20
The Respiratory System

Steve J. Gould

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 often needs 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 complications 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 is to release pleural air under water. This can often be achieved easily by immersing the 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 esophagus, tracheoesophageal fistulas. After removal of the esophagus, the form of the tracheal rings should be checked for either complete rings or rings with large posterior pars membranacea that might accompany tracheomalacia. My preference when examining for laryngeal anomalies, especially when suggested by the history or presence of pulmonary hyperplasia (vide infra), is to cut the larynx transversely into three or four blocks for 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 or abnormality of lung growth (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. While histoanatomic discussion inevitably dominates the approach to respiratory development, it is important to consider the maturation of vital biochemical pathways, the immaturity of which contributes significantly to the postnatal morbidity and mortality of preterm infants.

Upper Respiratory Tract

The nose and mouth commence development at 5 weeks postconceptional age and are derived from five main facial processes: a fused pair of frontonasal prominences, and 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 primitive mouth, or stomatodeum. On either side of the midline of the frontonasal process, thickening of the epithelium forms circular nasal disks 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 signaled epithelial differentiation (Ferguson et al. 1992; Rice et al. 2004).

The larynx develops separately but at the same time from the endodermal lining of the laryngotracheal tube and the mesenchyme of the fourth to sixth 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 esophagus occurs by ingrowth of tissue to form the tracheoesophageal 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 esophagus by the tracheoesophageal septum. In the embryonic phase, the lung appears as a ventral outpouching of the endodermal foregut by the fourth week after ovulation. This forms the epithelial components, but branching begins within mesenchyme that forms the walls of the airways and blood vessels. Segmental airways are present by 6 weeks. Although lung development is divided into different stages by different authors, there is agreement as to the main events and timing (Burri 1999; Hislop 2003).

Pseudoglandular Phase (7 to 17 Weeks)

Major lung components develop including bronchial glands, cartilage, and, toward the end of this period, ciliated epithelium. The bronchial buds divide dichotomously with completion of preacinar branching by 17 weeks, although most divisions are complete by 14 weeks' gestation and 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. 20.1). Mesenchyme is abundant, but capillaries are sparse and not closely apposed to epithelium. Respiration is not possible at this stage.

FIGURE 20.1. Lung from a 13-week spontaneous abortion showing pseudoglandular development.
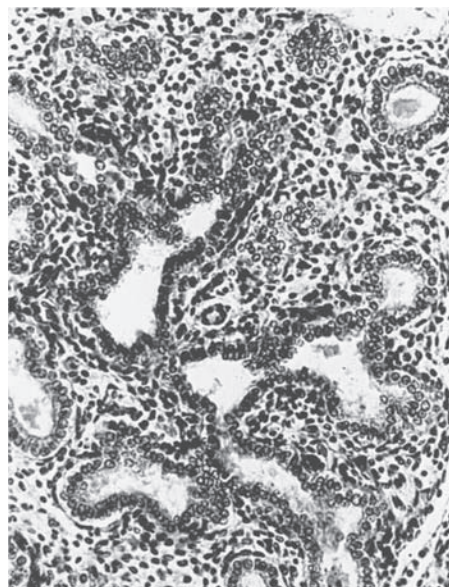

FIGURE 20.2. Early canalicular stage of development at 17 weeks' gestation. Vascularity is still poor and there is no blood–air barrier formation.

Canalicular Phase (17 to 27 Weeks)

Preacinar airways increase in diameter and, more peripherally, prospective respiratory bronchioles and then alveolar ducts begin to form. 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 afterward (McDougall and Smith 1975) (Fig. 20.2). Around 23 to 24 weeks' gestation, capillaries are pushing into the airways, the first blood–air barriers are forming (about 0.6 μm) and there is sufficient area for respiration to occur (Fig. 20.3).

Alveolar Phase (28 Weeks to Term)

This phase is characterized by rapid maturation of the acinus. Airway growth prenatally is linear. At the end of the canalicular phase, the terminal acinus is more in the form of a saccule. Some alveoli start to develop between 28 and 32 weeks
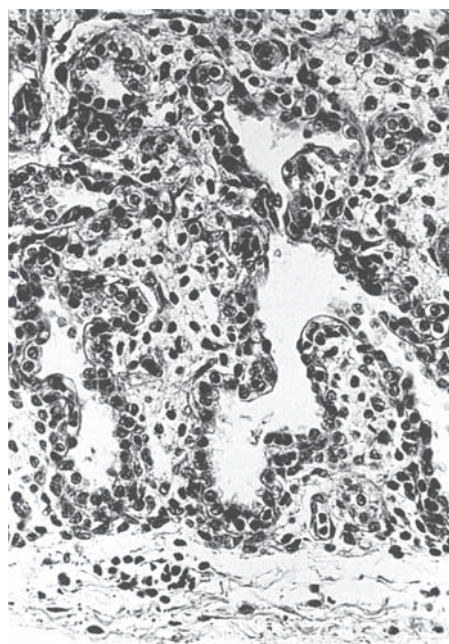
FIGURE 20.3. Canalicular stage lung at 23 weeks' gestation. Capillaries are starting to push into the airways, pulmonary epithelium is becoming attenuated and blood–air barriers are recognizable. Epithelium at distal sites, adjacent to the pleura remain cuboidal.
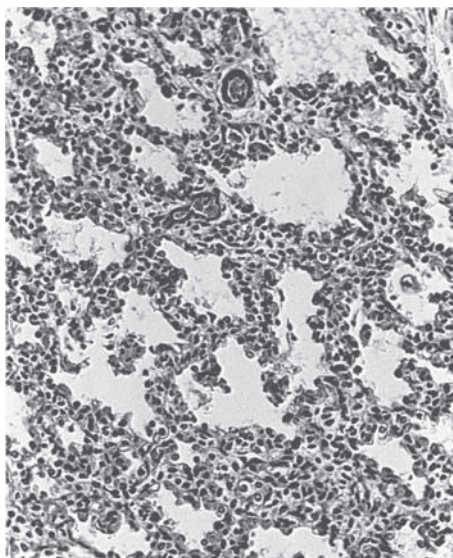
FIGURE 20.4. Terminal sac development at 28 weeks' gestation. Mesenchyme is less prominent and vascularization more marked.

but often retain a double capillary layer. Further septation leads to formation of true thin walled alveoli, and by 34 weeks mature cup-shaped alveoli line the elongated saccules. By term, between 30% and 50% of the adult number are present (Langston et al. 1984; Hislop et al. 1986; Hodson 1992). Alveolarization continues to about 8 years of age.

A characteristic of the late canalicular, early alveolar phase is the rapid differentiation of type 1 and type 2 pneumocytes (Fig. 20.4). 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 and Control

Rapid progress has been made in recent years in this complex field. Normal lung development and function is dependent on a wide variety of factors, many of them extrinsic to the lung itself. Some of these factors are more conveniently discussed in

the context of lung pathology, especially pulmonary hypoplasia.

The interaction between mesenchyme and the in-growing epithelial buds is fundamental. Indeed lung mesenchyme is a requirement for normal morphogenesis. The numerous factors involved in the complex interactions of short-range inducers in lung development have been subject to review (Shannon and Hyatt 2004; Groenman et al. 2005). 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 subunits 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, especially fibroblast growth factor 10, are critical from a very early stage possibly operating via sonic hedgehog, a regulatory molecule present in many organs and found especially at epithelial tips (Shannon and Hyatt 2004). Epidermal growth factor with receptor, and transforming growth factor-α, have been co-localized 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 mediated 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), which 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 minutes), suggesting a posttranslational effect. Of interest, androgens appear to block FPF production, which might partly account for the increased 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 antioxidants probably at the level of gene transcription rather than posttranscriptionally (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. While 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% to 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 labor. 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 needs to be 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, persistence of lung liquid may cause transient neonatal respiratory distress. Of greater importance to the pathologist is the evidence that 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 defense 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 by 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% to 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, partly as a result of increased oxygen

tension, 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. Associated changes that promote further pulmonary blood flow include ductal closure. In healthy infants, most blood flow alterations have occurred by 8 to 12 hours after birth. Subsequently, 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 cerebrocranial 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 midline defects are associated with trisomy 13 (see Chapter 26 p. 706).

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—the 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 abnor-

malities seen both individually or together. In the absence of other malformations they are commoner in males, but the sex incidence is approximately equal in the presence of nonfacial malformation. There is a considerable list of potential associations and syndromes (Winter et al. 1988), and the underlying causes are extremely varied. Some midline clefts have a clear underlying genetic association such as with trisomy 13, but environmental agents such as smoking or drug ingestion may also be involved (Murray and Schutte 2004). In the Pierre–Robin sequence 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 nine examples into three 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 pharyngotracheal duct, 1 mm in diameter. The cricoid is malformed and conical (Fig. 20.5).
- *Type 2*: The vestibule is normal and the arytenoid cartilages separate. The glottis is a blind cleft between the vocal folds, and the cricoid is 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.

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.
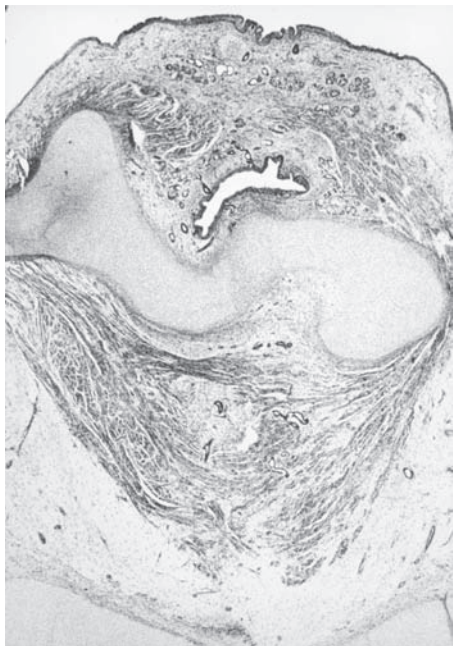
FIGURE 20.5. Transverse section across laryngeal atresia with abnormal, fused arytenoid cartilages. The pharyngotracheal duct passes dorsally and a mass of muscle is fused anterior to the cartilage.

Zaw-Tun (1988) 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. Laryngeal atresia can be inherited as a component of Fraser's syndrome (Slovotinek and Tifft 2002)

In the severe forms of atresia the lungs may be hyperplastic because lung liquid efflux is obstructed. Indeed, the presence of lung hyperplasia is often the feature that alerts the pathologist to the presence of a laryngeal anomaly (see below).

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. 20.6), 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). Although generally sporadic, a familial example of congenital subglottic stenosis has been described (Linna et al. 2004).
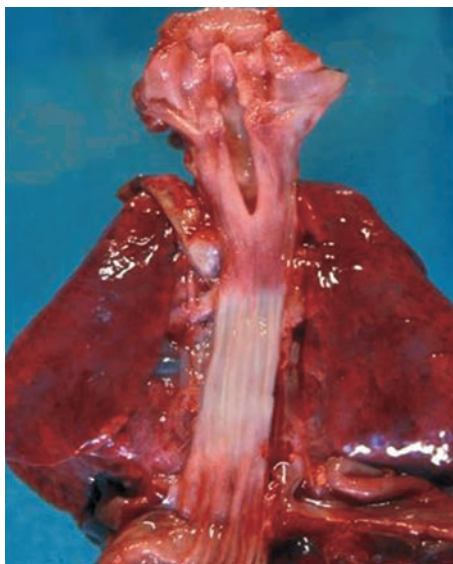
Laryngeal Clefts

Occasionally, clefts are anterior, but most laryngeal clefts are in the midline posteriorly and represent a failure of fusion of the tracheoesophageal septum. They have been classified as follows:

- 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)

Small clefts may be asymptomatic but neonates often suffer from stridor or respiratory distress (Fig. 20.7). For the more severe forms, mortality is high, and type 2 and 3 clefts require surgery for

FIGURE 20.6. Laryngeal stenosis. Coronal slice through the larynx shows an abnormal bar of cartilage obstructing the lumen. (Courtesy of Dr. S. Knowles.)

FIGURE 20.7. Laryngeal cleft (type 2) from a 34-week late neonatal death. (Courtesy of Dr. J. Keeling.)

survival (Samuel et al. 1997; Kubba et al. 2005). Up to 40% of type 1 clefts are associated with a tracheoesophageal 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 may be endodermal in origin and 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). Laryngoceles 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). Those cysts with a mesodermal component, which may be partly extrinsic, may be more difficult to treat (Forte et al. 2004).

Laryngomalacia

A frequent clinical, though rare pathological, diagnosis, laryngomalacia is one of the commonest causes of congenital laryngeal, usually inspiratory, stridor (Friedman et al. 1990). Sometimes stated to be due to a soft cartilaginous framework

of the larynx (Cotton and Richardson 1981), the pathology is very poorly defined and the histology may be normal or show little readily detectable abnormality (Manning et al. 2005). It has been suggested that stridor may result from a mild localized form of hypotonia due to neuromuscular dysfunction (Belmont and Grundfast 1984), although the neuromuscular problems may be more systemic (Chandra et al. 2001). Laryngomalacia resolves spontaneously during the second year in 90% of cases.

Trachea

There are about 22 cartilaginous 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. It results from ventral or dorsal displacement of the tracheoesophageal septum. The agenetic segment of trachea may be long or short, and sometimes the agenetic segment is replaced by a thin fibrous cord. The distal trachea or bronchi may arise from the esophagus (Fig. 20.8) (Diaz et al. 1989), which can be a conduit for ventilation in some cases in the immediate neonatal period. However, prognosis is very poor (Lander et al. 2004). It is commonly associated with tracheoesophageal fistulas (Floyd et al. 1962; Bray and Lamb 1988) and other congenital abnormalities, particularly in the cardiac or genitourinary 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, and it gradually becomes more stenotic. Common associations include a sling left pulmonary artery or pulmonary agenesis. Diffuse stenosis may also be caused by a solid cartilaginous 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. 20.9). Many are associated with other abnormalities, notably of the cardiovascular system (Bonnard et al. 2003). About a

FIGURE 20.9. Localized tracheal stenosis in a baby with aortic arch anomalies and congenital heart disease.

FIGURE 20.8. Tracheal agenesis in a 34-week gestation stillbirth. Laryngeal inlet appears relatively normal despite the absence of airway below the cricoid, and the bronchi are arising directly from the esophagus. Both lungs are of normal size.

third are diagnosed at birth, with a later presentation often being from dysphagia or nonspecific respiratory symptoms such as infection or respiratory distress.

Tracheoesophageal Fistula

A tracheoesophageal 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 tracheoesophageal fistula is a blind-ending, upper esophageal pouch associated with a fistulous connection between the lower esophagus and the trachea (Holder and Wooler 1970). Tracheoesophageal fistula is discussed more fully in the section on the gastrointestinal tract (see Chapter 18 p. 469).

Tracheo- and Bronchomalacia

Tracheo- and bronchomalacia are due to an inadequacy of the respective cartilaginous frameworks and cause a loss of airway patency at some point in the respiratory cycle. They may present clinically as stridor 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 cartilaginous 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 reported (Agosti et al. 1974), and an association with other congenital abnormalities, particularly congenital heart disease, is common. There does appear to be a significant association between these tracheobronchial abnormalities and chromosomal anomalies such as trisomy 21 and 22q deletions (Maeda et al. 2000; Huang and Shapiro 2000; Betrand et al. 2003).

Secondary tracheomalacia, in this context implying acquired damage to the trachea, is a rare complication of chronically ventilated preterm infants. Damage to the cartilaginous 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,
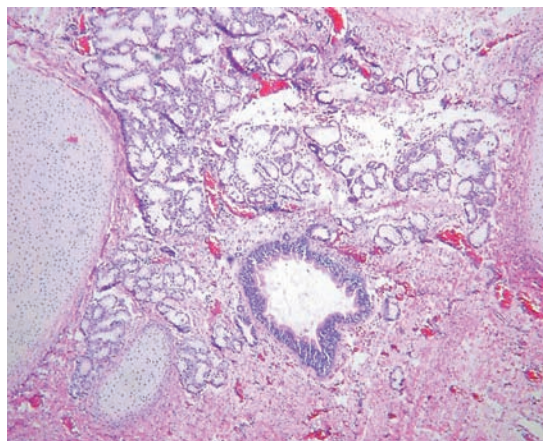
Figure 20.10. Atretic main bronchus in a 36-week-gestation baby. Lung distal to the atresia demonstrated solid (type 3) adenomatoid malformation.

especially of the heart (Landing 1984; Stewart et al. 1984; DeVine et al. 1991).

Isolated bronchial atresia is generally considered extremely rare and usually apical. Some atresias have been associated with bronchogenic cysts, and unrecognized bronchial atresia may underlie the pathology of a number of pulmonary cystic diseases (Fig. 20.10) (see below). Although this has suggested a malformative basis for atresia (Kuhn and Kuhn 1992; Mori et al. 1993), the presence of fibrotic material in some cases suggest that at least a few are "acquired."

Bronchial stenosis is rarely caused by an intrinsic abnormality (Chang et al. 1968) but 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. Unilateral agenesis may be associated with esophageal atresia and distal tracheoesophageal fistula. It has been suggested (Knowles et al. 1988) that unilateral pulmonary agenesis may

"replace" tracheoesophageal fistula as a component of the VACTERL association (vertebral defects, anal atresia, cardiac defects, tracheoesophageal atresia, renal anomalies, limb defects). The solitary lung may show the normal bronchial divisions, but a compensatory increase in alveolar number may produce mediastinal shift. Chromosomal abnormalities 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, in which there is right pulmonary venous drainage into the inferior vena cava (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. Presentation is also very variable, and while some may be symptomatic and present in the early neonatal period, a few may be discovered incidentally at autopsy. However, a significant proportion are now diagnosed in utero, often following routine anomaly ultrasound scan. At this early stage, there is a good argument for describing these lesions simply as cystic lung malformations (Bush 2001), as the precise diagnosis may need to await later pathological examination or other assessment. Indeed, although cystic lung disease is often described as a number of separate and seemingly distinct entities, there is often overlap.

Differential diagnosis typically includes adenomatoid malformation and sequestration with diaphragmatic hernia as the major nonpulmonary lesion. Cystic lung malformations can cause effusions or hydrops due largely to venous obstruction and mediastinal shift. Compression of adjacent normal lung may cause pulmonary hypoplasia (see below). Complications and management are more dependent on the size and extent of the lesion and factors such as the degree of mediastinal shift than precise subtype (Davenport et al. 2004). Increasing experience of antenatal detection indicates prognosis is not as bad as formerly thought, even in the presence of systemic complications. Pulmonary cysts may become less visible as gestation progresses and, by the time of birth, imaging may detect some lesions only with difficulty. Some argue that abnormal lung should always be resected, as it will almost invariably become symptomatic at some point in life (Laberge et al. 2005) and have a higher risk of malignancy (Ueda et al. 1977; Domitzio et al. 1990; Ribvet et al. 1995; Kaslovsky et al. 1997; MacSweeney et al. 2003). Others recommend postnatal follow-up with computed tomography (CT) scan for the first year, and resection only if the abnormality persists on imaging or is symptomatic (Calvert 2005). In this latter study 78% of infants diagnosed with cystic lung disease in utero required surgery in the their first year. It is likely that many cystic lung lesions go undetected and regress, although adult presentation is recorded (Lackner et al. 1996).

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. However, lesions with the histological characteristics of bronchogenic cysts have been described in a very wide range of locations, such as infradiaphragmatically or in subcutaneous tissues, often with little obvious connection with the respiratory tract. 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 esophageal cysts (Salyer et al. 1977).

Congenital Lobar Emphysema

This usually presents in the neonatal period or sometimes slightly later with respiratory distress due to lobar overexpansion and compression of adjacent tissues. In one study, approximately 50% presented in the first week of life and 80% by 6 months. It almost invariably affects the upper lobes, but multiple lobes can be involved (Mani et al. 2004). The key factor in congenital lobar emphysema (CLE) is largely related to partial obstruction of the airway and air trapping. Usually, the abnormality is intrinsic to the bronchus and bronchial stenosis, possibly due to a cartilage defect, as has been reported (Warner et al. 1982), but extrinsic bronchial compression with CLE has also been described (Engle et al. 1984). Histopathological findings are often limited. The affected lung shows overexpanded alveoli but the underlying structure is usually normal. Identifying the cause of the obstruction with confidence may be impossible.

Congenital lobar emphysema has been diagnosed in utero, and the overexpansion of the lung in this context is probably due to impaired lung liquid flow by bronchial obstruction. The alveoli may be simplified, large, and show increased elastic in the alveolar walls.

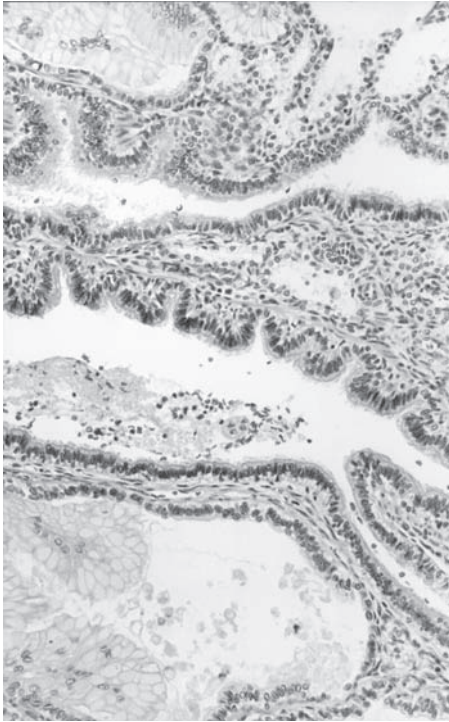## Congenital Pulmonary Adenomatoid Malformation

Although still widely described as congenital cystic adenomatoid malformation (CCAM), the general term *congenital pulmonary adenomatoid malformation* (CPAM) acknowledges that cystic change may not be a feature of some malformations. Adenomatoid malformation has been widely classified by the system (types 1 to 3) devised by Stocker et al. (1978) from pediatric lung resections to which two further subtypes (types 0 and 4) have been added more recently. However, it can be difficult to classify some adenomatoid malformations using this system, especially lesions seen in fetal life (Cha et al. 1997) or resected shortly after birth. Overlap with other lesions (Bale 1979; Fisher et al. 1982) occurs. While aspects of the pathogenesis remain incomplete, Langston (2003) places more emphasis on regarding some pulmonary cysts as part of a sequence that makes it easier for some lesions, which often have more than one pathology, to be more easily

FIGURE 20.11. Small cyst adenomatoid malformation (type 2) in part of a left lower lobe.
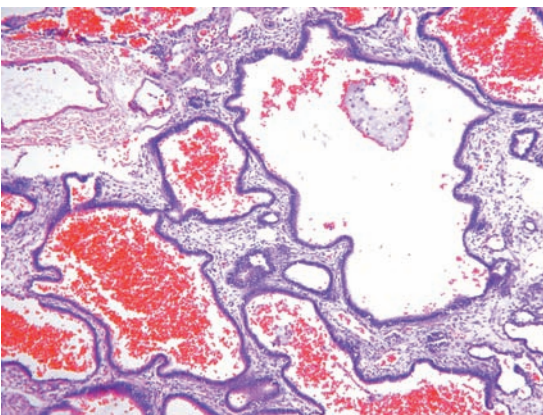
described and understood (Fig. 20.11). Bronchial atresia may be a common factor in a number of types of pulmonary cystic disease (Riedlingen et al. 2006). Classification is as follows:

- *Large cyst type (Stocker type 1):* Often affecting only a single lobe, these cysts may be up to 3 to 7 cm in some children. Even in small babies the cysts may be 2 cm in diameter, with smaller cysts merging with adjacent lung. The cysts can cause mediastinal shift or even hypoplasia of adjacent lung. These cysts communicate with the bronchial tree. Microscopically, cysts are lined by respiratory-type ciliated columnar epithelium, which may be flattened, or a mucigenic epithelium (Fig. 20.12). The wall comprises a thin fibromuscular layer, the cysts lie back to back, and small islands of cartilage may be present. Cysts with the appearance of enlarged alveoli may be interspersed between the larger cysts.

- *Small cyst type (Stocker type 2)*: Small cyst type adenomatoid malformation presents with a wide spectrum of appearance. Multiple, evenly spaced cysts may rarely occupy a whole lung but, more usually, only a lobe or part of a lobe. Small cystic disease may even be scattered throughout a lobe of lung. The epithelial lining and wall of the cysts usually resembles that of normal respiratory bronchioles (Fig. 20.13) and, on occasions may be difficult to distinguish from normal structures except that they are present to excess. Cartilage is not present. Detailed study suggests bronchial anomalies, especially atresia (Imai and Mark 2002), may be

FIGURE 20.12. Congenital cystic adenomatoid malformation (CCAM) type 1 showing typical epithelium with thin layer of fibromuscular tissue. Metaplastic, mucous epithelium is characteristic of type 1 but is not always found.
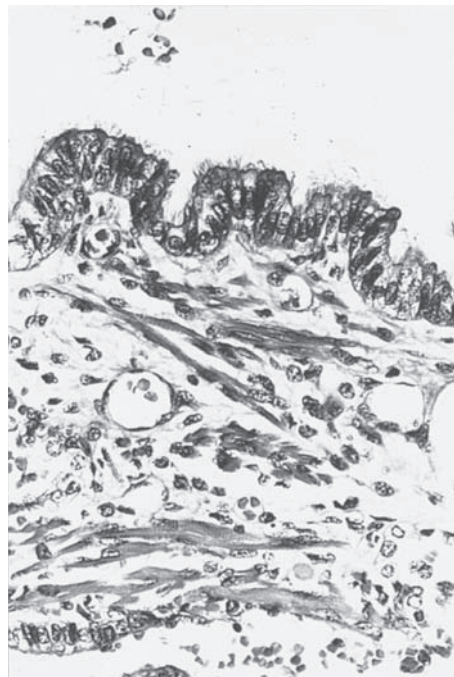
present, and indeed Langston (2003) considers that this abnormality is usually, if not always, secondary to early airway obstruction. Mucus and macrophages, within the cysts and sur-

rounding lung, suggesting airway obstruction, are common features of resected lung with small cyst disease. Very occasionally, striated muscle may be found randomly distributed throughout the malformation (Fig. 20.14). Of the three main subtypes, this type is most commonly associated with malformation elsewhere, especially of the renal tract (Pham et al. 2004).

- *Solid adenomatoid malformation (Stocker type 3)*: This subtype is formed of small cysts less than 0.5 cm in diameter, involving an entire lobe. Cyst lining is cuboidal epithelium on a very thin fibromuscular layer with no cartilage or mucigenic cells (Fig. 20.15). Due to the overall size of the affected lung, type 3 CCAM is more likely to produce significant mediastinal shift and carry a poor prognosis. This form of abnormality may have parallels with pulmonary hyperplasia due to airway obstruction (Langston 2003), and bronchial atresia has occasionally been demonstrated (Fig 20.10).
- *Peripheral cyst type (Stocker type 4)*: Proposed in 1994 (Stocker 1994), this type was considered a probable hamartomatous malformation of the
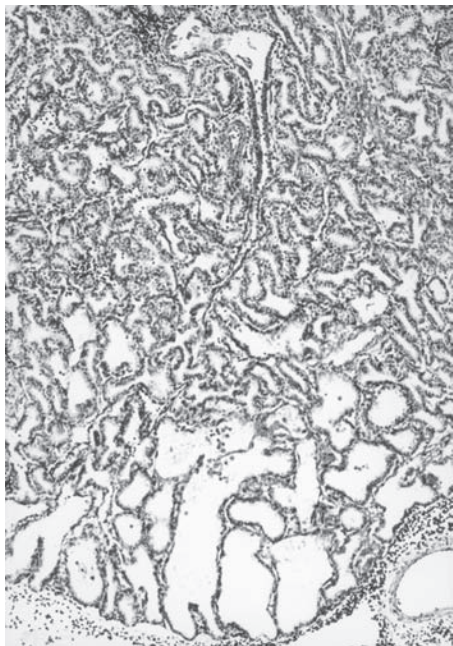

FIGURE 20.13. Small cyst adenomatoid malformation. Cysts are bronchiolar in appearance. This was an unexpected finding in a fetus terminated for renal agenesis.

FIGURE 20.14. Small cyst adenomatoid malformation with striated muscle cells in the wall. The striations are visible.

FIGURE 20.15. Solid, type 3 CCAM with uniform small cysts lined by cuboidal epithelium, which is surrounded by a very thin connective tissue layer.

distal acinus, often presenting as an asymptomatic incidental finding or sudden respiratory distress from spontaneous 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. However, it is likely many of these cysts are cystic pleuropulmonary blastomas, and the distinction may be extremely difficult (Mac-Sweeney et al. 2003). Indeed, because of the malignant potential of the latter, the diagnosis of a malformation should be made only with extreme caution (Hill et al. 2004; Miniati et al. 2006).

· *Acinar dysplasia (Stocker type 0)*: Initially reported as acinar dysplasia (Rutledge and Jensen 1986), this type has been proposed as a type 0 adenomatoid malformation. Incompatible with life, the macroscopic appearance is of a severely hypoplastic lung (Chambers 1991). It is described in association with cardiac anomalies and, in one case, renal anomalies (Gillespie et al. 2004). Microscopically, acinar development is extremely poor with terminal sacs lined

by pseudostratified, bronchial-type columnar epithelium with goblet cells (Fig. 20.16).

Pulmonary Sequestration

Sequestered lobes are abnormal masses of pulmonary tissue that do not communicate with the main pulmonary bronchial tree and are supplied by an anomalous artery usually arising from the descending aorta. Sequestration may be intrapulmonary (intralobar sequestration, ILS), or extrapulmonary (extralobar sequestration, ELS), when the sequestered lobe is invested by its own pleura. Extralobar sequestration may present in the fetus with hydrops, as an incidental finding by ultrasound, or postmortem associated with other anomalies. In infancy it may present with respiratory distress. Extralobar sequestration may lie anywhere in the thorax or even subdiaphragmatically. In ELS, small cyst type adenomatoid malformation is commonly present.

Intralobar sequestration is usually found within the left lower lobe. It has been suggested that, because ILS is rarely found in fetuses or neonates (Ng et al. 1994) and presentation is often late, only
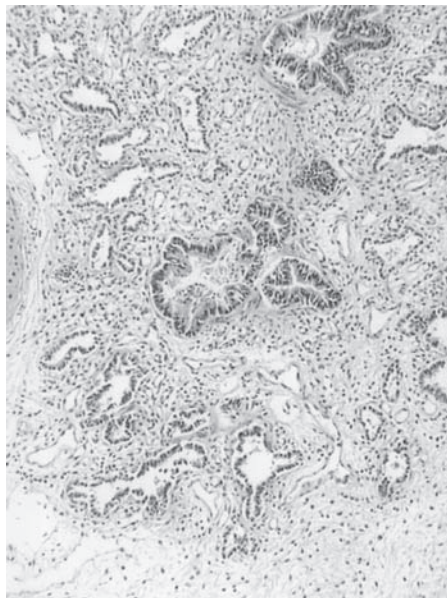
FIGURE 20.16. Acinar dysplasia from a term infant dying at 1 day of age. The central bronchiole is essentially normal, but distal to it there is no normal alveolar development. (Courtesy of Dr. C.J.H. Padfield, Nottingham, England.)
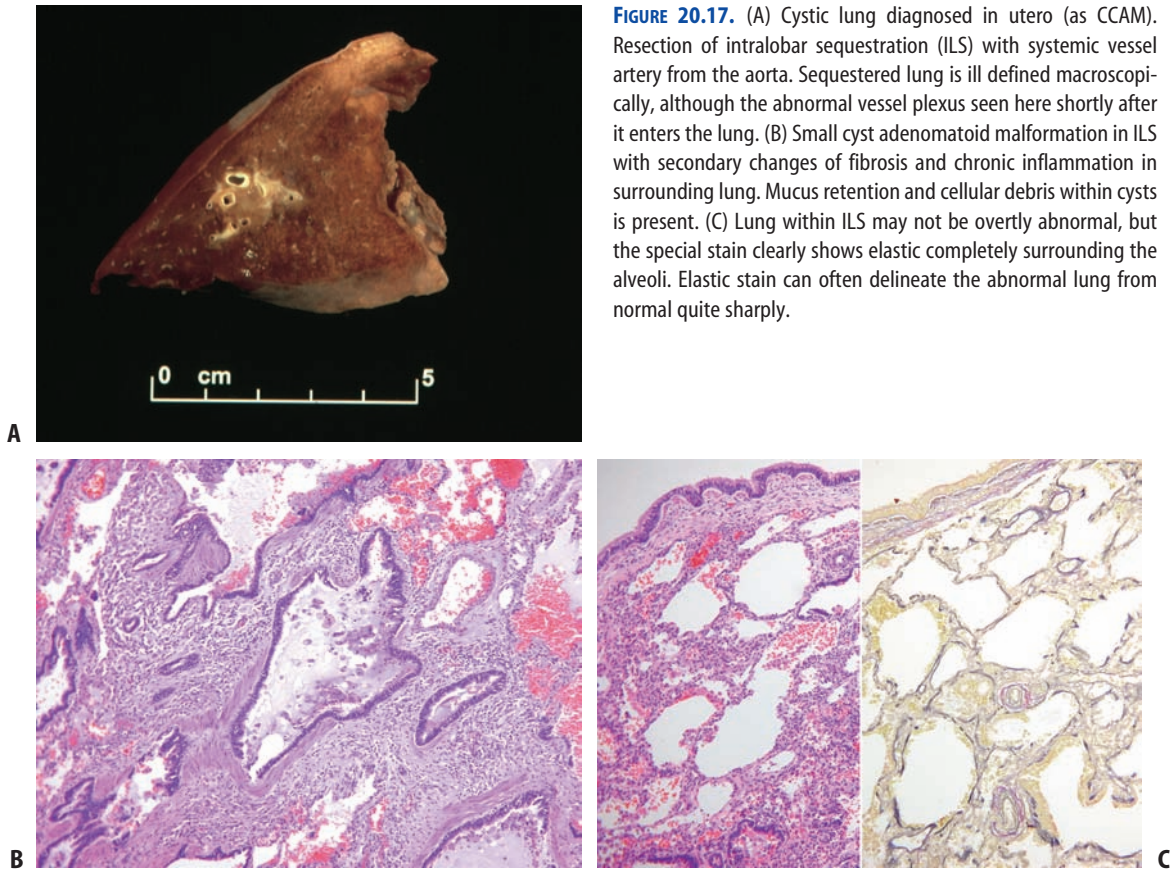
FIGURE 20.17. (A) Cystic lung diagnosed in utero (as CCAM). Resection of intralobar sequestration (ILS) with systemic vessel artery from the aorta. Sequestered lung is ill defined macroscopically, although the abnormal vessel plexus seen here shortly after it enters the lung. (B) Small cyst adenomatoid malformation in ILS with secondary changes of fibrosis and chronic inflammation in surrounding lung. Mucus retention and cellular debris within cysts is present. (C) Lung within ILS may not be overtly abnormal, but the special stain clearly shows elastic completely surrounding the alveoli. Elastic stain can often delineate the abnormal lung from normal quite sharply.

a few may be true malformations, and most are the result of infection (Stocker and Kagan-Hallet 1979). However, it is clear that a number of cystic pulmonary lesions, initially seen in utero by ultrasound, when resected postnatally are found to be supplied by a systemic artery (Walford et al. 2003) and conform to the definition of a sequestration (Fig. 20.17A) (Langston 2003; Orpen et al. 2003). In resected lung, small cysts are sometimes macroscopically visible in the resected specimen, but in others the adenomatoid component is only apparent histologically (Fig. 20.17B); mucus retention may be striking. The intervening lung parenchyma may also be abnormal; elastin stains may be very helpful in defining the extent of the abnormality (Fig. 20.17C).

Clements and Warner (1987) emphasize that a wide range of bronchial connection, arterial supply, and venous drainage may be found. The embryological origin of pulmonary sequestration is a matter of debate, although there does appear to be a consensus that other bronchopulmonary 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 esophagus or stomach, is generally termed a bronchopulmonary foregut malformation. It is generally right sided and presents in infancy either as an associated finding with other malformations or as a symptom related to infection (Srikanth et al. 1992).

Pulmonary Heterotopias/Hamartomas

Solid hamartomas are rare anomalies and may contain cartilage and adrenal (Bozic 1969); pancreatic heterotopia has also been described
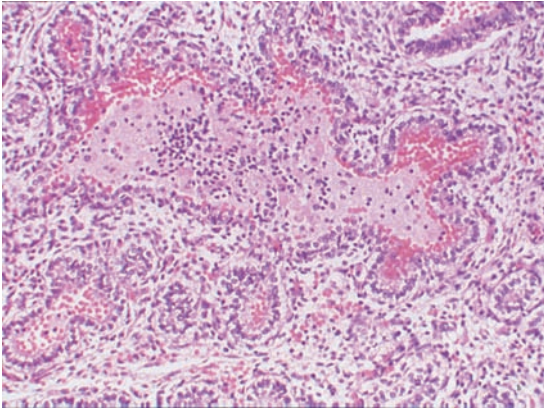
Figure 20.18. Heterotopic neural tissue in the airway of anencephalic fetus. This heterotopic material is probably aspirated.

(de Krijger et al. 2004). Glial and skeletal muscle masses are sometimes seen in anencephaly (Fig. 20.18) (Morgan et al. 2003). Rhabdomyomatosis or diffuse heteroplasia of skeletal muscle is described and is usually associated with a cardiovascular malformation (Chi and Shong 1982; Chellam 1988, Chen et al. 1991; Hardisson et al. 1997).

Alveolar Capillary Dysplasia

This dysplasia results from failure of normal alveolar capillarization, in which capillaries fail to push into the developing alveolar walls. The lungs are not hypoplastic but in some respects maturation appears arrested because of both the poor vascularization and the relative immaturity of the epithelium (Fig. 20.19A). It is associated with an
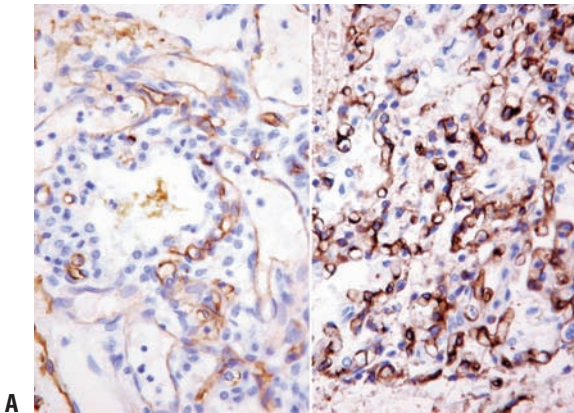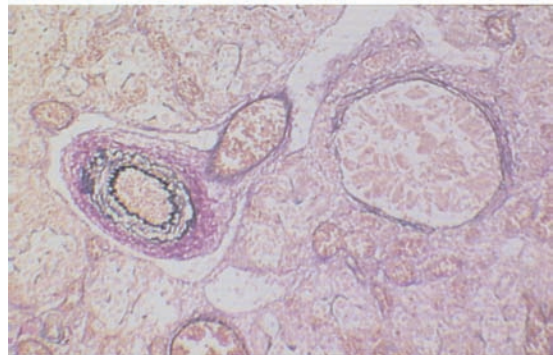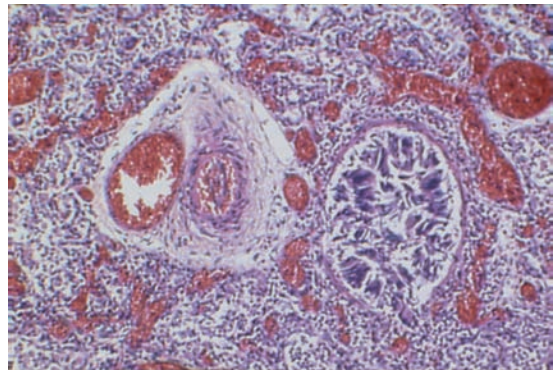
Figure 20.19. (A) Vascular pattern in alveolar capillary dysplasia (left) compared with normal lung at 33 weeks' gestation. CD-34 immunostain is used to highlight the capillaries. The capillaries in alveolar capillary dysplasia (ACD) are reduced in number and do not show the normal intimate relationship with the alveoli. The alveolar epithelium is immature for gestation. (B) Misalignment of the pulmonary veins in a term baby dying at 14 days with severe pulmonary hypertension of uncertain etiology. Highlighted in the elastic van Gieson (EVG) stain, the pulmonary vein accompanies the pulmonary artery adjacent to a terminal bronchiole. Although congested, dilated capillaries are present within the interstitium. There is an absence or severe reduction in capillaries pushing into the alveolar wall.

abnormality of the vascular bundle, sometimes known as misalignment of the pulmonary veins, such that there is both pulmonary artery and vein in the same adventitial coat (Fig. 20.19B). 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). An association with other malformations is being increasingly recognized, and there is evidence that some case are autosomal recessively inherited (Sen et al. 2004).

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 lymphangiectasia 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 here at some length, first, 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. 20.20). After removal as a block, the diaphragmatic surfaces of the lungs are not in line with the apex of the heart (Fig. 20.21). Another readily available measure is lung/body-weight ratio; a lung/body-weight ratio of 0.015 before 28 weeks' gestation, and one of 0.012 at 28 weeks' gestation or later is indicative of hypoplasia. The lungs should always be greater than 1.2% of body weight (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 broad patterns of histology in lung hypoplasia have been described (Wigglesworth et al. 1981), although these are not always sharply
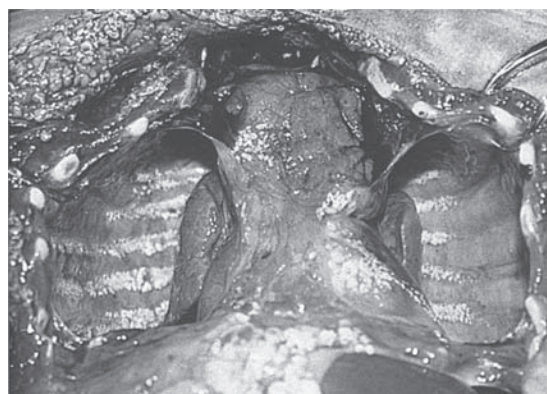
FIGURE 20.20. Thoracic contents of a 33-week early neonatal death with idiopathic fetal hydrops. The pleural effusions have been removed to show marked bilateral pulmonary hypoplasia.
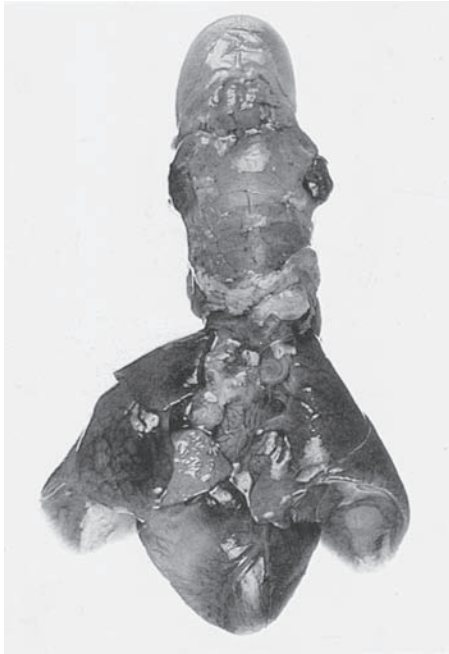
FIGURE 20.21. Hypoplastic lungs in relation to the size of the heart. Normally, the inferior surfaces of the lungs and apex of the heart should all be at approximately the same level. (From an early neonatal death at 26 weeks of gestation with renal agenesis.)

delineated (Nakamura et al. 1992). 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. Evidence of deficient surfactant production in the former suggests that 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 significantly to the functional impairment (Wilcox et al. 1997).

Mechanisms and Causes of Lung Hypoplasia

At first glance, the many associations and causes of lung hypoplasia have little in common, but the study of these seemingly disparate pathologies has contributed significantly to our understanding of normal lung growth (Wigglesworth 1987a,b). Pulmonary hypoplasia can be classified in a logical manner (Table 20.1) and based on factors that may impair normal growth. Some influences may be relatively subtle but operate early in development

TABLE 20.1. Mechanisms and causes of lung hypoplasia

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

(Maritz et al. 2005), and the following underlying molecular mechanisms are only beginning to be understood (Groenman et al. 2005):

- *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, for example, skeletal dysplasias; a space-occupying lesion, for example, an abnormal viscus associated with diaphragmatic hernia (Areechon and Reid 1963); eventration (Fig. 20.22); 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 that these movements allow influx of amniotic fluid or generate important pressure changes within the thorax (Wigglesworth 1987a; Kitterman 1984). The interrelationship among normal fetal breathing movements, lung liquid, and lung growth has been summarized (Hooper and Harding 1995). Pulmonary hypoplasia may also be seen when fetal breathing has been inhibited by severe brainstem injury (Endo et al. 2001) or other cerebral pathology (Matturri et al. 2003).
- *Oligohydramnios*: Oligohydramnios due to either 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. In oligohydramnios, a larger than normal pressure gradient between fetal lung and amniotic sac occurs and the efflux of fetal lung liquid may be 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. Another factor may be increased spinal flexion from uterine compression (Albuquerque et al. 2002). These hypotheses are not mutually exclusive.

The relevance of intraalveolar 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 (Fig. 20.23). The laryngeal anomaly prevents the loss of fetal lung liquid (Wigglesworth et al. 1987; Silver et al. 1988). However, attempts to reproduce this experimentally by plugging the trachea give mixed results. While lungs are larger, lung maturation remains impaired (Piedboeuf et al. 1997; Nardo et al. 1998; Chapin et al. 2005). In human fetuses, there are also indications that tracheal occlusion does not enhance maturation, but the increase in lung size is due mainly to emphysema and mucus pooling (Heerema et al. 2003).

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) should be examined for evidence of oligohydramnios and radiographs for possible skeletal dysplasia. Pathology or malformation involving the brainstem should also be specifically sought. 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
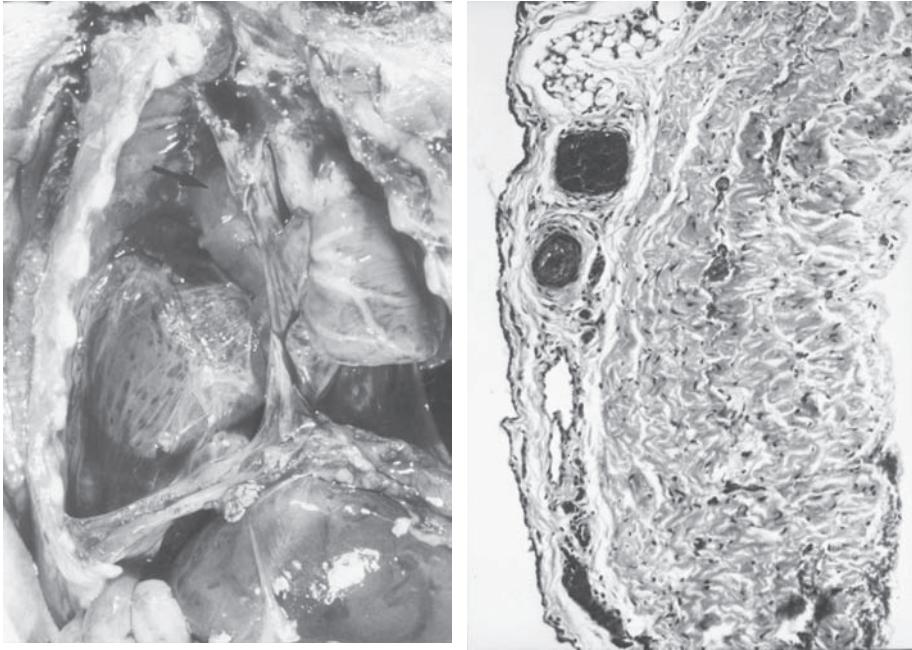
FIGURE 20.22. (A) Eventration. Right hemidiaphragm is a thin glistening membrane through which the right lobe of the liver can be seen. There is mediastinal shift, and the right lung is grossly hypoplastic (arrow). In this case, the left lung was also hypoplastic (not visible). From a term infant dying at a few hours of age. (B) The membrane comprises fibrous diaphragmatic tissue only with no muscle.
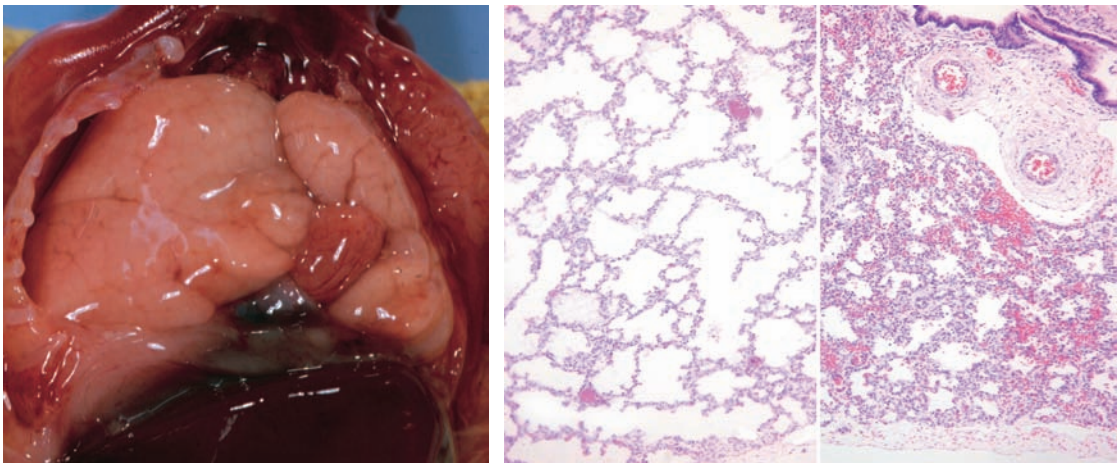
FIGURE 20.23. (A) Hyperplastic lungs at 19 weeks' gestation caused by laryngeal atresia. The bulky lungs cover the heart and the diaphragm is flattened. (B) Hyperplastic lung at 33 weeks' gestation (left) from a stillborn baby with laryngeal atresia compared with lung of similar gestation baby (right; same magnification). The hyperplastic lung appears inflated and more mature than might be expected.

immaturity, the consequences of birth asphyxia, or infection. Superimposed on this can be the effects of therapy, especially 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 are considered elsewhere (see Chapter 17).

Pathology of Immaturity

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

The lungs of most immature infants who have survived more than a few hours demonstrate pathological changes, but occasionally they are histologically normal. This is usually confined to the extremely preterm infant of around 23 to 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 describing an acute illness, generally developing within 4 to 6 hours of birth in a preterm infant. There is a constellation of symptoms: increased respiratory rate (>60 breaths/min), respiratory distress (sternal and subcostal recession), cyanosis, and grunting that does not resolve within 24 hours. Radiographically there may be pulmonary collapse and an air bronchogram. Approximately 1% of babies develop RDS, the risk of which is inversely proportional to gestational age, with some 50% developing the syndrome before 30 weeks' gestation. The incidence and outcome has been radically altered by the use of prenatal steroids and replacement surfactant.

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

Hyaline Membrane Disease

Hyaline membrane disease 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 is associated with prematurity and surfactant deficiency. However, it can also be associated with severe acute asphyxia, some forms of pulmonary infection, and pulmonary hemorrhage. It is almost invariably accompanied by respiratory distress, although the clinical syndrome may be obscured if the infant is ventilated, and some extremely preterm infants (<26 weeks' gestation) may become apneic rather than develop classic RDS. The natural clinical course has been further modified by the use of replacement surfactant, which may be used prophylactically very shortly after birth or as later rescue therapy (Halliday 2003).
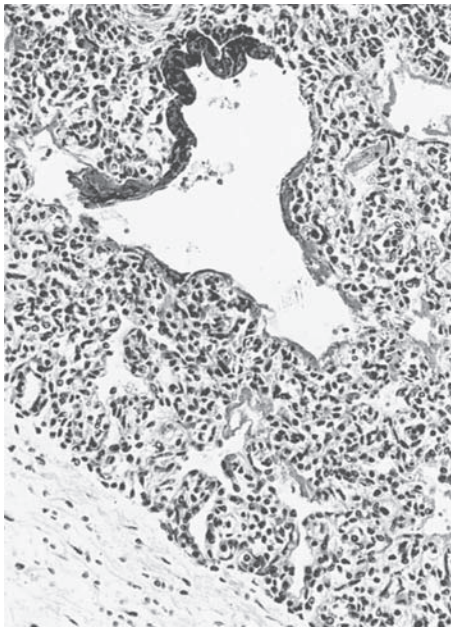
Hyaline membrane disease associated with surfactant deficiency, and not treated by replacement therapy, usually presents an hour or so after birth with respiratory distress. With the exception of the most immature infants, the majority of infants survive with appropriate ventilatory therapy, unless additional pathology such as intraventricular hemorrhage supervenes. Ventilation is often required for a few days, but toward the end of the first week, and presumably reflecting a resurgence in surfactant levels, ventilatory requirements decrease.

Should infants die within a few hours of onset of the disease, the lungs are collapsed, heavy and red/purple in color, 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 (HMs) develop (de la Monte et al. 1986). The membranes may become dislodged and plug more distal airways. The eosinophilic HMs lining
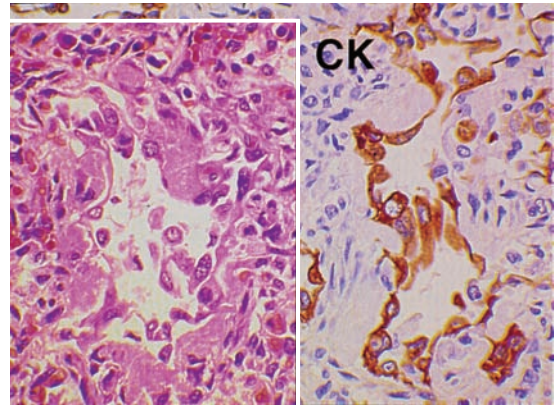
the terminal airways are present within an hour or so of birth and often contain nuclear debris of necrotic epithelium (Fig. 20.24). Membranes are not usually seen in the terminal sacs, which are collapsed. After a few hours the presence of polymorphs and macrophages in the interstitium is marked with 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. 20.25).

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

FIGURE 20.25. Hyaline membranes at 40 hours of age. Reactive macrophages and some fibroblasts are present below the membranes. Immunohistology for cytokeratin (CK) shows regenerating epithelial cells already covering the membranes; some membrane may be incorporated into the wall.

incorporation of albumen bound bilirubin into the hyaline membranes (Blanc 1976).

Pathogenesis

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 ischemia 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, that is, 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.

FIGURE 20.24. Hyaline membrane disease in a 26-week-gestation neonate dying at 12 hours 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.

Surfactant replacement therapy is now recommended for any infant less than 27 to 28 weeks' gestation while slightly more mature infants receive surfactant if their RDS is severe enough to require intubation (Halliday 2003). 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 hemorrhage, mainly with some artificial replacement surfactants (Halliday 2003). Where infants do die with respiratory distress syndrome, no major difference in the lung pathology between babies who have or who have not had surfactant replacement is described (Pinar et al. 1994; Thornton et al. 1994), although in my experience the membranes tend to be more scant and fragmented than in the natural disease.

Bronchopulmonary Dysplasia (Chronic Lung Disease)

Terms and Definition

The past 20 to 25 years has seen a variable and sometimes less than well defined use of the terms *bronchopulmonary dysplasia* (BPD) and *chronic lung disease* (CLD). Bronchopulmonary dysplasia was described by Northway et al. (1967) in the early days of neonatal intensive care and entailed a lung severely damaged by the therapies used to maintain respiration in the preterm infant. This damage usually occurred in the first few days of life during treatment of an acute lung disease, most commonly the surfactant-deficient hyaline membrane disease of preterm infants. Infants with BPD required intensive ventilatory support and had lungs that showed a spectrum of damage but that commonly included obliterated airways and an interstitial fibrosis. The infants commonly died from respiratory failure or complications directly attributable to fibrotic lungs such as cor pulmonale. With better management and advent of therapies such as surfactant replacement, this pattern of severe lung disease has largely disappeared, but a milder condition has emerged in which continued respiratory support is still required but at a much diminished level. In many cases, the early acute lung disease is relatively mild and there may be an interval between the apparent successful treatment of the acute disease and the onset of a chronic respiratory disease process.

The terms CLD and BPD have been used interchangeably clinically but with CLD gradually becoming the preferred description for this milder pattern of clinical disease, as many neonatologists preferred to avoid the connotations of severe fibrotic lung damage that accompanied the label BPD. However, there are now positive moves to return to BPD (sometimes prefixed by "new") as the preferred term, largely to reduce the potential for confusion between this specific disease of the neonatal period and other chronic lung diseases arising later in life (Jobe and Bancalari 2001; Sosenko et al. 2003; Greenough and Milner 2005).

"New" BPD is almost invariably a clinical diagnosis, and indeed is defined in clinical terms, and describes a baby requiring continued ventilatory support for a prolonged period. It usually follows a period of mechanical ventilation and supplemental oxygen, although there may be a period when no supplemental oxygen is required before oxygen requirements gradually increase and the infant becomes more dependent on ventilatory support. Most babies can eventually be weaned from this support, although a small minority gradually progress and die from respiratory failure. Specific definitions are usually only critical if comparative studies are being made. In babies <32 weeks' gestation, new BPD is classed as mild if oxygen >21% has been required for at least 28 days, but there has been a return to air breathing at 36 weeks postmenstrual age or discharge; BPD is considered severe when there has been a requirement for >30% oxygen at a similar time point. Unlike earlier clinical definitions of BPD, there is now no requirement for cystic changes to be present on chest x-ray or the need for a defined early acute lung disease (Jobe and Bancalari 2001).

For the pathologist, there is one further aspect that has changed while the nomenclature has cycled from BPD to CLD and back to new BPD. Old BPD had very distinctive features that usually allowed a confident pathological diagnosis at autopsy. The new BPD, however is, essentially, a clinical diagnosis based on the period of oxygen dependency. The pathology is far more subtle and is a difficult diagnosis to make on pathological
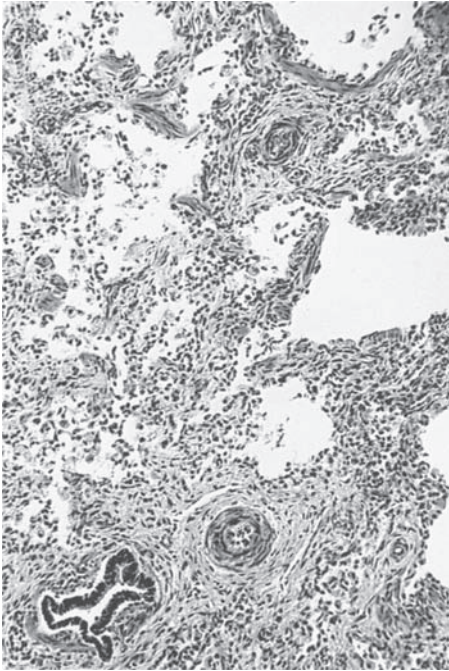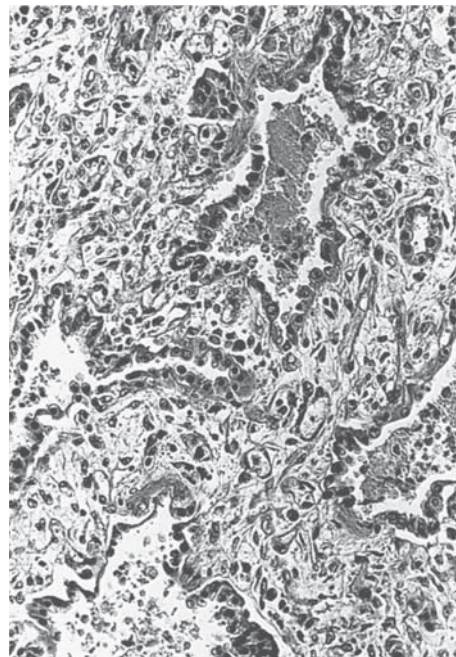
FIGURE 20.26. Bronchopulmonary dysplasia in an infant dying at 3 months of age. Interstitium shows striking fibrous thickening and the small pulmonary artery is thick walled. The adjacent terminal bronchiole is normal.

- *Major airway injury:* Severe bronchial and bronchiolar damage is characterized by necrosis 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 the ventilatory management that was then current, and the relatively high inflationary pressures. Severe acute major airway pathology is now highly unusual. 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 edema and fibrosis (Fig. 20.26) associated with cuboidal metaplasia (Fig. 20.27). Early ventilatory inequality may give rise to areas of relative collapse and fibrosis accompanied by more distended emphysematous lung (Fig. 20.28).

FIGURE 20.27. Striking cuboidal metaplasia associated with bronchopulmonary dysplasia.

grounds alone in the absence of the appropriate clinical setting; indeed, the milder variants are unlikely to be seen by the pathologist as they will not be fatal. The old and the new patterns of BPD will be described in these terms, although it should be emphasized that they still represent a spectrum of lung injury rather than distinct disease entities.
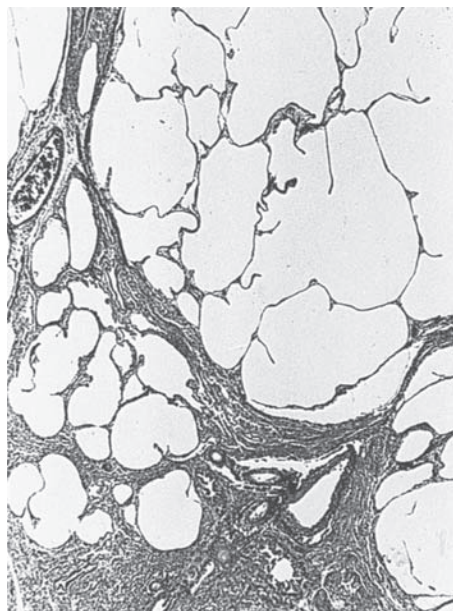
Bronchopulmonary Dysplasia (Old)

The 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, and a chronic fibroproliferative phase from the end of the first month. In the following 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:

FIGURE 20.28. Bronchopulmonary dysplasia. An area of emphysema.

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.

- *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. 20.26) (Hislop and Haworth 1990). In some cases, there is evidence of a reduction in peripheral arterial density, possibly due to failure of normal postnatal 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.

New Bronchopulmonary Dysplasia (Chronic Lung Disease)

Compared with the older pattern of disease, new BPD lungs show little or no major airway damage, and the small pulmonary arteries are relatively normal. Although an increase in elastic tissue can be detected with special stains, interstitial fibrosis

also appears minimal or absent. The damage is predominantly due to interference with normal alveolarization so that there are fewer, but larger and simpler, air spaces, leading to a significant decrease in surface area and a reduced abnormal pulmonary microvasculature (Jobe and Bancalari 2001; Thibeault et al. 2004; Galambos and DeMello 2007). Histologically these changes can be relatively subtle, and the relative increase in alveolar size easily missed by the casual observer. There is evidence that interference with the normal processes of septation and alveolarization occurs very early, and the normal collagen framework is affected by ventilation (Thibeault et al. 2003).

Etiology and Pathogenesis

The current and changing incidence of BPD is difficult to specify. It varies markedly depending on gestation and because the pattern of disease and definition of BPD has changed. However, there is some indication that the need for long-term ventilatory support is increasing, possibly because of averted neonatal death from improving therapies (Yu and Ng 1995). Approximately, 20% of very low birth weight babies (<1500 g) still require some supplementary oxygen at 36 weeks postmenstrual age (Sosenko et al. 2003). Clinically, the infants destined to develop BPD are not easy to identify at an early stage, although antenatal factors may be significant. These include early, prenatal lung inflammation (Watterberg et al. 1994; Matsuda et al. 1997). Bronchoalveolar lavage studies indicate a higher level of inflammatory and oxidant markers associated with the acute lung injury in those infants who progress to chronic lung disease (Contreras et al. 1996; Murch et al. 1996b) compared with those who do not.

Additional factors may include the use, too early, of intralipid during parenteral nutrition, which may interfere with oxygenation (Cooke 1991; Stahl et al. 1992); lung colonization with *Ureaplasma urealyticum* (Wang et al. 1995); and antenatal steroids (Jobe 2003).

Bronchopulmonary dysplasia, as a distinct entity, emerged primarily following the introduction of ventilatory support for the preterm infant and resulted from a combination of barotrauma and oxygen toxicity, which interfered with normal growth and repair mechanisms following acute

lung injury. Inflammation is an 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 is likely to be the most significant factor in the obliterative bronchiolar lesions (Taghizadeh and Reynolds 1976; Saugstad 1990) seen in old BPD.

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: 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 is enhanced in the presence of high oxygen concentrations and damage is accentuated in the absence of normal cellular antioxidant defenses. 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 organization. Platelet-derived growth factor may be produced by the interstitium in response to hyperoxia and stimulate early fibroblast hyperplasia (Han et al. 1992). Inactivation of surfactant may also be important (Merritt 1982; Saugstad 1990; Contreras et al. 1996). There is growing evidence that indicators of oxidative stress can be found very early, possibly only hours after birth (Saugstad 2003).

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. 20.29). 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.
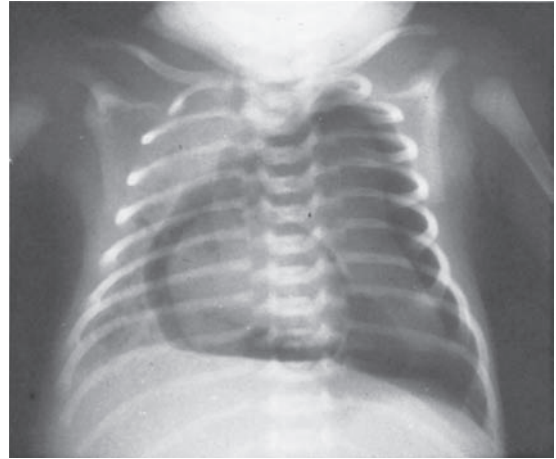
FIGURE 20.29. Chest radiograph from a baby at 28 weeks' gestation. There is air within the left pleural and pericardial cavities.

20.30). 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. 20.31). Often at
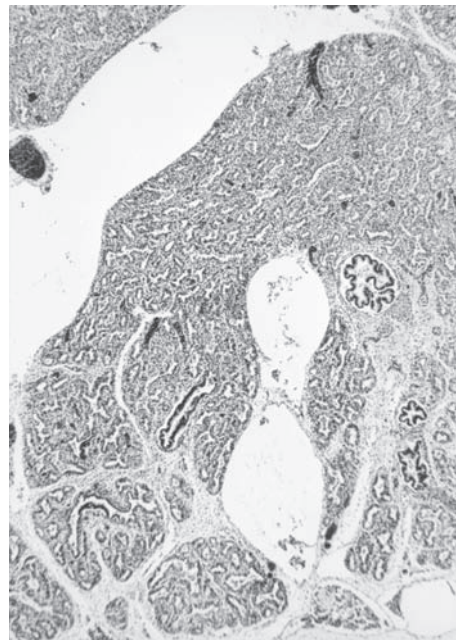
FIGURE 20.30. Lung from a 25-week early neonatal death showing emphysema and air within septal lymphatics tracking to the subpleural region.
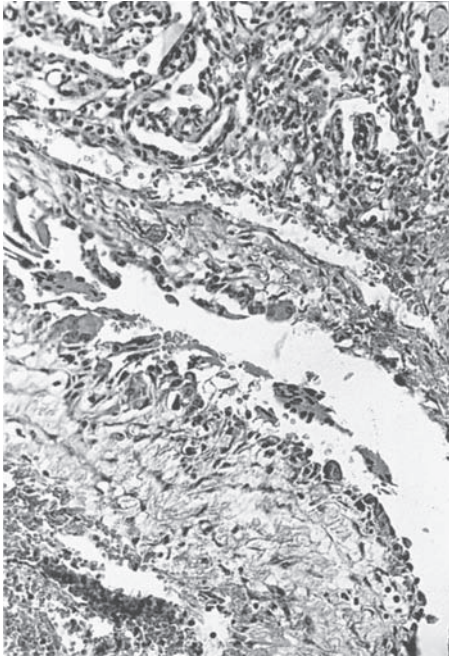
FIGURE 20.31. Partially collapsed old cyst resulting from interstitial emphysema. Cyst wall is formed of thick fibrous tissue and lined by macrophages including giant cells.

postmortem, due to resorption, PIE is less impressive than the premortem radiographs might lead one to expect. Severe PIE is seen much less frequently with modern therapies especially since the advent of surfactant therapy for HMD. Both pneumothorax and PIE are more likely in the presence of pulmonary hypoplasia.

Pulmonary Hemorrhage

In preterm infants dying during the acute phase of lung injury, some pulmonary hemorrhage is a common finding in the terminal sacs and pulmonary interstitium, especially associated with hyaline membrane disease (Coffin et al. 1993). Hemorrhage may also occur into the dilated pulmonary lymphatics. In some cases massive hemorrhage is a terminal event. It may be associated with birth asphyxia or hemorrhagic disease of the newborn. Although the pathogenesis is not certain, pulmonary hemorrhage may represent a hemorrhagic pulmonary edema (Cole et al. 1973; Amizuka et al. 2003) and reflect terminal heart failure.

Pathology of Birth Asphyxia

Birth asphyxia has been defined as a condition of impaired blood gas exchange leading to progressive hypoxemia and hypercapnia with a 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. 20.32). 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% to 15% of infants. It is rarely seen before 34 weeks, and if seen earlier may be associated with infection. Release has been attributed to reflex anal
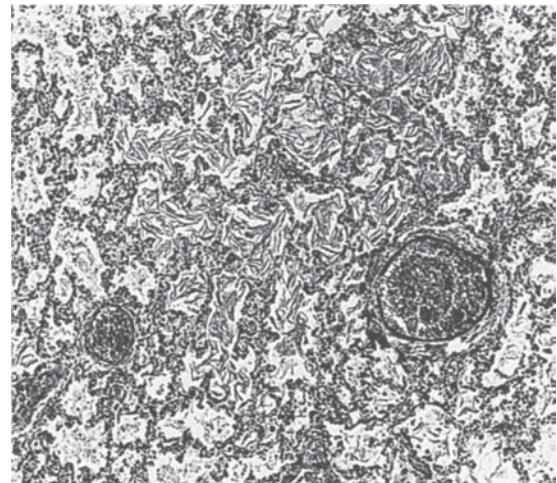
FIGURE 20.32. Lung from a fresh stillbirth at 37 weeks' gestation. Airways are unexpanded and aspirated squames are present in air spaces.

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 considerable debate as to the timing of meconium aspiration and its significance in relation to management and prevention (Wiswell et al. 1990; Katz and Bowes 1992; Ahanya et al. 2005). 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, that aspect of MAS due to pulmonary hypertension may reflect antepartum structural changes in pulmonary arterioles resulting from chronic intrauterine hypoxia (Murphy et al. 1984; Thureen et al. 1997).

At necropsy, asphyxia is suggested by petechial hemorrhages, sometimes confluent, on the pleural surfaces of the lungs. The cut surfaces may show congestion and edema. When substantial meconium aspiration has occurred, the lungs are heavy and mottled, and careful inspection may reveal areas of overdistention 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. 20.32). More rarely, meconium are also present as eosinophilic granular material, with small yellowish meconium bodies and mucus (Fig. 20.33). While a few macrophages may be associated with this material, a widespread acute inflammatory infiltrate is unusual, which may indicate that meconium aspiration is often an agonal event in
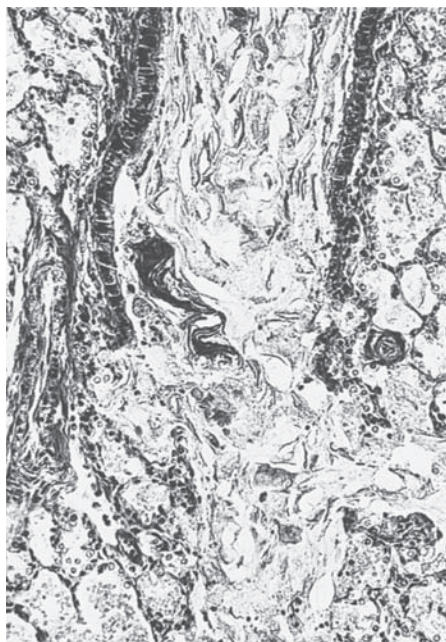
FIGURE 20.33. Terminal bronchiole from term infant containing squames, mucin, and granular material typical of meconium aspiration.

many stillborns. Chronic intrauterine aspiration of meconium associated with lung infarction has been reported (Kearney 1999).

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. There is evidence that meconium causes a chemical pneumonitis possibly due to the bile salt content (Oelberg et al. 1990), but features such as the patchy distribution of the inflammation that accompanies the meconium and the rarity of inflammation in the meconium stained lungs of stillborns suggest 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 (PPH) of the newborn reflects a failure to reduce or maintain a reduction in the normal postnatal fall in pulmonary vascular resistance. Increased pulmonary vascular resistance may be due to increased

muscularization of the pulmonary arteries, increased vascular reactivity, or decreased vascular bed because of poor lung growth; these factors are not mutually exclusive. Although there may be an initial period of apparent normality, PPH may be indicated by cyanosis and respiratory distress, which may develop after birth; the associated hypoxemia responds poorly to supplemental oxygen. There is right-to-left intrapulmonary shunting but also across the foramen ovale and the ductus arteriosus (if it remains patent). Because of this latter feature, it has been referred to as persistent fetal circulation (Gersony 1973).

Pulmonary hypertension may be associated with other abnormalities such as congenital heart disease or congenital alveolar capillary dysplasia (see above). Late presentation may occur rarely in babies with trisomy 21 even in the absence of a relevant structural cardiac defect. A more common association is lung hypoplasia, where 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 hypoglycemia. Rarely it may be idiopathic, although it has been argued this does not exist (Perlman et al. 1989).

Idiopathic PPH and the hypertension associated with MAS may be associated with vascular changes of prenatal origin, possibly due to intrauterine chronic hypoxia. The preacinar and intraacinar 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 fibers 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 restriction. Infection may be acquired in utero, intrapartum, or in the neonatal period, and while 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).
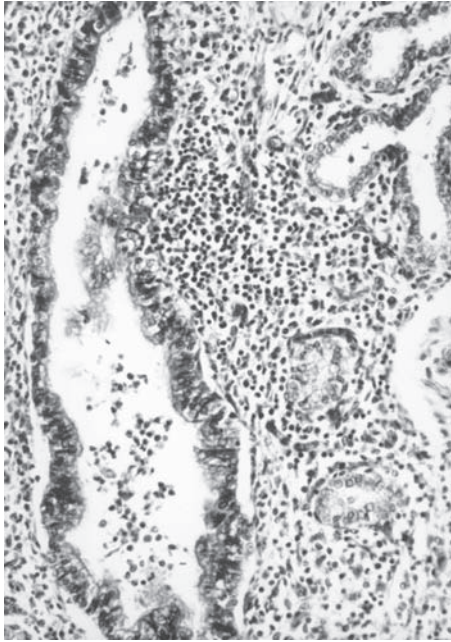
Ascending Infection

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% to 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 hemopoietic cells and lymphocytic aggregates (Fig. 20.34). The latter, which is 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 (GBS). *Candida* infection may produce superficially nonspecific but usually very florid pneumonia in which the characteristic hyphae can be seen (Fig. 20.35). 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.
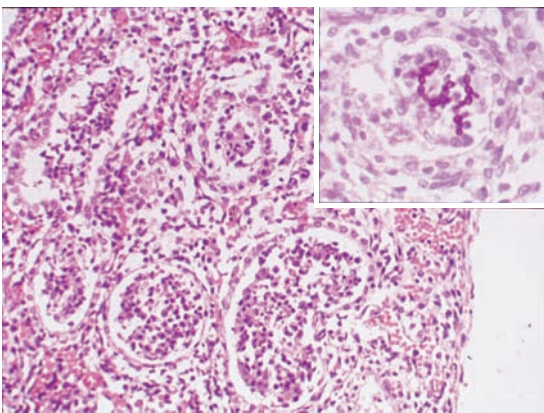
Neonate

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

FIGURE 20.34. Ascending infection in lung from 20-week-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.

hours after birth but can be delayed for up to 48 hours. Most bacterial infection produces a typical nonspecific bronchopneumonia, although some organisms produce characteristic features. Group B streptococcus, 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. Early GBS infection is not invariably associated with evidence of ascending infection in the placenta (De Paepe et al. 2004). Many of the cardiovascular effects of GBS may be mediated by tumor 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 edema. 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. 20.36).

The pathology of late-onset pneumonia is similar to that of early onset but with a different range of organisms. *Pseudomonas* is a frequent
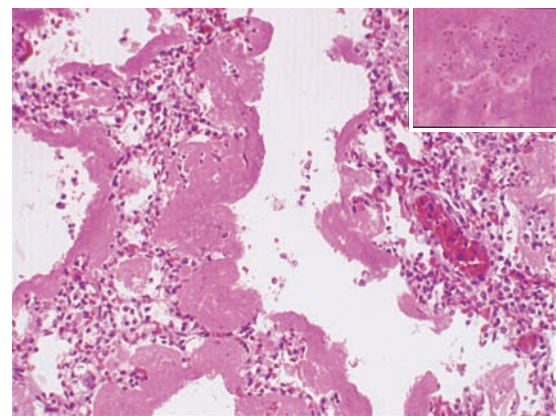

FIGURE 20.35. Florid pneumonia associated with ascending infection in a 17-week-gestation fetus. Inset shows typical *Candida* (periodic acid-Schiff stain).

FIGURE 20.36. Dense hyaline membranes in term infant dying at approximately 12 hours of age from overwhelming group B streptococcal infection. Under high power (inset) bacteria are visible in the membrane.

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 (Bonifacio et al. 2003). Hemorrhage 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" is usually only 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. 20.35). In systemic infection, the vasculature is usually the prime site of infection from septic emboli.

Viral Infection

Most viral infections can affect the lungs, but other tissues or organs 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
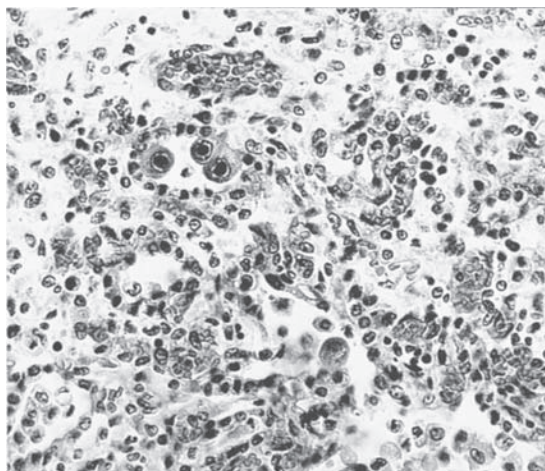

FIGURE 20.37. Cytomegalovirus inclusions in the lung of an infant dying from chronic lung disease. The infection is not congenital and was acquired while the infant was on the neonatal unit.

lung disease (Fig. 20.37). 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. 20.38).

Other viruses are generally very rare in the neonatal period. Respiratory syncytial virus (RSV) and metapneumovirus (Ulloa-Gutierrez et al. 2004) are normally seen in older infants, although RSV 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
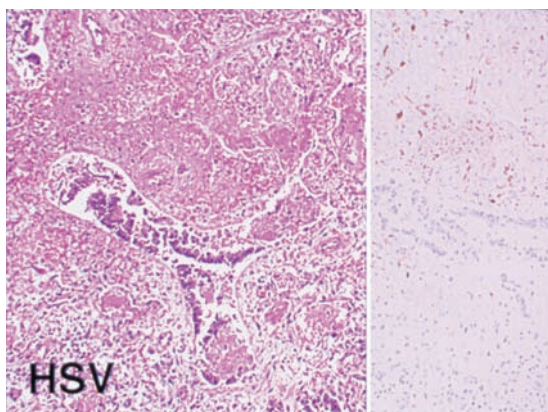
FIGURE 20.38. Herpes simplex virus (HSV) (type 2) in lung from an infant with disseminated disease. Inclusions are difficult to find, the necrosis is bland, and there is little associated inflammatory reaction. Immunohistology shows the presence of viral antigen confined mainly to the areas of necrosis.

(Modlin 1986; Abzug et al. 1990). The illness may be very severe and resemble a bacterial pneumonia clinically. There is a case report implicating a coronavirus associated with chronic lung disease (Sizun et al. 1994).

References

Ablow RC, Driscoll SG, Effman EL, et al. (1976) A comparison of early onset group B streptococcal neonatal infection and the respiratory distress syndrome of the newborn. N Engl J Med 294:65–70.

Abzug MJ, Beam AC, Gyorkos EA, Myron J (1990) Viral pneumonia in the first month of life. Pediatr Infect Dis J 9:882–885.

Agosti E, Filippi G, Chiussi F (1974) Generalized familial bronchomalacia. Acta Pediatr Scand 63:616–618.

Ahanya SN, Lakshmanan J, Morgan BL, Ross MG (2005) Meconium passage in utero: mechanisms, consequences, and management. Obstet Gynecol Surv 60:45–56.

Albuquerque CA, Smith KR, Saywers TE, Johnson C, Cock ML, Harding R (2002) Relation between oligohydramnios and spinal flexion in the human fetus. Early Hum Dev 68:119–126.

Amizuka T, Shimizu H, Niida Y, Ogawa Y (2003) Surfactant therapy in neonates with respiratory failure due to haemorrhagic pulmonary oedema. Eur J Pediatr 162:697–702.

Areechon W, Reid L (1963) Hypoplasia of lung with congenital diaphragmatic hernia. Br Med J 1:230–233.

Askenazi SS, Perlman M (1979) Pulmonary hypoplasia: lung weight and radial alveolar count as criteria of diagnosis. Arch Dis Child 54:614–618.

Bale PM (1979) Congenital cystic malformation of the lung. A form of congenital bronchiolar (adenomatoid) malformation. Am J Clin Pathol 71:411–420.

Belmont JR, Grundfast K (1984) Congenital laryngeal stridor (laryngomalacia). Etiologic factors and associated disorders. Ann Otol Rhinol Laryngol 93:430–437.

Benjamin B (1984) Tracheomalacia in infants and children. Ann Otol Rhinol Laryngol 93:438–442.

Bertrand P, Navarro H, Caussade D, Holmgren N, Sanchez I (2003) Airway anomalies in children with Down syndrome: endoscopic findings. Pediatr Pulmonol 36:137–141.

Blanc WA (1976) Commentary: yellow lung in premature infants. J Pediatr 89:131–132.

Bonifacio SL, Kitterman JA, Ursell PC (2003) Pseudomonas pneumonia in infants: an autopsy study. Hum Pathol 34:929–938.

Bonikos DS, Bensch KG, Northway WH Jr, Edwards DK (1976) Bronchopulmonary dysplasia: the pulmonary pathologic sequel of necrotizing bronchiolitis and pulmonary fibrosis. Hum Pathol 7:643–666.

Bonnard A, Auber F, Fourcade L, Marchac V, Emond S, Revillon Y (2003) Vascular ring abnormalities: a retrospective study of 62 cases J Pediatr Surg 38:539–543.

Booth JB, Berry CL (1967) Unilateral pulmonary agenesis. Arch Dis Child 42:361–374.

Bozic C (1969) Lesions dues a l'intubation endotrachéale des nouveau-nés. Helv Paediatr Acta 24:458–462.

Bray RJ, Lamb WH (1988) Tracheal stenosis or agenesis in association with tracheo-oesophageal fistula and oesophageal atresia. Anaesthesia 43:654–658.

Brown MJ, Olver RE, Ramsden CA, Strang LB, Walters DV (1983) Effects of adrenaline and of spontaneous labour on the secretion and absorption of lung liquid in the fetal lamb. J Physiol 344:137–152.

Burri PH (1999) Lung development and pulmonary angiogenesis. In: Gaulter C, Bourbon J, Post M (eds) Lung Development. Oxford University Press, New York, pp. 122–151.

Bush A (2001) Congenital lung disease: a plea for clear thinking and clear nomenclature. Pediatr Pulmonol 32:328–337.

Calvert JK, Boyd PA, Chamberlain PC, Said S, Lakhoo K (2006) Outcome of antenatally suspected congeni-

tal cystic adenomatoid malformation of the lung: 10 years' experience 1991–2001. Arch Dis Child Fetal Neonatal Ed 91:F26–28.

Cassell GH, Waites KB, Watson HL, Crouse DT, Harasawa R (1993) *Ureaplasma urealyticum* intrauterine infection: role in prematurity and disease in newborns. Clin Microbiol Rev 6:69–87.

Cater G, Thibeault DW, Beatty EC Jr, Kilbride HW, Huntrakoon M (1989) Misalignment of lung vessels and alveolar capillary dysplasia: a cause of persistent pulmonary hypertension. J Pediatr 114:293–300.

Cha I, Adzick NS, Harrison MR, Finkbeiner WE (1997) Fetal congenital cystic adenomatoid malformations of the lung: a clinicopathologic study of eleven cases. Am J Surg Pathol 21:537–544.

Chambers HM (1991) Congenital acinar aplasia: an extreme form of pulmonary maldevelopment. Pathology 23:69–71.

Chandra RK, Gerber ME, Holinger LD (2001) Histological insight into the pathogenesis of severe laryngomalacia. Int J Pediatr Otorhinolaryngol 19:31–38.

Chang N, Hertzler JH, Gregg RH, Lofti MW, Brough AJ (1968) Congenital stenosis of the right mainstem bronchus. A case report. Pediatrics 41:739–742.

Chapin CJ, Ertsey R, Yoshizawa J, et al. (2005) Congenital diaphragmatic hernia, tracheal occlusion, thyroid transcription factor-1, and fetal pulmonary epithelial maturation. Am J Physiol Lung Cell Mol Physiol 289: L44–52.

Chellam VG (1988) Rhabdomyomatous dysplasia of the lung: a case report with review of the literature. Pediatr Pathol 8:391–394.

Chen MF, Onerheim R, Wang NS, Huttner I (1991) Rhabdomyomatosis of the newborn lung. Pediatr Pathol 11:123–129.

Chen Y, Frank L (1993) Differential gene expression of antioxidant enzymes in the perinatal rat lung. Pediatr Res 34:27–31.

Chi JG, Shong Y-K (1982) Diffuse striated muscle heteroplasia of the lung. An autopsy case. Arch Pathol Lab Med 106:641–644.

Chu L, Gussack G, Orr JB, Hood D (1994) Neonatal laryngoceles: a cause for airway obstruction. Arch Otolaryngol Head Neck Surg 120:454–458.

Clements BS, Warner JO (1987) Pulmonary sequestration and related congenital bronchopulmonary-vascular malformations: nomenclature and classification based on anatomical and embryological considerations. Thorax 42:401–408.

Coffin CM, Schechtman K, Cole FS, Dehner LP (1993) Neonatal and infantile pulmonary hemorrhage: an autopsy study with clinical correlation. Pediatr Pathol 13:583–589.

Cogbill TH, Moore FA, Accurso FJ, Lilly JR (1983) Primary tracheomalacia. Ann Thorac Surg 35:538–541.

Cole VA, Normand ICS, Reynolds EO, Rivers RPA (1973) Pathogenesis of hemorrhagic pulmonary edema and massive pulmonary hemorrhage in the newborn. Pediatrics 51:175–186.

Contreras M, Hariharan N, Lewandoski JR, et al. (1996) Bronchoalveolar oxyradical inflammatory elements herald bronchopulmonary dysplasia. Crit Care Med 24:29–37.

Cooke RWI (1991) Factors associated with chronic lung disease in preterm infants. Arch Dis Child 66:776–779.

Cooney TP, Thurlbeck WM (1982) The radial alveolar count method of Emery and Mithal: a reappraisal. 2. Intrauterine and early postal lung growth. Thorax 37:580–583.

Cotton RT, Richardson MA (1981) Congenital laryngeal anomalies. Otolaryngol Clin North Am 14:203–218.

Cunningham ML, Mann N (1997) Pulmonary agenesis: a predictor of ipsilateral malformations. Am J Med Genet 70:391–398.

Danielian PJ (1994) Multiple parameters including meconium. In: Spencer JAD, Ward RHT (eds) Intrapartum Fetal Surveillance. RCOG Press, London, pp. 269–280.

Davenport M, Warne SA, Cacciaguerra S, Patel S, Greenough A, Nicolaides K (2004) Current outcome of antenally diagnosed cystic lung disease. J Pediatr Surg 39:549–556.

de Krijger RR, Albers MJ, Bogers AJ, Mooi WJ (2004). Heterotopic pancreatic tissue presenting as a solid and cystic lung lesion: a very unusual bronchopulmonary foregut malformation. Pediatr Dev Pathol 7:204–209.

de la Monte S, Hutchins GM, Moore GW (1986) Respiratory epithelial cell necrosis is the earliest lesion of hyaline membrane disease of the newborn. Am J Pathol 123:155–160.

De Paepe ME, Friedman RM, Gundogan F, Pinar H, Oyer CE (2004) The histologic fetoplacental inflammatory response in fatal perinatal group B-streptococcus infection. J Perinatol 24:441–445.

De Santo LW, De Vine KD, Weiland LH (1970) Cysts of the larynx. Classification. Laryngoscope 80:145–176.

De Vine WA, Debich DE, Anderson RH (1991) Dissection of congenitally malformed hearts, with comments on the value of sequential segmental analysis. Pediatr Pathol 11:235–260.

Devlieger H, Jaeken J, Moerman P, et al. (1994) Intractable asphyxia at birth: analysis of the underlying conditions. Eur J Obstet Gynecol Reprod Biol 54: 21–24.

Diaz EM, Adams JM, Hawkins HK, Smith RJH (1989) Tracheal agenesis. A case report and literature review. Arch Otolaryngol Head Neck Surg 115:741–745.

Domitzio P, Liesner RJ, Dicks-Mireaux C, Risdon RA (1990) Malignant mesenchymoma associated with a congenital lung cyst in a child. Case report and review of the literature. Pediatr Pathol 10:785–797.

Doolin EJ, Strande L, Attorri RJ (1995) Morphometry and histochemistry of pulmonary arteries in a hypoplastic lung model. J Surg Res 59:191–197.

Durham PL, Snyder JM (1995) Characterization of alpha-1, beta-1 and gamma-1 laminin subunits during rabbit fetal lung development. Dev Dynam 203:408–421.

Durham PL, Snyder JM (1996) Regulation of the beta-2 subunit chain of laminin in developing rabbit fetal lung tissue. Differentiation 60:229–243.

Emery JL, Mithal A (1960) The number of alveoli in the terminal respiratory unit of man during late intrauterine life and childhood. Arch Dis Child 35:544–547.

Endo A, Minato M, Takada M, et al. (2001) A case of pulmonary hypoplasia associated with intrauterine brainstem necrosis. Eur J Pediatr 160:675–676.

Engellenner W, Kaplan C, Van-de-Vegte GL (1989) Pulmonary agenesis association with nonimmune hydrops. Pediatr Pathol 9:725–730.

Engle WA, Lemons JA, Weber TR, Cohen MD (1984) Congenital lobar emphysema due to a bronchogenic cyst. Am J Perinatol 1:196–198.

Esterly JR, Oppenheimer EH (1970) Lymphangiectasis and other pulmonary lesions in the asplenia syndrome. Arch Pathol 90:553–560.

Farrell PM, Avery ME (1975) Hyaline membrane disease. Am Rev Respir Dis 3:657–688.

Ferguson MWJ (1991) The orofacial region. In: Wigglesworth JS, Singer DB (eds) Textbook of Fetal and Perinatal Pathology. Blackwell Scientific, Oxford, pp. 843–880.

Ferguson MWJ, Sharpe PM, Thomas BL, Beck F (1992) Differential expression of insulin-like growth factors I and II (IGF I and II), mRNA, peptide and binding protein 1 during mouse palate development: comparison with TGF-beta peptide distribution. J Anat 181:219–238.

Figa FH, Yoo SJ, Burrows PE, Turner-Gomes S, Freedom RM (1993) Horseshoe lung—a case report with unusual bronchial and pleural anomalies and a proposed new classification. Pediatr Radiol 23:44–47.

Fine ED, Dahms B, Arnold JE (1995) Laryngeal hamartoma: a rare congenital abnormality. Ann Otol Rhinol Laryngol 104:87–89.

Fisher JE, Nelson SJ, Allen JE, Holzman RS (1982) Congenital cystic adenomatoid malformation of the lung. A unique variant. Am J Dis Child 136:1071–1074.

Floyd J, Cambell DC, Dominey DE (1962) Agenesis of the trachea. Am Rev Respir Dis 86:557–560.

Forte V, Fuoco G, James A (2004) A new classification system for congenital laryngeal cysts. Laryngoscope 114:1123–1127.

France NE, Brown RJK (1971) Congenital pulmonary lymphangiectasis: report of 11 examples with special reference to cardiovascular findings. Arch Dis Child 46:528–532.

Frank L, Sosenko IRS (1987) Development of lung antioxidant enzyme system in late gestation: possible implications for the prematurely born infant. J Pediatr 110:9–14.

Frank L, Sosenko IRS (1991) Failure of premature rabbits to increase antioxidant enzymes during hyperoxic exposure: increased susceptibility to pulmonary oxygen toxicity compared with term rabbits. Pediatr Res 29:292–296.

Friedman EM, Vastola P, McGill TJI, Healy GB (1990) Chronic pediatric stridor: etiology and outcome. Laryngoscope 100:277–280.

Galambos C, DeMello DE (2007) Molecular mechanisms of pulmonary vascular development. Pediatr Develop Pathol 10:1–17.

Gersony WM (1973) Persistence of the fetal circulation. A commentary. J Pediatr 82:1103–1106.

Gibson RL, Redding GJ, Henderson WR, Truog WE (1991) Group B streptococcus induces tumor necrosis factor in neonatal piglets. Am Rev Respir Dis 143:598–604.

Gifford GH Jr, Swanson L, MacCollum DW (1972) Congenial absence of the nose and anterior nasopharynx. Plast Reconstr Surg 50:5–12.

Gillespie LM, Fenton AC, Wright C (2004) Acinar dysplasia: a rare cause of neonatal respiratory failure. Acta Paediatr 93:712–713.

Goldman AS (1992) Pathophysiology of congenital malformations. In: Polin RA, Fox WW (eds) Fetal and Neonatal Physiology. WB Saunders, London, pp. 36–46.

Gorenflo M, Vogel M, Obladen M (1991) Pulmonary vascular changes in bronchopulmonary dysplasia: a clinical pathologic correlation in short and long term survivors. Pediatr Pathol 11:851–866.

Gould SJ, Howard S (1985) The histopathology of the larynx in the neonate following endotracheal intubation. J Pathol 146:301–311.

Gould SJ, Isaacson PG (1993) Bronchus-associated lymphoid tissue (BALT) in human fetal and infant lung. J Pathol 169:229–234.

Gravett MG, Nelson P, DeRouen T, et al. (1986) Independent associations of bacterial vaginosis and *Chla-*

mydia trachomatis infection with adverse pregnancy outcome. JAMA 256:1899–1903.

Greenough A, Milner AD (2005) Chronic lung disease. In: Rennie JM (ed) Roberton's Textbook of Neonatology, 4th ed. Elsevier, New York, pp. 554–572.

Grigg J, Arnon S, Chase A, Silverman M (1993) Inflammatory cells in the lungs of premature infants on the first day of life: perinatal risk factors and origin of cells. Arch Dis Child 69:40–43.

Groenman F, Unger S, Post M (2005) The molecular basis for abnormal lung development. Biol Neonate 87:164–177.

Groneck P, Speer CP (1995) Inflammatory mediators and bronchopulmonary dysplasia. Arch Dis Child 73:F1–F3.

Gupta TGCM, Goldberg SJ, Lewis E, Fonkalsrud EW (1968) Congenital bronchomalacia. Am J Dis Child 115:88–90.

Gutierrez D, Rodriguez A, Palenzuela S, Forteza C, Rossella KLD (2000) Congenital misalignment of pulmonary veins with alveolar capillary dysplasia causing persistent neonatal pulmonary hypertension: report of two affected siblings. Pediatr Dev Pathol 3:271–276.

Haidar A, Ryder TA, Wigglesworth JS (1991) Epithelial cell morphology and airspace size in hypoplastic human fetal lungs associated with oligohydramnios. Pediatr Pathol 11:839–850.

Hall CB, Kopelman AE, Douglas RG Jr, Geiman JM, Meagher MP (1979) Neonatal respiratory syncytial virus infection. N Engl J Med 300:393–396.

Halliday H (2003) Respiratory distress syndrome. In: Greenhough A, Milner AD (eds) Neonatal Respiratory Disorders. Arnold, London, pp. 247–271.

Hamilton WJ, Boyd JD, Mossman HW (1972) Human Embryology. Williams & Wilkins, Baltimore, pp. 291–377.

Han RN, Buch S, Freeman BA, Post M, Tanswell AK (1992) Platelet-derived growth factor and growth related genes in rat lung. II. Effect of exposure to 85% O_2. Am J Physiol 262:L140–146.

Harding R, Hooper SB, Dickson KA (1990) A mechanism leading to reduced lung expansion and lung hypoplasia in fetal sheep during oligohydramnios. Am J Obstet Gynecol 163:1904–1913.

Harding R, Hooper SB, Han VKM (1993) Abolition of fetal breathing movements by spinal cord transection leads to reductions in fetal lung liquid volume, lung growth, and IGF-II gene expression. Pediatr Res 34:148–153.

Hardisson D, Garcia Jimenez JA, Jimenea Heffernan JA, Nistal M (1997) Rhabdomyomatosis of the newborn

lung unassociated with other malformations. Histopathology 31:474–479.

Haworth SG (1988) Pulmonary vascular remodelling in neonatal pulmonary hypertension. State of the art. Chest 93:133S–138S.

Heerema AE, Rabban JT, Sydorak RM, Harrison MR, Jones KD (2003) Lung pathology in patients with congenital diaphragmatic hernia treated with fetal surgical intervention, including tracheal occlusion. Pediatr Dev Pathol 6:536–546.

Heithoff KB, Sane SM, Williams JW, et al. (1976) Bronchopulmonary foregut malformations. A unifying concept. Am J Roentgenol 126:46–55.

Hicks BA, Contador M, Perlman JM (1996) Laryngeal atresia in the newborn: surgical implications. Am J Perinatol 13:409–411.

Hill DA, Dehner LP, Ackerman LV (2004). A cautionary note about congenital cystic adenomatoid malformation (CCAM) type 4. Am J Surg Pathol 28:554–555.

Hislop A (2003) Fetal and postnatal anatomical lung development. In: Greenough A, Milner AD (eds) Neonatal Respiratory Disorders. Arnold, London, pp. 3–11.

Hislop A, Hey E, Reid L (1979) The lungs in congenital bilateral renal agenesis and dysplasia. Arch Dis Child 54:32–38.

Hislop AA, Haworth SG (1990) Pulmonary vascular damage and the development of cor pulmonale following hyaline membrane disease. Pediatr Pulmonol 9:152–161.

Hislop AA, Howarth SG (1989) Airway size and structure in the normal fetal and infant lung and the effect of premature delivery and artificial ventilation. Am Rev Respir Dis 140:1717–1726.

Hislop AA, Wigglesworth JS, Desai R (1986) Alveolar development in the human fetus and infant. Early Hum Dev 13:1–11.

Hodson WA (1992) Normal and abnormal structural development of the lung. In: Polin RA, Fox WW (eds) Fetal and Neonatal Physiology. WB Saunders, London, pp. 771–782.

Holder MP, Wooler GH (1970) Tracheo-oesophageal fistula and oesophageal atresia: results of 30 years' experience. Thorax 25:406–412.

Hooper SB, Harding R (1995) Fetal lung liquid: a major determinant of the growth and functional development of the fetal lung. Clin Exp Pharmacol Physiol 22:235–247.

Huang RY, Shapiro NL (2000) Structural airway anomalies in patients with DiGeorge syndrome: a current review. Am J Otolaryngol 21:326–330.

Husain AN, Hessel RG (1993) Neonatal pulmonary hypoplasia: an autopsy study of 25 cases. Pediatr Pathol 13:475–484.

Imai Y, Mark EJ (2002) Cystic adenomatoid change is common to various forms of cystic lung diseases of children: a clinicopathologic analysis of 10 cases with emphasis on tracing the bronchial tree. Arch Pathol Lab Med 126:934–940.

Janney CG, Askin FB, Kuhn CK (1981) Congenital alveolar dysplasia—an unusual cause of respiratory distress in the newborn. Am J Clin Pathol 76:722–727.

Jobe AH (2003) Antenatal factors and the development of bronchopulmonary dysplasia. Semin Neonatol 8:9–17.

Jobe AH, Bancalari R (2001). Bronchopulmonary dysplasia. NICHD/NHLBI/ORD Workshop Summary. Am J Respir Crit Care Med 163:1723–1729.

Kaslovsky RA, Purdy S, Dangman BC, McKenna BJ, Brien T, Ilves R (1997) Bronchoalveolar carcinoma in a child with congenital cystic adenomatoid malformation. Chest 112:548–555.

Kassner EG, Kauffman SL, Yoon JJ, et al. (1981) Pulmonary candidiasis in infants: clinical, radiologic, and pathologic features. Am J Roentgenol 137:707–716.

Katz VL, Bowes WA (1992) Meconium aspiration syndrome: reflections on a murky subject. Am J Obstet Gynecol 166:171–183.

Kaufmann V, Kohler G (1995) Congenital posterior laryngotracheoesophageal cleft with subglottic stenosis: a case report. Pediatr Pathol 15:321–325.

Kearney MS (1999) Chronic intrauterine meconium aspiration causes fetal lung infarcts, lung rupture and meconium embolism. Pedatr Dev Pathol 2:544–551.

Keller MA, Sellers BB, Melish ME, et al. (1977) Systemic candidiasis in infants. Am J Dis Child 131:1260–1263.

Khong TY, Frappell J, Steel HM, Stewart CM, Burke M (1986) Perinatal listeriosis. A report of six cases. Br J Obstet Gynaecol 93:1083–1087.

Kitterman JA (1984) Fetal lung development. J Dev Physiol 6:67–82.

Kizilcan F, Tanyel C, Cakar N, Buyukpamukcu N, Hicsonmez A (1995) The effect of low amniotic pressure without oligohydramnios on fetal lung development in a rabbit model. Am J Obstet Gynecol 173(a):36–41.

Knowles S, Thomas RM, Lindenbaum RH, Keeling JW, Winter RM (1988) Pulmonary agenesis as part of the VACTERL sequence. Arch Dis Child 63:723–726.

Kubba H, Gibson D, Bailey M, Hartley B (2005) Techniques and outcomes of laryngeal cleft repair: an update to the Great Ormond Street Hospital series. Ann Otol Rhinol Laryngol 114:309–313.

Kuhn C, Kuhn JP (1992) Coexistence of bronchial atresia and bronchogenic cyst: diagnostic criteria and embryologic considerations. Pediatr Radiol 22:568–570.

Laberge JM, Puligandla P, Flageole H (2005) Asymptomatic congenital lung malformations. Semin Pediatr Surg 14:16–33.

Lackner RP, Thompson AB III, Rikkers LF, Galbraith TA (1996) Cystic adenomatoid malformation involving an entire lung in a 22-year-old women. Ann Thorac Surg 61:1827–1829.

Lamont RF, Taylor-Robinson D, Wigglesworth JS, et al. (1987) The role of mycoplasmas, ureaplasmas and chlamydiae in the genital tract of women presenting in spontaneous early preterm labour. J Med Microbiol 24:253–257.

Lander TA, Schauer G, Bendel-Stenzel E, Sidman JD (2004) Tracheal agenesis in the newborn. Laryngoscope 114:1633–1636.

Landing BH (1984) Five syndromes (malformation complexes) of pulmonary symmetry, congenital heart disease, and multiple spleens. Pediatr Pathol 2:125–151.

Landing BH, Dixon LG (1979) Congenital malformations and genetic disorders of the respiratory tract. Am Rev Respir Dis 120:151–185.

Landing BH, Wells TR (1973) Tracheobronchial anomalies in children. In: Rosenberg HS, Bolande RP (eds) Perspectives in Pediatric Pathology, vol 1. Year Book, Chicago, pp. 1–32.

Langston C (1991) Misalignment of pulmonary veins and alveolar capillary dysplasia. Pediatr Pathol 11:163–170.

Langston C (2003) New concepts in the pathology of congenital lung malformations. Semin Pediatr Surg 12:17–37.

Langston C, Kida K, Reed M, Thurlbeck WM (1984) Human lung growth in late gestation and in the neonate. Am Rev Respir Dis 129:607–613.

Laurence KM (1955) Congenital pulmonary lymphangiectasis. J Pathol Bacteriol 70:325–333.

Lauria MR, Gonik B, Romero R (1995) Pulmonary hypoplasia: pathogenesis, diagnosis, and antenatal prediction. Obstet Gynecol 86:466–475.

Liggins GC, Vilos GA, Campos GA, Kitterman JA, Lee CH (1981) The effect of bilateral thoracoplasty in lung development in fetal sheep. J Dev Physiol 3:275–282.

Lim TA, Spanier SS, Kohut RI (1979) Laryngeal clefts: a histopathologic study and review. Ann Otol Rhinol Laryngol 88:837–845.

Linna O, Hyrynkangas K, Kaukola T, Pajunen L (2004) Congenital subglottic stenosis in two unrelated pairs of siblings. Acta Paediatr 93:565–567.

Loeff DS, Filler RM, Vinograd I, et al. (1990) Congenital tracheal stenosis: a review of 22 patients from 1965–1987. J Pediatr Surg 25:492–495.

Low JA (1997) Intrapartum fetal asphyxia: definition, diagnosis and classification. Am J Obstet Gynecol 176:957–959.

MacSweeney F, Papagiannopoulos K, Goldstraw P, Sheppard MN, Corrin B, Nicholson AG (2003) An assessment of the expanded classification of congenital cystic adenomatoid malformations and their relationship to malignant transformation. Am J Surg Pathol 27:1139–1146.

Maeda J, Yamagishi H, Matsuoka, et al. (2000) Frequent association of 22q11.2 deletion with tetralogy of Fallot. Am J Med Genet 5:269–272.

Mani H, Suarez E, Stocker JT (2004) The morphologic spectrum of infantile lobar emphysema: a study of 33 cases. Paediatr Respir Rev 5(suppl A):S313–320.

Manning SC, Inglis AF, Mouzakes J, Carron J, Perkins JA (2005). Laryngeal anatomic differences in pediatric patients with severe laryngomalacia. Arch Otolaryngol Head Neck Surg 131:340–343.

Margraf LR, Tomashefski JF Jr, Bruce MC, Dahms BB (1991) Morphometric analysis of the lung in bronchopulmonary dysplasia. Am Rev Respir Dis 143:391–400.

Maritz GS, Morley CJ, Harding R (2005) Early developmental origins of impaired lung structure and function. Early Hum Dev 81:763–771.

Matsuda T, Nakajima T, Hattori S, et al. (1997) Necrotizing funisitis: clinical significance and association with chronic lung disease in premature infants. Am J Obstet Gynecol 177:1402–1407.

Matturri L, Lavezzi AM, Minoli I, et al. (2003) Association between pulmonary hypoplasia and hypoplasia of arcuate nucleus in stillbirth. J Perinatol 23:328–332.

McDougall J, Smith JF (1975) The development of the human type II pneumocyte. J Pathol 115:245–251.

McMillen WG, Duvall AJ (1968) Congenital subglottic stenosis. Arch Otolaryngol 87:272–278.

McNie DJM, Pryse-Davies J (1970) Tracheal agenesis. Arch Dis Child 45:143–144.

Mendelson CR, Boggaram V (1989) Regulation of pulmonary surfactant protein synthesis in fetal lung: a major role of glucocorticoids and cyclic AMP. Trends Endocrinol Metabol 1:20–25.

Merritt TA (1982) Oxygen exposure in the newborn guinea pig lung lavage cell populations, chemotactic and elastase response: a possible relationship to neonatal bronchopulmonary dysplasia. Pediatr Res 16:798–805.

Miniati DN, Chintagumpala M, Langston C, et al. (2006) Prenatal presentation and outcome of children with pleuropulmonary blastoma. J Pediatr Surg 41:66–71.

Mitchell DB, Irwin C, Bailey CM, Evans NG (1987) Cysts of the infants larynx. J Laryngol Otol 101:833–837.

Modlin JF (1986) Perinatal echovirus infection: insights from a literature review of 61 cases of serious infection and 16 outbreaks in nurseries. Rev Infect Dis 8:918–926.

Morgan T, Anderson J, Jorden M, Keller K, Robinson T, Hintz S (2003) Pulmonary glial heterotopia in a monoamniotic twin. Pediatr Pulmonol 36:162–166.

Mori M, Kidogawah H, Moritaka T, et al. (1993) Bronchial atresia: report of a case and review of the literature. Surg Today 23:449–455.

Moses D, Holm BA, Spitale P, et al. (1991) Inhibition of pulmonary surfactant function by meconium. Am J Obstet Gynecol 164:477–481.

Murch SH, Costeloe K, Klein NJ, et al. (1996a) Mucosal tumor necrosis factor-alpha production and extensive disruption of sulfated glycosaminoglycans begin within hours of birth in neonatal respiratory distress syndrome. Pediatr Res 40:484–489.

Murch SH, Costeloe K, Klein NJ, MacDonald TT (1996b) Early production of macrophage inflammatory protein 1 alpha occurs in RDS and is associated with poor outcome. Pediatr Res 40:490–497.

Murphy JS, Vawter GF, Reid LM (1984) Pulmonary vascular diseases in fetal meconium aspiration. J Pediatr 104:758–762.

Murray JC, Schutte BC (2004) Cleft palate: players, pathways and pursuits. J Clin Invest 113:1676–1678.

Nakamura Y, Harada K, Yamamoto I, et al. (1992) Human pulmonary hypoplasia. Statistical, morphological, morphometric and biochemical study. Arch Pathol Lab Med 116:635–642.

Nardo L, Hooper SB, Harding R (1998) Simulation of lung growth by tracheal obstruction in fetal sheep: relation to luminal pressure and lung liquid volume. Pediatr Res 43:184–190.

Ng KJ, Hasan N, Gray ES, Jeffrey RR, Youngson GG (1994) Intralobar bronchopulmonary sequestration: antenatal diagnosis. Thorax 49:379–380.

Nicolini U, Fisk NM, Rodeck CH, Talbert DG, Wigglesworth JS (1989) Low amniotic pressure in oligohydramnios—is this the cause of pulmonary hypoplasia? Am J Obstet Gynecol 161:1098–1101.

Nimrod C, Varela-Gittings F, Machin G, Campbell D, Wesenberg R (1984) The effect of prolonged membrane rupture on fetal development. Am J Obstet Gynecol 148:540–543.

Northway WH, Rosan RC, Porter DY (1967) Pulmonary disease following respiratory therapy for hyaline membrane disease. N Engl J Med 276:357–368.

Oelberg DG, Downery SA, Flynn MM (1990) Bile salt induced intracellular Ca accumulation in type 2 pneumocytes. Lung 168:297–308.

Oldenburg J, Van der Pal HJH, Schrevel LS, Blok APR, Wagenvoort CA (1995) Misalignment of lung vessels and alveolar capillary dysplasia. Histopathology 27:192–194.

Olver RE, Strang LB (1974) Ion fluxes across the pulmonary epithelium and the secretion of lung liquid in the foetal lamb. J Physiol 241:327–357.

Oppenheimer EH, Dahms BB (1981) Congenital syphilis in the fetus and neonate. In: Rosenberg HS, Bernstein J (eds) Perspectives in Pediatric Pathology, vol 6. Year Book Medical, Chicago, pp. 112–138.

Orpen N, Goodman R, Bowker C, Lakhoo K (2003) Intralobar pulmonary sequestration with congenital cystic adenomatous malformation and rhabdomyomatous dysplasia. Pediatr Surg Int 19:610–611.

Ostor AG, Stillwell R, Fortune DW (1978) Bilateral pulmonary agenesis. Pathology 10:243–248.

Page DV, Stocker JT (1982) Anomalies associated with pulmonary hypoplasia. Am Rev Respir Dis 125:216–221.

Pagon RA, Graham JM (1981) Coloboma, congenital heart disease and choanal atresia with multiple anomalies: CHARGE association. J Pediatr 99:223–227.

Perlman EJ, Moore GW, Hutchins GM (1989) The pulmonary vasculature in meconium aspiration. Hum Pathol 20:701–706.

Pham TT, Benirschke K, Masliah E, Stocker JT, Yi ES (2004) Congenital pulmonary airway malformation (congenital cystic adenomatoid malformation) with multiple extrapulmonary anomalies: autopsy report of a fetus at 19 weeks of gestation. Pediatr Dev Pathol 7:661–666.

Piedboeuf B, Laberge JM, Ghitulescu G, et al. (1997) Deleterious effect of tracheal obstruction on type II pneumocytes in fetal sheep. Pediatr Res 41:473–479.

Pinar H, Makarova N, Rubin LP, Singer DB (1994) Pathology of the lung in surfactant-treated neonates. Pediatr Pathol 14:627–636.

Podlech J, Richter J, Czygan P, Klein PJ, Muentefering H (1995) Bilateral agenesis/aplasia of the lungs: report of a second case in the offspring of one woman. Pediatr Pathol Lab Med 15:781–790.

Raine J, Hislop AA, Redington AN, Haworth SG, Shinebourne EA (1991) Fatal persistent pulmonary hypertension presenting late in the neonatal period. Arch Dis Child 66:398–402.

Ribvet ME, Copin MC, Soots JG, Gosselin BH (1995) Bronchioloalveolar carcinoma and congenital cystic adenomatoid malformation. Ann Thorac Surg 60:1126–1128.

Rice R, Spencer B, Connor EC, et al. (2004). Disruption of FgF10/Fgfr2b-coordinated epithelial-mesenchymal interactions causes cleft palate. J Clin Invest 113:1692–1700.

Riedlinger WFJ, Vargas SO, Jennings RW, et al. (2006) Bronchial atresia is common to extralobar sequestration, intralobar sequestration, congenital cystic adenomatoid malformation and lobar emphysema. Pediatr Develop Pathol 9:361–373.

Robertson B (1991) The origin of neonatal lung injury [editorial]. Pediatr Pathol 11:iii–vi.

Robson PJ, Smid M, Bannerjee S, Wigglesworth JS, Nicolini U (1993) Extreme prematurity or pulmonary hypoplasia: the inevitable consequences of second trimester premature rupture of membranes? J Obstet Gynaecol 13:320–328.

Romero R, Hanaoka S, Mazor M, et al. (1991) Meconium-stained amniotic fluid: a risk factor for microbial invasion of the amniotic cavity. Am J Obstet Gynecol 164:859–862.

Rooney SA (1989) Fatty acid synthesis in developing fetal lung. Am J Physiol 257:L195–L207.

Rutledge JC, Jensen P (1986) Acinar dysplasia: a new form of pulmonary maldevelopment. Hum Pathol 17:1290–1293.

Salyer DC, Salyer WR, Eggleston JC (1977) Benign developmental cysts of the mediastinum. Arch Pathol Lab Med 101:136–139.

Samuel M, Burge DM, Griffiths DM (1997) Prenatal diagnosis of laryngotracheoesophageal clefts. Fetal Diagn Ther 12:260–265.

Saugstad OD (1990) Oxygen toxicity in the neonatal period. Acta Paediatr Scand 79:881–892.

Saugstad OD (1997) Bronchopulmonary dysplasia and oxidative stress: are we closer to an understanding of the pathogenesis of BPD? Acta Pediatr 86:1277–1282.

Saugstad OD (2003) Bronchopulmonary dysplasia—oxidative stress and antioxidants. Semin Neonatol 8:39–49.

Schmidt B, Vegh P, Weitz J, et al. (1992) Thrombin/antithrombin III complex formation in the neonatal respiratory distress syndrome. Am Rev Respir Dis 145:767–770.

Sen P, Thakur N, Stockton DW, Langston C, Bejjani BA (2004) Expanding the phenotype of alveolar capillary dysplasia (ACD). J Pediatr 145:646–651.

Sgrignoli A, Yen DRL, Hutchins GM (1994) Giant cell and lymphocytic interstitial pneumonia associated with fetal pneumonia. Pediatr Pathol 14:955–965.

Shannon JM, Hyatt BA (2004) Epithelial-mesenchymal interactions in the developing lung. Annu Rev Physiol 66:625–645.

Sigurdson SL, Lwebuga-Mukasa MS (1994) Divalent cation-dependent regulation of rat alveolar epithelial cell adhesion and spreading. Exp Cell Res 213:71–79.

Silver MM, Thurston WA, Patrick JE (1988) Perinatal pulmonary hyperplasia due to laryngeal atresia. Hum Pathol 19:110–113.

Sizun J, Soupre D, Legrand MC, et al. (1994) Coronavirus infection in 19 infants admitted to intensive care. A retrospective study using immunofluorescence. Arch Pediatr 1:477–480.

Slovotinek AM, Tifft CJ (2002) Fraser syndrome and cryptophthalmos: review of the diagnostic criteria and evidence for phenotypic modules in complex malformation syndromes. J Med Genet 39:623–633.

Smith BT, Post M (1989) Fibroblast pneumocyte factor. Am J Physiol 257:L174–L178.

Smith II, Bain AD (1965) Congenital atresia of the larynx. A report of nine cases. Ann Otol Rhinol Laryngol 74:338–349.

Sosenko IRS, Bancalari E, Greenhough A (2003) Bronchopulmonary dysplasia. In: Greenough A, Milner AD (eds) Neonatal Respiratory Disorders. Arnold, London, pp. 399–422.

Sotomayor JJ, Godinez RI, Borden S, Wilmott RW (1986) Large airway collapse due to acquired tracheobronchomalacia in infancy. Am J Dis Child 140:367–371.

Srikanth MS, Ford EG, Stanley P, Hossein Mahour G (1992) Communicating bronchopulmonary foregut malformations: classification and embryogenesis. J Pediatr Surg 27:732–736.

Stahl GE, Spear ML, Hamosh M (1992) Lipid infusions and pulmonary function abnormalities. In: Polin RA, Fox WW (eds) Fetal and Neonatal Physiology. Saunders, London, pp. 346–352.

Stewart PA, Becker AE, Wladimiroff JW, Essed CE (1984) Left atrial isomerism associated with asplenia: prenatal echocardiographic detection of complex congenital cardiac malformations. J Am Coll Cardiol 4:1015–1020.

Stocker JT (1994) Congenital and developmental diseases. In: Dail DH, Hammar SP (eds) Pulmonary Pathology. Springer-Verlag, New York, pp. 155–190.

Stocker JT, Drake RM, Madewell JE (1978) Cystic and congenital lung diseases in the newborn. In: Rosenberg HS, Bolande RP (eds) Chicargo Year Book Publishers, Chicargo. Perspect Pediatr Pathol 4:93–154.

Stocker JT, Kagan-Hallet K (1979) Extralobar pulmonary sequestration. Am J Clin Pathol 72:917–925.

Strandjord TP, Clark JG, Guralnick DE, Madtes DK (1995) Immunolocalization of transforming growth factor-alpha, epidermal growth factor (EGF), and EGF-receptor in normal and injured developing human lung. Pediatr Res 38:851–856.

Swischuk LE, Richardson CJ, Nichols MH, Ingman MJ (1979) Primary pulmonary hypoplasia in the neonate. J Pediatr 95:573–577.

Taghizadeh A, Reynolds EOR (1976) Pathogenesis of bronchopulmonary dysplasia following hyaline membrane disease. Am J Pathol 82:241–264.

Teplitz C (1965) Pathogenesis of Pseudomonas vasculitis and septic lesions. Arch Pathol 80:297–307.

Thibeault DW, Mabry SM, Ekekezie II, Zhang X, Truog WE (2003) Collagen scaffolding during development and its deformation with chronic lung disease. Pediatrics 111:766–776.

Thibeault DW, Mabry SM, Norberg M, Truog WE, Ekekezie II (2004) Lung microvascular adaptation in infants with chronic lung disease. Biol Neonate 85:273–282.

Thompson DM, Kasperbauer JL (1994) Congenital cystic hygroma involving the larynx presenting as an airway emergency. J Nat Med Assoc 86:629–632.

Thornton CM, Halliday HL, O'Hara MD (1994) Surfactant replacement therapy in preterm neonates: a comparison of postmortem pulmonary histology in treated and untreated infants. Pediatr Pathol 14:945–953.

Thureen PJ, Hall DM, Hoffenberg A, Tyson RW (1997) Fatal meconium aspiration in spite of appropriate perinatal airway management: pulmonary and placental evidence of prenatal disease. Am J Obstet Gynecol 176:967–975.

Tucker GF, Ossoff RH, Newman AN, Holinger LD (1979) Histopathology of congenital subglottic stenosis. Laryngoscope 89:866–876.

Ueda K, Gruppo R, Unger F, Martin L, Bove K (1977) Rhabdomyosarcoma of the lung arising in a congenital adenomatoid malformation. Cancer 40:383–388.

Ulloa-Gutierrez R, Skippen P, Synnes A, et al. (2004) Life-threatening human metapneumovirus pneumonia requiring extracorporeal membrane oxygenation in a preterm infant. Pediatrics 114:e517–519.

Vawter GF (1981) Perinatal listeriosis. In: Rosenberg HS, Bernstein J (eds) Perspectives in Pediatric Pathology, vol 6. Year Book Medical, Chicago, pp. 153–156.

Virtanen I, Laitinen A, Tani T, et al. (1996) Differential expression of laminins and their integrin receptors in developing and adult human lung. Am J Respir Cell Mol Biol 15:184–196.

Wagenvoort CA (1986) Misalignment of lung vessels: a syndrome causing persistent neonatal pulmonary hypertension. Hum Pathol 17:727–730.

Walford N, Htun K, Chen J, Liu YY, Teo H, Yeo GS (2003) Intralobar sequestration of the lung is a congenital anomaly: anatomopathological analysis of four cases diagnosed in fetal life. Pediatr Dev Pathol 6:314–321.

Walters DV, Ramsden CA (1987) The secretion and absorption of fetal lung liquid. In: Walters DV, Strang LB, Geubelle F (eds) Physiology of the Fetal and Neonatal Lung. MTP Press, England, pp. 61–75.

Wang EEL, Ohlsson A, Kellner JD (1995) Association of *Ureaplasma urealyticum* colonization with chronic lung disease of prematurity: results of a metaanalysis. J Pediatr 127:640–644.

Warner JO, Rubin S, Heard BE (1982) Congenital lobar emphysema: a case with bronchial atresia and abnormal bronchial cartilage. Br J Dis Chest 76:177.

Watterberg KL, Carmichael DF, Gerdes JS, et al. (1994) Secretory leukocyte protease inhibitor and lung inflammation in developing bronchopulmonary dysplasia. J Pediatr 25:264–269.

Wells TR, Wells AL, Galvis DA, et al. (1990) Diagnostic aspects and syndromal associations of short trachea with bronchial intubation. Am J Dis Child 144:1369–1371.

Whyte RK, Hussain Z, De Sa DJ (1982) Antenatal infections with candida. Arch Dis Child 57:528–535.

Wigglesworth JS (1977) Expansion of the infant lung. Pathology of neonatal respiratory distress. Proc R Soc Med 70:861–863.

Wigglesworth JS (1987a) Pathology of the lung in the fetus and neonate, with special reference to problems of growth and maturation. Histopathology 11:671–689.

Wigglesworth JS (1987b) Factors affecting fetal lung growth. In: Walters DV, Strang LB, Geubelle F (eds) Physiology of the Fetal and Neonatal Lung. MTP Press, England, pp. 25–36.

Wigglesworth JS, Desai R (1981) Use of DNA estimation for growth assessment in normal and hypoplastic fetal lungs. Arch Dis Child 56:601–605.

Wigglesworth JS, Desai R (1982) Is fetal respiratory function a major determinant of perinatal survival? Lancet 1:264–267.

Wigglesworth JS, Desai R, Guerrini P (1981) Fetal lung hypoplasia: biochemical and structural variations and their possible significance. Arch Dis Child 56:606–615.

Wigglesworth JS, Desai R, Hislop AA (1987) Fetal lung growth in congenital laryngeal atresia. Pediatr Pathol 7:515–525.

Wilcox DT, Glick PL, Karamanoukian HL, Holm BA (1997) Contributions by individual lungs to the surfactant status in congenital diaphragmatic hernia. Pediatr Res 41:686–691.

Winter RM, Knowles SAS, Bieber FR, Baraitser M (1988) The Malformed Fetus and Stillbirth. John Wiley & Sons Ltd, New York.

Wiswell TE, Tuggle JM, Turner BS (1990) Meconium aspiration syndrome: have we made a difference? Pediatrics 85:715–721.

Wright JR, Clements JA (1987) Metabolism and turnover of pulmonary surfactant. Am Rev Respir Dis 136:426–444.

Yu VY, Ng P-C (1995) Chronic lung disease. Pulmonary problems in the perinatal period and their sequelae. Baillieres Clin Paediatr 3:147–170.

Zaaijman J du T, Wilkinson AR, Keeling JW, Mitchell RG, Turnbull AC (1986) Spontaneous premature rupture of the membranes: bacteriology, histology and neonatal outcome. J Obstet Gynaecol 2:155–160.

Zaw-Tun HIA (1988) Development of congenital laryngeal atresias and clefts. Ann Otol Rhinol Laryngol 97:353–358.