

# 7

## Acquired Nonneoplastic Neonatal and Pediatric Diseases

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The *lung biopsy* is an established procedure to procure a pathologic diagnosis in a child with a suspected pneumonic process of undetermined etiology. Improvements in pediatric anesthesia and surgery have reduced the operative complications to a minimum. A biopsy can usually be taken through a small intercostal incision when localization is not especially important in a patient with diffuse changes (see Chapter 1). The alternative method for tissue sampling is the endoscopic transbronchial biopsy. There is less risk to the patient, but the specimen is smaller and crush artifacts from the instrument are more common.

Rapid tissue processing of the biopsy for routine histologic preparation is preferred to a frozen-section consultation because these specimens in children are often very small and may be exhausted in the preparation. If the clinician is mainly interested in knowing whether granulomas or recurrent tumor is present, however, a frozen section can serve that immediate purpose. Another function of the frozen section is to give the surgeon some indication whether lesional tissue has been sampled. A number of series have been published and should be consulted about the results of open lung and transbronchial biopsies in children.<sup>1</sup>

Another diagnostic procedure is the *fine-needle aspiration biopsy*,<sup>2</sup> in which the needle is guided by computed tomography (CT) or ultrasonography. The application of fine-needle aspiration biopsy is mainly confined to the presence of a discrete mass with the clinical prospects of recurrent or metastatic tumor. A diagnosis by this biopsy technique has medical and economic advantages. If the changes in the lung(s) are diffuse in nature, rather than a single localized lesion, the positive yield in our experience has been quite low.

Some of the disease entities presented in this chapter are also discussed elsewhere in this volume for adult patients, and the reader is referred to those chapters. Many other entities discussed here, however, do not pertain to adults.

### Hyaline Membrane Disease

It is important to understand the difference between hyaline membrane disease (HMD) and the formation of hyaline membranes (HMs). The term *hyaline membrane disease* is used almost exclusively to describe the neonatal respiratory distress syndrome (RDS) associated with prematurity, which is due to the immature lungs' failure to synthesize adequate amounts of surfactant.<sup>3</sup> The risk of developing HMD is increased in males, infants of diabetic mothers, patients with preeclampsia,<sup>4</sup> and after cesarean section. In contrast, the formation of HM is associated with many other primary diseases such as infection (congenital or acquired), meconium aspiration, hemorrhage, and shock. Hyaline membrane disease in the classic form, as described by Lauweryns<sup>5</sup> in 1970, has been largely prevented by inhaled surfactant therapy on the first day of life, which has become the standard of care since the early 1990s. Today, HMD is seen as the cause of death, at autopsy, only infrequently, usually in the extremely premature infant (23 to 25 weeks' gestation) who dies in the first day or two of life. Infants who survive severe RDS for longer than 3 or 4 days before death usually display the changes of bronchopulmonary dysplasia (BPD) described below. Formation of hyaline membranes can also be seen in postmature infants. Seo and colleagues<sup>6</sup> described their occurrence in 17 of 21 postterm infants dying within 10 days of birth. Amniotic and meconium aspiration was present in 95% of these cases.

Clinically, RDS is characterized by tachypnea, intercostal retractions, and hypoxemia. Radiographically, there is a typical ground-glass appearance of the lungs with air bronchograms and diffusely scattered reticulogranular opacities. On gross examination the lungs are firm, atelectatic, and typically sink when placed in water. The pleura is smooth and deep tan to red. The cut surface reveals a deep red parenchyma that oozes bloody fluid and resembles liver more than lung.

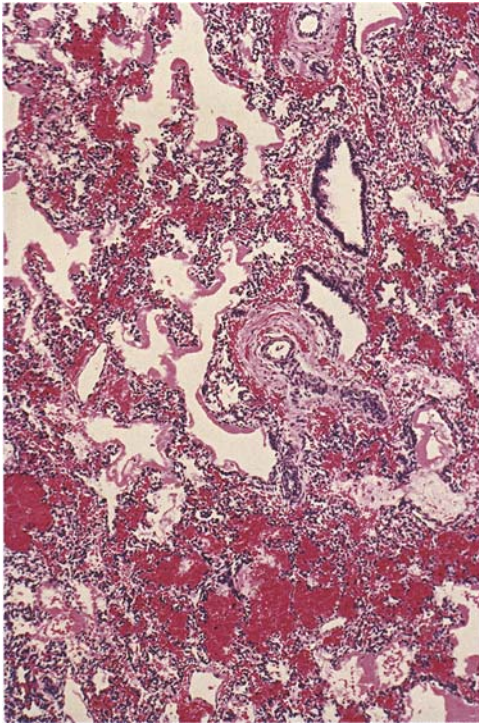


FIGURE 7.1. Hyaline membrane disease. Autopsy section of lung with hyaline membrane disease displays diffuse atelectasis of alveolar sacs and alveoli with slight overdilation of alveolar ducts and terminal bronchioles. Smooth hyaline membranes are closely applied to walls of these airways. Note the areas of focal interstitial and alveolar hemorrhage.

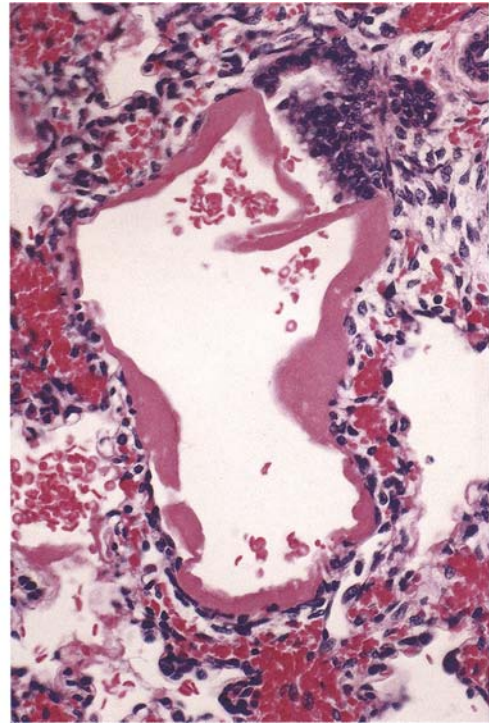


FIGURE 7.2. Hyaline membrane disease. In this 1-day-old infant's lung, homogeneous membranes cover the surface of the alveolar duct.

Microscopically there is a diffuse atelectasis that accentuates the bronchi and dilated bronchioles and alveolar ducts (Fig. 7.1). Smooth, homogeneous pink membranes, the HMs from which the disease derives its name lie free in the lumen or are closely applied to surfaces of respiratory bronchioles and alveolar ducts (Fig. 7.2). The membranes are composed of necrotic alveolar lining cells, plasma transudate, inhaled amniotic fluid, and, if hemorrhage is present, fibrin. Homogeneously pink or finely granular transudate is often present in alveolar saccules, occasionally extending to bronchiolar and bronchial levels. Hemorrhagic material may be present focally throughout the lung. Pulmonary lymphatics are dilated particularly around pulmonary veins.<sup>7</sup>

Hyaline membranes may be seen in infants dying as early as 1 to 4 hours after birth. Well-formed membranes are usually present by 12 to 24 hours, and by 36 to 48 hours, in cases of uncomplicated disease, organization of these membranes occurs with separation of the membrane from the underlying wall and engulfment of the material by macrophages (Fig. 7.3). Final repair of the bronchiolar and alveolar duct wall is accomplished by resurfacing of the wall by bronchiolar epithelial cells or type I and II alveolar lining cells.<sup>8,9</sup> In the majority of

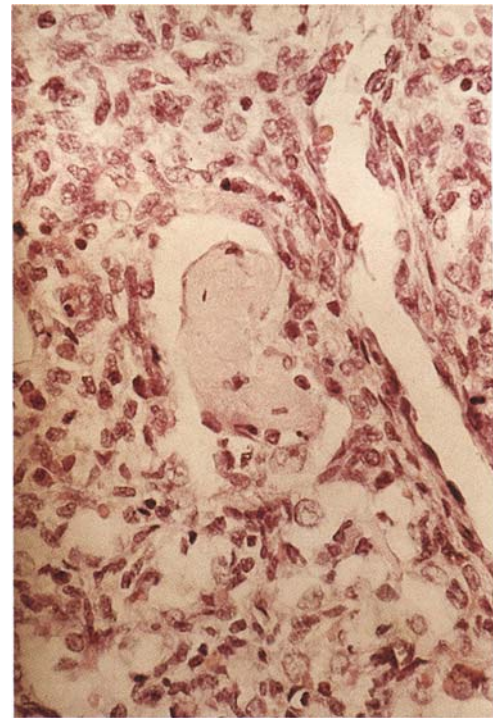


FIGURE 7.3. Hyaline membrane disease in 4-day-old infant. Hyaline membranes are undergoing organization by macrophages and regenerating alveolar lining cells, which separate membranes from the wall of the alveolar duct. Note "rounded-up" membrane material.

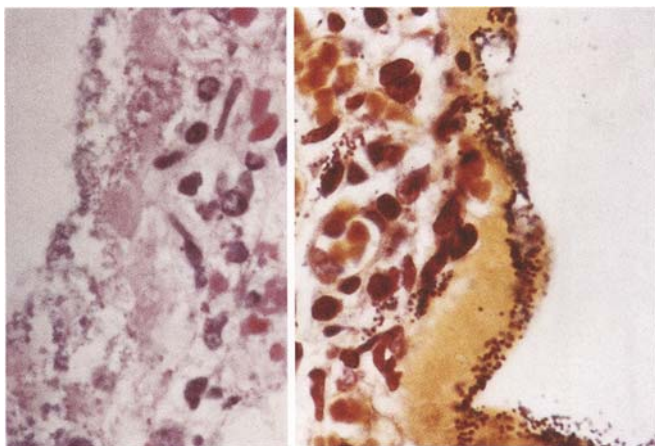


FIGURE 7.4. Hyaline membrane disease with superimposed bacterial growth. On left, irregular, granular hyaline membrane lines alveolar duct. With special stains (right) cocci can be seen covering surface of membrane. (Left, hematoxylin and eosin [H&E]; right, Humberstone stain.)

patients, the HMs resolve completely, resulting in a normal or near-normal functioning lung. Up to 30% of patients of less than 1000-g birth weight develop BPD.

The appearance of the hyaline membranes may be altered by the presence of bacteria that find the membranes an ideal culture medium. Gram stains of membranes that are fragmented, granular, and faintly basophilic often display the gram-positive cocci or gram-negative rods typical of streptococcal or *Escherichia coli* infections occasionally associated with this disease (Fig. 7.4). In infants with kernicterus, intraventricular hemorrhage, intrahepatic bile stasis, pulmonary hemorrhage, or disseminated intravascular coagulation who survive 3 days or longer, yellow HMs may be present. The yellow pigment, visible in unstained paraffin sections, is an unconjugated bilirubin.<sup>10,11</sup>

## Bronchopulmonary Dysplasia

Both the definition and pathology of BPD have evolved since the initial description by Northway et al.<sup>12</sup> and Nash et al.<sup>13</sup> in separate articles in 1967. Antenatal glucocorticoid therapy, postnatal surfactant therapy, and improved mechanical ventilation have minimized severe lung injury in all but the smallest of premature babies. Thus, BPD is now infrequent in treated infants with gestational age exceeding 30 weeks or birth weight more than 1200 g. However, when one looks at those areas of the world where such treatment is not available or possible, the classic form of BPD is still seen.

Clinically, a more extensive definition was proposed at the 2000 National Institutes of Health (NIH) BPD workshop, which uses oxygen dependency at 36 weeks post-

menstrual age, total duration of oxygen supplementation, positive pressure requirements, and gestational age of the infant to delineate the three degrees of severity: mild, moderate, and severe.<sup>14</sup> A subsequent study evaluated this new definition and concluded that it does offer a better description of underlying pulmonary disease and correlates with the infant's maturity, growth, and overall severity of disease.<sup>15</sup>

The incidence of BPD is dependent on multiple factors, the most important of which are gestational age, weight, and the definition used. Using the above definition, one retrospective study of very low birth weight (VLBW) infants looked at the mortality and incidence and severity of BPD in three groups of patients over time. Cohort A was from 1986 to 1990 (pre-surfactant era and use of conventional intermittent mandatory ventilation [IMV]); cohort B was from 1993 to 1994 (use of synthetic surfactant, nasopharyngeal continuous positive airway pressure [CPAP] and conventional IMV); and cohort C was from 2000 to 2001 (use of natural surfactant, early nasal prong CPAP, synchronized IMV with tidal volume monitoring, and high-frequency oscillatory ventilation). Bronchopulmonary dysplasia was classified as mild, moderate, or severe. The mean gestational ages and birth weights were 28 and 3/7 weeks and 1120 g for cohort A, 30 and 0/7 weeks and 1340 g for cohort B, and 29 and 1/7 weeks and 1200 g for cohort C. The use of partial or complete courses of antenatal corticosteroids increased over time. There was a 50% reduction of mortality between each time period with mortality rates of 30%, 14%, and 7%, while the overall incidence of BPD was 26%, 11%, and 19% in cohorts A, B, and C. Of note, moderate and severe forms of BPD decreased over time (11%, 3%, and 2%, respectively). Thus, changes in neonatal care of VLBW infants have resulted in dramatically improved survival rates over the past 15 years without increasing moderate to severe pulmonary morbidity.<sup>16</sup>

The pathogenesis of bronchopulmonary dysplasia is generally considered to be multifactorial.<sup>17</sup> The disease was first described in premature infants with severe respiratory distress syndrome who had been treated with high levels of oxygen (80% to 100%) and intermittent positive-pressure respirators for longer than 6 days.<sup>12,13,18</sup> Subsequent experimental studies have clearly demonstrated the toxic effects of prolonged exposure to high oxygen levels on the lungs of animals.<sup>19-23</sup> Considered of equal importance by many is the role of barotrauma from artificial ventilation to the developing immature lung, contributing not only to the interstitial emphysema, pneumothorax, and pneumomediastinum seen in infants with bronchopulmonary dysplasia but also directly injuring the acinus.<sup>24,25</sup> While most cases follow the treatment of the RDS, others may occur following pneumonia, meconium aspiration syndrome, tracheoesophageal fistula, and congenital heart disease.<sup>17</sup>

The initiation of mechanical ventilation in surfactant-treated preterm animals causes a proinflammatory response, suggesting that any mechanical ventilation of the preterm lung may be injurious.<sup>26</sup> Inflammation appears to be central to the development of BPD.<sup>14</sup> Multiple proinflammatory and chemotactic factors are present in the air spaces of ventilated preterm infants, and these factors are found in higher concentrations in the air spaces of infants who subsequently develop BPD.<sup>27</sup> Factors such as macrophage inflammatory protein-1 and interleukin (IL)-8 persist in the air spaces, and counterregulatory cytokines such as IL-10 may be decreased, resulting in unregulated and persistent inflammation. Infants exposed to antenatal infection/inflammation or fetal colonization with *Ureaplasma urealyticum* have proinflammatory indicators in their air spaces at delivery.<sup>28</sup> The activation of inflammatory cascades can result in a vicious cycle of inflammation, which resolves slowly. Microbial infections (group B streptococcus, *Ureaplasma urealyticum*, and *Escherichia coli*) activate nuclear factor  $\kappa$ B (NF- $\kappa$ B), induce proinflammatory cytokine production, stimulate inducible nitric oxide synthase (iNOS) expression, and increase vascular endothelial growth factor (VEGF) and intercellular adhesion molecule-1 (ICAM-1) expression and other inflammatory mediators in the host.<sup>29</sup> All these factors interact with each other. Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) can activate iNOS expression, promote ICAM-1 production, induce apoptosis, and upregulate NF- $\kappa$ B activation. After initial damage reparative processes begin that favor fibroproliferative changes in the lung. Several profibrotic factors such as transforming growth factor- $\beta$  (TGF- $\beta$ ), nitric oxide (NO), and VEGF have been shown to play roles in the development of chronic lung disease. This results in remodeling of lung tissue with disrupted lung morphology and architecture including interference with vascular and alveolar development.

Close coordination of growth between airways and vessels is essential for normal lung development. Thus it has been hypothesized that failure of pulmonary vascular growth during a critical period of lung growth (saccular or alveolar stages of development) could decrease septation and ultimately contribute to the lung hypoplasia that characterizes BPD.<sup>30</sup> Stachurski et al.<sup>31</sup> conducted a comparative analysis of the pulmonary vasculature in infants with BPD and age-matched controls using immunohistochemical, molecular, and bias-free stereologic volumetric techniques. They concluded that the total pulmonary volume of endothelial cells, reflecting the size of the peripheral microvasculature network, of BPD lungs parallels or exceeds that of age-matched controls. They speculated that the primary pathogenic factor in BPD is ventilation-induced type II pneumocyte cell death, rather than microvascular dysgenesis.

Because decreased numbers of alveoli are so striking in the lungs of very preterm infants who die of BPD,

understanding the developmental regulation of septation and alveolarization is a high priority in understanding the pathology of BPD. In experimental models, hyperoxia, hypoxia, or poor nutrition can decrease septation, as can glucocorticoid treatment.<sup>32</sup> In transgenic mice, overexpression of the cytokines TNF- $\alpha$ , TGF- $\beta$ , IL-6, or IL-11 also can interfere with alveolarization, suggesting that the proinflammatory environment of the air space of the preterm infant may contribute to the altered septation.<sup>33</sup>

Other factors involved in the development of bronchopulmonary dysplasia include pulmonary edema<sup>34</sup> and vitamin A deficiency.<sup>35</sup>

The treatment of infants with bronchopulmonary dysplasia is primarily supportive, since once it develops, it cannot be reversed. Thus there is intense focus on developing preventive measures. The evolution of BPD from a disorder of pulmonary injury affecting moderately preterm infants to one characterized by a developmental pulmonary arrest among survivors of extreme prematurity has important implications for BPD prevention. Recent recognition that the pathogenesis of BPD might have prenatal origins raises new challenges and opportunities for studies of BPD prevention; however, most current preventative strategies for BPD focus on respiratory management. Neither past nor current clinical trials have shown a conclusive benefit of a single preventive treatment strategy. Promising but still largely unproven preventative respiratory treatments include high frequency oscillatory ventilation, permissive hypercapnia, and inhaled NO. Other areas to be studied are postnatal low-dose corticosteroid treatment, superoxide dismutase, inositol, and  $\alpha_1$ -proteinase inhibitor. Only vitamin A has proven a safe and effective preventive treatment for BPD. Directed cytokine and genetic therapies are on the horizon.<sup>36</sup>

Survival of infants who develop severe bronchopulmonary dysplasia is associated with a 54% mortality and significant morbidity even in long-term survivors. Predictors of survival and outcome, not surprisingly, include degree of prematurity, duration of oxygen requirement, length of stay in the hospital, and severity of radiographic abnormalities.<sup>37</sup>

The pathology of the lungs of infants with BPD has to be considered in the context of how the patient was treated. The classic changes of BPD are still seen in those not treated with surfactant and newer forms of ventilation (pre-surfactant BPD), whereas the treated patients who still develop severe enough BPD that results in death have an arrest in lung development. These two forms of BPD will be described separately.

The pathology of pre-surfactant bronchopulmonary dysplasia<sup>38,39</sup> varies considerably depending on (1) the gestational age of the infant, specifically, the degree of immaturity of the lung; (2) the type, duration, and peak

TABLE 7.1. Pathologic features of bronchopulmonary dysplasia

	Acute	Reparative	LSHBPD
I. Trachea			
Mucosa	Dysplasia Necrosis	Metaplasia Metaplasia	Normal or metaplasia Metaplasia
Submucosa	Inflammation acute or chronic Necrosis or edema	Inflammation chronic Fibroplasia	Inflammation chronic Fibrosis (pseudopolyp)
Glands	Hypertrophy	Hyperplasia	Hyperplasia or normal
II. Bronchi			
Mucosa	Dysplasia	Metaplasia	Normal or metaplasia
Submucosa	Inflammation acute or chronic Edema	Inflammation chronic Muscular hyperplasia	Normal Normal
III. Bronchioles			
Mucosa	Luminal occlusion by hyaline membrane Dysplasia Necrosis	Organization Metaplasia Metaplasia	Normal Normal Normal
Submucosa	Necrotizing obstructive bronchiolitis Edema Inflammation acute and chronic	Intrinsic fibroplasia Muscular hyperplasia Extrinsic fibroplasia	Partial or complete obliteration Muscular hyperplasia Fibrosis
IV. Alveolar duct			
Mucosa	Hyaline membranes Dysplasia Necrosis	Organization Metaplasia Intrinsic fibroplasia	Normal Normal Fibrosis or obliteration
Submucosa	Necrosis and edema	Extrinsic fibroplasia	Fibrosis or obliteration
V. Alveolus			
Lining cells	Hyaline membranes Necrosis	Organization Fibroplasia	Normal Fibrosis or obliteration
Interstitial	Edema Necrosis	Edema Fibroplasia	Normal Fibrosis or obliteration
VI. Interlobular septa			
	Edema Interstitial emphysema—acute Interstitial emphysema—persistent	Edema Organization Giant cell reaction	Normal Normal Fibrosis
VII. Pulmonary arteries			
	Adventitial edema	Medial hyperplasia and adventitial edema	Medial hyperplasia or adventitial fibrosis

LSHBPD, long-standing healed bronchopulmonary dysplasia.<sup>39</sup>

pressures of artificial ventilation; (3) the duration and concentration of oxygen therapy; (4) the degree of pulmonary edema; and (5) the presence of intercurrent processes such as pneumonia, interstitial emphysema, or pneumothorax. Detailed description of all these variations is beyond the scope of this chapter, but the major changes in gross morphology and changes within the airways and acini are described and summarized (Table 7.1). These changes are divided into (1) acute, (2) reparative or healing, and (3) long-standing healed bronchopulmonary dysplasia. In the acute stages of the disease, following typical changes of hyaline membrane disease in the first 3 to 4 days of life, the lungs are bulky, firm, and heavy, and often two to four times the expected weight (Fig. 7.5). The pink-to-tan pleura may be smooth or mildly irregular with areas of depressed or atelectatic parenchyma producing an uneven surface. Cut section displays a solid-appearing parenchyma that exudes fluid when

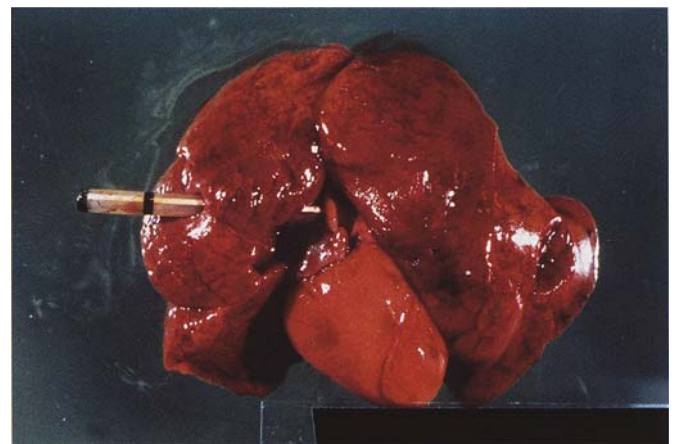


FIGURE 7.5. Pre-surfactant era bronchopulmonary dysplasia at 8 days of age. Lungs are bulky and expanded with mildly irregular surface. Note chest tube perforating the right lung.

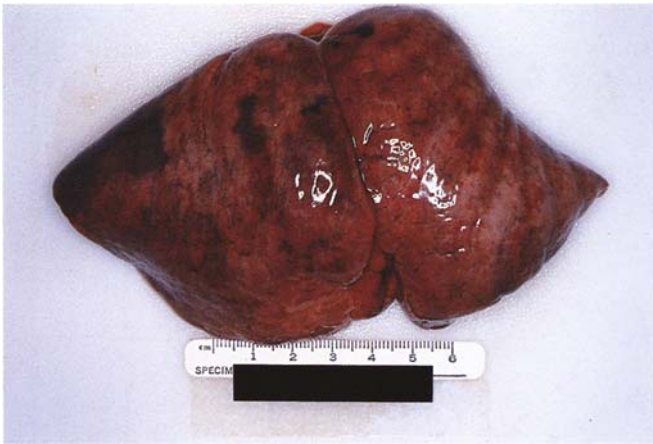


FIGURE 7.6. Pre-surfactant era bronchopulmonary dysplasia at 21 days. Pleura of lung is irregular with hyperexpanded acini bulging from surface. Not the rib impressions on the surface of the lung.

compressed. By 1 to 2 weeks, the lungs begin to show a typical cobblestone surface with the development of an intricate sublobulation beneath the pleura representing alternating areas of atelectasis, interstitial fibroplasia, or hyperexpansion of acini (Fig. 7.6). As the disease progresses to the healed stage at 1 to 3 months, this sublobulation becomes more accentuated with shallow and deep depressions dividing the lung into irregular lobules (Fig. 7.7). Some of these depressions may be large enough to be confused with the fissures between lobes of the lung. Hyperexpanded acini protrude from the surface of the lung with individual alveoli visible to the naked eye, implying an overexpansion of at least 5- to 10-fold.



FIGURE 7.7. Pre-surfactant era long-standing healed bronchopulmonary dysplasia at 2 months. Close-up view: Irregular depressions or fissures subdivide lung into multiple sublobules. Hyperexpanded acini protrude above pleura, further accentuating sublobules.



FIGURE 7.8. Pre-surfactant era long-standing healed bronchopulmonary dysplasia at 10 months. With growth of new parenchyma, pleural surface becomes smoother (compare with Fig. 7.7), but large fissures remain, producing bizarre lobular configuration.

Microscopically, the airways (trachea, bronchi, bronchioles) and gas-exchanging portions of the lung (alveolar ducts, saccules, and alveoli) undergo a series of acute changes followed by reparative processes that eventually lead to a static stage termed *long-standing healed bronchopulmonary dysplasia*.<sup>39</sup> These changes will be considered in turn at each level of the lung (Fig. 7.8).

The acute changes within the trachea range from mild mucosal dysplasia to frank necrosis.<sup>40,41</sup> The earliest changes may consist only of loss of cilia and disruption of the pseudostratification typical of respiratory epithelium (Fig. 7.9). Epithelial cells may appear dysplastic with enlarged nuclei. Focal mucosal necrosis, which may extend through the submucosa to the level of the tracheal cartilage rings, may occur and is possibly related to excessive pressure from an endotracheal tube. Acute and chronic inflammation in the submucosal connective tissue is usually present in varying degrees, and submucosal glands may be hypertrophied with dilated acini and ducts. In the reparative stages, the mucosa may undergo significant metaplastic changes eventually resembling noncornified stratified squamous epithelium, which is usually focal and noted predominantly in the lower trachea but may line the entire trachea extending into the ducts of the submucosal glands (Fig. 7.10). Chronic inflammation persists in

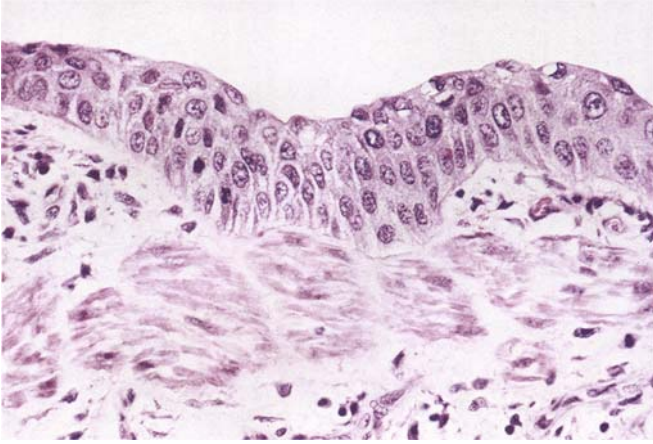


FIGURE 7.9. Pre-surfactant era bronchopulmonary dysplasia at 16 days. Normal pseudostratified ciliated columnar epithelium of the trachea is replaced by metaplastic squamous epithelium.

the submucosa, and glands may display hyperplasia producing a Reid index of 40% to 60% that may persist into the healed stage. Focal fibrous and muscular hyperplasia in the lower trachea may produce epithelial-covered polyps that may narrow or rarely occlude the lumen.



FIGURE 7.10. Pre-surfactant era long-standing healed bronchopulmonary dysplasia at 8 months. Squamous epithelium covers the surface and extends into the submucosal ducts of this segment of lower trachea. Note mild chronic inflammation.

Bronchial changes in the acute, reparative, and healed stages are similar to those noted in the trachea (Fig. 7.11). First- or second-division bronchi display mucosal dysplasia and occasionally necrosis. The submucosa is often edematous and mildly infiltrated by acute inflammatory cells. Submucosal glands may be hypertrophied in early stages, but hyperplasia infrequently occurs and is usually mild or nonexistent in the healed phase. Muscular hyperplasia may develop in the reparative stage and persist in distal bronchi in the healed phase.

The most striking changes of acute BPD occur at the level of the bronchioles and alveolar ducts, where several distinct lesions are observed. Total occlusion of a terminal or respiratory bronchiole by HMs or necrotic debris (Figs. 7.12, 7.13, and 7.14) may effectively remove access to, and thus protect, the acinus distal to the occlusion from exposure to oxygen tensions and ventilatory pressures. The occluded bronchiole may display an intact epithelial lining, submucosa, and muscular wall, or the bronchiole may be recognizable only by remnants of the muscular wall with partial or total destruction of the epithelium. As the lesions resolve, most of the occluded bronchioles are cleared of debris or recanalized. The epithelium may regenerate, leaving a normal-appearing, cuboidal to columnar epithelium and unremarkable wall. Some of the severely involved bronchioles may remain permanently obliterated.

Bronchioles in the acute stage that remain free of HMs and necrotic debris, or are only partially occluded, may display striking epithelial cell dysplasia with large irregular cells containing hyperchromatic nuclei with densely clumped chromatin and prominent nucleoli (Fig. 7.15). Focal necrosis may also be present. The submucosa is usually edematous and may be infiltrated by neutrophils and lymphocytes. As the lesion progresses, fibroblasts

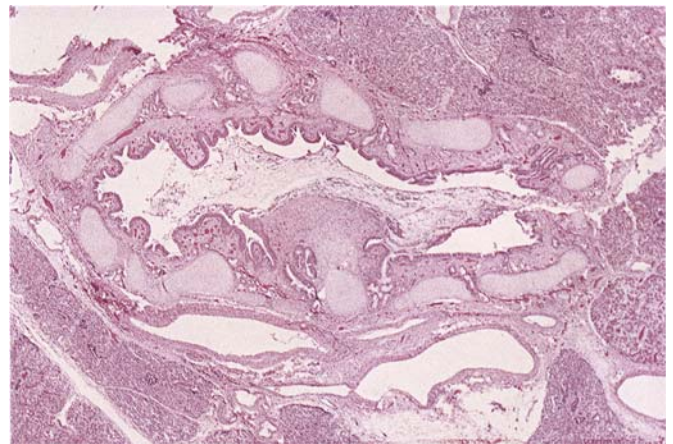


FIGURE 7.11. Pre-surfactant era long-standing healed bronchopulmonary dysplasia at 6 months. Lumen of a large mainstem bronchus is significantly narrowed by a polyp with a fibromuscular core.

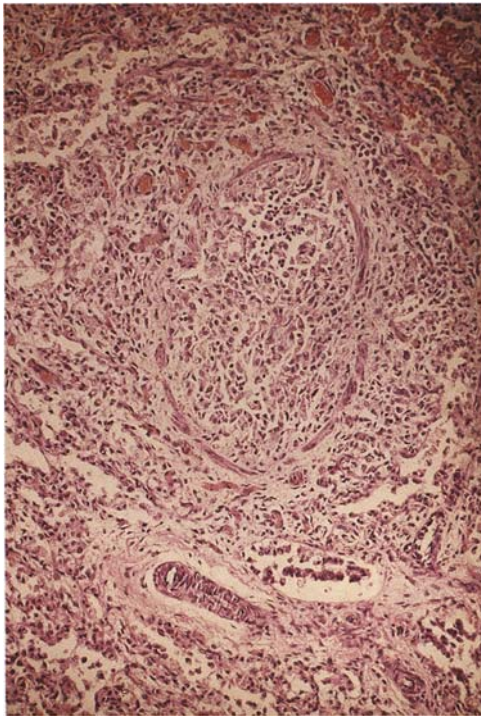


FIGURE 7.12. Pre-surfactant era bronchopulmonary dysplasia at 8 days. Mixture of hyaline material and amorphous necrotic debris occludes bronchiole (necrotizing bronchiolitis) in 700-g infant.

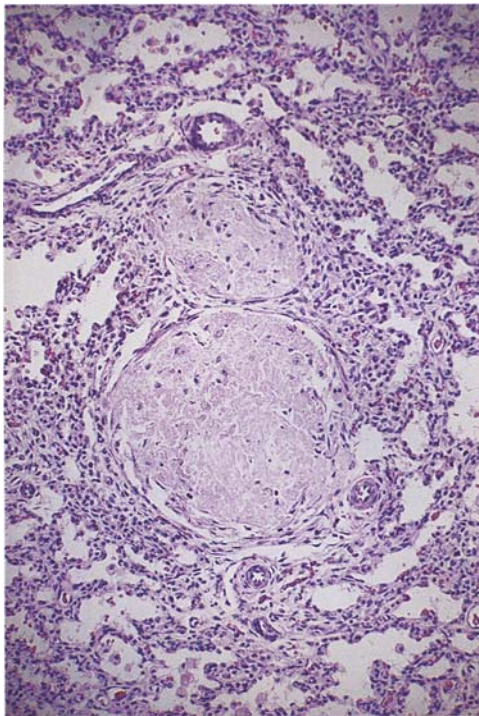
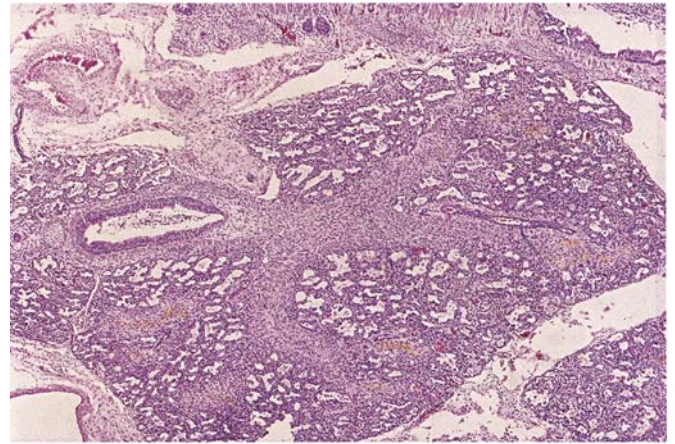
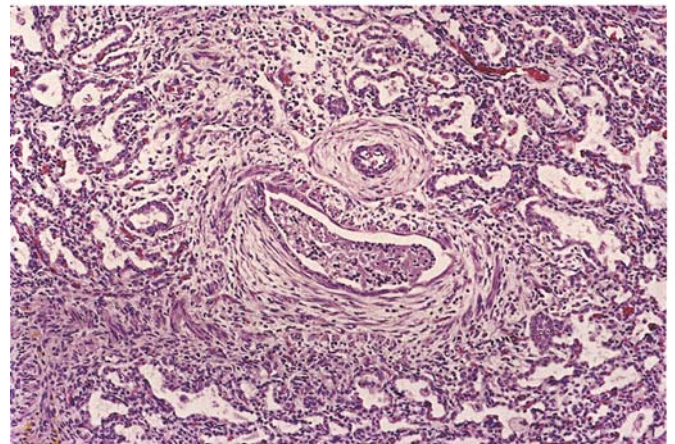


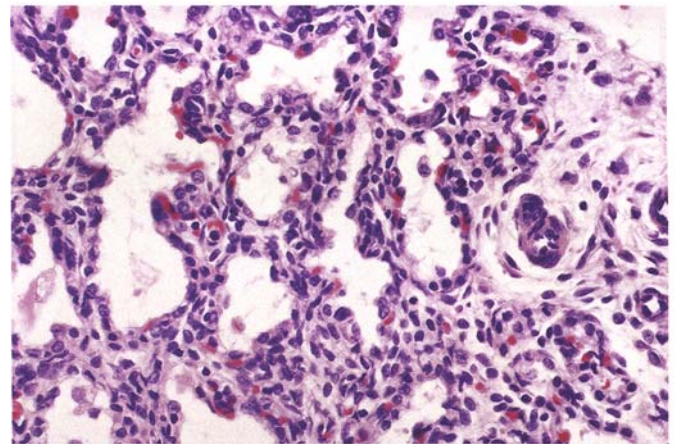
FIGURE 7.13. Pre-surfactant era bronchopulmonary dysplasia at 8 days. In slightly more mature lung (820-g infant) than in Figure 7.12, protective effect of occluded bronchiole is readily seen in absence of acinar dysplasia or fibroplasia.



A



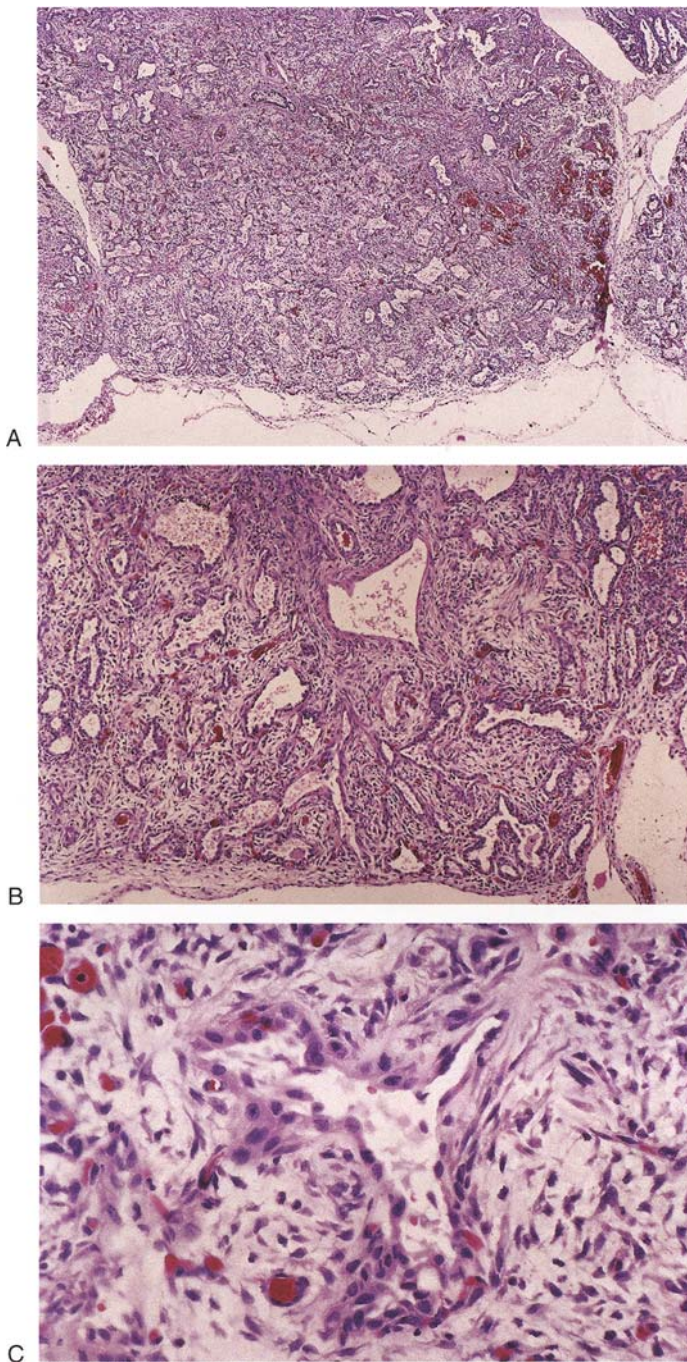
B



C

FIGURE 7.14. Pre-surfactant era bronchopulmonary dysplasia at 10 days. **A.** In this section of a lung with diffuse necrotizing bronchiolitis, the occluded bronchiole tree extends from an open bronchus (left) to multiple branches plugged with necrotic debris. **B.** At a higher magnification, an occluded bronchiole with its accompanying pulmonary artery are surrounded by immature but normal alveolar sacs (compare with Fig. 7.15B). **C.** The periphery of the acini displays widened alveolar septa, normal for the gestational age of this infant (compare with Fig. 7.15C).





**FIGURE 7.15.** Pre-surfactant era bronchopulmonary dysplasia at 10 days. **A.** In an adjacent section of the lung as displayed in Figure 7.14, and at the same magnification, a diffuse and uniform injury to the parenchyma is present. Note the scattered “open” bronchioles throughout the section. **B.** At a higher magnification, an open bronchiole (upper center) is surrounded by alveolar septa that are markedly widened and dysplastic all the way to the edge of the acinus (compare with Fig. 7.14B). **C.** This alveolar duct is compressed by the extensive fibroplasia surrounding it and extending into the alveolar septa (compare with Fig. 7.14C).

may proliferate within the submucosal connective tissue (intrinsic fibroplasia) or outside the muscular wall (extrinsic fibroplasia). With resolution of these injured bronchioles, the epithelium also returns to normal, but muscular hyperplasia of the wall may persist.

The alveolar ducts not protected by an occluded bronchiole in the acute phase display striking epithelial cell dysplasia (for which the disease is named) and focal necrosis. Edema in the subepithelial region gives way to prominent fibroplasia, which may extend into adjacent alveolar septa. This fibroproliferative process and associated edema may expand the duct wall, leading to varying degrees of occlusion of the lumen and partially protecting the distal acinus in a manner similar to that provided by occluded bronchioles. With resolution, the ductular wall becomes thickened by fibrous connective tissue.

Alveoli in acini with occluded bronchioles remain unremarkable (Fig. 7.14). In acini exposed to the high oxygen tensions and ventilatory pressures, however, alveoli have increased numbers of macrophages with hyperplastic and bizarre nuclei (Fig. 7.15). Alveolar lining cells may undergo necrosis or, more often, become hyperplastic, frequently forming a prominent cuboidal cell lining to the alveoli all the way to the periphery of the acinus. In cases with more severe injury, interstitial edema is present along with plump fibroblasts that may proliferate and, in extreme cases, virtually replace an acinus. Resolution of this process, depending on the degree of injury, may lead to interstitial fibrosis (Fig. 7.16) or possibly total loss of the acinus. The degree of acinar injury seems to correlate with the long-term survival of premature infants with bronchopulmonary dysplasia. Soboyna and colleagues<sup>38</sup> and Margraf and colleagues<sup>42</sup> noted a marked decrease in mean total alveolar number (less than 15% of expected) and internal surface area of the lung in long-term survivors.

Interstitial fibrosis, the hallmark of long-standing healed bronchopulmonary dysplasia (Fig. 7.17), is usually uniform within an acinus but may be extremely variable from one lobe of a lung to another or even from one acinus to another (Fig. 7.18).<sup>39</sup> The fibrous connective tissue within the alveolar wall separates the usually intermeshed capillary beds supplying the alveoli on either side of the wall. In cases with severe fibrosis, a third capillary bed may be present within the connective tissue separating the two alveolar capillary beds.

Changes in the vessels within the lung, other than those in the alveolar capillary bed, are mild. Pulmonary arteries at the level of the bronchi display adventitial edema early in the course of the disease, and medial hypertrophy is present during the reparative and healed stages, although changes beyond Heath and Edward grade I to II pulmonary hypertensive vascular disease are unusual.<sup>43</sup> Bronchial arteries and lymphatics show no significant changes. Changes within the interlobular septa and pleura are

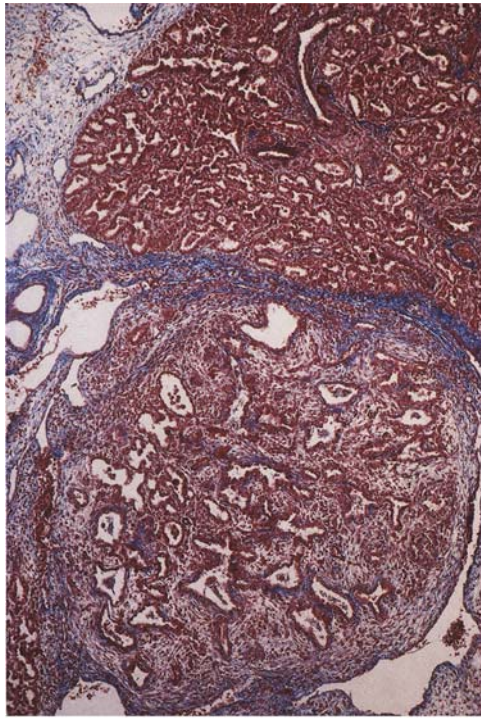


FIGURE 7.16. Pre-surfactant era bronchopulmonary dysplasia at 8 days. Acinus (upper) in this immature lung from a 700-g infant shows only mild atelectasis while the adjacent acinus (lower) displays marked interstitial edema and early fibroplasia (see Fig. 7.17 for later stage). (Masson trichrome.)

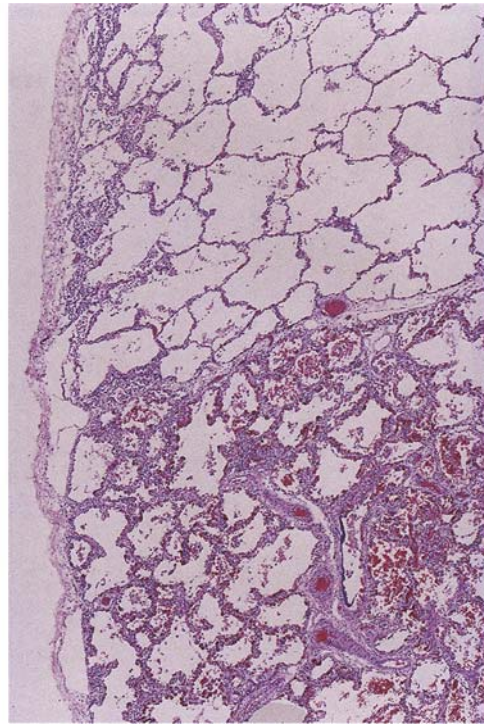


FIGURE 7.17. Pre-surfactant era long-standing healed bronchopulmonary dysplasia at 6 months. Acinus below displays diffuse alveolar septal fibrosis, while acinus at top, although hyperexpanded, shows little or no fibrosis (compare with Fig. 7.16).

seen only in cases in which acute or persistent interstitial pulmonary emphysema develops.

Hyperexpansion of acini may be present following the early stages of the disease, accounting for the cystic changes noted radiographically and the accentuated sublobulation seen grossly. The enlarged alveoli are usually in acini with little or, more frequently, no interstitial fibrosis. Alveoli may be expanded to 5- to 10-fold or more normal size, and rupture of the highly elastic walls may be noted. As with the interstitial fibrosis, the emphysema may be patchy with an acinus containing normal-sized alveoli lying adjacent to one with markedly distended alveoli. The sequential changes of bronchopulmonary dysplasia are presented schematically in Figure 7.19.

The pathology of post-surfactant BPD is significantly different from the above description. Necrotizing bronchiolitis and severe alveolar septal fibrosis are infrequently seen.<sup>44</sup> The few infants who now die from BPD display what might be best described as acinar simplification (Fig. 7.20). These simplified acini are characterized by uniformly dilated alveoli whose walls consist of thin

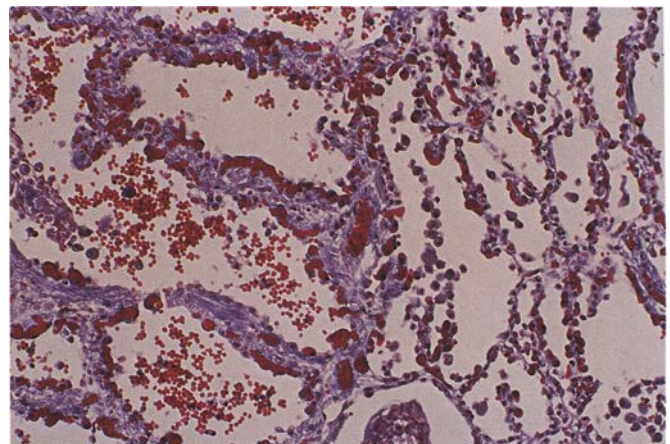
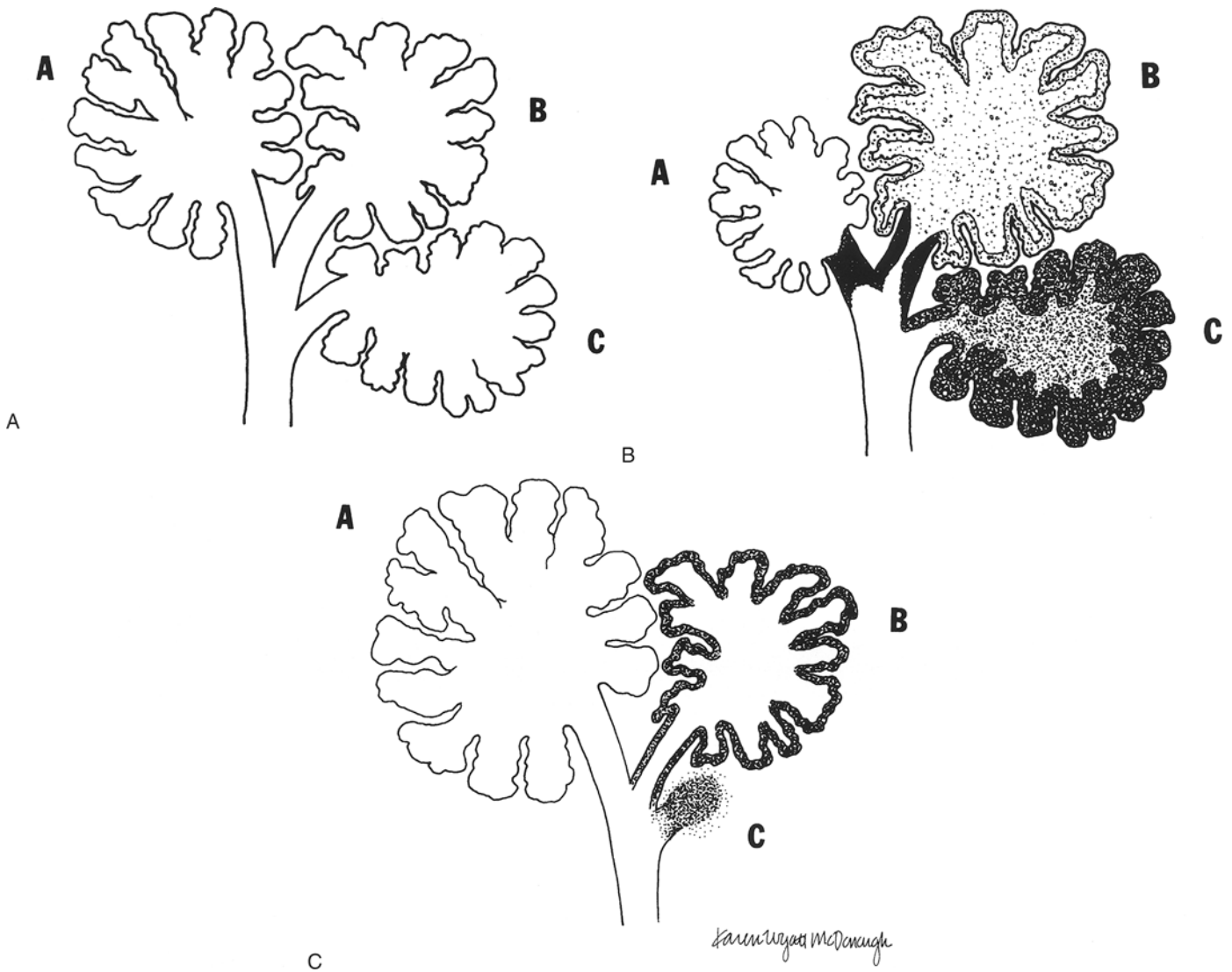


FIGURE 7.18. Pre-surfactant era long-standing healed bronchopulmonary dysplasia at 6 months. The distinct injury and fibrosis to the septa of an exposed acinus (left), the hallmark of long-standing healed bronchopulmonary dysplasia, is apparent when compared to an acinus (right) that had been protected by an occluded bronchiole and shows no alveolar septal fibrosis.

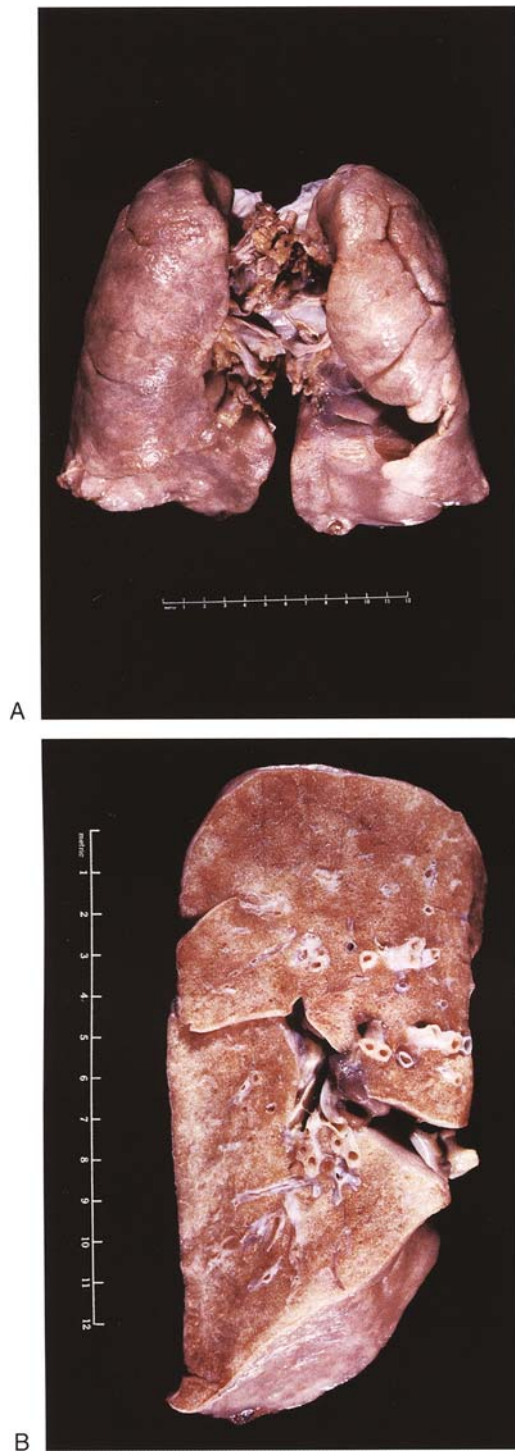


**FIGURE 7.19.** Pre-surfactant era bronchopulmonary dysplasia. **A.** Three normal acini (A, B, C) arise from terminal bronchiole in this schematic drawing. **B.** In acute stages of bronchopulmonary dysplasia, bronchiole leading to acinus A is occluded by material (hyaline membranes, necrotic debris, etc.), protecting acinus from ventilatory pressure and high oxygen tension. Bronchiole to acinus B is only partially occluded, allowing some injury to alveolar saccules and alveoli. Acinus C receives full ventilatory pressure and oxygen tension through widely patent

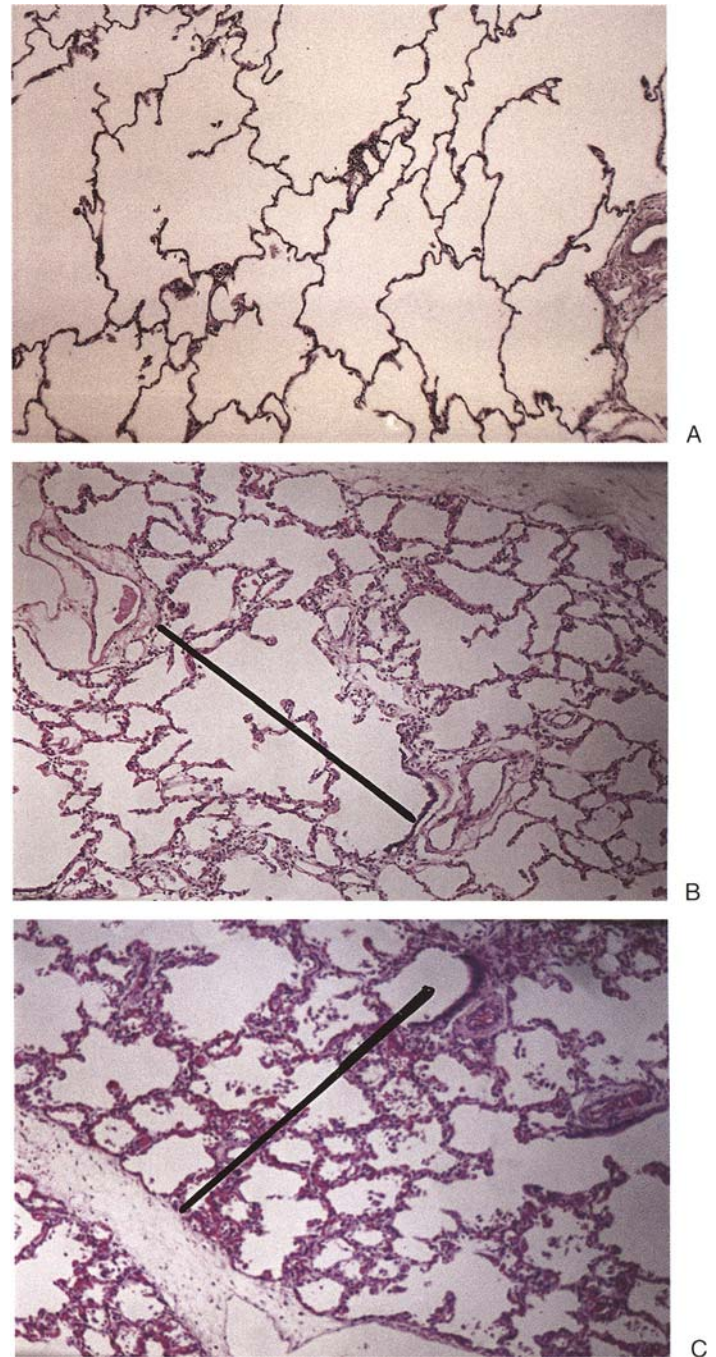
bronchiole, allowing extensive damage (dysplasia, inflammation, fibroplasia) to alveolar saccules and alveoli. **C.** With resolution and healing, bronchiole in A is reopened allowing expansion (or overexpansion) of uninjured acinus. Acinus B displays interstitial fibrosis atypical of healed bronchopulmonary dysplasia; the most severely injured acinus C may partially or completely disappear, leading to contraction and fissuring of pleura. (From Husain et al.<sup>45</sup> Copyright 1998, with permission from Elsevier.)

alveolar septa with little or no interstitial fibrosis (Fig. 7.21). The bronchioles are similarly unremarkable, with only an occasional mild increase in peribronchiolar musculature. These changes seem to represent an “arrest” of development of the acini, with a resulting markedly decreased number of alveoli within each acinus. As a result, the surface area of the lung is significantly decreased even in the absence of significant fibrosis or bronchiolitis.

Husain et al.<sup>45</sup> examined the lungs at autopsy of 22 patients with BPD, 14 of whom had received surfactant therapy, and compared them with 15 age-matched controls with no lung disease. Using readily available morphometric techniques (radial alveolar count [RAC] and mean linear intercept [MLI]), they observed a virtual arrest of alveolar development in both the surfactant-treated and non-surfactant-treated infants whether or not alveolar septal fibrosis was present. Incidentally, septal fibrosis



**FIGURE 7.20.** Surfactant treated bronchopulmonary dysplasia. **A.** The lungs of this 2-year-old child who was born at 26 weeks' gestation, received surfactant therapy, but still required oxygen supplementation until he died, display mild hyperexpansion but little if any of the pseudofissuring characteristic of the pre-surfactant bronchopulmonary dysplasia era (compare with Figs. 7.7 and 7.8). **B.** The cut section of this child's lung shows a uniform parenchyma with enlarged alveoli visible to the naked eye.



**FIGURE 7.21.** Surfactant treated bronchopulmonary dysplasia. **A.** A microscopic section of the lung in Figure 7.20 displays overdistracted alveoli surrounded by thin alveolar septa (compare with Figs. 7.17 and 7.18). **B.** A radial alveolar count (performed by dropping a perpendicular line from the opening of a terminal/respiratory bronchiole to the nearest acinar edge) in this infant displays a count number of 3, well below that expected for a 2-year-old and even less that that of a normal term infant (**C**), indicating an arrest of acinar development.

was infrequently seen in surfactant-treated BPD patients even though their disease was severe enough to be the underlying cause of their death. The RAC/MLI ratio (an indicator of the number of alveoli) in the BPD patients who lived weeks to months was virtually unchanged from that expected at the infants' birth. In other words, an infant born at 28 weeks' gestation who developed HMD and BPD and lived for 12 weeks, whether treated with surfactant or not, had the same number of alveoli as one born at 28 weeks' gestation and died immediately after birth.

Although high concentrations of oxygen over prolonged periods of time are known to cause alveolar cell hyperplasia and necrotizing bronchiolitis with resulting alveolar septal fibrosis, it is possible that low levels of oxygen (25% to 35%) in very immature infants may inhibit growth of new alveolar ducts and alveoli. Although the lung appears to mature histologically (alveolar septa thin and expand to resemble the septa of term infants) there is no accompanying significant increase in the surface area of the lung through increase in number of alveoli (Fig. 7.22). Thus, although recent advances in

mechanical ventilation have limited the amount of injury to the bronchiole (i.e., no necrotizing bronchiolitis), the continued patency of all bronchioles throughout the course of therapy allows equal injury to all acini from even low levels of oxygen therapy, which should be compared with the even lower in utero oxygen levels to which the developing lung is exposed to.

Complications of BPD include cor pulmonale, sudden unexpected death, higher incidence of cardiac arrhythmias, and a markedly increased susceptibility to pulmonary infections (both viral and bacterial).

## Interstitial Pulmonary Emphysema

Interstitial pulmonary emphysema is the presence of air within the connective tissue, and possibly the lymphatics, of the perivascular and interlobular septa of the lungs.<sup>46</sup> Interstitial pulmonary emphysema develops along the interlobular septa of the lungs following the overdistention and rupture of the alveolar base, the segment of an alveolus directly contiguous to the fluid-rich tissue surrounding blood vessels. This allows air to leak into the septal connective tissue.<sup>47</sup> The air may remain localized to the septa, or dissect centrally along vessels to the mediastinum producing pneumomediastinum, or to the pericardium producing pneumopericardium, or peripherally to and through the pleura producing a pneumothorax.<sup>48</sup>

Interstitial pulmonary emphysema had once been seen in as many as 20% of all preterm infants ventilated for the respiratory distress syndrome. But it has also been observed in low birth weight infants who breathed spontaneously and did not need mechanical ventilation<sup>49-51</sup> or required only limited assistance such as nasal prong oxygen supplementation.<sup>52</sup> Interstitial pulmonary emphysema has also been noted following *Staphylococcus aureus* pneumonia,<sup>53</sup> and, in a 15-year-old boy in association with a pulmonary metastasis from a synovial sarcoma.<sup>54</sup>

Prior to the advent of surfactant therapy, infants weighing less than 1500 g showed an incidence of nearly 33%, and infants weighing less than 1000 g showed an incidence as high as 42%.<sup>55</sup> Mortality in these infants was higher (greater than 50%), again primarily (95%) in those infants with birth weights less than 1500 g (64%) or who develop interstitial pulmonary emphysema on the first day of life (>75%). Since the advent of surfactant therapy and the use of high-frequency oscillatory ventilation, the incidence of interstitial pulmonary emphysema in premature infants has fallen dramatically,<sup>56-58</sup> with one study noting an incidence of 6% in a group of 18 premature infants (median birth weight of 1010 g) vs. 39% in a control group of nonsurfactant, continuous positive airway pressure treated infants.<sup>59</sup>

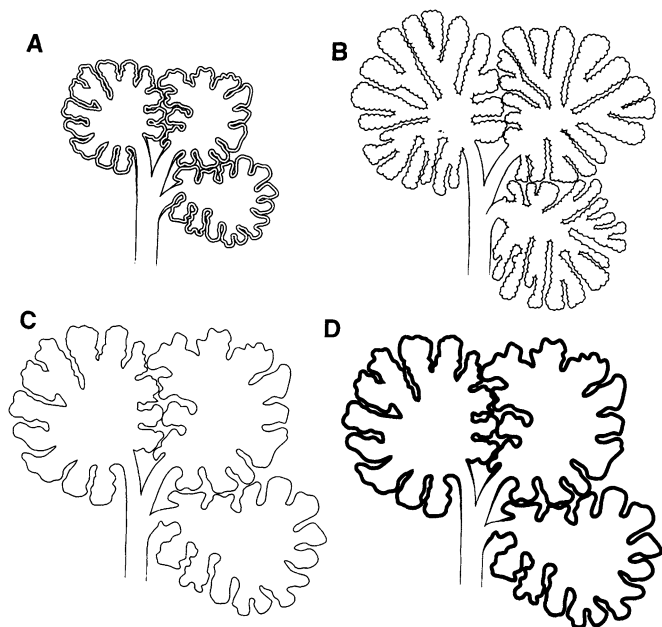


FIGURE 7.22. Surfactant treated bronchopulmonary dysplasia. **A.** The acini display the normal thickening of an immature lung at the time of birth. **B.** With uneventful growth, the acini increase in size and complexity. **C.** With the acinar arrest of surfactant treated bronchopulmonary dysplasia, the acini are distended but few if any new alveoli develop. **D.** If the supportive therapy needed (oxygen, ventilation) results in injury to the acini, a uniform, though mild, alveolar septal fibrosis may develop. (From Husain et al.<sup>45</sup> Copyright 1998, with permission from Elsevier.)

Pneumothorax, pneumomediastinum, and pneumopericardium frequently accompany interstitial pulmonary emphysema (40% to 77%) and contribute significantly to the mortality of preterm infants.<sup>60</sup> Pneumothorax and interstitial pulmonary emphysema are also seen in full-term infants, primarily in association with meconium aspiration<sup>61</sup> or pulmonary hypoplasia.

Radiographically, interstitial pulmonary emphysema presents as lucent linear streaks with prominent interstitial markings and cystic spaces that tend to radiate from the hilum.<sup>62</sup> Large subpleural lucent cystic spaces may be seen, being particularly noticeable if a pneumothorax is present. If interstitial pulmonary emphysema persists, radiographs may display an expanded multicystic pattern of one or more lobes. If it is localized to one lung, mediastinal shift and depression of the diaphragm may occur. Compression atelectasis of lung adjacent to the cysts will further accentuate the air-filled spaces.<sup>63</sup> Solitary unilocular cysts of the lung may be seen with persistence of acute interstitial pulmonary emphysema even if the initial episode of interstitial emphysema is undetected for days or weeks.<sup>64</sup>

The treatment of infants with bilateral interstitial pulmonary emphysema is difficult and varied. Reduction in ventilatory pressures is effective and alleviates the influx of air into interstitial tissues but may also prove inadequate to ventilate the infant. High-frequency ventilation has been shown to be helpful in these infants. Many modes of therapy have been employed in the treatment of infants with persistent unilateral interstitial pulmonary emphysema, including selective bronchial intubation, lateral decubitus positioning, extracorporeal membrane oxygenation, alveolar lavage during flexible bronchoscopy, artificial pneumothorax and pneumotomy, partial liquid ventilation,<sup>65</sup> and lobectomy.<sup>46</sup> Persistent interstitial pulmonary emphysema in recent years has become

an indication for pulmonary resection in the newborn period.<sup>62</sup>

Interstitial pulmonary emphysema pathologically occurs in two forms (Table 7.2): an acute usually diffuse form noted in the first few days of life, and a persistent form seen in either a localized or diffuse pattern in infants more than 1 week old.<sup>46,66</sup>

Acute interstitial pulmonary emphysema (AIPE) appears grossly as round-to-oval gas-filled spaces around bronchovascular bundles or along interlobular septa (Fig. 7.23). These spaces are usually visible beneath the pleura but are almost always limited to those areas in which the interlobular septa extend to the pleura. This is a major reason for establishing that the gas, for the most part, is within the connective tissue of the interlobular spaces rather than within lymphatics, which could lead to a lateral distribution of air within subpleural lymphatics.<sup>46</sup> The parenchyma adjacent to the interstitial pulmonary emphysema is often atelectatic and firmer than areas of uninvolved lung.

Microscopically, interstitial pulmonary emphysema is characterized by spherical cysts within the interlobular septa (Fig. 7.24). The walls of the cysts are composed of thin fragments of connective tissue or, more frequently, the walls of collapsed alveoli of lobules adjacent to the interlobular septa. The cysts usually have no discernible lining, although rarely endothelial cells of interlobular septal lymphatics may be incorporated into some of the cysts. Other lymphatics, however, along with pulmonary veins, may be compressed by the interstitial cysts. Subpleural lymphatics, as previously mentioned, are rarely involved by this process. Adjacent parenchyma may display the changes of the HMD and BPD so frequently associated with interstitial pulmonary emphysema.

Persistent interstitial pulmonary emphysema (PIPE) is now seen most frequently in its localized form presenting

TABLE 7.2. Comparison of forms of interstitial pulmonary emphysema

Features	AIPE	PIPE	
		Localized	Diffuse
Patient's age (days)	<7	>7	>7
Mediastinal shift	+	++	—
Pneumothorax	++	+	++
Average size of interstitial air spaces (cm)	0.2	1.3	0.7
Shape of interstitial air spaces	Spherical cysts	Irregular cysts	Channels and cysts
Fibrosis of cyst wall	—	++	+
Giant cell reaction along wall	—	++	+
Parenchymal disease	+	+	++

AIPE, acute interstitial pulmonary emphysema; PIPE, persistent interstitial pulmonary emphysema.

Source: Stocker et al.,<sup>63</sup> with permission of Springer Science and Business Media.

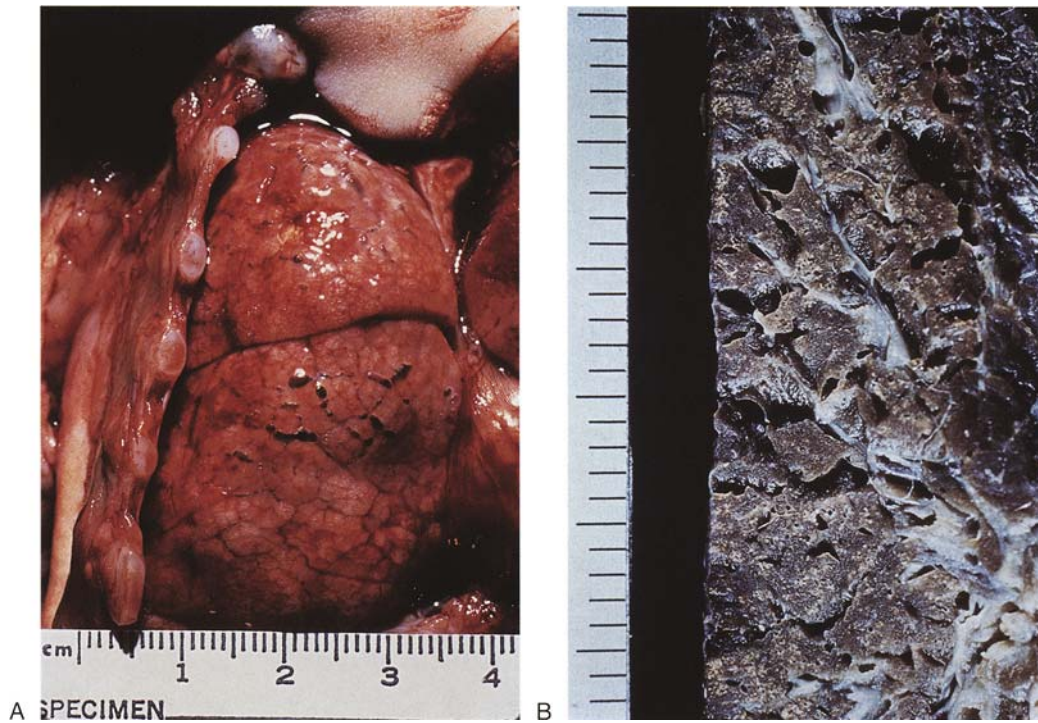


FIGURE 7.23. **A,B.** Acute interstitial pulmonary emphysema. Air-filled cysts are present within interlobular septa extending radially from the hilum (**B**, right) to the subpleura.

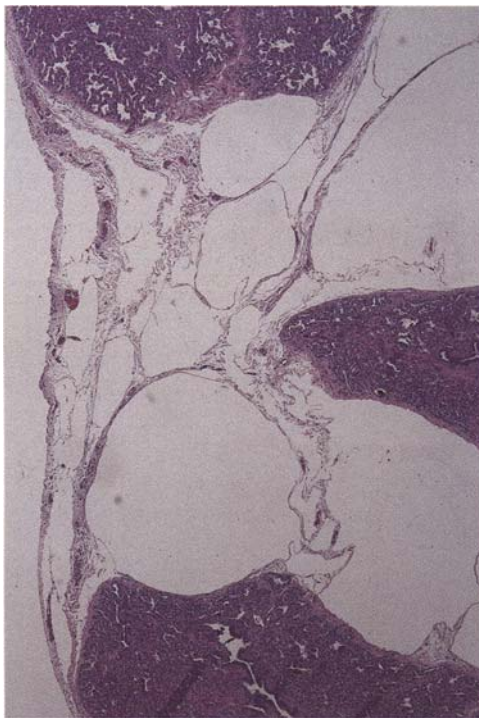


FIGURE 7.24. Acute interstitial pulmonary emphysema. Air-filled spaces markedly widen the interlobular septum beneath the pleura (left) and compress intervening pulmonary parenchyma.

grossly with a picture of multiple intercommunicating cysts 0.2 to 2.0 cm in diameter, resembling, in some cases, congenital pulmonary airway malformation.<sup>46</sup> The cysts, again limited to interlobular septa, are often irregular and appear to be lined by a smooth membrane overlying atelectatic parenchyma (Fig. 7.25). Microscopically, the cysts display a thin to occasionally prominent fibrous connective tissue wall studded with multinucleated foreign-

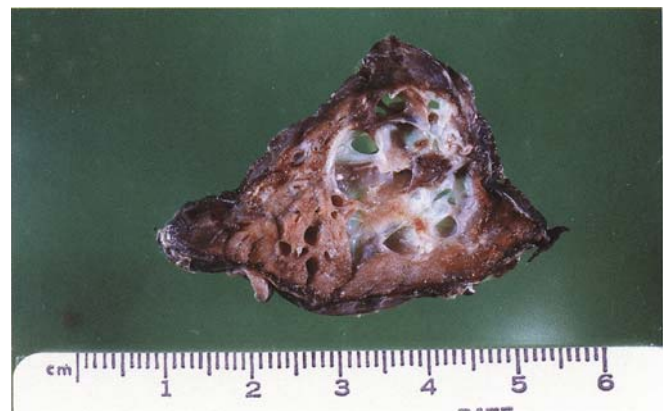
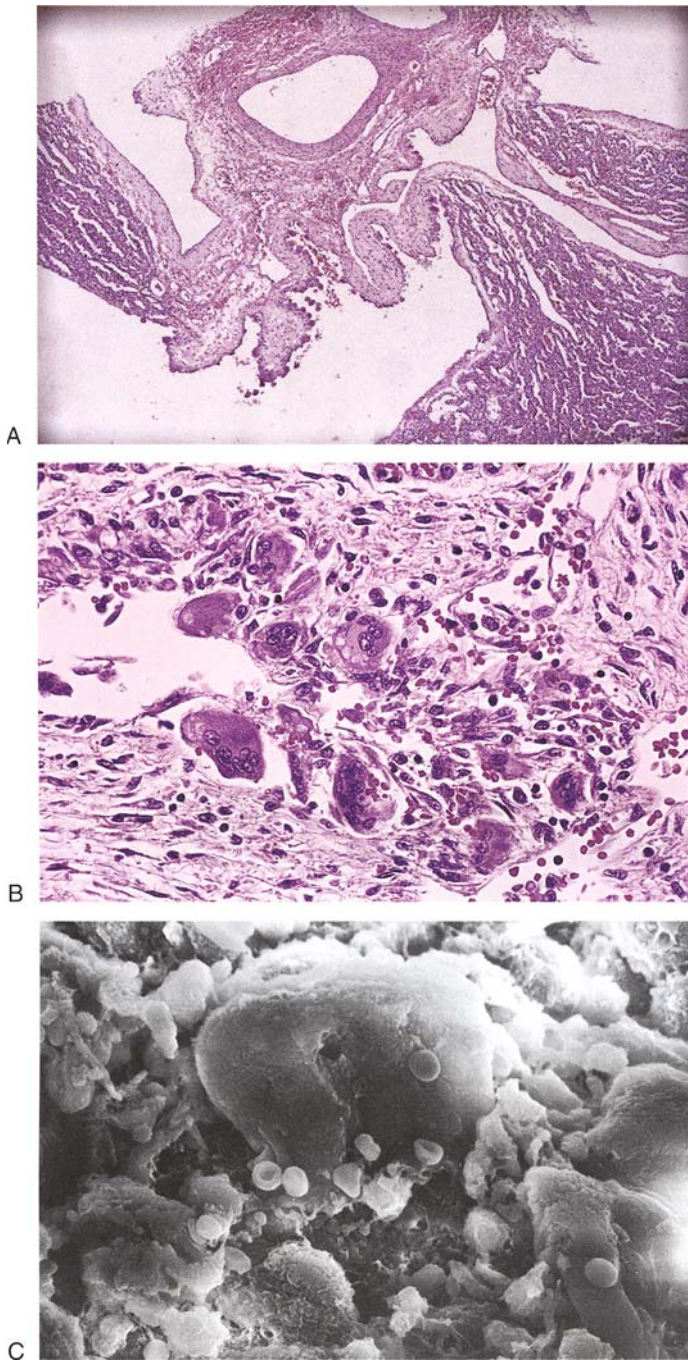


FIGURE 7.25. Persistent interstitial pulmonary emphysema. A cross section of lung displays many distorted interconnecting irregular air-filled cysts varying from 0.2 cm to more than 1 cm in diameter.



**FIGURE 7.26.** Persistent interstitial pulmonary emphysema. **A.** Irregular air-filled spaces within the interlobular septa compress a bronchovascular bundle. Note the thickened fibrous walls of the cysts and the giant cells scattered along them. **B.** Foreign-body-type giant cells, the hallmark of the persistent form of interstitial pulmonary emphysema, line portions of interlobular septal cyst walls. The foreign-body giant cells contain 3 to 25 eccentrically placed nuclei and finely granular cytoplasm rarely displaying demonstrable foreign material. **C.** Cyst, scanning electron microscopy. Foreign-body-type giant cells are randomly scattered along the surface. Thin strands of fibrous connective tissue crisscross the wall. Note the concave red blood cells on and adjacent to the giant cell.

body giant cells (Fig. 7.26). These giant cells, the hallmark of persistent interstitial pulmonary emphysema,<sup>46</sup> may occur singly or in clusters along the surface of the cyst or within the connective tissue of the cyst wall, the latter probably reflecting an area of collapsed and scarred former cyst.<sup>51</sup> The cells are 20 to 150  $\mu\text{m}$  or more in diameter with two to 35 or more round-to-oval eccentrically placed nuclei, each with a prominent nucleolus. The abundant cytoplasm is smooth to finely granular or vesicular and only rarely contains any identifiable or stainable material, as with hemosiderin.

The tissue in the walls of the cysts ranges from plump fibroblasts with prominent capillaries in young infants to dense collagenized connective tissue in older infants. Foci of hemosiderin-laden macrophages, probably reflecting old hemorrhage, and chronic inflammatory cells may also be present. Rarely, a direct communication between the interstitial cysts and a bronchiole or alveolar duct may be demonstrated with cuboidal epithelial lining cells extending from the bronchiole into the cyst.<sup>47</sup> Adjacent lung parenchyma may be entirely normal or display focal atelectasis, fibrosis, or pneumonia. Persistent interstitial pulmonary emphysema is still occasionally seen in its diffuse form with three or more lobes involved and in close association with chronic lung disease of the premature infant (bronchopulmonary dysplasia). The lung is firm, reflecting the underlying alveolar septal fibrosis of BPD but in addition, small (0.1 to 0.4 cm in diameter), irregular gas-filled spaces are present as long thin channels around bronchovascular bundles and along interlobular septa. The channel walls are composed of loose fibrous connective tissue along which giant cells are seen. They occur, however, far less frequently than in the localized form of PIPE. The underlying pulmonary parenchyma usually displays the characteristic features of BPD.

The cyst walls of PIPE, particularly in the localized form, are virtually identical to those seen in pneumatosis intestinalis and pneumatosis vaginalis.<sup>46</sup> The giant cells apparently reflect a reaction of the connective tissue to air, a foreign substance, which when present in the tissue for more than 7 days elicits this response.<sup>67</sup>

While lymphatics may be incorporated into the walls of the interstitial cysts through fibrosis or contribute to the lining of a small portion of the cysts, it is unlikely that the cysts represent only intralymphatic air. As previously mentioned, interstitial air is rarely seen in the subpleural region except for the area in direct continuity with the interlobular septum. In cases of bronchopulmonary dysplasia with AIPE or PIPE, the large subpleural lymphatic bed is uninvolved and in most cases appears virtually normal. Also, the air-containing cysts of interstitial pulmonary emphysema are many times the size of normal lymphatics and the dilated lymphatics of congenital lymphangiectasis, which, incidentally, does involve subpleural



as well as interlobular lymphatics. Finally, an endothelial lining, as present in lymphatics, cannot be identified with any consistency in the interstitial cysts.<sup>46</sup>

## Tracheomalacia

While congenital tracheomalacia is a relatively rare disorder (see Chapter 6), acquired tracheomalacia has been seen in premature infants requiring prolonged nasotracheal intubation as part of the treatment for the RDS.<sup>68,69</sup> Damage to the lower trachea and mainstem bronchi has also been noted with aggressive airway suctioning through naso- or orotracheal tubes.<sup>70</sup> Tracheal perforation, in fact, may occur as a complication of vigorous nasotracheal intubation.<sup>71</sup> Damage to the trachea with resultant tracheomalacia has been reported in children treated for recurrent laryngotracheal papillomatosis.<sup>72</sup> Tracheomalacia and gastroesophageal reflux presenting as cough in neonates has also been noted.<sup>73</sup> Surgical repair with resection of the involved area, aortopericardiosternotomy, use of an extratracheal splint, or insertion of a stent has been done in treatment.<sup>74-79</sup>

Radiographically, tracheomalacia may be noted as an extremely mobile trachea that is more dilated and oval (or even collapsed) than normal.<sup>70,80</sup> Grossly the trachea is pliable and easily compressed and flattened. The internal diameter of the lumen may be enlarged, with an increased width of the posterior fibromuscular membrane completing the cartilage ring.

Microscopically, squamous metaplasia of the epithelium is usually prominent, either focally or around the entire internal diameter of the trachea. Focal ulceration and necrosis may also be present.<sup>68</sup> The underlying fibromuscular connective tissue may display an acute or chronic inflammatory infiltrate, and mucous glands may be increased, occupying more than 50% of the area between the cartilage rings and epithelium. The cartilage rings (and plates in the bronchi) may be narrowed or thinned, with rare foci of inflammation and necrosis, but in most cases they are histologically unremarkable.

## Pulmonary Changes in Extracorporeal Membrane Oxygenation

The development of extracorporeal membrane oxygenation (ECMO) and its use in the often successful treatment of meconium aspiration,<sup>81</sup> congenital heart malformations, and diaphragmatic hernia (among other causes of pulmonary hypoplasia) have produced a unique set of pathologic changes in the lung. Extracorporeal membrane oxygenation is not, unfortunately, successful in a variety of the pulmonary dysplasia disorders such as alveolar capillary dysplasia, surfactant protein B and C

deficiency, and pulmonary lymphangiectasia.<sup>82</sup> Chou and colleagues<sup>83</sup> described the autopsy finding in 23 patients receiving ECMO therapy and noted the presence of interstitial and intraalveolar hemorrhage with HM formation during the first few days of therapy. Hyperplasia of type II alveolar cells and bronchial epithelial cells was noted after 2 days of ECMO therapy in some patients and by 7 days in all patients. Bronchial epithelium displayed squamous metaplasia in most cases. Clusters of calcified material were noted in the alveoli of 7 of 23 cases. Interstitial fibrosis was a consistent finding after 7 days of ECMO therapy. In three patients treated for 15, 19, and 21 days, there was replacement of the terminal airways and alveoli by tall columnar and mucin-producing epithelium.<sup>83</sup>

## Pulmonary Hemorrhage

Hemorrhage into the alveoli or interstitium of the lung is a rather common histologic finding at autopsy or in tissue removed at surgery for various reasons. In the latter situation, one must remember the possibility that intraoperative manipulation may have produced the hemorrhage. This section is concerned primarily with the clinicopathologic entities of *massive pulmonary hemorrhage of the newborn* and the so-called *alveolar hemorrhage syndromes* (Fig. 7.27).<sup>84-86</sup> In some cases these two disease categories may converge as pathogenetically identical processes<sup>87</sup> (Table 7.3). The alveolar hemorrhage syndromes include Goodpasture syndrome, Wegener granulomatosis, the collagen vascular diseases complicated by hemorrhage, and idiopathic pulmonary hemosiderosis.<sup>88</sup> The designation *pulmonary renal syndromes* has been applied as a collective appellation to this same basic group of diseases with



FIGURE 7.27. Massive pulmonary hemorrhage in a newborn boy is present throughout the left lung and is noted in focal areas of the right lung.

TABLE 7.3. Conditions associated with hemoptysis or pulmonary hemorrhage in children

Relatively common	
Foreign-body aspiration	
Infection	
Cystic fibrosis	
Bronchiectasis	
Tuberculosis	
Nonpulmonary origin	
Upper airway bleeding	
Hematemesis	
Less common	
Trauma	
Accidental	
Related to tracheostomy	
Deliberate (suffocation)	
Cardiac	
Congenital heart disease	
Pulmonary hypertension	
Pulmonary emboli	
Rare	
Tumor, etc.	
Adenoma	
Carcinoid	
Arteriovenous fistula	
Nonpulmonary origin	
Primary hematologic bleeding diseases	
Bleeding in immunocompromised children	
Very rare	
Pulmonary-renal syndromes	
Goodpasture syndrome	
Systemic lupus erythematosus	
Wegener granulomatosis	
Microscopic polyangiitis	
Henoch-Schönlein purpura	
Idiopathic pulmonary hemosiderosis	
Factitious hemoptysis	

Source: Modified from Godfrey,<sup>87</sup> with permission from John Wiley & Sons.

the exception of idiopathic pulmonary hemosiderosis.<sup>89</sup> In the pediatric age population, the concerns are mainly focused on neonatal pulmonary hemorrhage and idiopathic pulmonary hemosiderosis.

If surfactant deficiency is the most common cause of neonatal respiratory distress, massive pulmonary hemorrhage is one of the least frequent. There is little to distinguish massive pulmonary hemorrhage from other etiologies of severe respiratory insufficiency in the early clinical stages until there is bleeding from the tracheobronchial tree. The changes on the chest radiograph are generally nonspecific. Herein lies the problem of massive pulmonary hemorrhage and whether there is such a specific entity. An unmistakable impression from recent studies is that massive pulmonary hemorrhage is a diagnosis of exclusion, because there are other conditions such as disseminated intravascular coagulation, pneumonia, and congestive heart failure that produce a clinicoradiologic picture of massive pulmonary hemorrhage.

The estimated frequency of massive pulmonary hemorrhage in neonates is 0.1% of live births, a figure derived from the British Perinatal Mortality survey.<sup>90</sup> This incidence increases dramatically to 5% to 7% in VLBW infants with respiratory distress.<sup>85</sup> As viewed from the perspective of an autopsy finding in neonates, the frequency of pulmonary hemorrhage is more difficult to assess since the quantitative aspects may not be explicitly addressed in each published study. Hanzlick,<sup>91</sup> however, examined infant lung samples (four sections/cases) obtained by medical examiner pathologists from infants dying from forensic and nonforensic causes. The lung sections were scored as to the extent of alveolar hemorrhage on a scale of 0 to 7. In the cohort of 60 cases, 40 (67%) displayed some degree of pulmonary hemorrhage, although none of the deaths was attributed to the hemorrhage.

A number of mechanisms or etiologies have been proposed including surfactant deficiency, aspiration of maternal blood (confirmed with the Kleihauer-Betke test),<sup>92</sup> viral or bacterial infections, hypothermia, coagulopathy, hemolytic disease of the newborn, early HMD, oxygen toxicity, birth asphyxia, ECMO, pulmonary hypertension secondary to patent ductus arteriosus, pulmonary capillaritis, and congenital hyperammonemia.<sup>89,93-99</sup> Yeung<sup>100</sup> examined 35 neonates who came to autopsy after culture-proven bacterial infections during life; massive pulmonary hemorrhage was found in the lungs in 19 cases. It may be fair to conclude that massive pulmonary hemorrhage is a tissue response to a variety of systemic and localized conditions. One suggestion is that massive pulmonary hemorrhage is a nonspecific terminal event, a viewpoint that is difficult to refute.

The infants who develop massive pulmonary hemorrhage may be premature or low weight for dates; others are full term or weigh in excess of 2500 g at birth.<sup>101</sup> This variability in the clinical profile of neonates with massive pulmonary hemorrhage is best explained by the differences in etiology and pathogenesis. Since most studies are drawn from autopsy experiences, the conclusion might be made that massive pulmonary hemorrhage is universally fatal. However, there are, more recently, reports of survivors who have been treated with high-frequency ventilation or activated recombinant factor VII.<sup>85,97</sup> As with many diseases in infancy, massive pulmonary hemorrhage might best be treated by preventing the situations that lead to the hemorrhage, for example, surfactant replacement in premature infants to prevent hypoxia and alveolar cell damage.<sup>102,103</sup>

Hemorrhage producing consolidation of at least two lobes of the lung is a definition of massive pulmonary hemorrhage that was proposed by Esterly and Oppenheimer<sup>104</sup> in their classic study. They emphasized the confluent nature of the hemorrhage, although focal areas of more normal-appearing parenchyma may be identi-

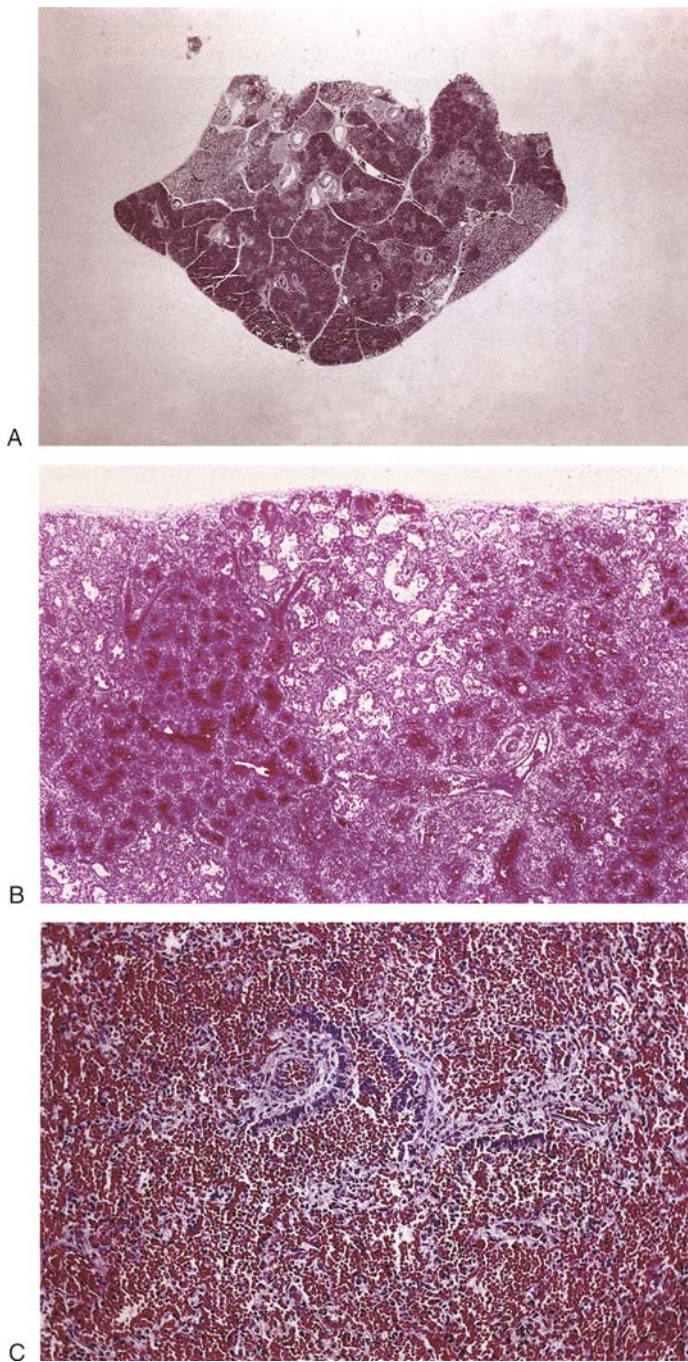


FIGURE 7.28. Pulmonary hemorrhage. **A.** Red cells within alveoli distend acini and produce consolidation of the lung. **B.** Alveolar septa are readily visible between the alveoli filled with red blood cells in this immature lung. **C.** Red blood cells fill a bronchiole (center) and extend into alveolar ducts, alveolar saccules, and alveoli.

fied. The cut surface of the specimen releases a hemorrhagic and often frothy fluid. Adamson et al.,<sup>105</sup> who examined the bloody liquid from the trachea of two neonates with massive pulmonary hemorrhage, found that the hematocrit of the fluid was very low, and concluded

that the blood was a plasma filtrate. Microscopically, the hemorrhage is typically found in the alveoli and interstitium; however, the alveolar extravasation is generally more apparent than the interstitial hemorrhage (Fig. 7.28). Many alveoli, in addition to the blood, contain palely staining fluid that is the predominant finding in some fields. The interlobar septa are often widened as the result of hemorrhage and edema. It is often difficult to be certain whether the changes in the alveolar septa are congestion or actual extravasation. When an area of lung is collapsed, there are further problems in the interpretation of the microscopic findings.

When the lungs are examined, it is important to evaluate them for the presence of other abnormalities that may be as important, if not more so, in explaining the cause of death. Focal bronchopneumonia, fibrin thrombi in arteriolar or capillary-sized vessels, and aspirated material should be carefully searched for in the sections.<sup>100,106</sup> Fibrin thrombi are an indication of disseminated intravascular coagulopathy; an examination of other organs such as the kidney, adrenal, and intestine often discloses the presence of thrombi as well. Hyaline membrane formation is found in a minority of cases.

## Idiopathic Pulmonary Hemosiderosis

Idiopathic pulmonary hemosiderosis (IPH) presents with symptoms including iron-deficiency anemia,<sup>107</sup> hypoxemia (85%), dyspnea, and hemoptysis (65%).<sup>108</sup> It occurs primarily in children 3 to 6 years of age, but can be seen in children as young as 4 to 6 months of age.<sup>109</sup> Consanguinity and environmental factors may be involved in its development.<sup>110</sup> The incidence is equal in both sexes, and 15% to 20% of cases occur in adolescents and young adults. Less specific nonpulmonary symptoms include fever (in as many as 79% of cases), lymphadenopathy, hepatomegaly, and splenomegaly. Radiographically, early stages are characterized by patchy or diffuse pulmonary infiltrates or massive confluent shadows that may rapidly clear (Fig. 7.29).<sup>108,111</sup> In later stages of the disease there is a perihilar reticulation or a pattern of diffuse interstitial disease. The clinical triad of hemoptysis, iron deficiency anemia, and diffuse parenchymal infiltrates is strongly suggestive of IPH.<sup>110</sup>

Hypochromic microcytic anemia is seen in virtually all cases of IPH, and eosinophilia is present in 12% to 15% of patients.<sup>110,112</sup> Bone marrow examination shows reactive erythroid hyperplasia and depleted iron stores. Levels of serum iron are low, and total iron-binding capacity is increased. Most patients with IPH have normal renal function without circulating autoantibodies.

Associations with celiac disease, juvenile idiopathic arthritis, cardiomyopathy, and antineutrophil cytoplasmic antibodies have also been reported.<sup>113-117</sup> A considerable

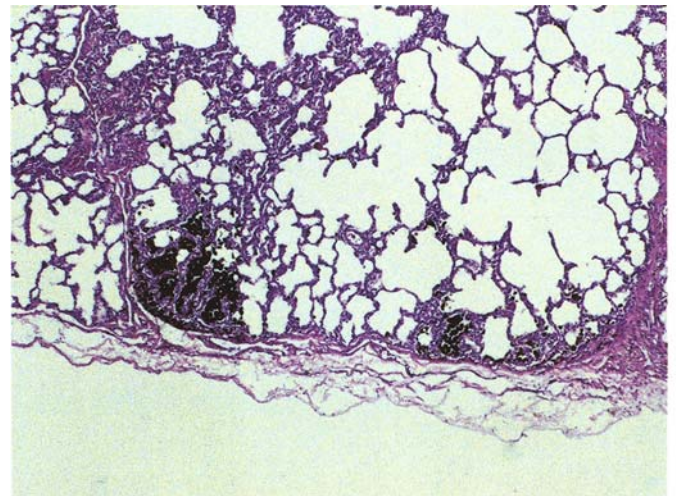


FIGURE 7.29. Idiopathic pulmonary hemosiderosis in 2½-year-old girl presented with shortness of breath, weakness, and iron-deficiency anemia. Admission chest radiograph shows multiple infiltrates and fluffy densities in both lung fields.

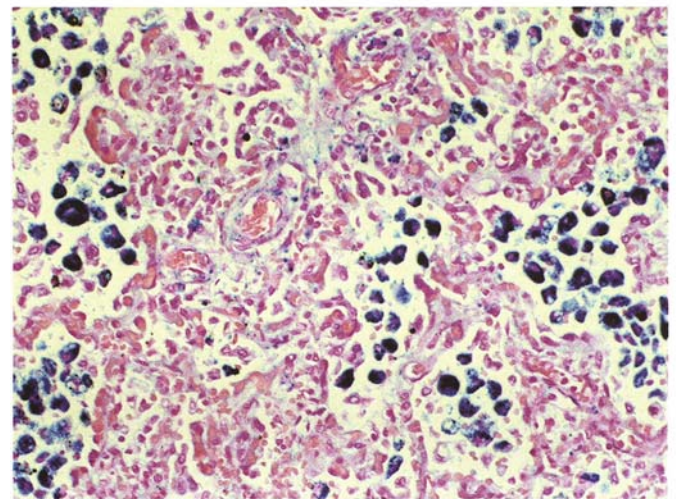
amount of debate has surrounded the possibility that the saprophytic fungus *Stachybotrys chartarum* may be an etiologic agent of pulmonary hemosiderosis.<sup>118–121</sup> After a number of reports of outbreaks of IPH in Cleveland and Chicago, and the discovery of *S. chartarum* in the homes of many of the children (and in the bronchoalveolar lavage of one child<sup>122</sup>), an association was suggested.<sup>123</sup> Subsequent reviews of the initial reports by the Centers for Disease Control and Prevention (CDC), however, found shortcomings in the conduct of the studies, and a new study is currently underway to identify cases with a narrow definition of the disease (evidence of blood in the airway, age  $\leq 1$  year, absence of medical disease related to pulmonary hemorrhage, and severe respiratory distress or respiratory failure)<sup>124</sup> and then see if these cases show a distinct correlation with *S. chartarum*.

While some children with IPH may die of massive hemorrhage shortly after presentation, other patients have a history of progressive respiratory insufficiency leading to death 2 to 5 years after diagnosis.<sup>125</sup> Treatment with corticosteroids has been successful,<sup>126,127</sup> including a reported 5-year survival of 86% in 17 patients receiving corticosteroids and other immunosuppressant agents.<sup>109</sup> Recurrence of IPH has been reported in a 19-year-old man 3 years after undergoing bilateral lung transplantation.<sup>128</sup>

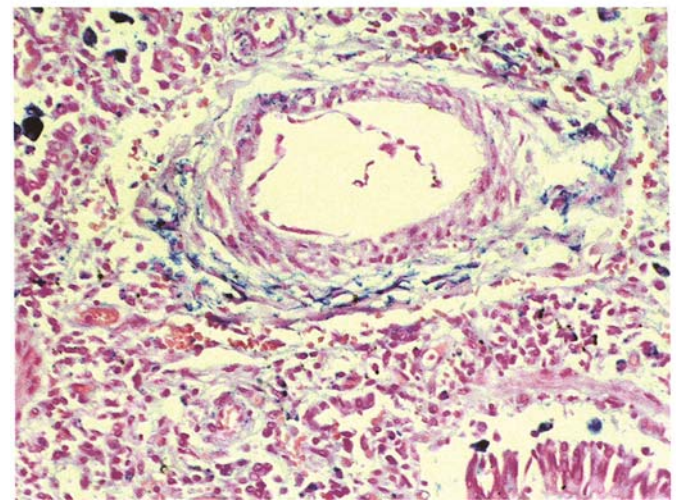
Bronchoalveolar lavage demonstrates hemosiderin-laden alveolar macrophages in large numbers.<sup>108,129</sup> Lung biopsy and autopsy specimens show varied involvement.<sup>107</sup> Focal areas of consolidation are common due to massive accumulations of hemosiderin-laden macrophages, which obliterate alveolar spaces and are associated with interstitial fibrosis (Fig. 7.30). Corrin and



A



B



C

FIGURE 7.30. Idiopathic pulmonary hemosiderosis (IPH). **A.** Lung biopsy shows collections of hemosiderin-laden macrophages in alveoli primarily beneath the pleura. Changes are not specific for IPH, but this diagnosis is strongly suspected in the presence of appropriate clinical and radiographic findings. **B.** Prussian blue stain for iron demonstrates hemosiderin-laden macrophages. Prussian blue. **C.** Similar Prussian blue staining material is present adjacent to collagen fibers surrounding a pulmonary artery. (Prussian blue.)

colleagues<sup>130</sup> describe capillary endothelial swelling and focal thickening of the basement membrane. Stainable iron is present in alveolar and tissue macrophages, free in connective tissues and encrusting elastic fibers of small blood vessels and alveolar septa. There is mild to moderate alveolar cell hyperplasia, peribronchial lymphoid hyperplasia, and alveolar septal mastocytosis.<sup>131</sup> Immunofluorescence is negative for immunoglobulin complement and antibasement membrane antibodies.<sup>131</sup>

## Goodpasture Syndrome

Whereas IPH is ordinarily regarded as a pediatric condition, Goodpasture syndrome is usually diagnosed in young men (see Chapter 29). Cases have, however, been reported in children, including a 10-year-old girl.<sup>89</sup> An immunoglobulin G (IgG) autoantibody to glomerular basement membrane, which cross-reacts with the alveolar basement membrane, is the sine qua non for the diagnosis of Goodpasture syndrome. However, pulmonary hemorrhage and glomerulonephritis of an immune complex type are more common than Goodpasture syndrome. Henoch-Schönlein purpura, Wegener granulomatosis, and poststreptococcal glomerulonephritis with hemorrhagic pulmonary edema produce a Goodpasture-like syndrome in children.<sup>132</sup> When the lung biopsy is examined by immunofluorescence, fine linear staining for IgG is present in the region of the alveolar basement membrane in a pattern virtually identical to the glomerular basement membrane.<sup>133</sup> Hyaline membranes, capillaritis in the alveolar septum, and a mononuclear infiltration of the interstitium, in addition to the alveolar hemorrhage, are other features in the lung biopsy of antibasement

membrane antibody-associated Goodpasture syndrome (Fig. 7.31).

## Congenital and Acquired Surfactant Deficiency

Surfactant deficiency is a common and consistent feature of prematurity, but may also occur from damage to type II pneumocytes resulting from pulmonary hemorrhage, pneumonia, atelectasis, or pulmonary edema.<sup>93</sup> The hypoplastic lungs of infants with congenital diaphragmatic hernia may also show a temporary deficiency of surfactant.<sup>134</sup> Replacement of the temporarily depleted surfactant and support of the infant until the type II pneumocytes recover (or mature) is often sufficient for a good outcome.<sup>93</sup>

It has only been in the last 10 to 15 years that congenital deficiencies of the surfactant proteins have been identified, starting with Noguee et al.<sup>135</sup> in 1993, when they noted a deficiency of surfactant protein B in a case of congenital alveolar proteinosis. Subsequently deficiencies of surfactant proteins B and C have been reported.<sup>136-144</sup>

Inherited deficiency of surfactant protein B (SP-B) is a fatal autosomal recessive disorder of lung cell metabolism caused most frequently by a frameshift mutation in codon 121 of the SP-B gene (*121ins2*) with an approximate gene frequency of 1 in 3000 to 5000 individuals.<sup>145</sup> The disease is characterized by rapidly progressive respiratory failure immediately after birth associated with a diffuse ground-glass appearance to the lungs radiographically along with markedly prominent interlobular septa.<sup>146,147</sup> Other novel mutation sites have also been described.<sup>148</sup> Chorionic villous sampling can be used to identify the homozygous state in utero.<sup>149</sup> Less frequently, abnormalities of surfactant proteins A and C may occur in association with SP-B deficiency,<sup>150-152</sup> but only recently had a true deficiency state of surfactant protein C been described.<sup>153,154</sup> Lung transplantation has been successful, although patients may develop an antisurfactant protein antibody.<sup>155</sup>

Grossly the lungs in congenital surfactant deficiency are heavy and appear consolidated. Microscopically in the early stages, alveoli are lined by a continuous layer of cuboidal alveolar lining cells (Fig. 7.32). As the disease progresses, alveoli may be filled with eosinophilic granular material admixed with desquamated alveolar cells and macrophages resembling congenital alveolar proteinosis (Fig. 7.33). In the later stages, alveolar septa are widened by fibroblasts producing alveolar septal fibrosis, although the alveolar cell hyperplasia persists (Fig. 7.34). Immunohistochemical stains of type II alveolar lining cells with SP-B or -C may be used to establish the appropriate deficiency state.

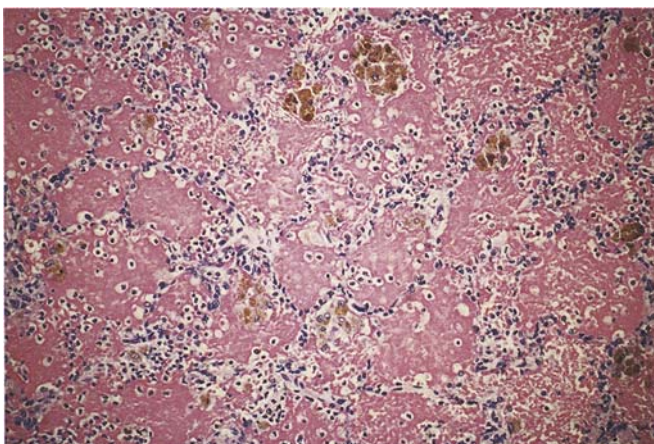
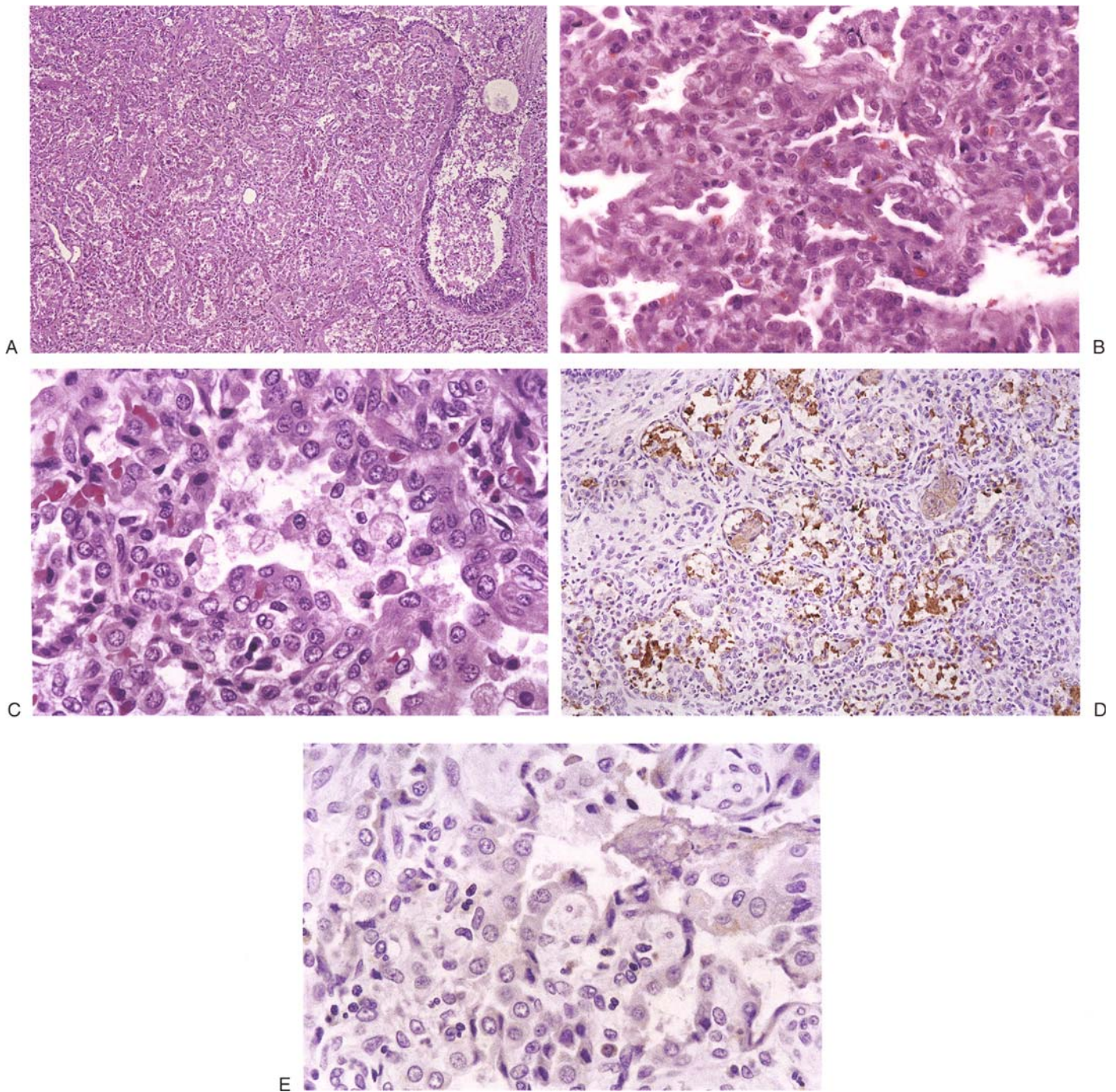


FIGURE 7.31. Goodpasture syndrome. Fresh, diffuse alveolar hemorrhage and evidence of older hemorrhage with hemosiderin-laden macrophages are present.



**FIGURE 7.32.** Congenital surfactant protein B deficiency. **A.** This 3-week-old girl with persistent respiratory distress since birth displays a consolidated lung, primarily due to a proliferation of type II alveolar lining cells. **B.** The alveolar septa are lined by side-by-side plump-type II alveolar lining cells. **C.** The alveolar lining cells display a plump pink cytoplasm. Note the desquama-

tion of some of these cells into the alveolar lumen. **D.** Staining for surfactant protein A is markedly positive. (Immunohistochemical surfactant protein A.) **E.** Staining for surfactant protein B, however, is negative. (Immunohistochemical surfactant protein B.)

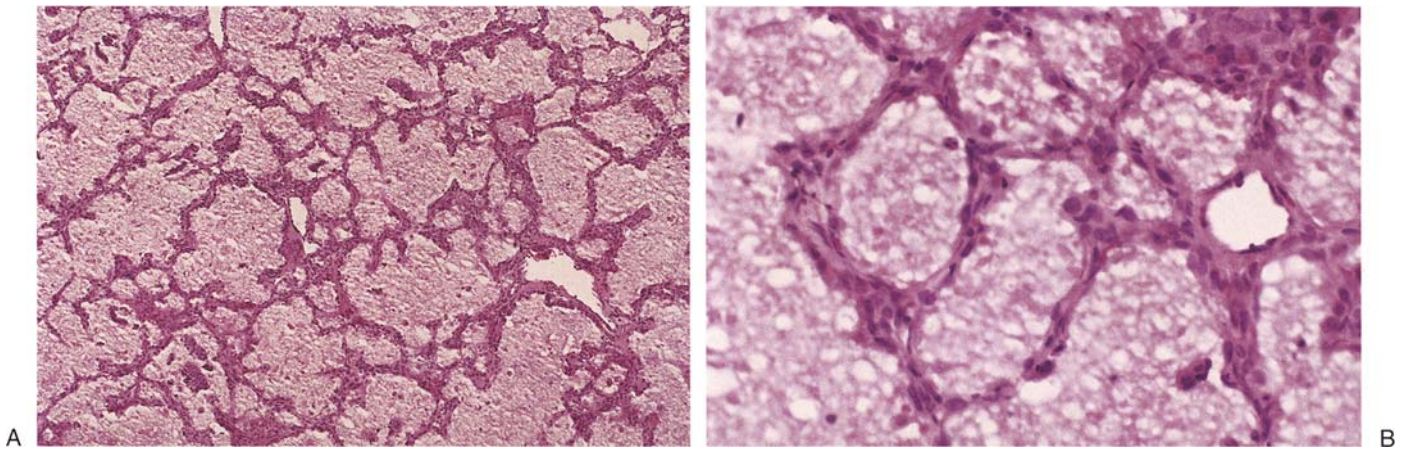


FIGURE 7.33. Surfactant protein B deficiency and pulmonary alveolar proteinosis. **A.** Alveoli are distended by a foamy pink material. **B.** The acellular nature of the material can be seen along with a few residual alveolar type II lining cells.

## Perinatal, Neonatal, and Infantile Infections

Pneumonia is one of the most common serious infection in newborn infants.<sup>156</sup> There are four basic categories of pneumonia in the fetus and neonate, based on the time and mode of acquiring the infection: (1) transplacental (generalized infection), (2) intrauterine pneumonia (a stillborn fetus or an infant who has survived for a few days), (3) perinatal pneumonia (acquired in the birth canal), and (4) postnatal pneumonia.<sup>157</sup> The latter is a complication of nursery or other environmental exposures. Incidence figures of congenital-perinatal pneumonia vary among series, but it is estimated that 10% to 20% of all neonatal deaths are attributed to pneumonia. Neonatal sepsis is accompanied by pneumonia in virtually all cases.<sup>157</sup> Only

a minority of pulmonary infections are acquired transplacentally; the majority are secondary to an ascending infection through prolonged ruptured membranes, birth asphyxia, or a contaminated birth canal.<sup>158</sup> Because the clinical manifestations are predominantly those of respiratory distress in the neonate, it is difficult to differentiate pneumonia from hyaline membrane disease.

## Congenital and Perinatal Infection

A congenital infection results when the fetus comes into contact with a potential pathogen; the acquisition of the infection is either by the transplacental hematogenous route or shortly before delivery through the ascending route. In the latter case, the distinction between a congenital and perinatal infection is not always possible or necessary. A perinatal infection may be generalized or localized to one system, in contrast to a congenital infection, which is usually systemic and may have teratogenic effects if it occurs early in development. Congenital pneumonia secondary to an organism crossing the placenta is well documented or strongly suggested for the following pathogens: cytomegalovirus, rubella, herpes simplex, *Toxoplasma gondii*, coxsackievirus B, *Treponema pallidum*, and *Listeria monocytogenes*.<sup>157</sup> Vaginal flora gain access to the amniotic sac with prolonged rupture of membranes and produce chorioamnionitis with or without an acquired congenital pneumonia; these organisms include various gram-negative coliform bacteria, *Candida albicans*, *L. monocytogenes*, and group B  $\beta$ -hemolytic streptococcus. Delivery through an infected birth canal may expose the infant not only to the aforementioned organisms but also to cytomegalovirus, herpes simplex, *S. aureus*, *Chlamydia trachomatis*, *Ureaplasma*, and *Mycoplasma*.<sup>157</sup> Aspiration of these organisms into the respiratory tract or sepsis is

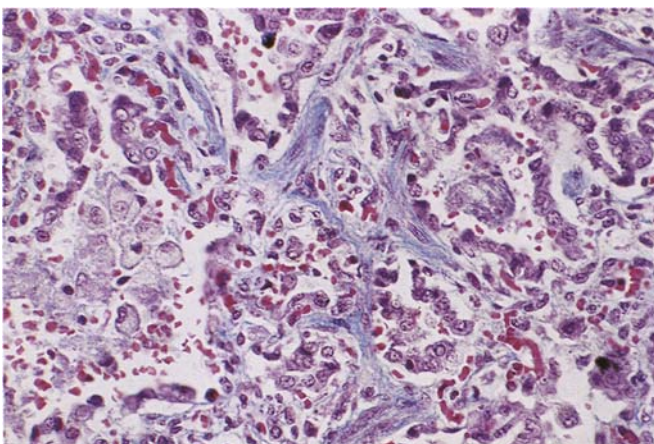


FIGURE 7.34. Surfactant protein C deficiency. In this 1-year-old boy who died after prolonged respiratory distress, alveolar septal fibrosis is noted along with alveolar cell hyperplasia. (Masson trichrome.)

the mode of infection. If the inflammatory exudate in the lungs is accompanied by amniotic contents, such as squamous cells or meconium, this supports the conclusion that aspiration occurred in a distressed fetus.

### Cytomegalovirus

Epidemiologic studies based in part on seroconversion in mothers and children and detection of virus in the urine have established that the cytomegalovirus (CMV) is the most commonly transmitted pathogen in utero.<sup>159,160</sup> It has been estimated that there are 33,000 cases of congenital CMV per year in the United States; only 5% to 10% of these infants actually become symptomatic.<sup>161</sup> The incidence of congenital CMV varies among series, which reflects differences in a number of important socioeconomic factors; the range is 0.24% to 2.2% for liveborn infants, and the highest rates of congenital CMV are found in those maternal populations with the greatest pre-pregnancy exposure to the virus.<sup>162-164</sup> It appears that these maternal reactivation infections are transmitted to the fetus, but their effects are ameliorated when compared to the more serious fetal consequences of a primary maternal infection. Viral exposure of the fetus to a reactivation infection is less likely than is the primary infection to result in microcephaly, neonatal hepatitis, growth retardation, thrombocytopenia, deafness, and chorioretinitis.<sup>165</sup>

Interstitial pneumonitis occurs in only 1% or less of symptomatic congenital CMV, whereas it is a more common manifestation of a perinatally or neonatally acquired infection. These infants are infected by secretions from the birth canal, from mother's milk, or from a contaminated blood transfusion. Viruria in perinatal CMV is not present for several weeks, this being the incubation period for CMV. The frequency (5% to 10%) of a clinically apparent infection in children with perinatal CMV is basically identical to congenital CMV. Unlike the multisystem involvement in congenital CMV, interstitial pneumonitis may be the only clinical expression of perinatal CMV. Stagno and associates<sup>166</sup> prospectively evaluated 45 infants with perinatal CMV, and four had interstitial pneumonitis.

In addition to CMV, copathogens such as *Chlamydia*, *Ureaplasma*, and *Pneumocystis jiroveci* have been isolated in a minority of cases.<sup>167</sup> When these children in the first few months of life present with fever, poor feeding, and tachypnea, a diagnosis of CMV pneumonitis is not an initial consideration since the exposure to the virus is invariably a subclinical event.

The lung is regarded as the site with the highest yield for the identification of the characteristic 5- to 10- $\mu$ m intranuclear inclusions in the enlarged (25- to 40- $\mu$ m) epithelial cells or in the commonly infected exfoliated alveolar macrophages (Fig. 7.35).<sup>168</sup> Cytoplasmic inclusions have a linear or curved configuration; they are

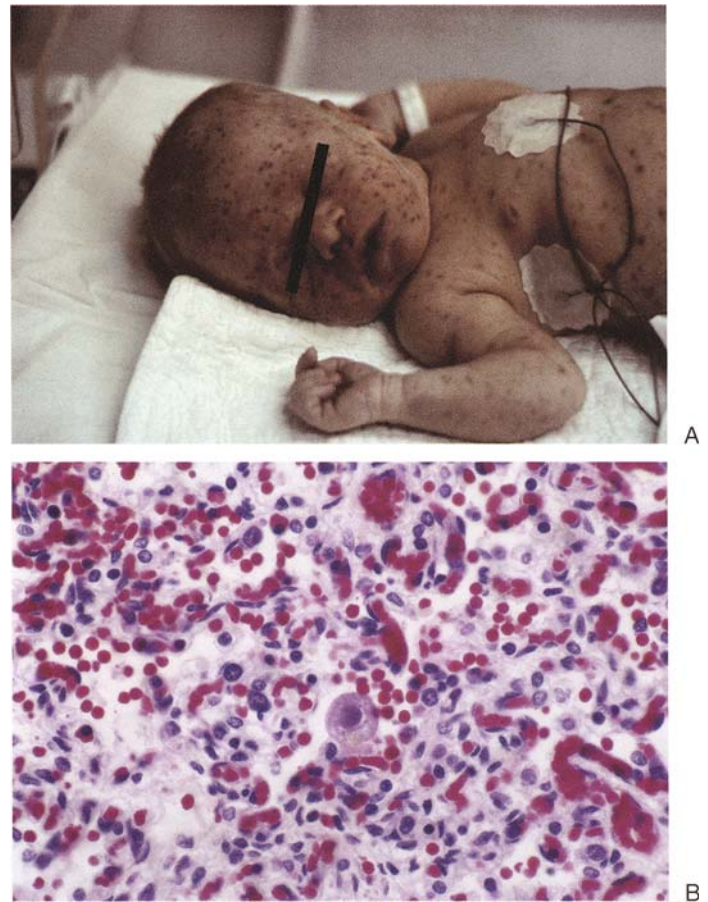


FIGURE 7.35. Congenital cytomegalovirus. **A.** At birth this infant was noted to have numerous petechiae over his body. X-rays of his head showed marked hydrocephalus with periventricular calcifications. **B.** In the lung, along with many other organs, typical large cells with intranuclear inclusions were identified. Prominent interstitial and alveolar cellular reaction was also present.

usually periodic acid-Schiff (PAS) positive, somewhat amphophilic, and are often aggregated opposite to the inclusion-bearing nucleus. When the specimen is an autopsied lung, there is usually little difficulty in the identification of CMV since it is possible to liberally sample the material. Even in a macerated stillborn fetus, the CMV-bearing cells are sufficiently well preserved in an otherwise autolyzed background to make a diagnosis possible.<sup>168,169</sup> Although the CMV inclusion is easily recognized as such in most cases, an enlarged amphophilic nucleolus in a reactive alveolar lining cell or other types of inclusions may evoke uncertainty that can be resolved by immunohistochemistry. It is unnecessary in most cases to resort to the latter technique except to confirm the diagnosis. We have found immunohistochemistry especially helpful in the demonstration of the less apparent cytoplasmic inclusions. The in situ polymerase chain



reaction has also been employed on fixed specimens for the diagnosis of cytomegalovirus infection.<sup>170</sup>

Most experience with CMV pneumonitis is confined to lung biopsies from institutions with larger populations of immunocompromised children and adults.<sup>171-175</sup> In addition to an interstitial inflammatory infiltrate,<sup>176</sup> evidence of alveolar damage with plump lining cells, hyaline membranes, hemorrhage, and macrophages are common histologic features even in the neonate.<sup>170</sup> However, these inflammatory and reactive changes are inconspicuous in the lungs of stillborn infants with CMV. Because the lungs have not inflated in the stillborn, we have found it difficult to judge the presence of an interstitial inflammatory reaction. Focal lymphocytic collections in a peribronchiolar location or a minimal lymphocytic or plasmacellular infiltration in the interstitium is seen more frequently in the neonatal lung.

The pneumonitis in perinatal acquired CMV more closely resembles the infection of later childhood.<sup>171,177</sup> A flocculent alveolar exudate may be the clue to a co-infection by *P. jiroveci*, but even in the absence of these changes, a methenamine silver stain is a justified routine. Necrosis in the lung should also alert one to the possibility of a co-infection since CMV pneumonitis alone is rarely accompanied by necrosis. Congenital lobar emphysema, eventration of the diaphragm, and hypoplasia of the lung are other less common intrathoracic complications of congenital-perinatal CMV.<sup>178</sup>

## Herpes Simplex

Most neonates with herpes simplex virus (HSV) infection have clinical manifestations, unlike the majority of infants with the more common cytomegalovirus. A minority of cases of HSV are acquired in utero (congenital)<sup>179-182</sup>; exposure to genital secretions during the second stage of delivery accounts for the predominant HSV-2 infection (80% of cases).<sup>183,184</sup> Risk factors for neonatal HSV disease include first-episode maternal infection in the third trimester, invasive monitoring, delivery before 38 weeks, and maternal age of less than 21 years.<sup>185</sup> After the neonate is infected with HSV, an incubation period of 2 to 12 days (occasionally 2 to 4 weeks) culminates in symptoms and signs in the first 2 weeks of life.<sup>186</sup> The severity of the neonatal infection, as with cytomegalovirus, is determined to some degree by the type of maternal infection, whether primary or recurrent. However, there is any number of cases of neonatal HSV in which viral shedding was not apparent or recognized at birth. These are the unfortunate de novo cases.

Neonatal HSV is either generalized (40% to 65% of cases) or localized to the brain, eyes, skin, or oral mucous membranes (35% to 60% of cases).<sup>187</sup> The central nervous system is infected in approximately 80% of infants with disseminated HSV.<sup>188-191</sup> Cutaneous vesicles are often the

first sign, followed by the constitutional symptoms.<sup>192</sup> Only one organ may be the predominant site of clinical abnormalities or the infection may severely compromise several organs, resulting in multisystem failure. Pneumonia (Fig. 7.36) is reported as one of the less common presenting features of HSV<sup>193</sup>; it is usually accompanied by other, often more serious extrapulmonary manifestations.<sup>192</sup> If the infection is confined to the skin, the prognosis is excellent.<sup>194</sup> The use of antiviral agents in cases at which neonates are at risk for developing generalized herpes simplex infection has markedly reduced the incidence of this disease and has even decreased the mortality (from 85% to 29%) in those infants who do develop generalized infection.<sup>186,194-198</sup>

The lungs are heavier than normal, have petechiae on the pleural surfaces, and are variably hemorrhagic or consolidated on the cut surface.<sup>199</sup> Bloody fluid exudes from the surface. Necrosis is generally not apparent from the gross inspection, but diffuse parenchymal nodularity may

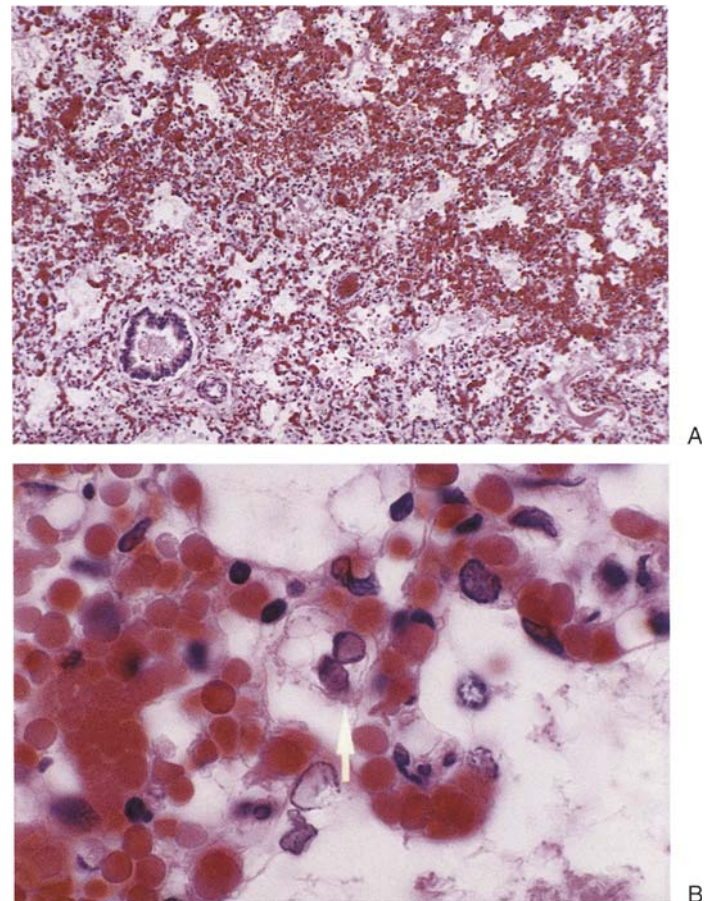


FIGURE 7.36. Congenital herpes virus. **A.** Areas of coagulative necrosis (upper right) are associated with alveolar capillary congestion. **B.** Epithelial cells at the edge of the necrotic area display smooth pink intranuclear inclusions that are not associated with an enlarged nucleus or cell.

indicate that secondary bronchopneumonia has occurred. The herpetic inclusions vary in appearance from a sharply delineated acidophilic structure surrounded by a halo and margined chromatin to a smudged, amphophilic inclusion replacing the nucleoplasm. Both mononuclear and multinucleated cells contain the inclusion(s). Cytomegaly is not a feature of the infected cells. If needed, immunohistochemistry or polymerase chain reaction for HSV can be performed.<sup>200,201</sup>

Focal necrosis and a background of alveolar damage and hemorrhage should suggest the possibility of HSV pneumonitis even before the characteristic inclusions are found. The inclusions are present in alveolar macrophages and interstitial cells at or near the margins of necrosis. It may be necessary to examine several microscopic sections before the inclusions are identified. In a few cases, even in the presence of inclusions in other organs (adrenals, liver, brain, skin), the diagnostic cells may be difficult to find in the lungs because of extensive necrosis; careful search may be required.

The lung may also have features of massive pulmonary hemorrhage, diffuse alveolar damage with hyaline membranes, fibrin thrombi in small vessels, or nonspecific interstitial pneumonitis. Neutrophils in the peripheral air spaces may indicate secondary bacterial pneumonia in an infant who has survived long enough to develop this complication.

### Varicella-Zoster

The herpesvirus varicella-zoster had been a very common contagious childhood infection until the advent of a varicella vaccine<sup>202</sup>; now most cases seen are in immunocompromised or immunosuppressed patients.<sup>203–206</sup> Only one case of varicella-zoster is reported in every 7500 pregnancies.<sup>207</sup> Varicella embryopathy (hypoplasia of extremities, cutaneous scarring, growth retardation, and neuro-ophthalmic damage) occurs in fetuses who are infected between the eighth and 19th week of gestation.<sup>208</sup> An infection in the last 4 days of gestation or within 2 days of birth results in severe generalized varicella with a very poor prognosis. Beyond this period, the infection is mild. Fewer than 100 cases of varicella have been reported in the perinatal-neonatal period.<sup>209–211</sup>

The pathologic findings in the lungs are similar if not indistinguishable from herpes simplex pneumonitis, including the appearance of the intranuclear inclusions.<sup>171</sup> Diffuse alveolar damage, hyaline membranes, and interstitial inflammation and focal necrosis are the principal microscopic features.

### Rubella

While vaccination for rubella has been utilized for years, isolated infection and epidemics still occur.<sup>212–215</sup> Classic

rubella embryopathy (cataracts, deafness, and congenital heart disease including patent ductus arteriosus, ventricular septal defect, and central and peripheral pulmonic stenosis) is the consequence of an in utero infection during the first two trimesters.<sup>216</sup> If the mother is seronegative in a nonepidemic period, 1 per 25,000 pregnancies is complicated by rubella embryopathy.<sup>217</sup> The expanded syndrome is manifested by thrombocytopenia purpura, neonatal hepatitis, encephalitis, and pneumonitis. Respiratory distress may be apparent soon after birth, or may be delayed for several weeks or months in infants with rubella pneumonitis. Gradual resolution of symptoms and signs is generally the case. Rosenberg and associates<sup>218</sup> indicated that pneumonitis with the late lesions of congenital rubella is probably a superimposed infection rather than rubella itself.

Interstitial pneumonitis with or without fibrosis is the less than specific finding in the lung. Multinucleated measles giant cells may be striking in some cases (Fig. 7.37). It is safe to conclude that a diagnosis of rubella

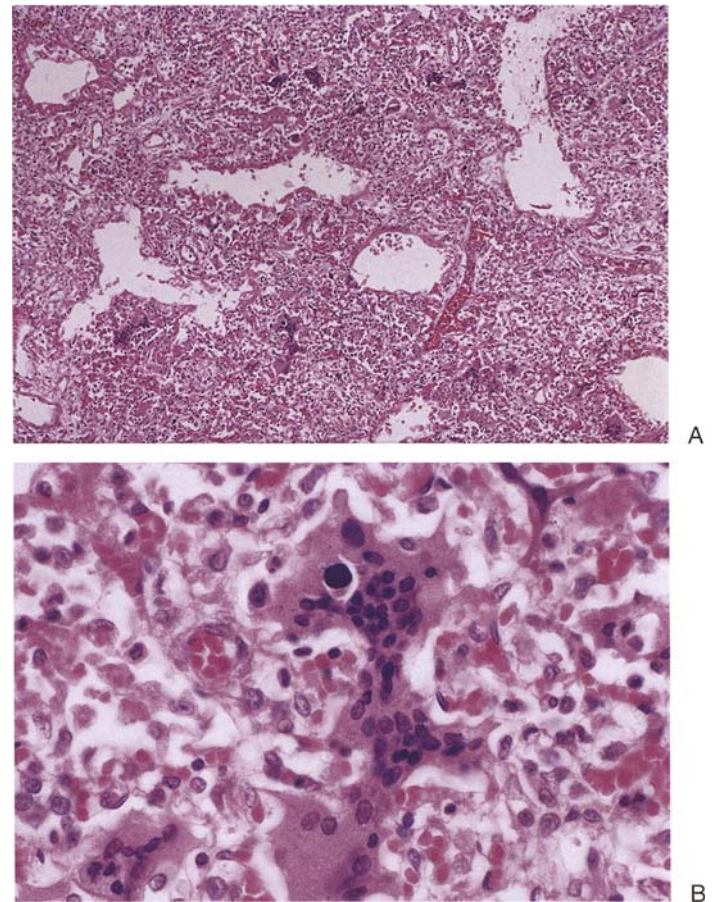


FIGURE 7.37. Measles giant cell pneumonia. **A.** The lung is diffusely consolidated with alveoli filled with giant cells visible even at low magnification. **B.** The giant cells contain 10 to 25 nuclei and abundant pink cytoplasm.

pneumonitis is only possible with appropriate supporting clinical and laboratory observations.

### Listeria monocytogenes

*Listeria monocytogenes*, a gram-positive rod, is one of the three nonviral organisms (the others are *Toxoplasma gondii* and *Treponema pallidum*) that spread from an infected mother through the placenta resulting in fetal sepsis.<sup>219,220</sup> However, the infant may be infected through the amniotic cavity, at the time of delivery through an infected birth canal, or in an infrequent nursery epidemic.<sup>221,222</sup> Lallemand and associates<sup>223</sup> documented the presence of listeriosis in 3% of second-trimester abortions. A spontaneous abortion occurred shortly after the mother had become febrile. The clinical manifestations of fetal, perinatal, and neonatal listeriosis vary, but cutaneous pustules, respiratory distress, and hepatic dysfunction are among the more common features.<sup>157,224</sup> In the premature infant with respiratory symptoms, BPD and streptococcal pneumonia are plausible considerations.<sup>224</sup> Later-onset listeriosis at 2 to 3 weeks of age is characterized by meningitis.<sup>225</sup>

Villitis and focal necrosis or abscess formation in the placenta are the hallmarks of intrauterine septicemia<sup>226</sup>; chorioamnionitis and decidual abscesses are more typical of the ascending infection. Abscesses are present in multiple organs, including the lungs, in the septic fetus.<sup>227</sup> Aspiration of infected vaginal secretions produces bronchopneumonia with necrotizing and hemorrhagic features.

### Treponema pallidum

Congenital syphilis is a complex disease with a host of clinical signs and symptoms.<sup>228</sup> The transmission of the spirochetes from an infected mother to the fetus may occur at any time during pregnancy.<sup>229</sup> The resurgence of syphilis in the United States over the past two decades (and the high prevalence throughout the developing countries of the world) has also been manifested by an increase in the incidence of congenital syphilis.<sup>230-233</sup> Poor or nonexistent prenatal care and substance abuse by mothers have contributed significantly to the virtual epidemic of congenital syphilis.<sup>234-236</sup> The diagnosis of congenital syphilis may be unsuspected initially, but should be considered in a stillborn with evidence of non-immune hydrops fetalis, hepatomegaly, and cutaneous lesions.<sup>237-239</sup>

So-called pneumonia alba is one of the classic pathologic features of congenital syphilis. There is delayed maturation of the lung and a severe fibrosing process with a zonal distribution.<sup>240</sup> The inflammatory reaction mainly consists of scattered lymphocytes and plasma cells in the interstitium. These infiltrates may be confused with extramedullary hematopoiesis. A superimposed bacterial

pneumonia is suggested by the presence of neutrophils. Spirochetes are often present in large numbers.

### Toxoplasma gondii

Toxoplasmosis is the most common parasitic infection in the United States, according to some investigators.<sup>241,242</sup> The facultative intracellular coccidia, *Toxoplasma gondii*, produces a number of clinical syndromes, ranging from a flu-like illness to an overwhelming septic infection affecting multiple organs including the brain, heart, and eye. An infection during pregnancy is usually inconsequential to the mother but may have drastic effects on the fetus, depending on the time during gestation when the organisms pass through the placenta.<sup>219,243</sup> The fetus of a seronegative primipara with an acute mononucleosis syndrome has a 25% to 40% chance of being infected. Maternal toxoplasmosis between the third and sixth months of gestation is the most vulnerable period for a severe fetal infection.<sup>244</sup> Only 10% to 20% of seropositive infants are clinically ill at birth.<sup>245</sup> The complex of congenital toxoplasmosis (cerebral calcifications, chorioretinitis, thrombocytopenia) is similar to congenital cytomegalovirus.<sup>184</sup> Pneumonitis is present in 35% to 40% of neonates with generalized toxoplasmosis.<sup>246</sup> These children have respiratory distress, which may constitute a significant problem in management.

Unless and until the encysted organisms are identified in the lung, the pulmonary changes are indistinguishable from other interstitial pneumonitides.<sup>247</sup> There is widening of the alveolar septa by a mixed inflammatory infiltrate, and focal collections of alveolar macrophages are present in distal air spaces. The cysts are found in macrophages, endothelium, smooth muscle, and epithelial cells.

### Metapneumovirus

In 2001, van den Hoogen and colleagues<sup>248</sup> isolated a paramyxovirus from 28 children in the Netherlands that they identified as a tentative new member of the *Metapneumovirus* genus based on virological data, sequence homology, and gene constellation. Subsequent studies have shown it to be a major cause of acute respiratory tract disease in normal infants and children worldwide, with a seasonal occurrence and spectrum of clinical illness most similar to the closely related respiratory syncytial virus.<sup>249</sup> The greatest prevalence of severe disease requiring hospitalization in otherwise healthy children appears to be in those aged between 6 and 12 months, older than the peak age of hospitalizations for respiratory syncytial virus.<sup>250</sup> Currently there is no rapid diagnostic assay, and reverse-transcriptase polymerase chain reaction is the most widely used method in confirming the diagnosis.<sup>251,252</sup>

*Metapneumovirus* is thought to account for about 6% to 10% of respiratory tract infections in which a common respiratory virus, such as respiratory syncytial virus (RSV), or influenza or parainfluenza viruses, could not be detected.<sup>250,253</sup> In a study of 1505 children with respiratory infection, Bosis et al.<sup>254</sup> detected metapneumovirus in 42 children (2.8%), RSV in 143 (9.5%), and influenza viruses in 230 (15.3%). Of the 42 metapneumovirus-positive samples, one was also positive for RSV and six for influenza viruses, for a co-infection rate of 16.7%. In addition, the authors noted that metapneumovirus was identified only in patients with acute respiratory infection, whereas RSV and influenza viruses were also detected in patients with different clinical manifestations.<sup>254</sup> Symptoms associated with metapneumovirus include cough, dyspnea, wheeze, and hypoxia.

The viral infection appears to primarily affect airway epithelium with the epithelial cells undergoing degeneration and necrosis, eliciting a neutrophilic response and increased mucus production.<sup>255</sup> Bronchoalveolar lavage (BAL) may show the respiratory epithelial cell degeneration or necrosis along with ciliocytophthoria and round red cytoplasmic inclusions. Other features of the BAL include alveolar macrophages containing hemosiderin, abundant neutrophils, and prominent mucus.<sup>255</sup> The clinical and pathologic picture may be confused with that of severe acute respiratory syndrome–associated coronavirus (SARS-CoV) infection (see below and Chapter 11).<sup>256–258</sup>

### Severe Acute Respiratory Syndrome–Associated Coronavirus

Originating in Guangdong, southern China, at the end of 2002, severe acute respiratory syndrome spread to regions all over the world and affected well over 8000 people.<sup>259</sup> The causative virus, a novel coronavirus, was identified by a World Health Organization (WHO)-led network of laboratories.<sup>257,260</sup>

Zeng et al.<sup>261</sup> studied 33 children with this syndrome in the Guangzhou area of China. The infection affected boys and girls equally with an age range of 3 months to 13 years. Five (15%) of the cases had an evident history of being exposed to a SARS patient before the symptoms occurred. The clinical features included fever (100%), often higher than 39°C, and cough (91%), both productive and nonproductive. The white blood count was normal or low in 67% of the cases. The predominant cell was the lymphocyte. Chest radiographs showed rapidly changing patchy infiltrates, with both unilateral and bilateral involvement. Supportive treatment included isolation and antibiotics to prevent bacterial infection, and resulted in the recovery of all the children.<sup>261</sup>

The lung pathology, fortunately, is rarely seen in children because of their frequent recovery. However, in

adults who have died, diffuse alveolar damage is commonly seen, with other morphologic changes including bronchial epithelial denudation, loss of cilia, and squamous metaplasia.<sup>256</sup> Less frequent findings include giant-cell infiltrate, pronounced increase in macrophages in the alveoli and the interstitium of the lung, and hemophagocytosis. Electron microscopy revealed viral particles in the cytoplasm of epithelial cells corresponding to coronavirus (see also Chapter 11).<sup>256</sup>

### Human Immunodeficiency Virus

Acquired immunodeficiency syndrome (AIDS) is the eventual consequence in most individuals of a human immunodeficiency virus (HIV-1 or, infrequently, HIV-2) infection. Approximately 2% of all reported AIDS cases in the United States are diagnosed in individuals younger than 13 years old.<sup>262</sup> The overwhelming majority of pediatric cases (80% to 90%) throughout the world are recognized in children 2 years old or younger who had acquired HIV through vertical transmission from an infected mother.<sup>263</sup> In countries where appropriate treatment of the mother is available, the rate have fallen to as low as 2%.<sup>264–266</sup> Some infants are seemingly infected in utero, but other neonates may acquire the virus intra- or peripartum. Even though the virus is transmitted across the placenta in some or most cases, neither villitis nor other pathologic evidence of infection, including pneumonia, has been documented in the fetus or neonate.<sup>267</sup> The remaining HIV–AIDS cases in the pediatric age population are the results of an infected blood transfusion (uncommon in the United States) or sexual contact with a HIV-infected individual; these patients are more commonly older children or adolescents.

Pulmonary complications of HIV–AIDS are manifested in 70% or more of infected children, especially among infants.<sup>268–270</sup> Rather than opportunistic microorganisms, infants often have recurrent bacterial infections from *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *S. aureus*, or mucosal candidiasis.<sup>271</sup> Among the serious opportunistic infections, *P. jiroveci* pneumonia is one of the most common in children and has been reported in almost 40% of pediatric cases.<sup>272</sup> Organisms are often identified in a BAL or transbronchial biopsy.<sup>273</sup> A frothy alveolar exudate with abundant cysts is very often absent, and in its place is seen a pattern of diffuse alveolar injury and even granulomas of an epithelioid type without caseous necrosis.<sup>274</sup> Measles, herpes simplex, varicella, and RSV are known to cause severe, if not fatal, pneumonia in HIV-infected children, just as these viruses are responsible for pneumonitis in children with one of the primary immunodeficiency syndromes.<sup>275</sup>

## Perinatal and Neonatal Infection

The infections in the previous sections are typically acquired at some point during gestation, even during the first stage of delivery. This section is concerned principally with those infections that are acquired perinatally and are manifested in the first days or weeks of life. Most of these infections are ultimately traced to the mother, and occasionally to the father. Mothers can infect their children postnatally, but extramaternat sources (the nursery and its personnel, mechanical devices, and other family members) are important in the etiology of neonatal pneumonias. The incidence of pneumonia is particularly high in premature infants in the presence of chorioamnionitis.<sup>276</sup>

### Group B $\beta$ -Hemolytic Streptococcus

Two bacteria, group B  $\beta$ -hemolytic streptococcus (GBS) and *Escherichia coli*, are together responsible for the

majority of cases of neonatal sepsis, pneumonia, and meningitis.<sup>277</sup> The overall incidence of GBS disease is 2 to 3 cases per 1,000 live births; premature or low-weight-for-date infants have an even greater risk of infection.<sup>278</sup> There is a correlation between the degree of cervicovaginal colonization and the acquisition rate of GBS disease in the neonate.<sup>279</sup> Prolonged rupture of membranes and low birth weight enhance the risk for infection. Early-onset GBS disease in the first day of life is characterized by symptoms and signs of respiratory distress and radiographic changes resembling early BPD. The infection evolves very rapidly and terminates in death in 50% to 75% of cases unless quickly diagnosed and appropriately treated. When GBS disease has a delayed onset, the prognosis is more favorable.<sup>280</sup> A documented association of GBS disease is the delay in the clinical presentation of a right-sided diaphragmatic hernia.<sup>281,282</sup>

The pathologic findings of GBS in the lungs (Fig. 7.38) have been carefully delineated by Craig.<sup>283</sup> In the early stages, the lungs both grossly and microscopically are

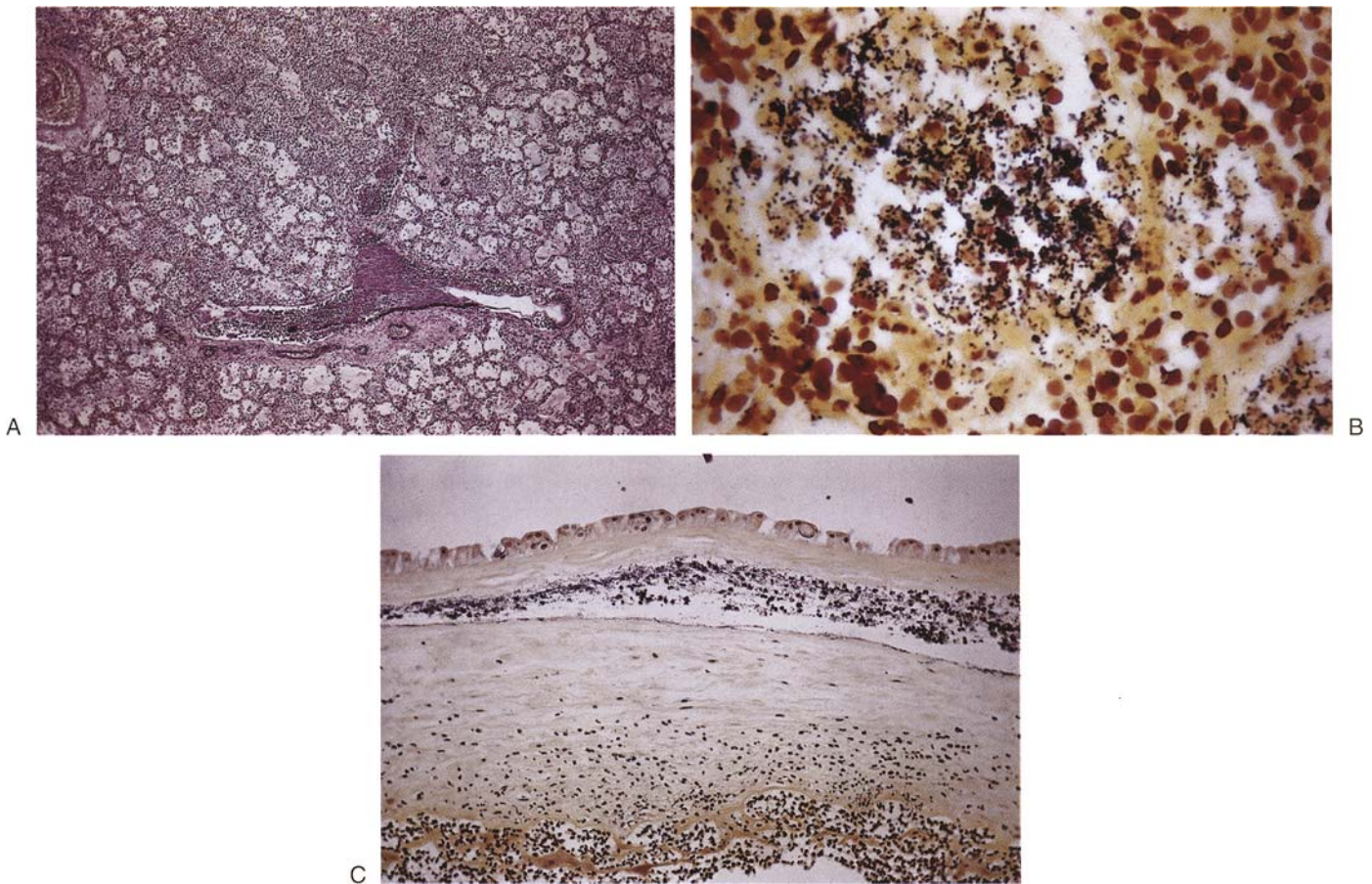


FIGURE 7.38. Congenital pneumonitis and chorioamnionitis. **A.** The bronchioles, alveolar ducts, alveolar saccules and alveoli are filled with neutrophils. **B.** A Gram stain of the alveolar contents displays clusters and chains of small cocci, typical

of group B  $\beta$ -hemolytic streptococcus. (Humberstone stain.) **C.** Similar cocci are present within the amnion and chorion of this infant's placental membranes. (Humberstone stain.)

similar to BPD with a hypoaerated appearance and widespread HMs in underexpanded air spaces. Diffuse alveolar and interstitial hemorrhage simulates massive pulmonary hemorrhage of the newborn. There is a minimal neutrophilic infiltrate in the first few hours of the infection; the Gram stain shows clumps of gram-positive cocci in the air spaces and within the HMs, and appropriate bacteriologic cultures establish the diagnosis. Antibiotic therapy may interfere with the results of culture and the demonstration of the bacteria. A focal or confluent neutrophilic exudate in the alveoli is present in the lungs of infants who survive 12 to 24 hours. Abscesses are usually not found.

### *Chlamydia trachomatis*

*Chlamydia* has long been known as the etiologic agent of neonatal inclusion conjunctivitis, but its role in genital tract infections in adults has been the subject of recent interest.<sup>284</sup> At the time of delivery, the cervix is infected by *Chlamydia* in approximately 10% of mothers.<sup>285,286</sup> Conjunctivitis is the most typical form of *Chlamydia* infection (20% to 25%); it is encountered in 1 to 4 infants per 1000 live births.<sup>287</sup> Pneumonitis occurs in 3% to 18% of cases and is preceded by conjunctivitis in a number of infants.<sup>288-290</sup> Approximately 30% to 40% of all infectious pneumonitides in the first 6 months of life are caused by *Chlamydia*. Most of these cases are clinically mild; however, 25% of infants have moderate-to-severe respiratory distress.<sup>291</sup> Bilateral interstitial or reticulonodular infiltrates and hyperexpanded segments are the radiographic findings. The overall prognosis is excellent.<sup>288</sup>

The diagnosis of *Chlamydia* is based on the results of tissue culture and the detection of the specific IgM antibody. Infected cells contain an intracytoplasmic inclusion on Giemsa-stained material from the eye or nasopharynx. Fortunately, there are very few opportunities to examine lung tissue from these patients. Various case reports report a necrotizing bronchiolitis and a mononuclear cell infiltrate (Fig. 7.39). An interstitial pneumonia without specific histologic features was seen by Beem and Saxon<sup>292</sup> in open lung biopsies from two infants. Too few cases of chlamydia pneumonitis have been described to allow any definite characterization (see also Chapter 12).<sup>293</sup>

### *Mycoplasma pneumoniae*

The presence of *Mycoplasma pneumoniae*, *Mycoplasma hominis*, and *Ureaplasma urealyticum* in the lower genital tract explains the occasional neonatal pneumonia caused by one of these organisms. *Mycoplasma pneumoniae* is generally uncommon in children less than 6 months old, but it occurs in 4 children per 1000 between the ages of 5 and 9 years and, in Japan over a period of 4 years it was

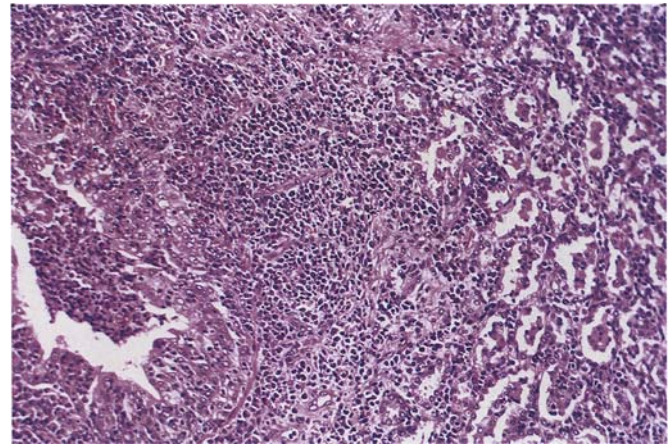


FIGURE 7.39. Chlamydial pneumonia. A diffuse inflammatory infiltrate is associated with necrotizing bronchiolitis (left) and a prominent lymphocytic response. (Courtesy of Fred Askin, Johns Hopkins Hospital, Baltimore, MD.)

noted in over 30% of children hospitalized with acute pneumonia.<sup>294-296</sup>

There are a few descriptions in the literature of the pathologic findings of *Mycoplasma pneumoniae*; most of these are in adults and a few prepubertal children. Luminal exudate in the bronchioles, peribronchiolar lymphoplasmacytic infiltrate, interstitial mononuclear infiltrate, and alveolar damage are characteristic features. Wang et al.,<sup>297</sup> however, reported five children who had a prolonged fever and severe respiratory distress, and had developed a necrotizing pneumonia. Kim et al.<sup>298</sup> also noted bronchiolitis obliterans in young patients with *Mycoplasma pneumoniae* pneumonia. The Swyer-James syndrome (unilateral hyperlucent lung) has also been described following an infection (see Chapter 25).<sup>299</sup>

### *Mycobacterium tuberculosis hominis*

Tuberculosis has always been prevalent in the less developed countries of the world, where it is endemic. In the United States, tuberculosis was until recently regarded as a disease under control; however, the status quo has been altered substantially, in part because of the growing number of new cases in HIV-infected individuals.<sup>300,301</sup> New cases of tuberculosis in children are most prevalent in those under 5 years of age<sup>302,303</sup>; most of these infections are airborne spread.

Infrequent examples of congenital tuberculosis have been documented and defined by active maternal disease and a primary complex in the liver of the infant.<sup>304</sup> Machin and associates<sup>305</sup> reported their experience with perinatally acquired tuberculosis and summarized the previous 13 cases in the literature. Infected secretions from mothers with pulmonary and genital tuberculosis are the source of the organisms.<sup>306</sup> Although there is a miliary pattern of

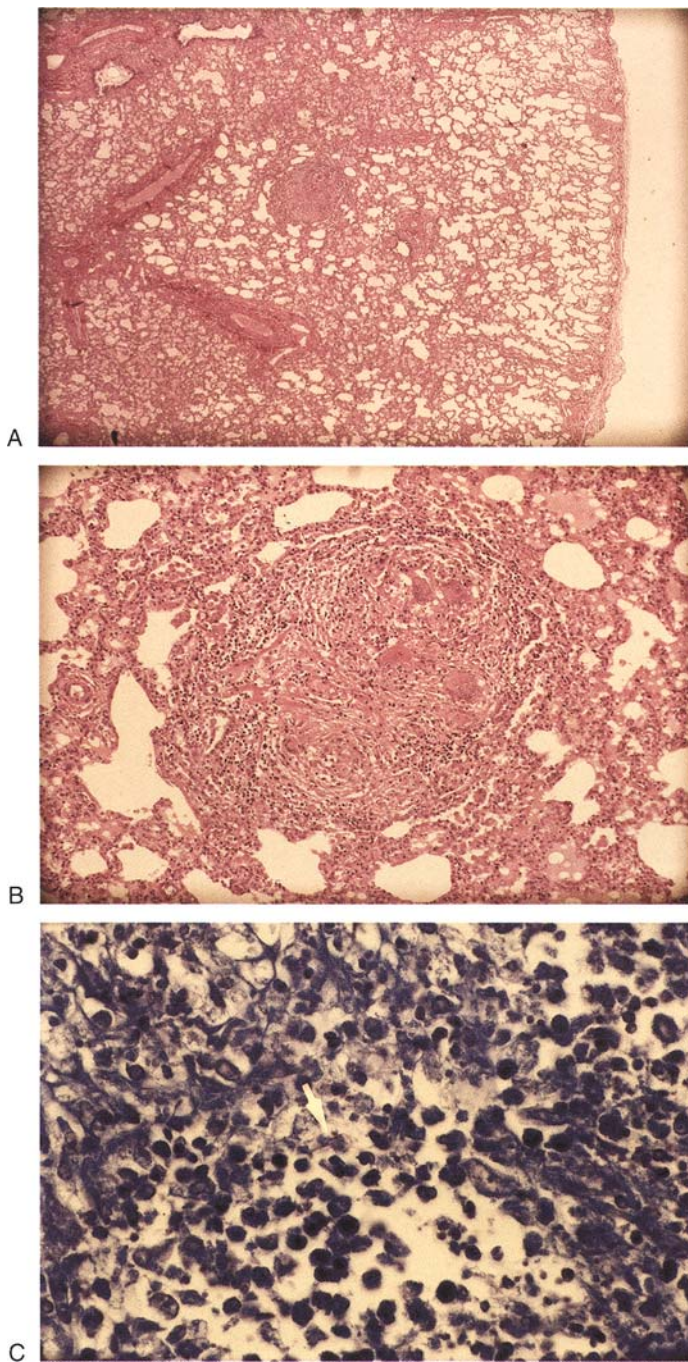


FIGURE 7.40. Pulmonary tuberculosis. **A.** Two small granulomata are noted (center) near the periphery of the lung of an 11-month-old infant male. **B.** The center of the granulomas is focally necrotic and surrounded by epithelioid cells, lymphocytes, and scattered giant cells. **C.** A Ziehl-Neelsen stain identifies a tubercular bacillus (arrow).

dissemination to the various organs including the lungs, caseous granulomas are uncommon (Fig. 7.40). Collections of histiocytes are present in the terminal air spaces in a distribution like bronchopneumonia, but there is an absence of neutrophils, lymphocytes, and plasma cells.

## Candida albicans

Candidiasis is the most common fungal infection of the neonatal period. Most of these infants have a localized infection in the oral cavity known as thrush. Approximately 4% of neonates develop thrush, which is probably acquired from organisms in the maternal cervicovaginal secretions.<sup>307</sup> In the past several years, candidiasis in premature infants has emerged as an important complication in neonatal intensive care units. These infants are extremely vulnerable to infections, and the parenteral route from intravascular catheters is well established both clinically and pathologically. Low birth weight infants, however, are at a much higher risk of developing pulmonary candidiasis, with Frezza et al.<sup>308</sup> noting an incidence of 8.6% in 233 infants with a birth weight under 1250g. There are a few examples of intrauterine infections from organisms in the vagina gaining access to the amniotic cavity and producing chorioamnionitis.<sup>309</sup> These infants have the expected early onset of respiratory distress, usually related to BPD. Symptoms and signs of sepsis ensue, and the radiographic findings are the combination of progressive bronchopulmonary dysplasia and focal or patchy parenchymal consolidation.<sup>310</sup> The latter may evolve into diffuse consolidation (Fig. 7.41). Aggressive antibiotic therapy and other supportive measures are imperative to avoid the inevitable outcome.

The gross and microscopic changes in the lungs may vary by virtue of the mode of candidal spread via the bronchopulmonary, vascular emboli, or systemically disseminated routes. Among the 14 autopsy cases that Kassner et al.<sup>310</sup> examined, 50% of the infants had embolization of an infected thrombus from a major vein or right-sided heart valve to the lungs with one or several peripheral hemorrhagic infarcts.<sup>311,312</sup> The lungs were diffusely consolidated and hemorrhagic in those cases of systemic candidiasis. Nodularity on palpation of the gross specimen may suggest the presence of abscesses or secondary bronchopneumonia. A shaggy, fibrinopurulent exudate alternating with denuded tracheobronchial mucosa in association with parenchymal consolidation was present in those cases of direct extension from the oropharynx.

Yeasts and pseudohyphae are easily identified in the mucosal exudate, but the invasive organisms may be obscured by the hemorrhage and necrosis. Occluded pulmonary vessels in the region of an infarct are often highlighted by a dense tangle of pseudohyphae invading the vessel wall in a similar manner as does *Aspergillus* or *Mucor*. Microabscesses with a minimal exudative component and rarely a granulomatous reaction are the features of capillary invasive candidiasis. An occasional case has more than one pattern of pulmonary involvement by *Candida*, or several simultaneous processes may be present as well, including BPD and secondary bacterial

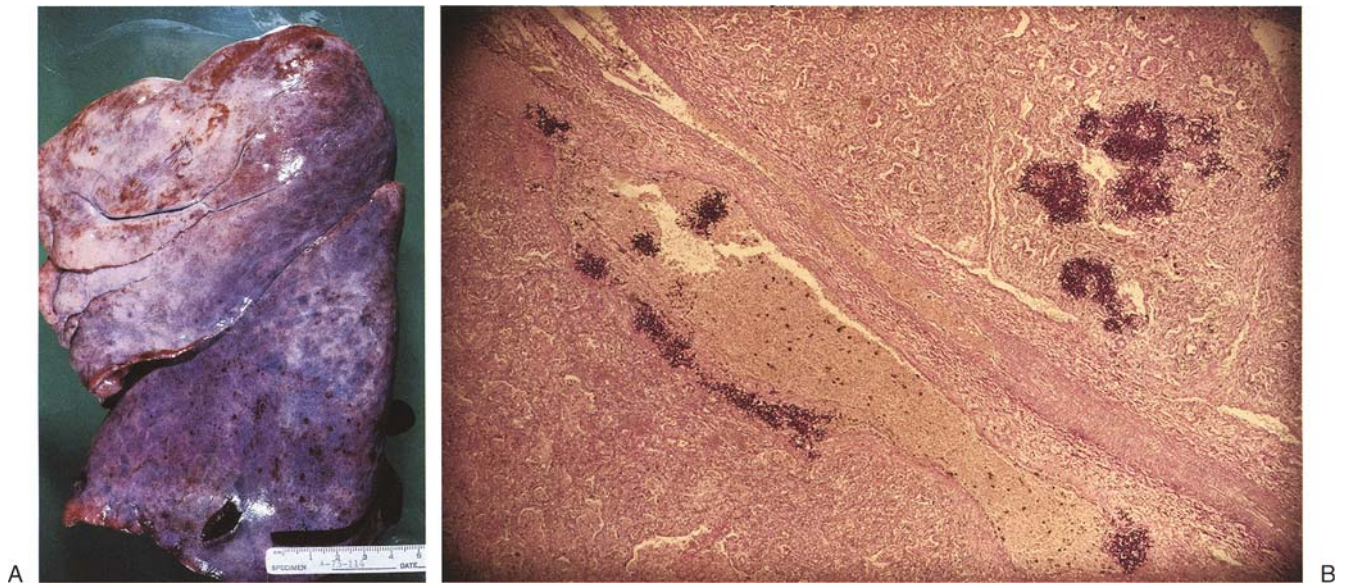


FIGURE 7.41. Candidal pneumonia. **A.** This 2-month-old boy died of overwhelming candidal sepsis. The lungs are consolidated with focal areas of necrosis. **B.** The clumps of fungal hyphae stain readily with periodic acid-Schiff stain.

pneumonia. Separation of the various pathologic findings in the lung is a difficult and complicated problem that is best approached with a thorough knowledge of the clinical events (see also Chapter 10).

### Other Fungal Infections

Fungal infections other than candidiasis in the neonatal-early infancy period are extremely rare.<sup>313</sup> Pulmonary cryptococcosis is highly unusual in children unless they are immunosuppressed or have AIDS.<sup>314</sup> Four cases of coccidioidomycosis in infants younger than 3 months old were reported by Child and associates.<sup>315</sup> Their review identified 17 cases, inclusive of their four cases of neonatal coccidioidomycosis. Occasional examples of histoplasmosis, aspergillosis, and phycomyces can be found in the literature.

### *Pneumocystis jiroveci*

Today, *Pneumocystis jiroveci* pneumonia is generally an opportunistic infection in children with primary or secondary immunodeficiency states. However, the earliest reports of this infection were nursery epidemics in poorly nourished, low-birth-weight infants who developed plasma cell pneumonia. Very few epidemics of nursery pneumocystosis are reported in the developed countries of the world.<sup>272</sup> HIV-infected children are the source of most cases of pulmonary pneumocystosis and may account for 40% or more of the deaths in patients under 1 year of age.<sup>272</sup> Those infants and young children who are HIV infected and present with *P. jiroveci* pneumonia have a

shorter period of survival when compared to HIV-infected children with some other initial clinical presentation.<sup>172</sup> Severe respiratory distress, tachypnea, apneic episodes, and small reticulonodular infiltrates on chest radiographs are the clinical manifestations.<sup>316</sup> The organism is acquired from environmental exposure early in life; approximately one third of children have antibodies to *Pneumocystis* by 1 year of age and 75% by 4 years of age.

The interstitium of the lung is heavily infiltrated by mature plasma cells in classic infantile pneumocystosis (Fig. 7.42). A flocculent, intraalveolar exudate containing the encysted organisms and a nonspecific, variably dense interstitial inflammatory infiltrate are the microscopic features usually associated with *Pneumocystis* pneumonia. However, a number of other tissue reactions accompany the infection, including poorly formed granulomas, diffuse alveolar damage, and dystrophic calcification. Touch imprints from a positive lung biopsy or material from a bronchoalveolar and tracheal aspiration stained with methenamine silver demonstrate the 1- to 2- $\mu$ m round to crescent-shaped organisms in clustered or individual cysts (see Chapter 13).<sup>317</sup>

### Respiratory Syncytial Virus

The respiratory syncytial virus, a RNA virus, is the single most important lower respiratory tract pathogen in childhood; it is responsible for the largest number of hospitalizations in the first year of life, and it results in 3000 to 4000 deaths in the United States each year.<sup>318</sup> The peak incidence of lower respiratory tract infections in children occurs in the first year of life, and by 2 to 3 years of age



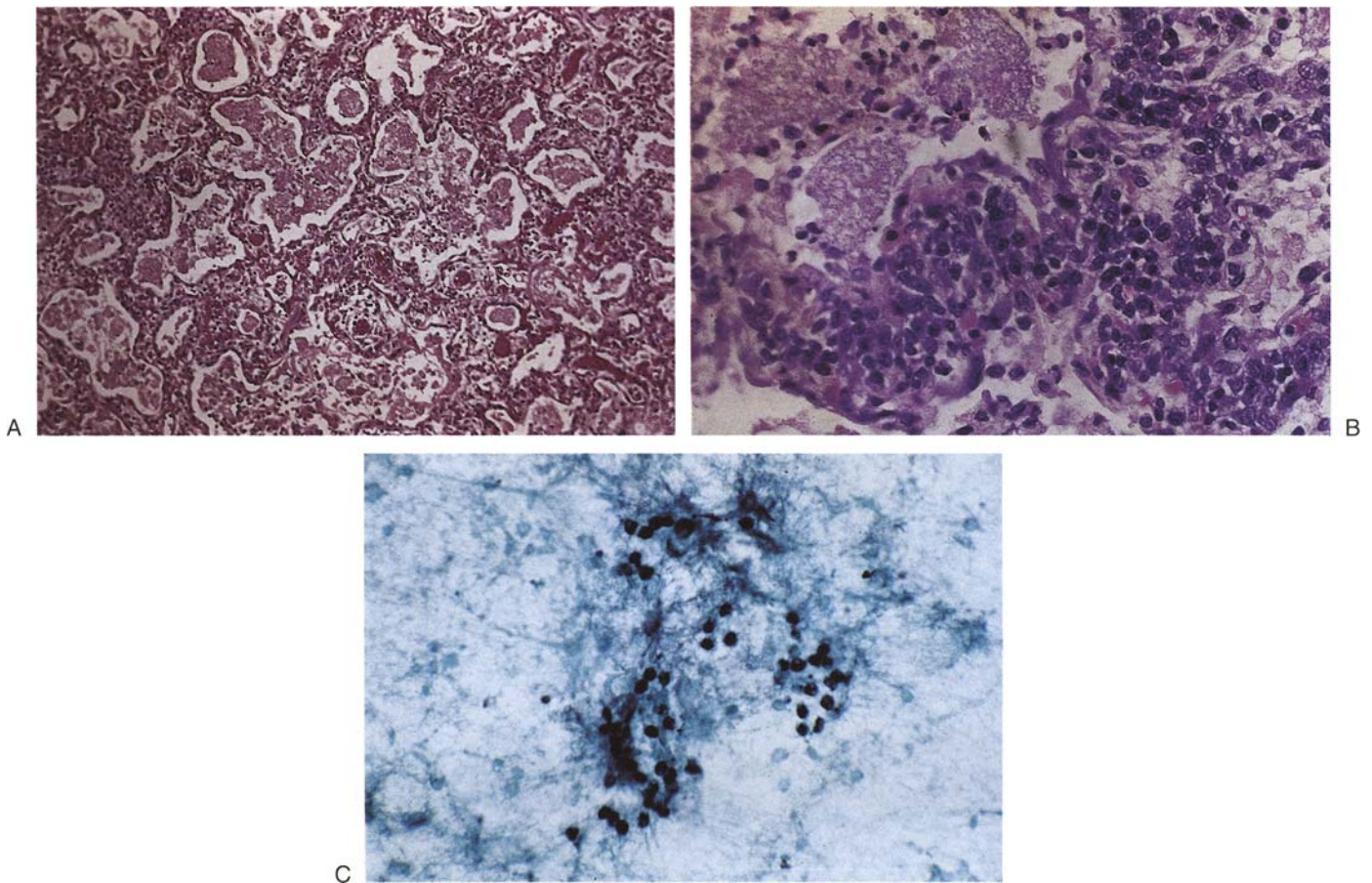


FIGURE 7.42. *Pneumocystis jiroveci* pneumonia in a malnourished child. **A.** The alveoli of this grossly firm lung are filled with a finely granular material and occasional nuclei. **B.** The alveolar material (upper left) is composed of amorphous pink material.

Note the many plasma cells in the alveolar septa, a feature not typically seen in immunocompromised children with *P. jiroveci* pneumonia. **C.** A silver stain demonstrates the saucer-shaped organisms. (Gomori methenamine silver.)

virtually 100% of children have been infected.<sup>318</sup> The spectrum of pulmonary clinical manifestations ranges from mild upper tract illness, which progresses to apnea in premature infants, pneumonia, and bronchiolitis. The pediatric population at risk for increased mortality and morbidity during RSV infection includes premature infants, infants with cyanotic congenital heart disease, HIV-infected subjects, and patients on intensive immunosuppressive therapy especially after bone marrow transplant.<sup>319,320</sup> The symptomatology of classic RSV-associated bronchiolitis is coughing and wheezing, except in infants under 4 weeks of age, who are more likely to have an atypical pneumonia.<sup>321</sup> Co-infection with other viruses, particularly metapneumovirus, has been documented and apparently increases the severity of the bronchiolitis and the need for hospitalization.<sup>322-325</sup> For older children with underlying chronic disease or an HIV-infected child, the prognosis is poorer than for the immunologically intact child.<sup>326</sup>

The pathologic anatomy of RSV is discussed at length in Chapter 11. Papillary hyperplasia of bronchiolar epi-

thelium and distal mucous plugging are the principal microscopic features (Fig. 7.43).

### Papillomavirus

Human papillomavirus is the general designation for a family of related DNA viruses with a number of distinct serotypes having a tropism for keratinizing epithelium. One subtype of human papillomavirus, type 6, is the etiologic agent for condyloma acuminatum and juvenile laryngeal papillomatosis.<sup>327</sup> Fewer than 0.1% of infants develop laryngeal papillomatosis, but in those with lesions, 50% or more of their mothers have documented genital tract involvement. There is a predilection for first-born infants. The initial lesions are found on the true vocal cords. The natural history is characterized by multiple local recurrences and even spread beyond the larynx into the hypopharynx, trachea, and even the lung (Fig. 7.44).<sup>328</sup> There are rare examples of spontaneous or induced malignant transformation.<sup>329-331</sup>

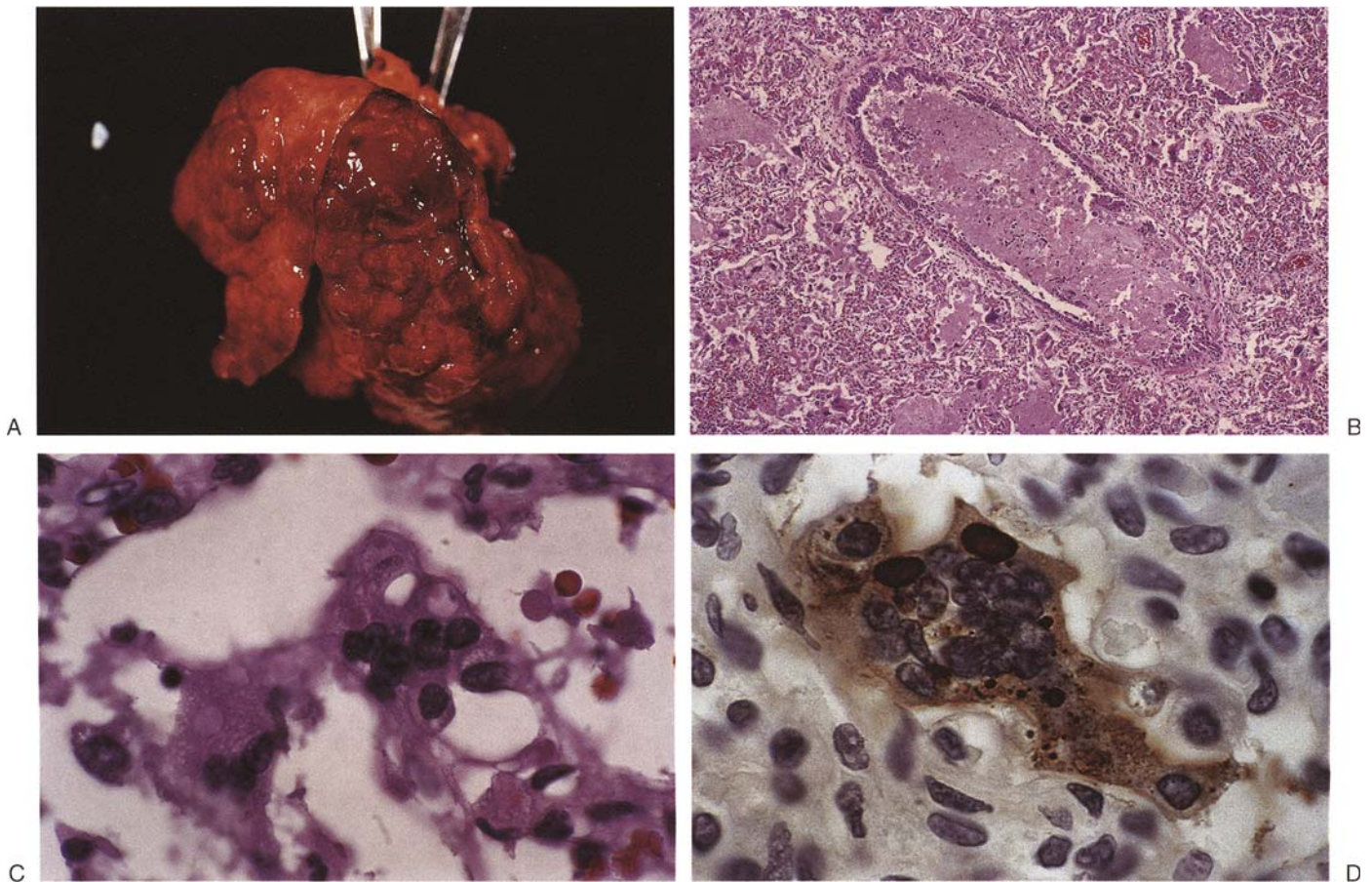


FIGURE 7.43. Respiratory syncytial virus bronchiolitis and pneumonia. **A.** The lung is alternately atelectatic and hyperexpanded due to the occlusion of scattered bronchioles. **B.** A bronchiole is filled with amorphous debris, which extends into alveolar ducts. Note the giant cells in adjacent alveoli. **C.** The giant cells are fused epithelial cells and contain both multiple nuclei and

a granular pink cytoplasm with focal round smooth areas about the size of a red blood cell and usually located near nuclei. **D.** Immunoperoxidase stain for respiratory syncytial virus (RSV) demonstrates the positivity of the cytoplasmic inclusions noted in **C** as well as many other smaller RSV positive granules.

Pulmonary involvement by papillomatosis is the consequence of fragmentation or contiguous extension into the tracheobronchial tree (Fig. 7.44).<sup>329</sup> The proliferation of squamous epithelium retains its papillomatous configuration in the bronchus. Hyperplastic squamous epithelium with surface koilocytosis with accompanying cytologic atypia is the characteristic microscopic appearance. In some cases, the cellular atypia is sufficiently disturbing as to suggest carcinoma in situ. It is best to reserve the diagnosis of carcinoma for those cases with an unequivocal invasion.

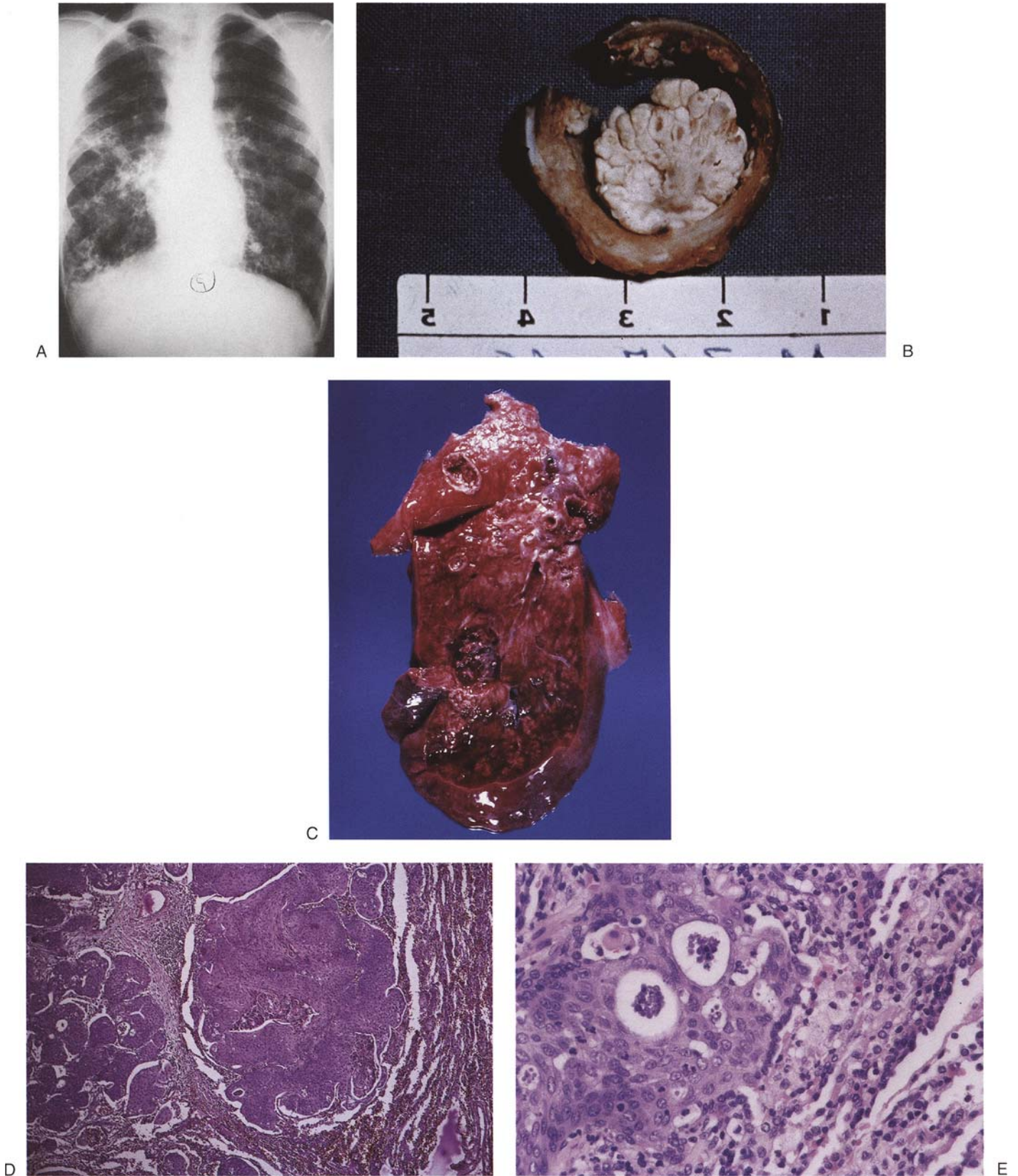
### Other Viral Infections

Many different types of major and minor viruses have been reported as etiologic agents of pneumonia in the neonatal period. Adenovirus (Fig. 7.45) has been implicated in the development of bronchiolitis obliterans,<sup>332</sup>

and adenovirus type 7h was reported in 29 children (83% under 1 year of age) with pneumonia and bronchiolitis (see Chapter 11).<sup>333</sup> The enteroviruses, echovirus and Coxsackie, are responsible for isolated cases of pneumonia in the newborn period.

### Other Bacterial Infections

Virtually all the gram-negative enteric bacilli, particularly *E. coli*, are causes of perinatal pneumonia.<sup>334,335</sup> *Streptococcus pneumoniae* sepsis is a rare infection of the neonatal period<sup>336</sup>; Bergqvist and Trovik<sup>337</sup> reported three cases that simulated GBS infection. Nursery epidemics of *S. aureus* are manifested as necrotizing bronchopneumonia. *H. influenzae* type B is one of the important causes of meningitis in infancy, but it is also the etiologic agent for a segmental pneumonia in children between 3 and 12 months of age.<sup>338</sup> The pathologic appearance is one of



**FIGURE 7.44.** Laryngeal papillomatosis with dissemination to lung. **A.** Chest x-ray of this 14-year-old boy displays hilar enlargement and multiple indistinct infiltrates in the lower portion of both right and left lungs. **B.** At autopsy, the larynx is partially occluded by a papillary growth arising from the mucosa. **C.** The gross lung contains multiple cyst-like areas filled with soft red-tan tissue. **D.** Sections of the lung lesions in **C** display

clusters of squamous epithelium growing along alveolar septa (left) and, as a solid mass (center), pushing aside the parenchyma. **E.** The metaplastic squamous epithelium that has fragmented from the laryngeal papillomatosis and lodged in the lung grows along alveolar septa and is dysplastic with hyperchromatic nuclei and prominent mitoses.

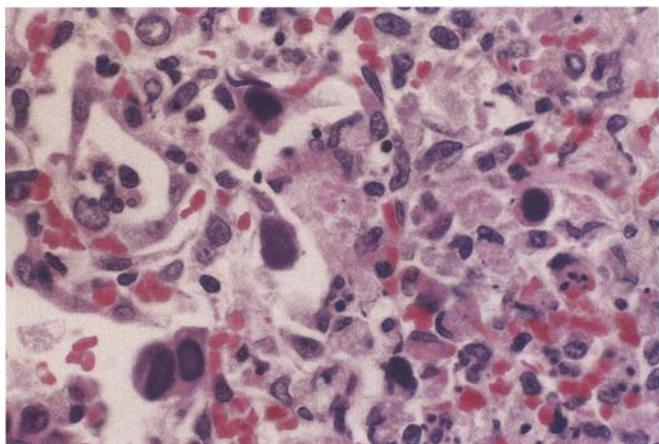


FIGURE 7.45. Adenovirus pneumonia. Alveolar epithelial cells are enlarged with nuclei distended by "smudged" inclusions.

necrotizing pneumonia. *Legionella pneumophila* has been isolated in rare cases of sepsis and pneumonia in immunocompromised infants.<sup>339</sup>

### Postinfarction and Down Syndrome–Associated Peripheral Cysts

The development of small subpleural cysts of the lung has been described in patients with Down syndrome and others with pulmonary artery thrombosis.<sup>340–344</sup>

Gonzalez and colleagues<sup>345</sup> analyzed autopsies of 98 patients with Down syndrome and found small subpleural cysts in 19 patients. They suggested that the cysts result from reduced postnatal production of peripheral small air passages and alveoli, reflecting the slow rate of cell proliferation seen in Down syndrome. Stocker and colleagues<sup>341,346</sup> believe that the peripheral cysts develop through liquefaction necrosis of the lung secondary to hypoperfusion of that area, as the result of either pulmonary artery occlusion or possibly altered blood flow associated with a cardiovascular anomaly (Figs. 7.46 and 7.47).

Preservation of the central portion of the lung is accomplished through an intact bronchial artery circulation supplying both the bronchial tree and adjacent pulmonary parenchyma through direct bronchopulmonary arteries and anastomoses between pulmonary arteries and bronchial arteries (Table 7.4; also see Fig. 6.6 in Chapter 6). The walls of the cysts represent preserved interlobular septa, which also receive their blood supply through the bronchial artery circulation. The cysts are 0.1 to 0.6 cm in diameter after reabsorption of the necrotic debris, and are most prominent in the upper lobes, suggesting a possible relationship to the cysts of idiopathic spontaneous pneumothorax noted in other patients.<sup>346</sup> The air-filled cysts of older infants as well as adults with idiopathic spontaneous pneumothorax, are lined by low cuboidal to attenuated epithelial cells overlying a vascular connective tissue wall.

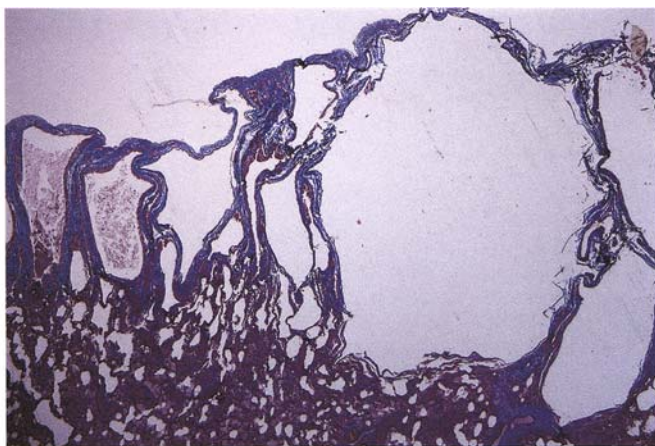


FIGURE 7.46. Peripheral pulmonary cysts. **A.** Smooth-walled subpleural air-filled cysts are delimited by residual interlobular septa following reabsorption of infarcted parenchyma. This 2-year-old child died suddenly of nonpulmonary causes. **B.** The

cyst walls are formed by the pleura (top) and interlobular septa. Normal lung parenchyma is present below the cysts. (Masson trichrome.)

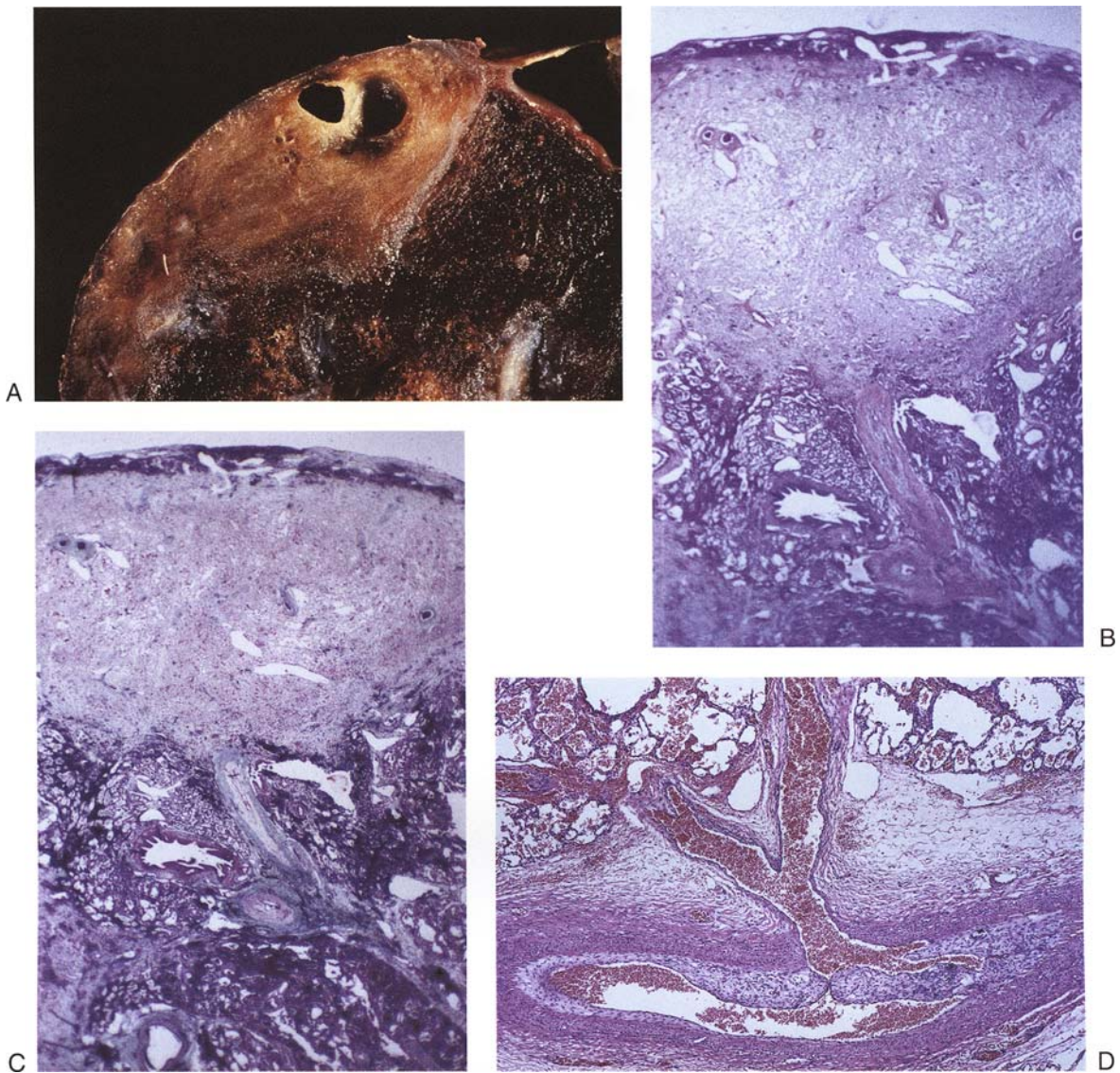
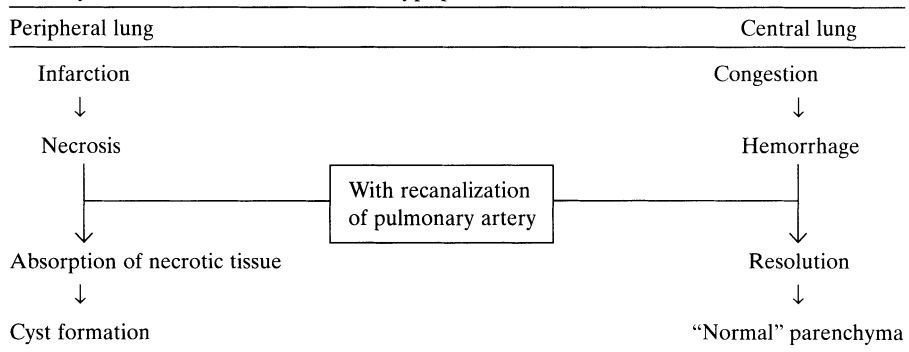


FIGURE 7.47. Postinfarction peripheral cysts. **A.** A lobe removed from a 1-month-old infant displays a subpleural collection of necrotic and partially liquefied material. **B.** Only amorphous debris (top) remains of the peripheral acini after infarction of the periphery of the lung. **C.** In this connective tissue stain note

intact pleura at the top of the field, and residual arterioles in the necrotic debris below the pleura. (Movat pentachrome.) **D.** Near the hilum of the lobe in **B** and **C**, a pulmonary artery branch (bottom) displays fragments of an organizing thrombus.

TABLE 7.4. Sequence of events in development of subpleural cysts secondary to pulmonary arterial occlusion or severe hypoperfusion<sup>a</sup>



<sup>a</sup>Pulmonary arterial occlusion or severe hypoperfusion with intact bronchial arteries, bronchopulmonary arteries, and bronchopulmonary arterial anastomosis.  
 Source: Modified from Stocker et al.,<sup>346</sup> with permission from John Wiley & Sons.)

## Intralobar Sequestration

An intralobar sequestration is a segment of pulmonary parenchyma invested along with the normal right or left lung by visceral pleura and supplied by a systemic artery (Fig. 7.48). The segment is usually isolated from the tracheobronchial tree but may be partially air containing.<sup>347</sup>

Intralobar sequestration is seen slightly more frequently in males than females (1.1:1). Symptoms of cough, sputum production, and recurrent pneumonia are noted in 85% of patients, approximately 25% of whom present before the age of 10.<sup>348-350</sup> Intralobar sequestration, however, is rarely seen in infants. In a review by the first author (J.T.S.) of 42,000 autopsies of infants less than 2 months of age, not a single case of intralobar sequestration was noted, while 12 cases of extralobar sequestration were seen.<sup>351</sup> Intralobar sequestration has been described in only about 20 infants under 5 years of age.<sup>352-354</sup>

Radiographic findings are variable. Cystic areas, some with fluid levels, are present in homogeneous or inhomogeneous shadows.<sup>350</sup> Bronchography displays the lack of connection to the bronchial system in about 85% of cases, with the remaining cases displaying some communication between the bronchial tree and the sequestration. Nuclear lung scan may show collateral ventilation of an intralobar

sequestration when direct communication cannot be demonstrated.<sup>355</sup> Arteriography demonstrates the single (84%) or multiple (16%) systemic arteries supplying the sequestration, the basis on which the diagnosis of intralobar sequestration is made.<sup>356,357</sup>

Arterial supply is via the thoracic aorta in 74% of cases, the abdominal aorta or celiac axis in 20%, and the intercostal arteries in 4% (Fig. 7.49).<sup>348,358,359</sup> Supply via the subclavian, internal thoracic, innominate, coronary, and pericardiophrenic arteries may rarely be noted.<sup>360-362</sup> An unusual intralobar sequestration was described by Eustace et al.<sup>363</sup> in a 29-year-old man with an endobronchial carcinoid tumor occluding the bronchus to the left lower lobe. The sequestered lobe shared the parasitized systemic vessels supplying the tumor.

Venous return in intralobar sequestration is via the normal pulmonary veins in more than 95% of cases<sup>356</sup>; the remaining cases drain partially or completely into the hemiazygos, azygos, or intercostal veins, or the inferior or superior vena cava.<sup>348</sup> Walford et al.<sup>364</sup> described the presence of abnormal systemic arteries supplying the lower lobe of the lung in four fetuses examined with in utero ultrasound and, following elective termination of the pregnancy, in the anatomic specimen. The systemic artery of three of the fetuses arose from the thoracic aorta and the fourth from the celiac axis. Two additional cases from this hospital went to term, were delivered and were asymptomatic, although the persistence of the abnormal



FIGURE 7.48. Intralobar pulmonary sequestration. **A:** A composite drawing of an intralobar sequestration of the right lower lobe with cysts with air-fluid levels apparent on x-ray and in the gross specimen. Note the systemic artery arising from the aorta and supplying the sequestered portion of the lung.

**B:** The pulmonary ligament artery (arrow) arising from the aorta (A) is more readily visible in this drawing. (**A:** Copyright James A. Cooper, MD; **B:** From Frazier et al.,<sup>350</sup> with permission.)

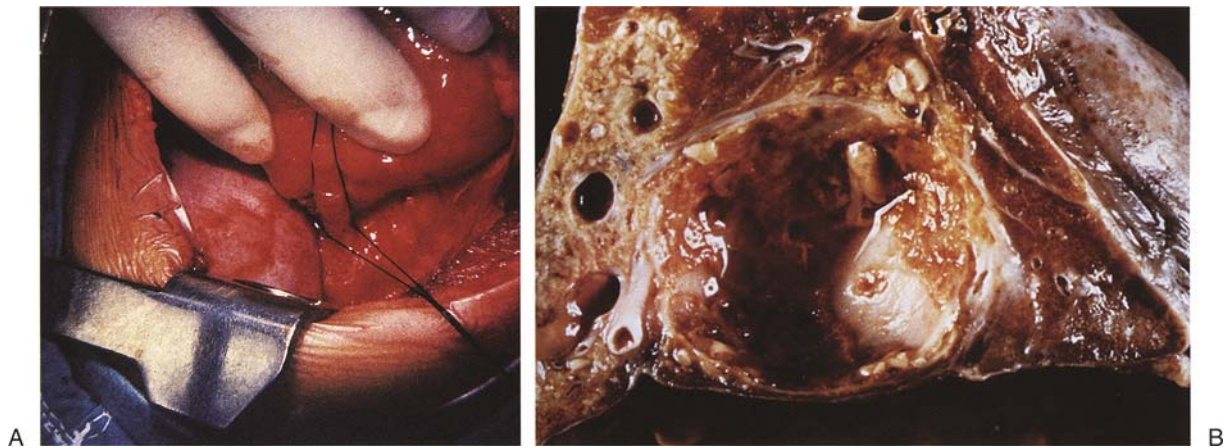


FIGURE 7.49. Intralobar pulmonary sequestration. **A.** At surgery the pulmonary ligament artery is identified and isolated. **B.** Cut section of a resected lower lobe reveals a densely fibrotic and multicystic mass.

artery was confirmed by computed tomography (CT).<sup>352</sup> None of these six cases involved a sequestered portion of the lung (i.e., a section of lung within the normal pleural investment of the lung but anatomically separated from lung) and they represent vascular abnormalities. Similar vascular abnormalities have been noted by other investigators,<sup>365</sup> and all of these involved a normal pulmonary venous return from the involved segment of lung.<sup>366</sup>

Intralobar sequestrations are located on the left side in 55% of cases and on the right in 45%. Bilateral involvement has rarely been reported. The lower lobes are involved in 98% of cases with the posterobasal segment affected in 81%. Upper-lobe involvement has been reported in only eight cases.<sup>347</sup> Associated anomalies are present in approximately 12% of patients with intralobar sequestration (see below).

Grossly the sequestered segment of lung displays a thickened pleura with adhesions between mediastinal structures, the diaphragm, and/or parietal pleura. Cut section reveals a consolidated parenchyma that frequently contains a single or multiple cysts varying in size from a few millimeters to 5 cm or longer in diameter and filled with thin to viscid yellow-white fluid or gelatinous material (Fig. 7.49).

Microscopically, chronic inflammation and fibrosis replace the normal pulmonary parenchyma (Fig. 7.50). The cysts noted grossly are lined by cuboidal, columnar, or, rarely, squamous epithelium and are filled with amorphous eosinophilic debris or foamy macrophages. Remnants of bronchi and bronchioles are surrounded by fibrous connective tissue infiltrated by lymphocytes, plasma cells, and macrophages. Lymphoid aggregates, some with germinal centers, may be present.

Remnants of alveolar ducts and alveoli are present as cuboidal epithelial-lined structures amid loose-to-dense

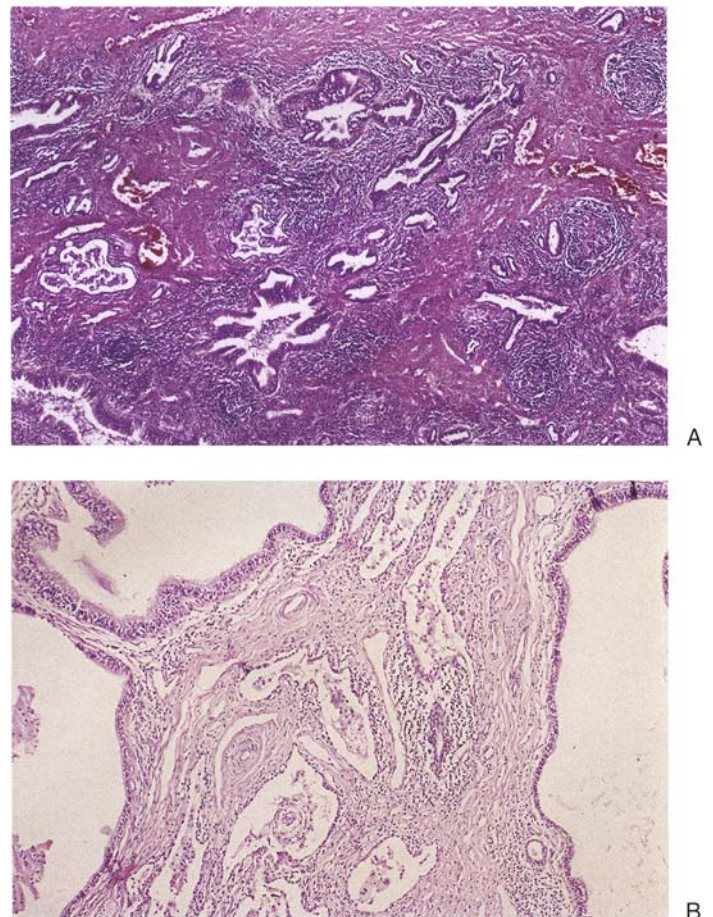


FIGURE 7.50. Intralobar pulmonary sequestration. **A.** Pulmonary parenchyma is distorted and largely replaced by dense fibrosis and chronic inflammation. Scattered bronchial-like structures lined by cuboidal-to-columnar epithelium are present. **B.** Irregular bronchiole-like structures are separated by fibrous connective tissue and alveolar-like structures that are heavily infiltrated by chronic inflammatory cells.

TABLE 7.5. Theories of origin of intralobar sequestration

Traction by anomalous branch of aorta on segment of developing lung results in separation from normal lung	Pryce, 1946 <sup>384</sup>
Persistence of thoracic aortic arteries secondary to insufficient pulmonary arterial supply; systemic blood pressure causes cystic degeneration of the lung	Smith, 1956 <sup>385</sup>
No causal relationship between nonfunctioning lung and systemic artery	Boyden, 1958 <sup>386</sup>
Acquired disease secondary to localized infectious process	Gebauer and Mason, 1959 <sup>368</sup>
Failure of normal embryonic organizer control	Blesovsky, 1967 <sup>387</sup>
Accessory lung bud develops in embryo and either becomes incorporated into normally developing lung (intralobar) or remains separate (extralobar); suggested term <i>congenital bronchopulmonary foregut malformation</i>	Gerle et al. 1968 <sup>388</sup>
Intralobar sequestration is collection of bronchogenic cysts associated with a systemic artery	Moscarella and Wylie, 1968 <sup>389</sup>
Acquired disease utilizing normally occurring pulmonary ligament arteries	Stocker and Malczak, 1984 <sup>369</sup>

Source: Modified from Stocker and Malczak,<sup>369</sup> with permission.

connective tissue infiltrated by inflammatory cells. Foamy macrophages again may fill these structures. Elastic and muscular arteries may be noted within the interstitium, and show varying degrees of medial hypertrophy, thrombosis, arteritis, and, in older patients, atherosclerosis. The edge of the lesion may be sharply separated from the normal parenchyma by connective tissue or may blend diffusely with it, occasionally encompassing areas of normal parenchyma. Foci of acute bronchopneumonia

may be present. Lymphatics are usually unremarkable. Two patients, a 36-year-old woman and a 69-year-old man, developed squamous cell carcinoma within an intralobar sequestration.<sup>367</sup>

Because of the presence of one or more systemic arteries to an intralobar sequestration, the lesion has long been considered to be a congenital malformation (Table 7.5). Gebauer and Mason<sup>368</sup> in 1959, however, suggested that intralobar sequestration resulted from a “destructive bronchial pulmonary disease.” In 1984, Stocker and Malczak<sup>369</sup> described the presence of normally occurring pulmonary ligament arteries in 90% of infants and children, and postulated that these arteries could be parasitized in the formation of an intralobar sequestration (Fig. 7.51). Under circumstances of bronchial obstruction and a chronic pneumonia with partial or complete interruption of the pulmonary artery supply to the infected portion, parasitization could occur through the development of a pleuritis and formation of a richly vascular granulation tissue deriving its blood supply from the hypertrophied pulmonary ligament arteries or, if the diaphragmatic surface of the lung is involved, the diaphragmatic vessels, that is, the phrenic arteries via the celiac axis (Fig. 7.52).

With progression and resolution of the pneumonia, accentuated by recurring bouts of pneumonia, one or more systemic arteries assume a substantial supply to the chronically infected segment of lung. The lack of systemic arteries other than the bronchial arteries available for parasitization by a chronic upper-lobe pneumonia accounts for the rare occurrence of intralobar sequestration in the upper lobes (less than 2% and likely overreported because of their rarity). Chronic pneumonia of the upper lobes, histologically similar to intralobar sequestration, is not, however, an unusual occurrence.

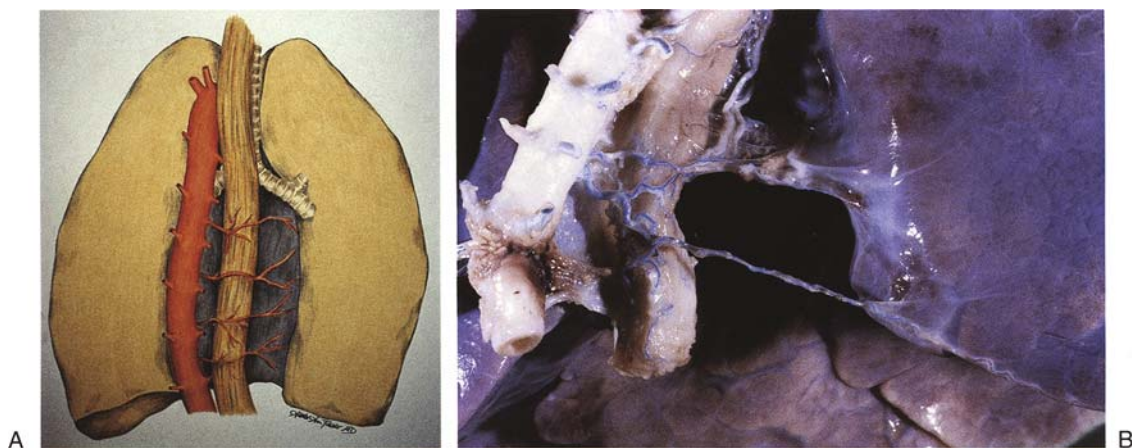


FIGURE 7.51. Pulmonary ligament arteries. **A.** Multiple pulmonary ligament arteries, most of which supply the esophagus, send small extensions to the pleura of the lower lobes. (From Stocker and Malczak,<sup>369</sup> with permission.) **B.** After injection

with blue latex, dissection through the pulmonary ligament artery to the right lower lobe reveals a very small artery rising from the aorta (left) supplying the esophagus and ramifying in the pleura.



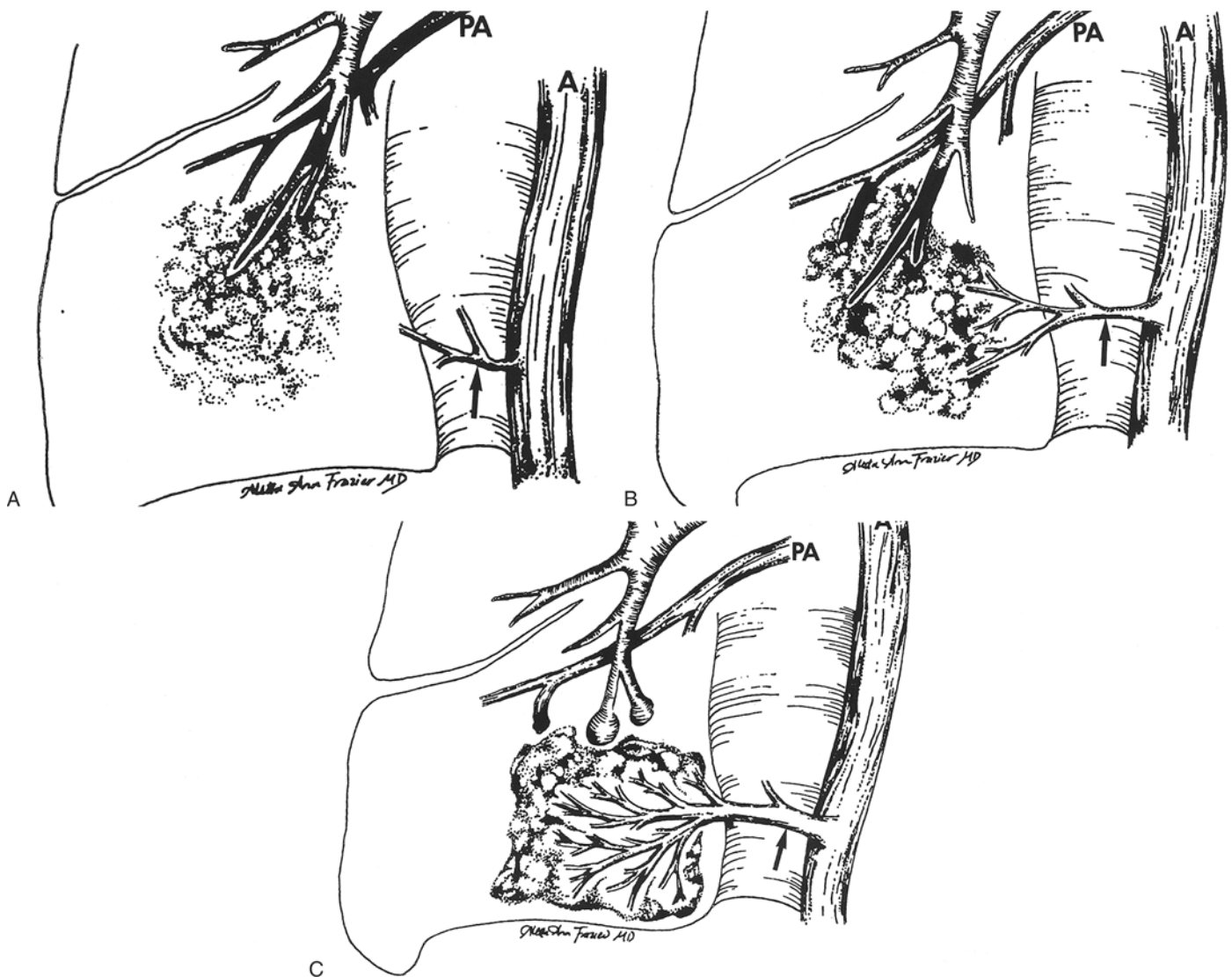


FIGURE 7.52. Sequence of events leading to formation of intralobar sequestration. **A.** Bronchial occlusion (by aspiration, inflammatory debris, etc.) leads to development of pneumonia distal to obstruction. Note small pulmonary ligament artery that is normally present. **B.** As pneumonia progresses, obstruction of pulmonary artery may occur, promoting hypertrophy of pulmo-

nary ligament artery as inflamed lung seeks oxygenated blood to aid in resolution of pneumonia. **C.** As pneumonia resolves, progresses, or recurs, involved segment of lung may derive its major arterial supply from single (or multiple) hypertrophied pulmonary ligament artery. (Modified from Stocker and Malczak,<sup>369</sup> with permission.)

Intralobar sequestration, as noted, is very unusual in infants, with the notable exception of bronchopulmonary foregut malformations and the rare case of pulmonary vascular malformation producing congestive heart failure, both clearly congenital lesions. This absence supports the theory of an acquired origin of this lesion. So also does the relative infrequency of associated anomalies (6% to 12%)<sup>347</sup> when compared with the anomalies seen in association with extralobar sequestration (49% to 67%), congenital pulmonary lymphangiectasis (85%), infantile lobar emphysema (42%), and congenital cystic adenomatoid malformation (26%).<sup>63</sup> In addition, the occurrence

of intralobar sequestration in older patients with no evidence of previous lung disease, and the presence in the lesion of an unusual infectious process such as the formation of a mycetoma, further suggests the acquired nature of the lesion.<sup>370-372</sup> Finally, the fact that intralobar sequestrations drain via the normal pulmonary veins in 95% of cases, and may be partially air containing, again suggests a fluctuating inflammatory process superimposed on a developmentally normal lung. It is possible, however, that some intralobar sequestrations develop in other preexisting malformations, such as congenital pulmonary airway malformation of a lower lobe, that become infected.<sup>373</sup>

## Lung Transplantation

Pediatric lung transplantation is relatively uncommon; it accounts for about 5.4% of all lung transplants (57 of 1053 in year 2001), with heart-lung transplantation being extremely rare in the United States.<sup>374,375</sup> Thus, much of what we have learned about the pathology of lung transplantation comes from the experience in adults gained over the last two decades (see also Chapter 23). The data accumulated from pediatric recipients indicates that the pathology of rejection is similar or identical to that in older patients. However, there are significant differences in primary diseases, size of the allograft, repeat hospitalization, recurrent disease, impact on growth and development, and mortality.<sup>376</sup>

Eighty-five percent of pediatric recipients are between 11 and 17 years of age, with the nadir between 2 and 7 years of age. Among the younger aged pediatric recipients, the first year of life is the most likely time for lung transplantation. In the infant age group, congenital heart disease was the most common indication for lung transplantation, but thereafter the most common indication is cystic fibrosis (67% of adolescents). Other indications include pulmonary hypertension, interstitial fibrosis, and bronchiolitis obliterans.<sup>375</sup>

The increasing scarcity of donor lungs, especially for pediatric recipients, has stimulated the development of downsizing techniques (split lung, lobar and peripheral segmental transplantation) of cadaveric lungs, which have proven to be reliable procedures providing equal results compared to standard lung transplantation.<sup>377</sup> In addition, living-donor lobar lung transplantation has also provided organs for patients considered too ill to await cadaveric transplantation, with at least comparable if not better survival.<sup>378,379</sup>

Transbronchial biopsies are an integral part of the posttransplant monitoring for rejection or infection, and adequate lung tissue for histologic diagnosis can be obtained safely and effectively from pediatric patients of all ages via flexible bronchoscopy.<sup>380</sup> The histology of both acute and chronic lung rejection is similar to that seen in adults, and the 1996 Working Formulation for the Classification of Pulmonary Allograft Rejection is used for grading (see Chapter 23).<sup>381</sup> Morbidity is common after pediatric lung transplantation, with these patients being at high risk for developing graft failure, adenoviral pneumonia and other infections, diabetes, hypertension, and bronchiolitis obliterans (BO). Bronchiolitis obliterans continues to be the leading cause of late morbidity and mortality, with only 45% of 5-year survivors being free of disease.<sup>375,382</sup> Because of the nature of indications for pediatric lung transplantation, recurrence of primary disease in the allograft is not an issue (in contrast to adults, e.g., sarcoidosis).

The outcome after pediatric lung transplantation has not improved significantly over the last 15 years, except for the trend toward increased survival in infants. Overall pediatric survival is 66% at 1 year, 57% at 2 years, 48% at 3 years, and 31% at 9 years.<sup>374,383</sup>

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