events at the biochemical or functional level. For instance, the percentage of type 2 pneumocytes is similar in oligohydramnios associated hypoplastic lungs compared with normal controls. However, evidence of deficient surfactant production in the former, suggests there may be functional impairment of this cell type (Haidar et al. 1991). Functional impairment of type 2 pneumocytes may also occur in the hypoplastic lungs associated with congenital diaphragmatic hernia, particularly in the ipsilateral lung, and surfactant deficiency may contribute signficantly to the functional impairment (Wilcox et al. 1997).

Mechanisms and Causes of Lung Hypoplasia At first glance, the long list of associations and causes of lung hypoplasia show little in common, but the study of these seemingly disparate pathologies has contributed significantly to our understanding of normal lung growth (Wigglesworth 1987a, b) such that they can be classified in a more logical manner (Table 17.1).



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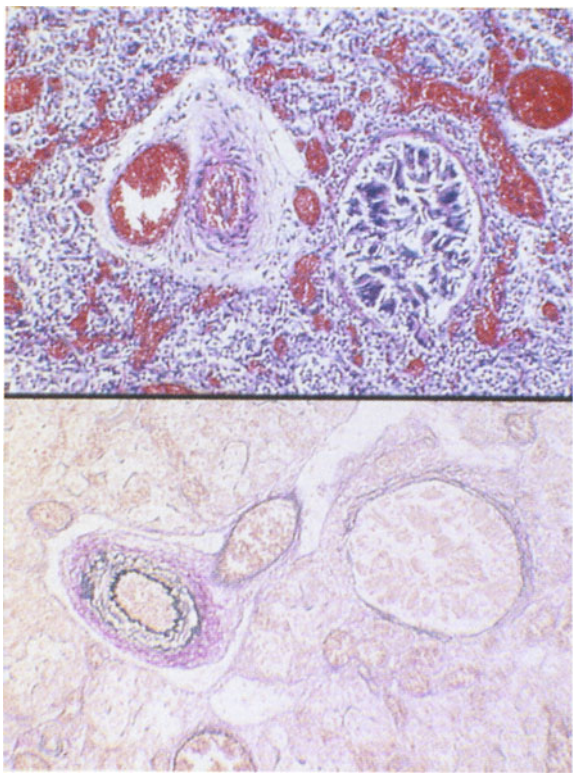


b

Fig. 17.14. **a** Heterotopic neural tissue in the airway of anencephalic fetus. This heterotopic material is probably aspirated. **b** Alveolar capillary dysplasia or misalignment of the pulmonary veins in a term baby dying at 14 days with severe pulmonary hypertension of uncertain aetiology. Pulmonary vein accompanies the pulmonary artery adjacent to a terminal bronchiole (Elastic van Gieson stain on right). Although congested, dilated capillaries are present within the interstitium, there is an absence or severe reduction in capillaries pushing into the alveolar wall.

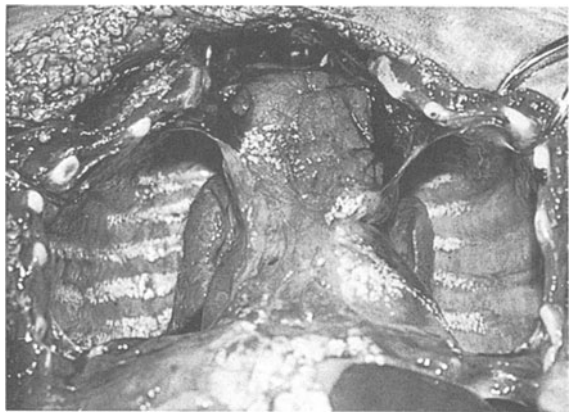


Fig. 17.15. Thoracic contents of a 33-week early neonatal death with idiopathic fetal hydrops. The pleural effusions have been removed to show marked bilateral pulmonary hypoplasia.

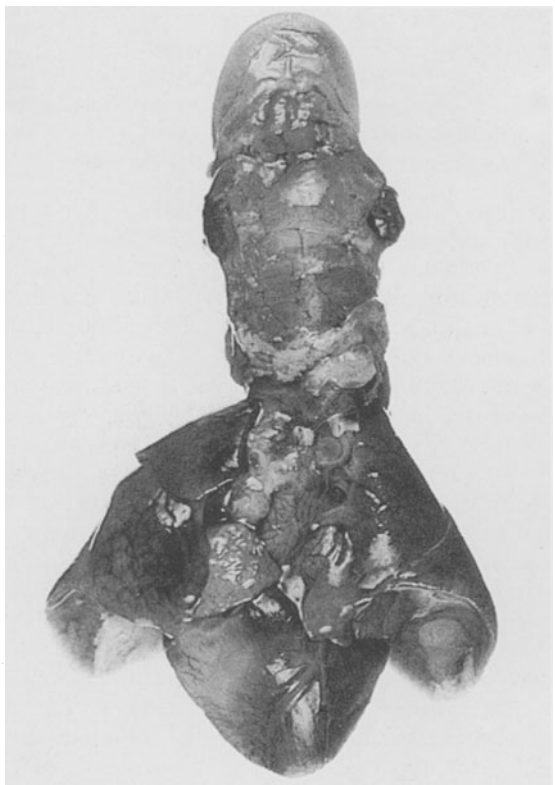
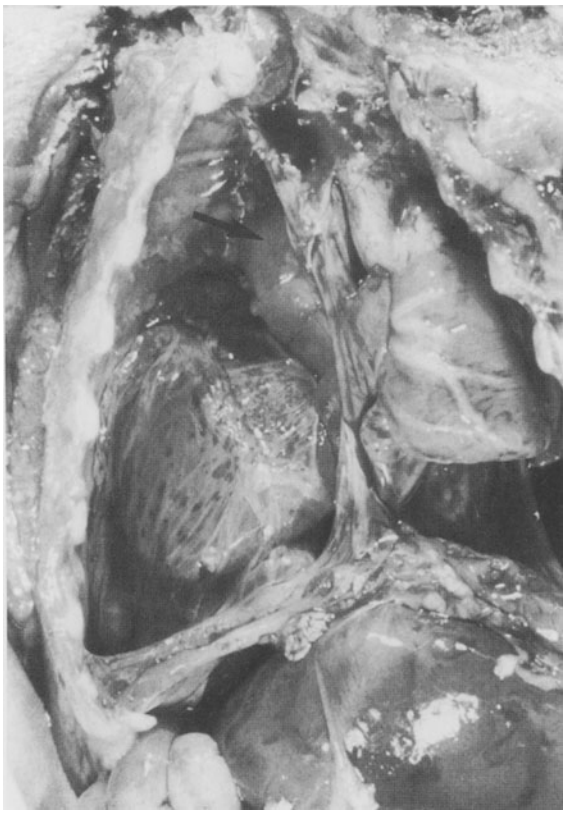


Fig. 17.16. Hypoplastic lungs in relation to the size of the heart. Normally, the inferior surfaces of the lungs and apex of the heart should all be at approximately the same level. From an early neonatal death at 26 weeks' gestation with renal agenesis.



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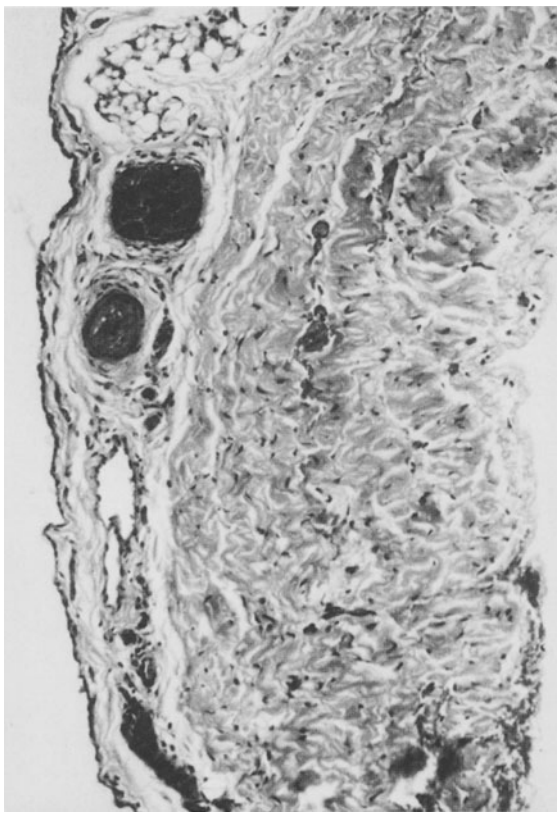

b

Fig. 17.17. **a** Eventration. Right hemidiaphragm is a thin glistening membrane through which the right lobe of the liver can be seen. There is mediastinal shift and the right lung is grossly hypoplastic (arrowed). In this case, the left lung was also hypoplastic (not visible). From a term infant dying at a few hours of age. **b** The membrane comprises fibrous diaphragmatic tissue only with no muscle.

Table 17.1. Mechanisms and causes of lung hypoplasia

Reduction in thoracic volume	Skeletal dysplasias	Thanatophoric dysplasia Achondrogenesis Asphyxiating thoracic dysplasia
	Pleural space lesions (often unilateral hypoplasia)	Diaphragmatic hernia Eventration Pleural effusions, e.g. in hydrops
Impairment of fetal breathing	CNS damage	Anencephaly involving brain stem Hypoxic–Ischsaemic injury
	Congenital muscular disease	Congenital muscular dystrophy
Oligohydramnios	Reduced production	Renal agenesis Renal cystic dysplasia Urinary tract obstruction
	Increased loss	Prolonged rupture of membranes
Primary/other	Idiopathic Cytogenetic Familial Growth retardation	Trisomy

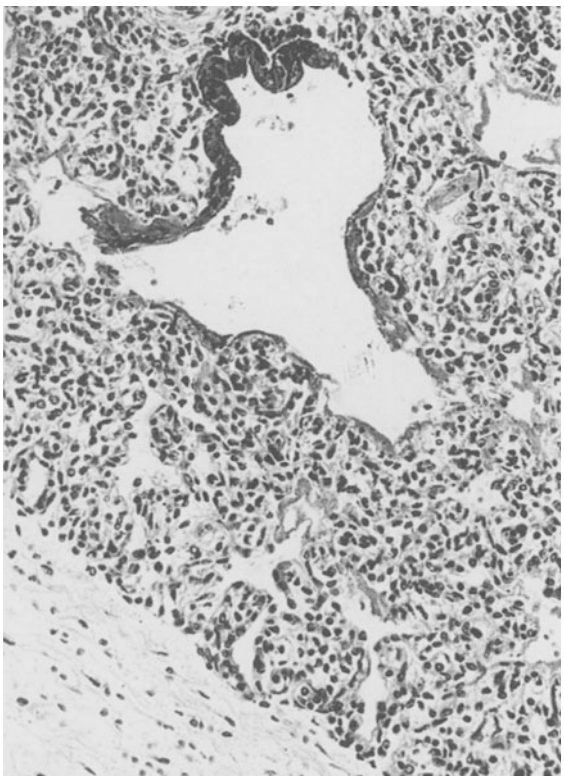

Fig. 17.18. Hyaline membrane disease in a 26 week's gestation neonate dying at 12 h of age. Necrotic respiratory bronchiolar epithelium lines part of a dilated airway. Hyaline membrane is also present at this level and more distally. In the most distal part of the lung, the air sacs adjacent to the pleura are collapsed but do not contain membrane.

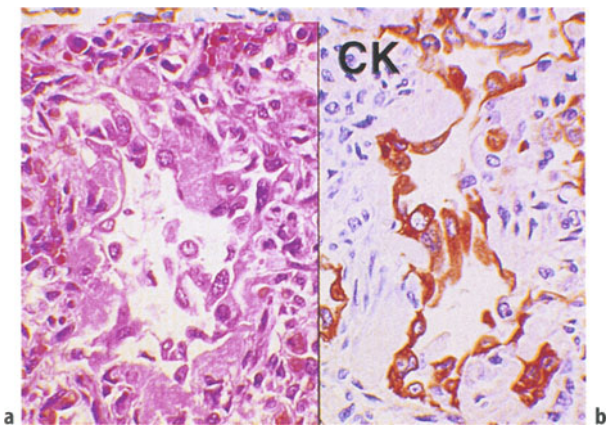

Fig. 17.19. a Hyaline membranes at 40 h of age. Reactive macrophages and some fibroblasts are present below the membranes. **b** Immunohistology for cytokeratin shows regenerating epithielial cells already covering the membranes – some membrane may be incorporated into the wall.

- Adequacy of thoracic volume: Not surprisingly, for lung to grow normally, it must have sufficient space in which to do so. Reduction in thoracic volume can be caused by poor rib growth, e.g. skeletal dysplasias; any space occupying lesion, e.g. an abnormal viscus associated with diaphragmatic hernia (Areechon and Reid 1963), eventration (Fig. 17.17) or pleural effusion associated with hydrops. With hernias and eventration, the hypoplasia is typically unilateral.
- *Fetal breathing*: In utero, the fetus normally makes bursts of rapid, but low-amplitude breathing movements, primarily diaphragmatic in origin. It is not entirely clear how or why such movements should be important to lung growth, but that they are, is strongly suggested by lung hypoplasia in conditions associated with their absence, or by experimental work in which the effects of fetal breathing are negated (Liggins et al. 1981). It has been suggested they allow influx of amniotic fluid or generate important pressure changes within the thorax (Wigglesworth 1987a; Kitterman 1984). The inter-relationship between normal fetal breathing movements, lung liquid and lung growth has recently been summarized (Hooper and Harding 1995).
- *Oligohydramnios*: Oligohydramnios due either to insufficient production or excessive loss of fluid (Hislop et al. 1979; Nimrod et al. 1984), is probably the commonest recognized single cause of lung hypoplasia. In the presence of premature membrane rupture, pulmonary hypoplasia is one of the main determinants of survival, especially in the very premature (Robson et al. 1993, Lauria et al. 1995). The mechanism is unclear. Previously thought to result from compression of the fetal thorax by the uterus, recent evidence suggests that, in oligohydramnios, a larger than normal pressure gradient between fetal lung and amniotic sac occurs and the eflux of fetal lung liquid is too rapid (Nicolini et al. 1989; Harding et al. 1990; Kizilcan et al. 1995). Lung liquid, retained within fetal airways and developing respiratory units, might act as a "stent" around which alveoli form.

The importance of intra-alveolar pressure can be seen in a rare combination of abnormalities sometimes found in Fraser's syndrome – laryngeal atresia or stenosis and renal agenesis. Despite the oligohydramnios due to renal agenesis which would be expected to cause lung hypoplasia, the lungs are not hypoplastic but are either of normal size or even hyperplastic. The laryngeal anomaly prevents the rapid loss of fetal lung liquid (Wigglesworth et al. 1987; Silver et al. 1988). This effect can be repro-

duced experimentally (Nardo et al. 1998) and is proposed as a possible approach to the in utero correction of pulmonary hypoplasia associated with, for instance,diaphragmatic hernia. Whether lung maturation is normal in these circumstances is uncertain (Piedboeuf et al. 1997).

It is rare for a specific cause of lung hypoplasia not to emerge from careful study although instances of "primary" pulmonary hypoplasia are recorded (Swischuk et al. 1979). Before a diagnosis of idiopathic or primary lung hypoplasia is entertained, some aspects of a case may be worth reassessing. In particular, the face (Potter's facies) or placenta (amnion nodosum) for evidence of oligohydramnios and radiographs for possible skeletal dysplasia. Pathology or malformation involving the brainstem should also be specifically looked for. Primary muscle disease may also be very easily overlooked (Devlieger et al. 1994).

In some instances there is evidence that there is a genetic basis for the poor lung growth; hypoplasia has been associated with chromosomal abnormality such as trisomy 21 and 18 (Page and Stocker 1982), recorded in families and sets of twins.

Acquired Pathology

Broadly, the acquired pathology of the respiratory tract can be related to pulmonary immaturity, the consequences of birth asphyxia or infection. Superimposed on this can be the effects of therapy especially, with respect to the lungs, ventilation. Where the underlying pathology of lung and pathology of therapy are inextricably combined, it will be described here. A more detailed discussion of underlying mechanisms and pathology such as the direct effects of intubation will be considered elsewhere (Chap. 14).

Pathology of Immaturity

As discussed above, there are two aspects of pulmonary immaturity which together lead to respiratory problems: physical immaturity with inadequate surface area for efficient gaseous exchange and, as importantly, biochemical immaturity. Surfactant production may be inadequate and a lack of antioxidant defences may increase susceptibility to injury.

The lungs of most immature infants who have survived more than a few hours will demonstrate pathological changes but occasionally they will be histologically normal. This is usually confined to the extremely preterm infant of around 23–25 weeks' gestation, in whom death has occurred within minutes or hours of birth. Death may be attributable to pulmonary immaturity alone.

Respiratory Distress Syndrome

The terms respiratory distress syndrome (RDS) and hyaline membrane disease (HMD) are frequently used interchangeably. However, for clarity, RDS should be considered a clinical term reflecting respiratory insufficiency in the premature infant. It describes a constellation of symptoms: increased respiratory rate, sternal and subcostal recession, cyanosis and grunting which does not resolve within 24 h. Radiographically there may be pulmonary collapse and an air bronchogram.

The majority of cases (75–80%) are associated with hyaline membrane disease, but, among others, respiratory distress can be caused by infection, birth asphyxia, massive pulmonary haemorrhage and cerebral intraventricular haemorrhage

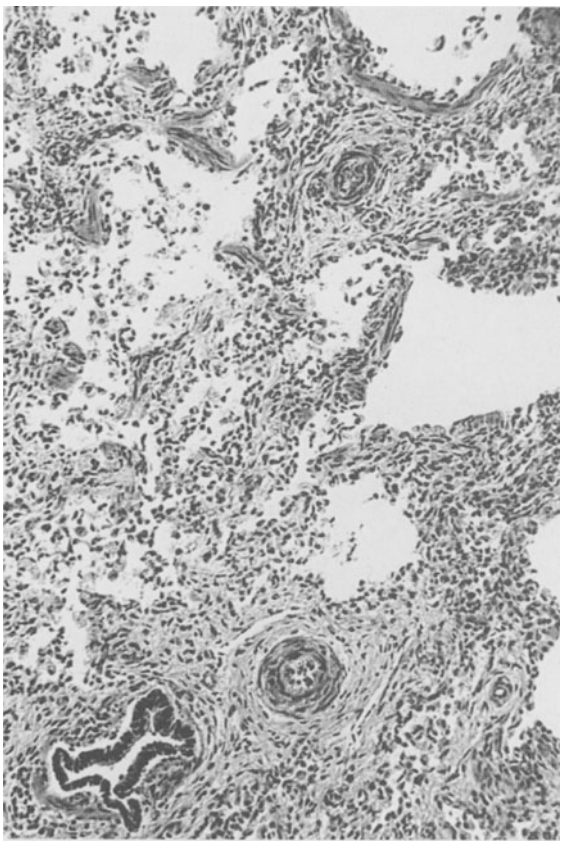

Fig. 17.20. Bronchopulmonary dysplasia in an infant dying at 3 months of age. Interstitium shows striking fibrous thickening and the small pulmonary artery is thick walled. The adjacent terminal bronchiole is normal.

(Wigglesworth 1977). It is possible that some babies die from other major problems before hyaline membranes develop.

Hyaline Membrane Disease

Hyaline membrane disease (HMD) is a pathological term describing the presence of eosinophilic amorphous material lining the terminal airways of the neonate. It is usually seen in the lungs of very preterm infants (Farrell and Avery 1975), and most commonly associated with surfactant deficiency. However, it can also be associated with severe acute asphyxia, some forms of pulmonary infection and pulmonary haemorrhage. It is almost invariably accompanied by respiratory distress although the clinical syndrome may be obscured if the infant is ventilated.

HMD associated with surfactant deficiency, usually presents an hour or so after birth with respiratory distress. With the exception of the most immature, the majority of infants will survive with appropriate ventilatory therapy, unless additional pathology such as intraventricular haemorrhage supervenes. Ventilation is often required for a few days, but towards the end of the first week, and presumably reflecting a resurgence in surfactant levels, ventilatory requirements decrease.

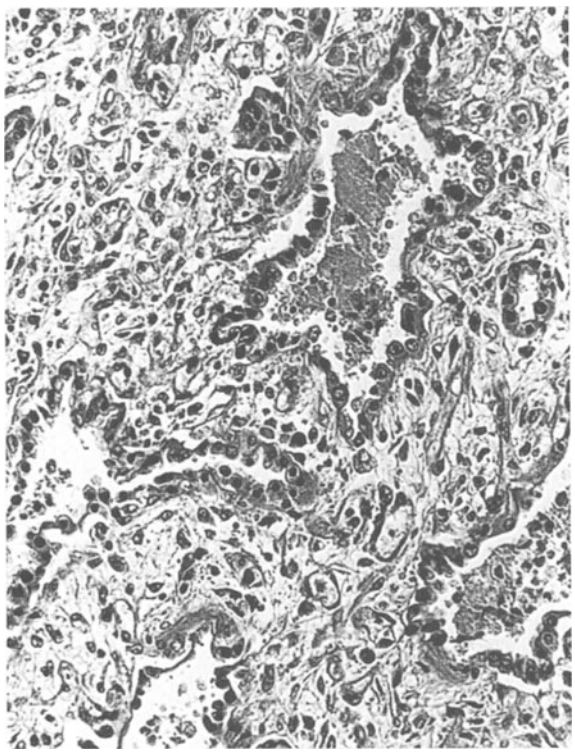

Fig. 17.21. Striking cuboidal metaplasia associated with bronchopulmonary dysplasia.

Should infants die within a few hours of onset of the disease, the lungs are collapsed, heavy and red/purple in colour – their texture resembling that of liver. Microscopically, the lungs are collapsed, but with many dilated terminal airways. Necrotic bronchial or bronchiolar epithelium is the earliest feature and may be seen before hyaline membranes develop (de la Monte 1986). They may become dislodged and plug more distal airways. The eosinophilic HMs lining the terminal airways are present within an hour or so of birth and often contain nuclear debris of necrotic epithelium (Fig. 17.18). Membranes are not usually seen in the terminal sacs, which are collapsed. After a few hours the presence of polymorphs and macrophages in the interstitium is marked with some spillage into the airways, although the inflammatory changes may not be conspicuous by routine histology (Murch et al. 1996a).

In infants dying at a day or two of age, the lungs show evidence of repair and regeneration. Macrophages ingest membrane (membranophages) but also accompany the fibroblasts proliferating beneath the HMs. Subsequently, regenerating cuboidal epithelium (type 2 pneumocytes) is apparent, often growing over residual HMs which are incorporated into the bronchiolar walls (Fig. 17.19).

In some cases, the hyaline membranes may be bright yellow, particularly on the luminal surface. Jaundice is not always present, but is due to the incorporation of albumen bound bilirubin into the hyaline membranes (Blanc 1976).

Pathogenesis of Hyaline Membrane Disease Hyaline membranes are composed of necrotic debris, and a proteinaceous precipitate of plasma including some fibrin. For the pathologist, they are the most outward expression of a complex pathophysiological process. The acute transudation from capillaries adjacent to the terminal airways reflects damage to epithelium and endothelium, whose integrity is necessary to form an impermeable barrier between the vasculature and the airways. What produces the damage is not entirely clear. It is presumed that either in the infant's attempts to breathe or because of the positive pressure from the ventilator, the terminal airways expand and shear forces damage the lining epithelium (Robertson 1991). The toxic effect of oxygen might also contribute or the epithelial damage may reflect a "reflow" injury following a period of local ischaemia. That ischaemia may be contributory in some instances is suggested by evidence of increased pulmonary intravascular

coagulation (Schmidt et al. 1992). The very terminal parts of the respiratory units, i.e. the air sacs, fail to expand because surface tension, which acts to collapse these small "spheres", is too great to overcome in the absence of surfactant.

Recent years have seen the almost universal adoption of surfactant replacement therapy to treat HMD in the immature infant. Its use has seen a major reduction in morbidity and perinatal mortality of up to 65% with no significant complications except perhaps a slight increase in pulmonary haemorrhage (Greenough and Roberton 1996). Where infants do die with clinical HMD, other than a possible reduction in the amount of hyaline membranes, no difference in the lung pathology can be detected between babies who have or who have not had surfactant replacement (Pinar et al. 1994; Thornton et al. 1994).

Bronchopulmonary Dysplasia and Chronic Lung Disease

The terms bronchopulmonary dysplasia (BPD) as described by Northway et al. (1967), and chronic lung disease (CLD) are frequently used interchangeably with CLD currently tending to be the more preferred term. Definitions of CLD are clinical, and while the precise definition varies from study to study, it implies an infant that: has appropriate chest radiological change; requires some form of ventilatory support, such as an oxygen requirement for more than a defined period, usually about 28 days; the ventilatory support follows a defined acute lung disease in the first week of life requiring mechanical ventilation. In most cases this will be hyaline membrane disease. Consequently, the incidence varies depending on definition but it does appear to be increasing, possibly because of averted neonatal death from improving therapies (Yu and Ng 1995).

Early pathological descriptions of BPD describe lung changes in three phases: an exudative phase from days 3 to 9; a subacute fibroproliferative stage from days 10 to the end of the first month; a chronic fibroproliferative phase from the end of the first month. In these descriptions, the more aggressive, early phases of BPD barely imply "chronic" lung disease at all. The more florid early stages are now very rarely seen pathologically and this reflects the significantly improved early management of the immature lung. Further, it is questionable that many of the infants, that eventually die with chronic lung disease, have ever passed through clearly recognizable exudative or fibroproliferative phases.

Clinically, the infants destined to develop CLD may not always be easy to identify at an early stage. There may be a more severe acute episode of respiratory disease after which, although the early ventilatory requirements fall, pulmonary permeability fails to return to normal and the infant continues to require ventilatory support. Broncho-alveolar lavage studies indicate a higher level of inflammatory and oxidant markers associated with the acute lung injury in those infants that progress to chronic lung disease (Contreras et al. 1996; Murch et al. 1996b) compared with those that do not. The infant may eventually die after many months either because support is withdrawn or the development of pulmonary hypertension and cor pulmonale.

Factors suggested to be associated with increase risk of CLD includes early, prenatal lung inflammation (Watterberg et al. 1994; Matsuda et al 1997), the too early use of intralipid during parenteral nutrition which may interfere with oxygenation (Cooke 1991; Stahl et al. 1992) and lung colonization with *Ureaplasma urealyticum* (Wang et al. 1995).

Pathology

- *Major airway injury:* Severe bronchial and bronchiolar damage is characterized by necrosis

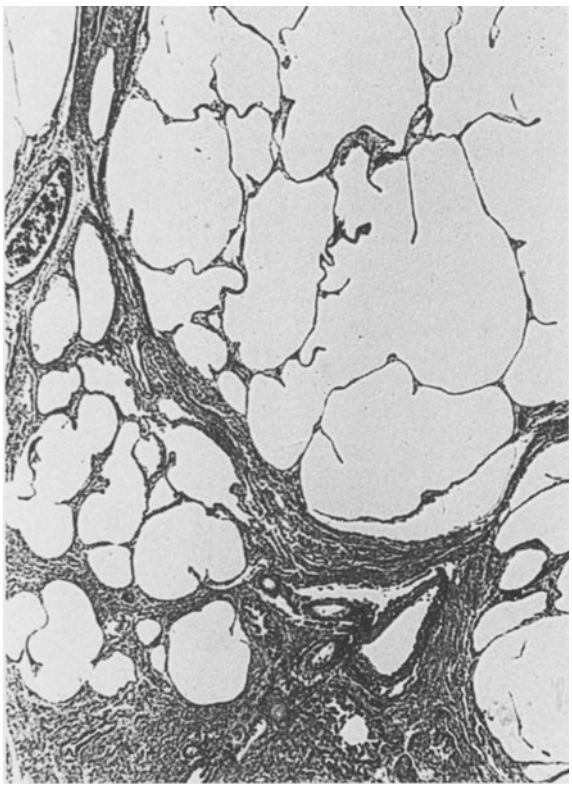

Fig. 17.22. Bronchopulmonary dysplasia. An area of emphysema.

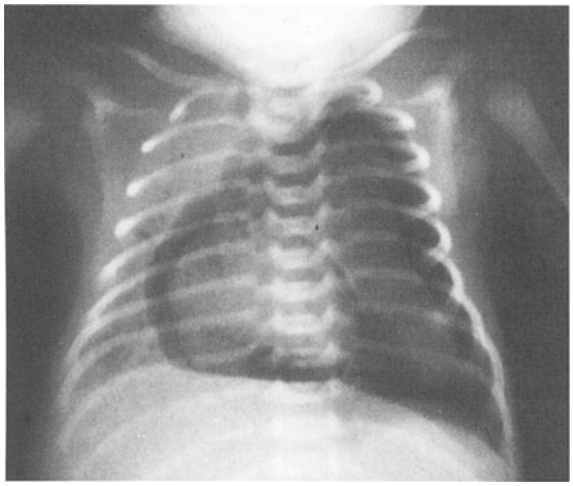

Fig. 17.23. Chest radiograph from a baby at 28 weeks gestation; there is air within the left pleural and pericardial cavities.

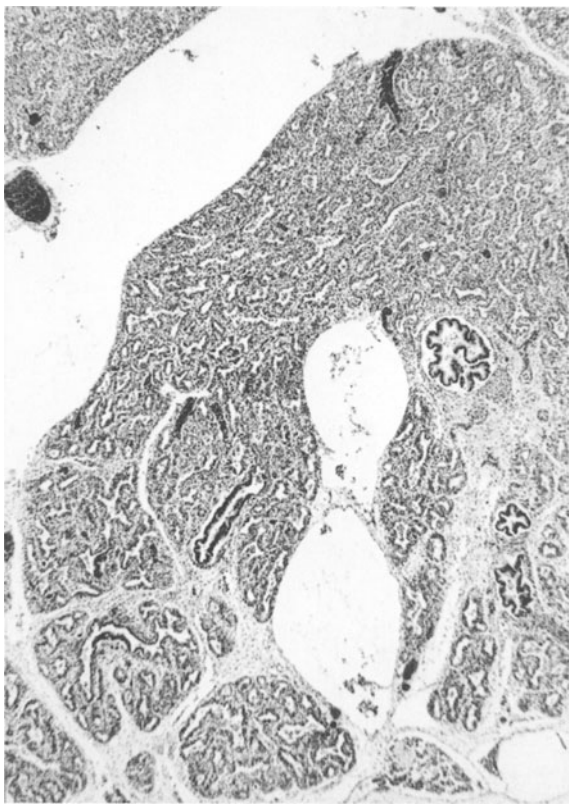

Fig. 17.24. Lung from a 25-week early neonatal death showing emphysema and air within septal lymphatics tracking to the subpleural region.

associated with an obliterative bronchiolitis, squamous metaplasia and collapse of lung tissue distal to the obstructed airway (Bonikos et al. 1976; Taghizadeh and Reynolds 1976). It is a relatively acute phenomenon, with the necrosis occurring in the first few days of life. Its frequency in earlier descriptions of BPD probably reflects ventilatory management then current, and the relatively high inflationary pressures. In infants who now die with chronic lung disease and demonstrate an obliterative bronchiolitis a history of severe difficulty in maintaining ventilation can usually be obtained. Morphometric study suggests that the major persistent airway lesions identifiable are bronchial gland hyperplasia and peribronchiolar smooth muscle hyperplasia (Hislop and Howarth 1989; Margraf et al. 1991)

- *Distal respiratory unit and interstitium:* The most prominent component of the lung injury is a widespread but occasionally patchy interstitial oedema and fibrosis (Fig. 17.20) associated with cuboidal metaplasia (Fig. 17.21). Early ventilatory inequality may give rise to areas of relative collapse and fibrosis accompanied by more distended emphysematous lung (Fig. 17.22). Special stains will show increase in the elastic tissue usually in the form of thick plaques at points of bronchiolar or alveolar duct division. The interstitial damage forms a continuum with the repair processes associated with the acute lung injury. Some infants dying after a number of months, may show relatively little overt alveolar damage. There may be a dramatic increase in the size of alveoli reflecting impaired development and an increase in connective tissue can sometimes be demonstrated by special stains.
- *Vasculature:* Arterial muscular hypertrophy and adventitial thickening of small pulmonary arteries may come to be the most significant component of the infant with chronic ventilator dependence (Fig. 17.20) (Hislop and Haworth 1990). In some cases, there is evidence of a reduction in peripheral arterial density, possibly due to failure of normal post-natal recruitment (Gorenflo et al. 1991). Eventually, pulmonary hypertension and cor pulmonale develop, although there may not always be good correlation between the occurrence of cardiac complications and the pulmonary histology.
- *Pathogenesis:* BPD as a distinct entity, emerged primarily following the introduction of ventilatory support. It results from a combination of barotrauma and oxygen toxicity that interferes with normal growth and repair mechanisms following acute lung injury. Inflammation is an

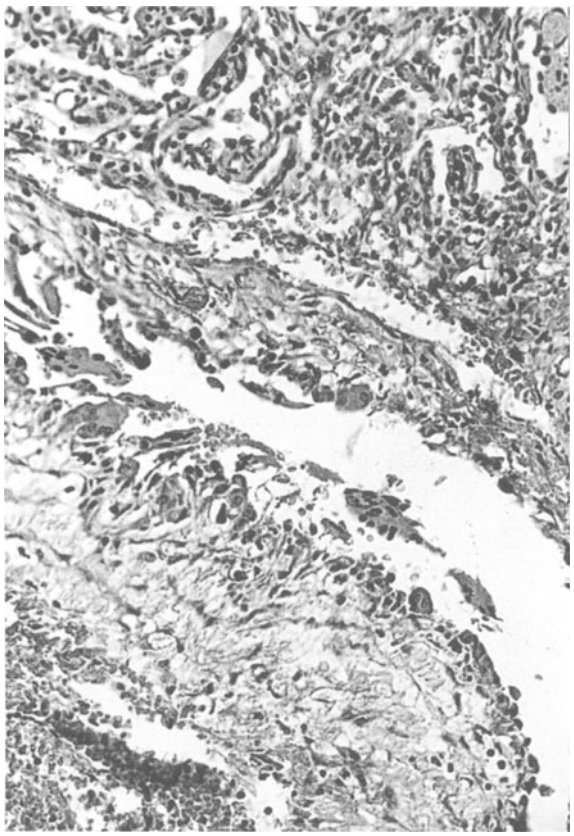

Fig. 17.25. Partially collapsed old cyst resulting from interstitial emphysema. Cyst wall is formed of thick fibrous tissue and lined by macrophages including giant cells.

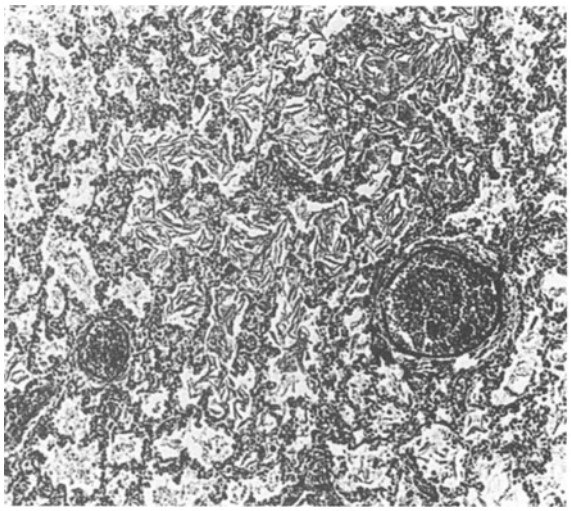

Fig. 17.26. Lung from a fresh stillbirth at 37 weeks gestation. Airways are unexpanded and aspirated squames are present in air spaces.

Fig. 17.27. Terminal bronchiole from term infant containing squames, mucin, and granular material typical of meconium aspiration.

early response to mechanical injury , and an increase in a wide range of cellular and chemical mediators can be demonstrated (Groneck and Speer 1995; Saugstad 1997). While it is not possible to dissociate entirely the mechanical effects of ventilation from the effects of hyperoxia, high inflationary pressure may well be the most significant factor in the obliterative bronchiolar lesions (Taghizadeh and Reynolds 1976; Saugstad 1990).

Cellular metabolism produces oxygen related toxic radicals such as OH^- and O_2^- and singlet oxygen. In the lung, there are probably two main sources of toxic radicals: from neutrophils or macrophages as a product of inflammation, and as a by-product of normal pulmonary epithelial or endothelial metabolism. Tissue production of free radicals will be enhanced in the presence of high oxygen concentrations and damage accentuated in the absence of normal cellular antioxidant defences. The precise mechanism by which tissue damage leads to interstitial fibrosis is unclear,

but it may cause an increase in capillary permeability, and fluid leakage with subsequent organisation. Platelet-derived-growth-factor may be produced by the interstium in response to hyperoxia and stimulate early fibroblast hyperplasia (Han et al. 1992). Inactivation of surfactant may also be important (Saugstad 1990; Contreras et al. 1996; Merritt 1982).

Air Leaks

The use of positive pressure to maintain lung inflation during hyaline membrane disease, may lead to tearing of delicate respiratory tissues. Air leakage into the pleural cavities can be a cause of sudden collapse (Fig. 17.23). Particularly if under tension, a pneumothorax can interfere with venous return and seriously impair cardiac output causing intracerebral complications. Rapid drainage of air is important, but occasionally drains may damage pulmonary parenchyma.

Pulmonary interstitial emphysema (PIE), when air passes into pulmonary tissues, may track in pulmonary lymphatics and, by compression of adjacent lung, seriously impair ventilation (Fig. 17.24). Clinically, it may produce a dilemma as excessive ventilatory pressure may exacerbate PIE, whereas the same pressure may be necessary to maintain lung expansion elsewhere. Persistent PIE may loculate and stimulate a giant cell reaction and fibrosis (Fig. 17.25). Often at postmortem, due to resorption, PIE is less impressive than the pre-mortem radiographs might lead one to expect.

Pulmonary Haemorrhage

In pretem infants dying during the acute phase of lung injury, some pulmonary haemorrhage is a common finding in the terminal sacs and pulmonary interstitium, especially associated with hyaline membrane disease (Coffin et al. 1993). Haemorrhage may also occur into the dilated pulmonary lymphatics. In some cases massive haemorrhage is a terminal event. It may be associated with birth asphyxia or haemorrhagic disease of the newborn. Although the pathogenesis is not certain, pulmonary haemorhage may represent a haemorrhagic pulmonary oedema (Cole et al. 1973) and reflect terminal heart failure.

Pathology of Birth Asphyxia

Birth asphyxia has recently been defined as a condition of impaired blood gas exchange leading to progressive hypoxaemia and hypercapnia with a

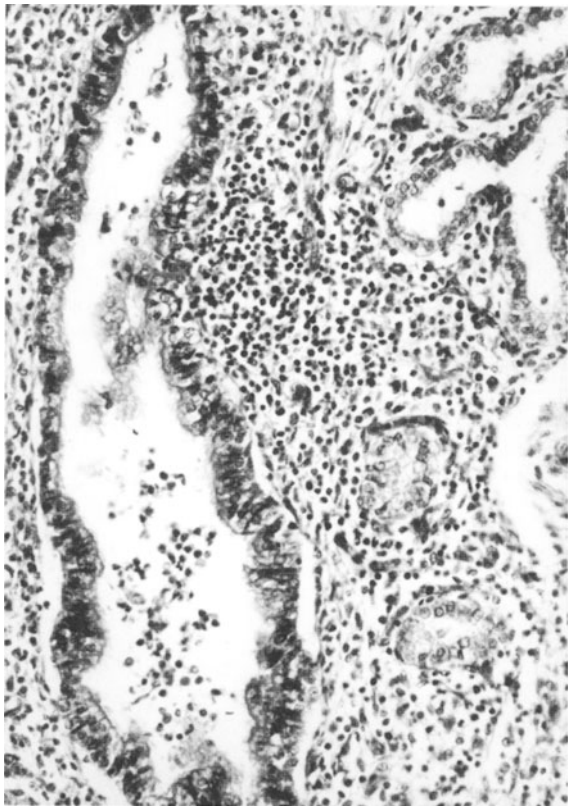

Fig. 17.28. Ascending infection in lung from 20 week's gestation spontaneous abortion. A few polymorphs are visible in the airway and evidence of a more chronic response is present with an adjacent interstitial lymphocytic aggregate.

significant metabolic acidosis (Low 1997). It typically presents in the term neonate, but may occur in the premature infant and compound the effects of organ immaturity. Evidence of acute asphyxia may also be observed in the lungs of stillborns.

Hypoxia stimulates deep gasping movements allowing movement of amniotic fluid into the airways and more terminal respiratory units (Harding et al. 1990). Amniotic fluid normally contains fetal squames and these are readily visible in the lungs of stillborns and neonates (Fig. 17.26). A few squames are a common finding and may not be very informative, but large plugs do suggest the occurrence of acute asphyxia, often as a terminal event.

Meconium Aspiration Syndrome

Meconium aspiration syndrome (MAS) is the major respiratory complication of acute asphyxia. Meconium is released from the fetal gut into the amniotic fluid near term in approximately 10–15% of infants. It is rarely seen before 34 weeks and if

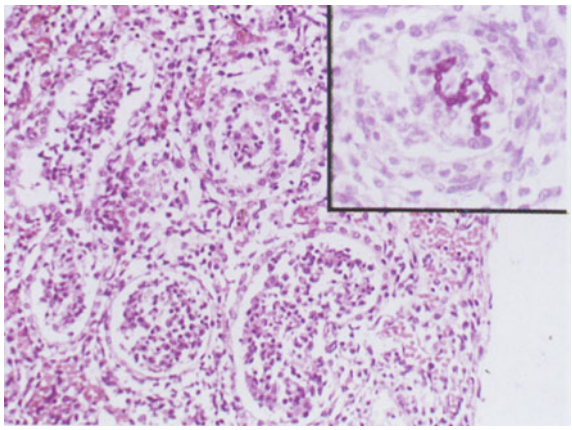

Fig. 17.29. Florid pneumonia associated with ascending infection in a 17 week's gestation fetus. Inset shows typical *Candida* (PAS stain).

seen earlier may be associated with infection. Release has been attributed to reflex anal dilatation from acute hypoxia but this is disputed (Danielian 1994) and meconium-stained liquor may simply reflect maturity. Only a small proportion of infants born with meconium stained liquor will exhibit evidence of aspiration and meconium in the liquor may only be of significance if it is thick and heavily stained.

In neonates, meconium aspiration causes respiratory distress from a number of mechanisms including airway obstruction with distal pulmonary collapse or pneumothorax; inhibition of surfactant (Moses et al. 1991) and predisposition to infection (Romero et al. 1991). Pulmonary hypertension may be a serious complication due, at least in part, to hypoxic vasoconstriction of pulmonary arteries.

There is unresolved debate as to the usual timing of meconium aspiration (Wiswell et al. 1990; Katz and Bowes 1992). On the basis that aspiration occurred at birth, resuscitation strategies to prevent meconium passage into the lungs have met with limited success, and many authors have stressed that aspiration is an antepartum event associated with evidence of antepartum hypoxia elsewhere such as in the placenta (Thureen et al. 1997). Further, the clinical part of MAS due to pulmonary hypertension, may reflect antepartum structural changes in pulmonary arterioles resulting from chronic intra-uterine hypoxia (Murphy et al. 1984; Thureen et al. 1997).

At necropsy, asphyxia is suggested by petechial haemorrhages, sometimes confluent, on the pleura surfaces of the lungs. The cut surfaces may show congestion and oedema. When substantial meconium aspiration has occurred, the lungs are heavy, mottled and careful inspection may reveal areas of overdistension with yellow–green meconium expressible from airways.

In stillborn infants, acute asphyxia may precipitate amniotic fluid inhalation with substantial plugs of fetal squames throughout the lung (Fig. 17.27). More rarely, meconium will also be present as eosinophilic granular material, with small yellowish meconium bodies and mucus (Fig. 17.27). While a few macrophages may be associated with this material, an acute inflammatory infiltrate is rare.

In neonates, meconium aspiration may be accompanied by patchy hyaline membranes associated with the acute hypoxia. If the infant survives the early neonatal period, an acute inflammatory response may develop although it may not uniformly accompany the meconium. The cause of this pneumonia is not entirely clear. It is probable that meconium causes a chemical pneumonitis possibly due to the bile salt content (Oelburg et al. 1990) but features such as the patchy distribution of the inflammation and rarity of inflammation in the meconium stained lungs of stillborns suggests that in many situations the pneumonia is due to infection. Typically the vascular changes of pulmonary hypertension are also present (see below).

Persistent Pulmonary Hypertension

Persistent pulmonary hypertension of the newborn reflects a failure to reduce or maintain a reduction in the normal post-natal fall in pulmonary vascular resistance. Cyanosis and respiratory distress may develop after birth, although there may be an initial period of apparent normality. There is right to left intrapulmonary shunting but also across the foramen ovale and the ductus arteriosis (if it remains patent). Because of this latter feature, the condition is often referred to as persistent fetal circulation (Gersony 1973).

Usually it is associated with other abnormalities such as congenital heart disease or congenital alveolar capillary dysplasia (see above). A more common association is lung hypoplasia where, it is assumed, there is a failure of the normal development of the pulmonary circulation and a reduced vascular bed. Other, mechanisms may also be involved (Doolin et al. 1995). It may also occur in association with sepsis, pneumonia, hyperviscosity, acute hypoxia with meconium aspiration, and hypoglycaemia. Rarely it may be idiopathic although it has been argued this does not exist (Perlman et al. 1989).

Idiopathic PPHN and the hypertension associated with MAS may be associated with vascular changes

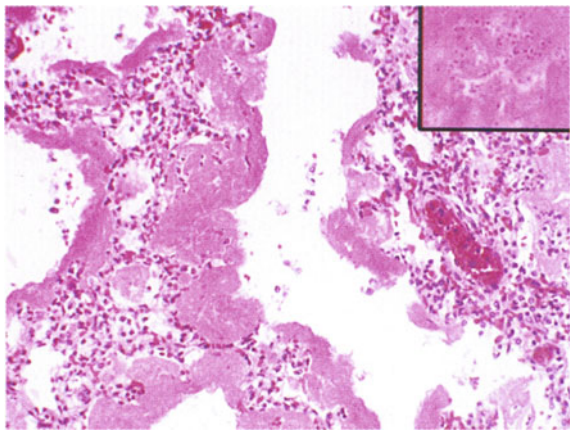

Fig. 17.30. Dense hyaline membranes in term infant dying at approximately 12 h of age from overwhelming Group B streptococcal infection. Under high power (inset) bacteria are visible in the membrane.

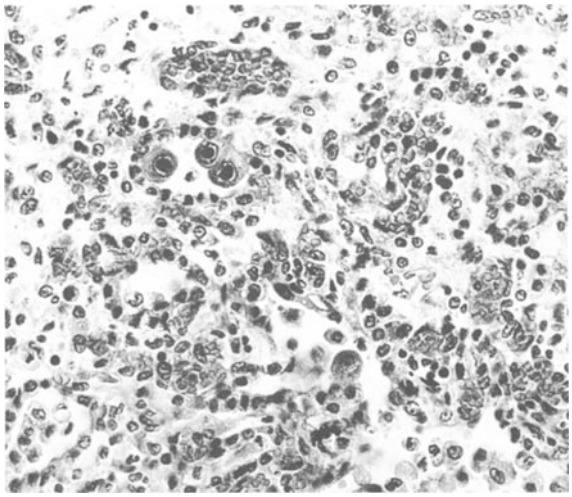

Fig. 17.31. Cytomegalovirus inclusions in the lung of an infant dying from chronic lung disease. The infection is nor congenital and was acquired whilst the infant was on the neonatal unit.

of prenatal origin, possibly due to intrauterine chronic hypoxia. The preacinar and intra-acinar pulmonary arteries and arterioles show medial hyperplasia with extension of smooth muscle into precapillary vessels (Murphy et al. 1984; Raine et al. 1991; Thureen et al. 1997). Nerve fibres have been found at a more distal location than normal (Raine et al. 1991).

Infection

The newborn infant is susceptible to infection, particularly if very preterm or suffering from growth retardation. Infection may be acquired in utero, intrapartum or in the neonatal period and, whilst the lung may not always demonstrate the most significant pathology, pulmonary involvement is frequent. In utero, transmission to the fetus is by two main routes – ascending through the maternal uterine os and transplacentally from the maternal circulation (Zaaijman et al. 1986).

Ascending Infection

Abortion and Stillbirths Evidence of an ascending infection is a common feature of spontaneous abortions particularly before 24 weeks' gestation, and chorioamnionitis may be found in up to 20–30% of cases. There are often no specific macroscopic features although effusion, which may be blood-stained may be associated with infection in stillborns. It should not be mistaken for the effusions associated with maceration.

Microscopically, the fetal lung may show a few polymorphs within the airways only or the infiltrate may be sufficient to be designated a pneumonia. Acute interstitial reaction is usually present but less obvious histologically. Studies have shown the airway cellular reaction is fetal in origin, not aspirated maternal cells as formerly believed (Grigg et al. 1993). A more chronic reaction may occur in the interstitium with both haemopoietic cells or lymphocytic aggregates (Fig. 17.28). The latter, which are typically closely applied to the bronchial epithelium, has parallels with the Peyer's patch of the gut. These infiltrates are probably always a reaction to ascending infection even if an acute reaction is not detectable (Gould and Isaacson 1993; Sgrignoli et al. 1994).

The infecting organism may be a common gastrointestinal commensal such as *Escherichia coli*, or a vaginal commensal such as Group B streptococcus. *Candida* infection may produce superficially non-specific but usually very florid pneumonia in which the characteristic hyphae can be seen (Fig. 17.29). Frequently, especially in abortuses, no organism is cultured despite florid histological evidence of infection. *Mycoplasma*, *Ureaplasma* or even *Chlamydia* (Gravett et al. 1986; Lamont et al. 1987; Cassell et al. 1993) may be involved in a proportion of cases.

Neonate Neonatal infections are frequently divided, clinically, into early or late onset. Early-onset pneumonia reflects an ante or intrapartum acquired organism. Symptoms usually start within a few hours after birth but can be delayed for up to 48 h. Most bacterial infection produces a typical

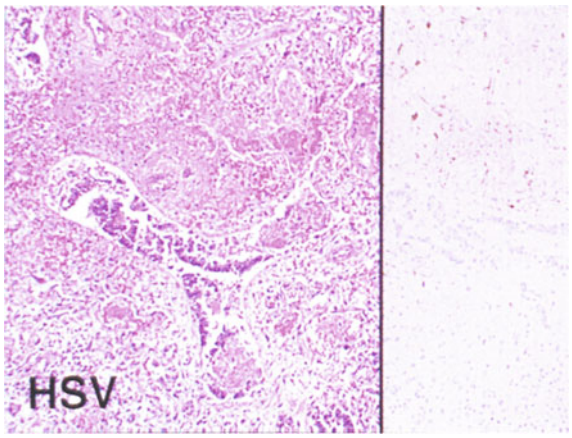

Fig. 17.32. Herpes simplex virus (type 2) in lung from an infant with disseminated disease, Inclusions are difficult to find, the necrosis is bland and there is little associated inflammatory reaction. Immunihistology shows the presence of viral antigen confined mainly to the areas of necrosis.

non-specific bronchopneumonia although some organisms produce characteristic features. Group B streptococcus (GBS) , normally an innocuous vaginal commensal, is a particularly virulent organism in the neonate. Death may be very rapid following acute collapse and may mimic perinatal asphyxia. Developing pulmonary infection may cause respiratory distress, indistinguishable clinically and radiographically, from surfactant deficient hyaline membrane disease (Ablow et al. 1976). Subsequent problems include pulmonary hypertension, reduced cardiac output and systemic hypotension. Many of the cardiovascular effects of GBS may be mediated by tumour necrosis factor (Gibson et al. 1991). Although usually sensitive to antibiotics, deterioration and death from GBS may supervene before effective control has been achieved.

If onset of infection and death are very rapid, the lungs may show surprisingly little by way of pathology other than congestion and oedema. Small patches of inflammation within major airways may be suggestive and careful examination with a gram stain, may reveal a few organisms. Longer survival is associated with the more typical picture of bronchopneumonia although hyaline membranes, often containing abundant stainable organisms giving a blue tinge to the membranes, may dominate some areas (Fig. 17.30).

The pathology of late onset pneumonia is similar to that of early onset but with a different range of organisms. *Pseudomonas* is a frequent colonizer of neonates but can cause a severe pneumonia. Histologically, areas of more typical pneumonia may be associated with striking growth of the organism in vessel walls. Haemorrhage and infarction can result from vessel thrombosis (Teplitz 1965). *Proteus* may do the same.

Other bacterial infections with characteristic appearances include *Listeria monocytogenes* . Involved as part of disseminated disease, the lung may show the typical granulomatous abscesses involving parenchyma and vessels as seen in other tissues (Vawter 1981; Khong et al. 1986). Congenital syphilis is not common in most developed countries, but should be considered as a cause of a congenital pneumonia where there are interstitial infiltrates of lymphocytes, plasma cells and "onion-skinning" of pulmonary arteries (Oppenheimer and Dahms 1981). This "pneumonia alba" will usually only be one manifestation of the disease and histological evidence of syphilis is likely to be present elsewhere such as in the liver or pancreas.

Fungal Infection

Pulmonary *Candida* occurs either as a manifestation of an ascending infection and amniotic fluid infection, or as a component of systemic candidiasis (Keller et al. 1977; Kassner et al. 1981; Whyte et al. 1982). In the former case, the infection is a typical bronchopneumonia in which fungal hyphae can be identified (Fig. 17.29). In systemic infection, the vasculature will usually be the prime site of infection from septic emboli.

Viral Infection

Most viral infections can affect the lungs, but other tissues or organs will often demonstrate more characteristic or extensive damage. Particularly in abortuses or stillbirth, however, pulmonary histology is often better preserved than elsewhere and useful to detect parvovirus.

Congenital cytomegalovirus (CMV) may produce a pulmonary interstitial infiltrate of mononuclear cells associated with the typical inclusions in macrophages and epithelial cells. More commonly, CMV is encountered in infants who have been long-term residents of the neonatal unit, having required ventilation for chronic lung disease (Fig. 17.31). The inclusions may be sparse and in the context of some cases it may be difficult to determine the contribution of the CMV to the lung damage.

Herpes simplex virus may be acquired antenatally or during passage through the birth canal. Babies typically present at the start of the second week of life. The organs most typically affected and showing virally induced necrosis are the liver and adrenals, but the lung also may be involved. The lung may appear normal macroscopically or show

small white necrotic foci. Microscopically, there may be a pneumonitis or hyaline membrane disease. The necrosis is often bland and the extent of the viral infection not readily apparent unless specific immunohistology performed (Fig. 17.32).

Other viruses are generally very rare in the neonatal period. Respiratory syncytial virus (RSV) is normally seen in older infants but may be found in neonates in association with chronic lung disease or congenital heart disease (Hall et al. 1979). Features include bronchiolar plugging with mucus, epithelial desquamation, inflammatory changes and giant cells lining distal airways. Enteroviruses, including Coxsackie and echovirus subtypes have all been reported as causing an acute neonatal pneumonitis probably acquired during birth from maternal secretions (Modlin 1986; Abzug et al. 1990). The illness may be very severe and resemble a bacterial pneumonia clinically. Coronavirus has been implicated in one report associated with chronic lung disease (Sizun et al. 1994).

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