11
Pulmonary Disease in the Pediatric Age Group

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Pediatric lung pathology offers a unique opportunity to study a wide variety of pathologic phenomena taking place in an adapting, fast-growing, maturing host. These pathologic changes are modified by different therapeutic modalities, frequently making interpretation difficult. A list of pulmonary diseases that occur in the pediatric population is presented in Display 11-1.

HYALINE MEMBRANE DISEASE

After the important work of Lauweryns in 1970, hyaline membrane disease (HMD) has been regarded as the anatomic counterpart of the respiratory distress syndrome (RDS).[1] The pathologist is infrequently confronted with the pure or classic form of HMD; most cases feature a combination of HMD with related oxygen toxicity and reparative changes, such as bronchopulmonary dysplasia (BPD).[2]

Most cases of HMD are seen in premature newborns with signs of respiratory failure and a typical radiologic ground-glass appearance with air bronchogram and reticulonodular infiltrates; laboratory tests commonly reveal hypoxemia. There is a higher incidence in boys than girls and in Caucasian than non-Caucasian patients. However, in Wigglesworth's experience, about 25% of infant deaths with a clinical picture of RDS did not reveal HMD at autopsy.[3] HMD has also occurred in postmature infants.[4] There are cases in which pulmonary hyaline membranes are identified at autopsy in patients with pulmonary infections or without an antecedent clinical history of RDS.[5]

Morphologically, three stages are recognized.[2] In stage I, from 0 to 8 hours, the gross examination reveals moderate congestion, compact appearance, and minimal evidence of aeration, mainly in the anterior parts. Microscopically, the earliest lesion of HMD is necrosis of the respiratory epithelium in terminal and respiratory bronchioles, which occurs within a few minutes after birth. From the standpoint of forensic pathology, this change can constitute evidence of spontaneous or artificial attempts to expand the lungs.[5] However, Lumadue and Hutchins reported necrosis of the respiratory epithelium in 3.4% of 500 autopsied stillborn infants.[6] The histologic appearance of the necrotic material is that of a basophilic deposit, positive to the Feulgen reaction. Necrosis precedes the appearance of hyaline membranes, which are formed by cellular debris and transudation of proteins as a consequence of alveolar-capillary damage (Fig. 11-1).

In stage II, from 12 to 36 hours, the lungs are deeply congested with a rubberlike consistency resembling liver tissue (Color Fig. 11-1). Microscopically, hyaline membrane formation reaches its peak at this stage. The basophilic necrotic bronchiolar debris is no longer present; bronchioles are dilated, and necrosis extends to the alveolar epithelium. The septa are intensely congested and show prominent cellularity (Fig. 11-2). Electron microscopic studies have revealed a marked reduction in the number of lamellar bodies in type II pneumocytes.[3,6] Features proper to stage III may be seen from 24 to 48 hours, because no sharp temporal demarcation separates the three stages. At this stage begins a cellular reaction characterized by histiocytic infiltration of the hyaline membranes, expansion of atelectatic alveoli, and regeneration of type II pneumocytes, which exhibit numerous lamellar bodies. Bronchiolar epithelial regeneration is also observed.

Bilirubin staining accounts for the development of yellowish hyaline membranes (Color Fig. 11-2). This occurs in patients with associated hyperbilirubinemia when bilirubin leaks into the airways, as demonstrated by Cho and Sastre by means of the Hall stain and is more frequently encountered in infants surviving longer periods.[7]

A histologic picture similar to that of HMD is seen in cases of perinatal infection with β-hemolytic group B streptococci, which

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DISPLAY 11-1. PULMONARY DISEASE IN THE PEDIATRIC AGE GROUP

Hyaline membrane disease
Bronchopulmonary dysplasia
Bronchiectasis
Cystic fibrosis
Primary ciliary dyskinesia
Young syndrome
Idiopathic pulmonary hemosiderosis
Hereditary hemorrhagic telangiectasia

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produces hyaline membranes associated with an inflammatory reaction of variable intensity and with masses of streptococci in the hyaline membranes. This condition is probably related to ascending infection, because it usually follows a history of premature rupture of placental membranes.[3]

With the application of modern therapeutic technologies, the lesions of RDS are likely to undergo still further modifications. An example is the pulmonary pathology reported by Chou and colleagues that was associated with extracorporeal membrane oxygenation therapy, which is currently used for neonates with HMD and meconium aspiration syndrome.[8] These investigators described interstitial and intraalveolar hemorrhages, hyaline membrane formation, hyperplastic type II pneumocytes, squamous metaplasia, and mucinous metaplasia. The latter term refers to groups of ciliated mucous cells in peripheral pulmonary acini.

Most cases of HMD of the newborn are believed to result from ineffective surfactant activity, normally provided by the tensioactive secretions of type II pneumocytes and Clara cells in the alveoli and bronchioles.[9]

The fetal lung is filled with secretions of the respiratory epithelium admixed with amniotic fluid, which is introduced to the airways through breathing movements beginning at 12 weeks of gestational age. Infants born by cesarean section without a trial of labor are at an increased risk of HMD, possibly due to the absence of high glucocorticoid production and catecholamine

levels associated with the onset of labor. Such hormonal surges are believed to be central to the biosynthesis of surfactant.[9] In cesarean births, the conceptus lacks the physiologic compression of the thorax exerted by the uterine contractions of parturition, and the amount of intrapulmonary fluid is increased over that of vaginally delivered infants. An appropriate transition from this aqueous medium to a gaseous atmosphere implies a rapid absorption of this intrapulmonary fluid, which takes place most efficiently across the thin cytoplasm of type I pneumocytes before reaching the peribronchiolar lymphatic vessels. During the immediate postnatal period, adjustment to an air-breathing physiology depends on the ability to maintain the alveolar spaces open against a high surface tension. Avoidance of complete alveolar collapse is achieved by the special surface-tension–lowering product (i.e., surfactant) of type II pneumocytes and Clara cells. The grunting of a nonintubated surfactant-deficient infant is an attempt to prevent alveolar collapse by increasing the expiratory airway resistance through a semicomplete closure of the glottis.[5]

Pulmonary surfactant is a complex of phospholipids and proteins that forms a monomolecular film that spreads over the alveolar and terminal conducting epithelial lining and reduces the surface tension of the air-liquid interphase. Surfactant production starts at about 23 to 24 weeks of gestational age. It appears as large lipid inclusions (i.e., lamellar bodies) in pre-type II pneumocytes. The most abundant phospholipid found in surfactant is phosphatidylcholine, in the form of dipalmitoylphosphatidylcholine.

Proteins are also important participants in surfactant structure and represent approximately 10% of its total mass. Three of these proteins have been designated surfactant proteins A (SP-A), B (SP-B), and C (SP-C). SP-A is encoded by a gene located in chromosome 10, and SP-B and SP-C are encoded by unrelated genes located in chromosome 2.[9]

All these compounds can be found in amniotic fluid, and their levels may be used to determine the functional maturity of fetal lungs.[10] Monoclonal and polyclonal antibodies directed against surfactant proteins have been used in various studies of HMD.[11] Ultrastructurally, the maturation process of surfactant secretion has been described as starting in the rough endoplasmic reticulum of type II pneumocytes, whose products of synthesis are
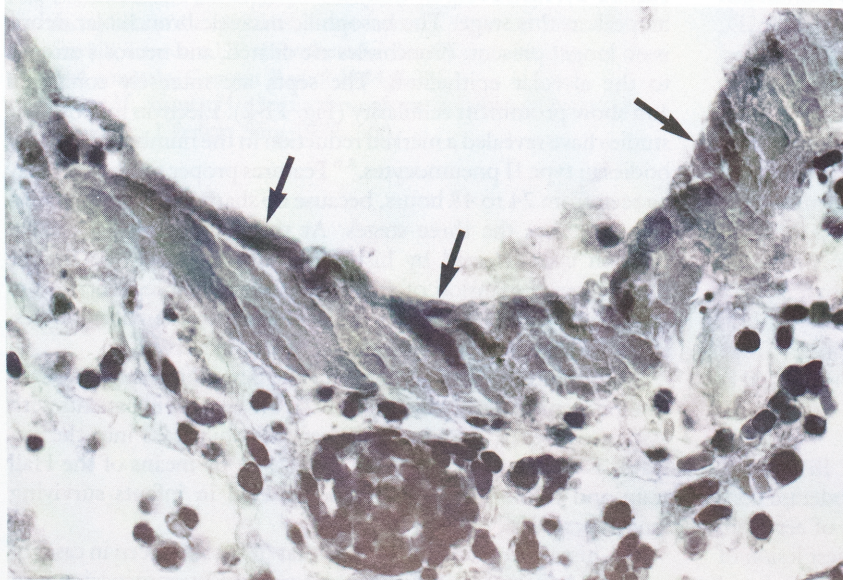

FIGURE 11-1. In the early stage of hyaline membrane formation, a superficial basophilic layer (*arrows*) covers an incipient hyaline membrane within a bronchiole. Bronchiolar epithelium is absent. (H & E stain; intermediate magnification.)
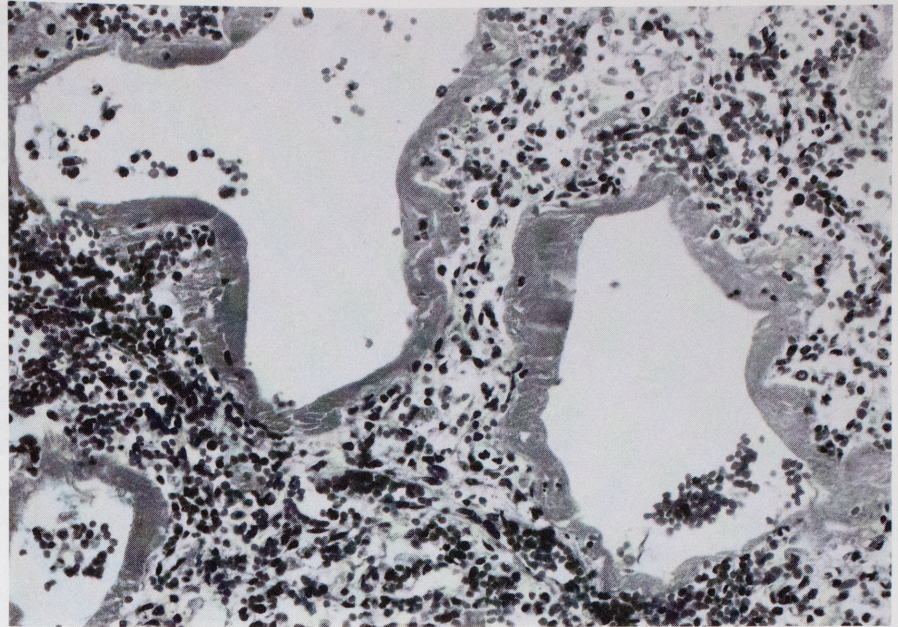
FIGURE 11-2. In stage II of hyaline membrane disease, the distended alveolar ducts are lined by well-developed eosinophilic hyaline membranes. There is marked atelectasis of the intervening alveolar tissue. (H & E stain; intermediate magnification.)

passed to the Golgi complex and then secreted as lamellar bodies and transformed into tubular myelin, apparently due to hydration changes between the lipid layers with the participation of the surfactant proteins (see Chap. 1). Tubular myelin is absent in infants with HMD.[12]

Several factors have been implicated in the deficient production of pulmonary surfactant. Immaturity is the most important factor, but others may participate, such as asphyxial episodes (*e.g.*, in the second twin of double pregnancies who is at high risk of developing HMD), hyperinsulinism in infants of diabetic mothers, and other endocrinologic dysfunctional states.[2,3,5] Stress has been known to enhance the synthesis of surfactant. Patients delivered when premature rupture of placental membranes occurs late in pregnancy or patients with intrauterine infections and other states that cause increased glucocorticoid production have a relatively lower risk.[3]

BRONCHOPULMONARY DYSPLASIA

BPD may be considered a relatively new disease, because it came about with advances in therapeutic technology. The first description of BPD did not appear until 1967, when Northway and colleagues studied 32 patients with severe RDS treated with artificial ventilation with high oxygen (80%–100%) for at least 24 hours.[13]

In the original description, the diagnosis of BPD was based mainly on sequential radiographic changes occurring in neonates with RDS. The disease was then divided into acute and chronic phases, each having certain clinical, radiologic, and pathologic appearances. The acute phase comprises the first three stages: stage I, between 2 and 3 days of life; stage II, between 4 and 10 days of life; and stage III, between 10 and 20 days of life. The chronic phase equals stage IV and occurs beyond 1 month of life. Many studies have been restricted to patients in stages III and IV, because many infants in stages I and II do not progress further. Because clinical and pathologic changes are temporally discrepant, Stocker and Dehner have divided the morphologic changes into

acute, reparative (*i.e.*, healing), and long-standing or healed BPD, and these are briefly reviewed here.[14]

In the acute phase, there is an increase in weight and consistency of the lungs. The pleura develops depressed areas, resulting in an uneven surface. Microscopically, the trachea and bronchi show cilia loss, dysplastic epithelial cells, edema, acute or chronic inflammation, and glandular hypertrophy in the mucosa and submucosa. The trachea may also have ulcerations, often after intubation.

Bronchioles and alveolar ducts exhibit the most impressive changes. There is extensive squamous metaplasia associated with acute and chronic inflammation and fibroblastic organization of the hyaline membrane exudate (Fig. 11-3). The hallmark of the lesion is dysplastic epithelium (Fig. 11-4), which in some cases can be very striking and is associated with many mitoses. In some bronchioles, there may be a histologic picture of necrotizing obstructive bronchiolitis. Well-ventilated alveoli are lined by ribbons of regular cuboidal cells, representing hyperplastic type II pneumocytes that have become detached from their basal membrane—a characteristic feature of oxygen toxicity (Fig. 11-5). Air may have leaked into the interlobular connective tissue septa, giving rise to interstitial emphysema.

In the reparative or healing stage, the pleural surface is finely nodular (*i.e.*, cobblestoned) as a result of the combination of overinflation and retraction of the underlying lung tissue by atelectasis and fibrosis (Fig. 11-6). Squamous metaplasia in the trachea can extend to the ducts of the submucosal glands. There is fibrosis within the bronchiolar lumen (*i.e.*, intrinsic fibrosis) or around its wall (*i.e.*, extrinsic fibrosis). Some bronchioles show evidence of maturing (*i.e.*, keratinizing) squamous metaplasia (Fig. 11-7). Patches of interstitial fibrosis are seen in alveolar tissue (Fig. 11-8). The interstitial emphysema is frequently associated with a foreign-body giant cell response. Muscular hyperplasia of pulmonary arteries is observed.

The pleural surface in the long-standing or chronic phase of BPD frequently appears coarsely nodular due to the same combination of overexpansion and fibrosis (Fig. 11-9). Some bronchi may show foci of residual squamous metaplasia, but most of them
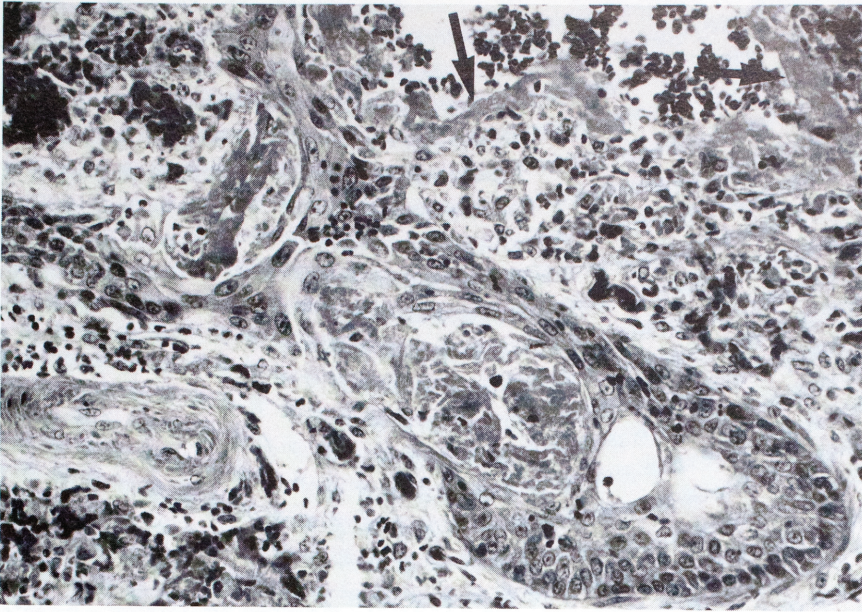
FIGURE 11-3. In the acute phase of bronchopulmonary dysplasia, a bronchiole with squamous metaplasia is surrounded by loose fibroblastic proliferation, including the remains of hyaline membranes (*arrows*). (H & E stain; intermediate magnification.)

are normal. Bronchioles may exhibit submucosal fibrosis and muscular hyperplasia. Alveoli demonstrate a varied histology, depending on the intensity of the prior injury; some show restitution of normal structure, and others are obliterated by fibrosis. Capillary vessels may proliferate, giving rise to an extracapillary bed unassociated with the alveolar septa.[14]

Several factors have been implicated in the pathogenesis of BPD, and no complete agreement has been reached. However, no researcher disagrees that oxygen and barotrauma provide the most significant contributions to the development of this condition.

High concentrations of oxygen are markedly toxic for the lungs. The first mention of oxygen toxicity, as early as 1785, is attributed to Lavoisier, who described an inflammatory action in the guinea pig lung.[14] The susceptibility to oxygen damage in experimental animals and human patients varies with age; younger subjects are more vulnerable than older ones. The difference is probably due to the lack in the young of well-developed enzymatic

systems to block toxic oxygen metabolites, mainly O_2 free radicals (see Chap. 15).

The second most significant contributing factor to BPD is barotrauma, which is the response of the lung to pressure or force. Although the precise mechanism by which barotrauma induces injury is unknown, the small and highly compliant bronchioles and respiratory ducts are prone to be ruptured and damaged by inflation pressure.[15]

Most investigators believe that neither oxygen alone nor barotrauma by itself is able to induce BPD. A combination of these injurious influences associated with other factors such as immaturity, surfactant deficiency, pulmonary edema, patent ductus arteriosus, severe and prolonged inflammatory response, altered elastase and α_1-proteinase inhibitor activity, and a deficiency of vitamins A and E propitiate the development of this disease.

Northway and associates described the late pulmonary functional sequelae of BPD in the surviving patients of their original
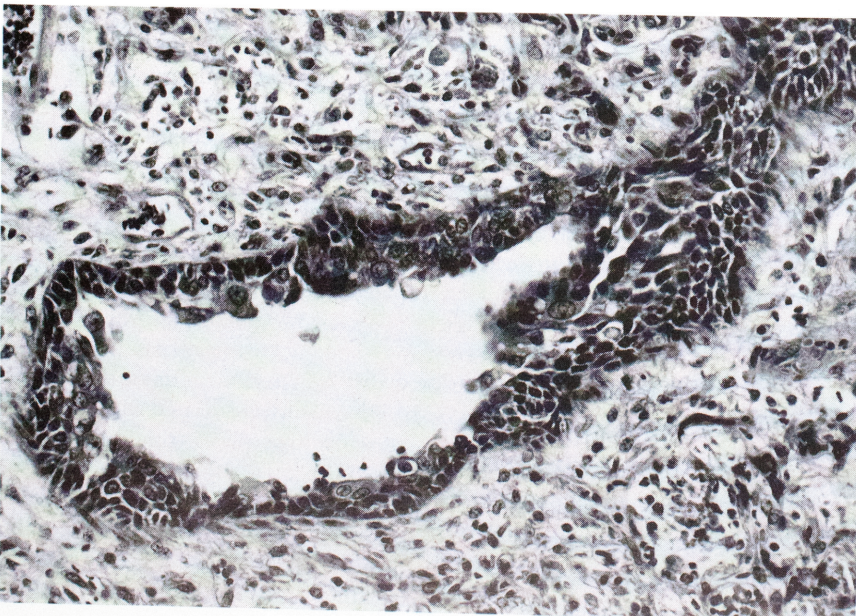

FIGURE 11-4. In the acute phase of bronchopulmonary dysplasia, there is regenerating bronchiolar epithelium with cytologic atypia (*i.e.*, dysplasia), a degree of fibroblastic proliferation and chronic inflammation is seen in the surrounding lung tissue. (H & E stain; intermediate magnification.)
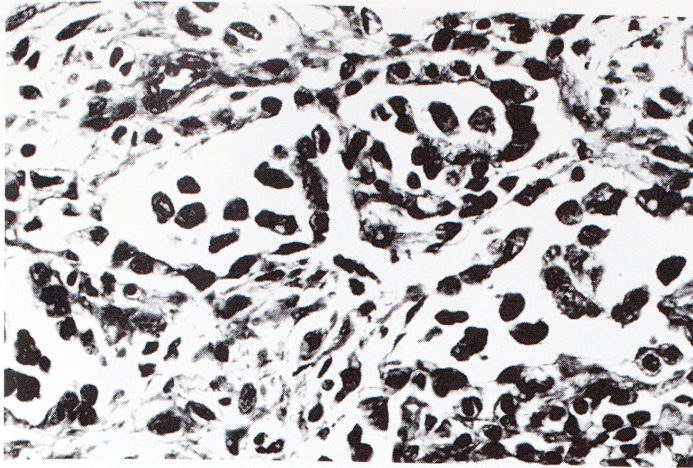
FIGURE 11-5. In the acute phase of bronchopulmonary dysplasia, ribbons of hyperplastic, type II alveolar cells line the alveoli; this is a characteristic feature of oxygen toxicity. (H & E stain; intermediate magnification; from Chou P, Shen-Schwarz S, Gonzalez-Crussi F, Reynolds M. Pulmonary changes following extracorporeal membrane oxygenation. Autopsy study of 23 cases. Hum Pathol 1993;24:405.)
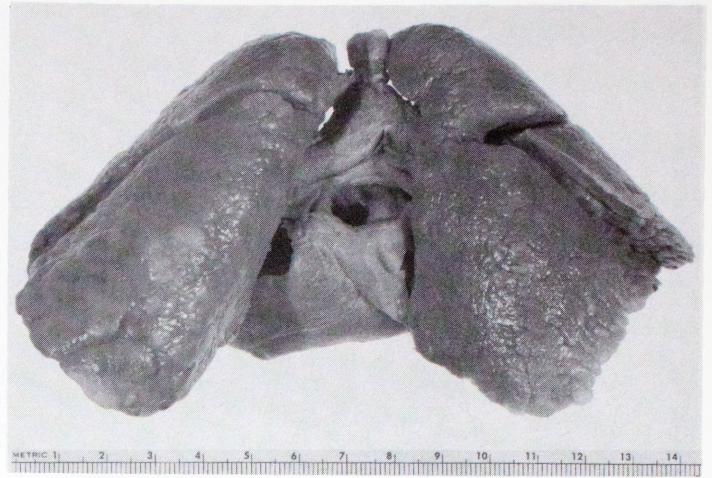

FIGURE 11-6. In this rear view of the lungs in the reparative stage of bronchopulmonary dysplasia, there is fine cobblestoning of the pleural surface with some deeper indentations (*left*). (Contributed by the editor.)

1967 report.[16] Late changes consist of obstruction, hyperreactivity, and hyperinflation of the airways, although these abnormalities are usually asymptomatic and the physiologic impact is not severe. Nonetheless, the overall mortality of infants with this disease is about 40%, which is far from insignificant.[17]

BRONCHIECTASIS

Bronchiectases are defined as abnormal and permanent dilatations of bronchi (see Chap. 28). Conditions such as cystic fibrosis (CF), primary ciliary dyskinesia (PCD), and the Young syndrome classically show these lesions. Less common acquired causes of bronchiectases in children are foreign body aspiration and tuberculosis, with airway obstruction by enlarged lymph nodes.[18] Before measles vaccination became available, this viral infection was mentioned as one of the most important predisposing diseases for the development of bronchiectasis in children.[19,20] Severe adenovirus infections have led to extensive bronchiectasis.[21]

A deficiency of bronchial cartilaginous plates has been reported as the primary cause of bronchiectases developing in children after mild respiratory infections, measles, or pneumonia. This represents the Williams-Campbell syndrome, whose pathologic findings other than bronchiectases include panlobular emphysema and inflammatory bronchial changes.[21-23] Children with a congenital deficiency of bronchial cartilage may suffer obstruction of the small airways caused by an abnormally high bronchial compliance, resulting in bronchial collapse during coughing.[21] Most affected children exhibit chest deformity, clubbed fingers, and short stature. Adult examples of this entity have been reported, but they are rare.[24]

An unusual disorder associated with bronchiectases is the yellow nail syndrome, which is characterized by discolored nails, primary lymphedema, and pleural effusion. Impaired peripheral and pulmonary lymphatic drainage with increased susceptibility
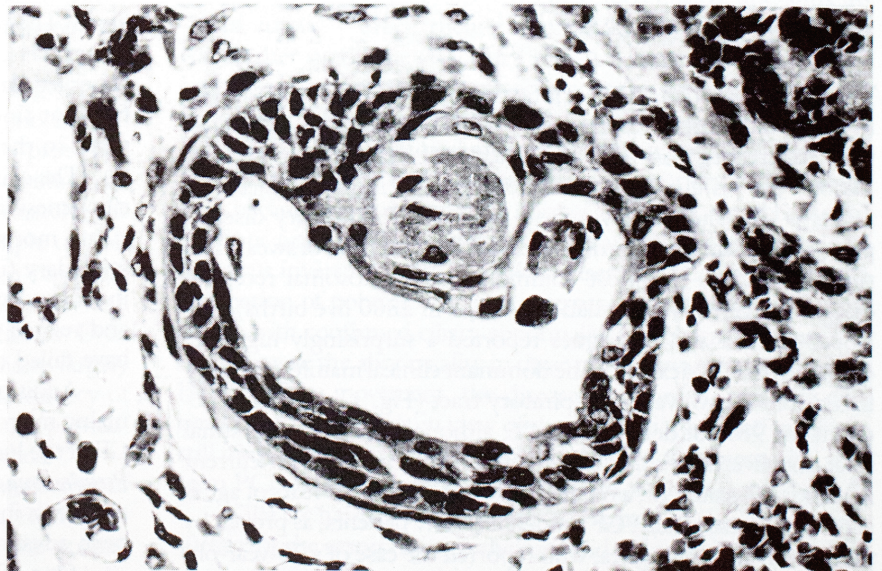

FIGURE 11-7. In the reparative stage of bronchopulmonary dysplasia with squamous metaplasia of the bronchiole, chronic inflammation and fibrosis of the surrounding tissue are present. (H & E stain; intermediate magnification; from Chou P, Shen-Schwarz S, Gonzalez-Crussi F, Reynolds M. Pulmonary changes following extracorporeal membrane oxygenation. Autopsy study of 23 cases. Hum Pathol 1993;24:405.)
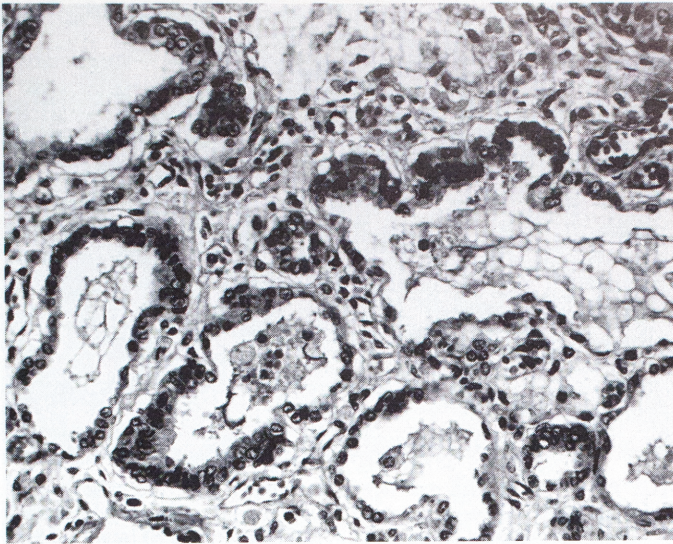
FIGURE 11-8. In the reparative stage of bronchopulmonary dysplasia, there is a focus of interstitial inflammation and fibrosis with prominent cuboidal metaplasia of the alveolar epithelial lining. (H & E stain; low magnification; from Chou P, Shen-Schwarz S, Gonzalez-Crussi F, Reynolds M. Pulmonary changes following extracorporeal membrane oxygenation. Autopsy study of 23 cases. Hum Pathol 1993;24:405.)


FIGURE 11-9. In the lung and heart of a patient with healed bronchopulmonary dysplasia, the cobblestone appearance of the pleura had progressed to coarse nodularity with sublobulations of the lung tissue. (Contributed by the editor.)

to infections and insufficient airways defenses against microorganisms may explain the respiratory damage.[18,25]

Bronchiectases can be seen in patients with disorders that affect the synthesis of different connective tissue proteins, such as collagen and elastin, as in the Ehlers-Danlos and Marfan syndromes, respectively.[18]

Bronchiectasis in the Maori is a special type of bronchiectasis that was described by Hinds in 1958.[26] It affects the Maoris, a Polynesian ethnic group. Hinds' study showed that saccular and cystic forms of bronchiectasis were strikingly frequent in these patients, compared with Europeans. Several alterations have been reported in the cilia of Polynesian patients suffering from bronchiectasis, including the complete or partial absence of dynein arms and microtubular abnormalities.[27,28]

CYSTIC FIBROSIS

The first comprehensive description of CF was made by Anderson in 1938, although an isolated case of meconium ileus associated with pancreatitis had been published by Landsteiner as early as 1905.[29,30] This disease, also named mucoviscidosis by Farber in 1944, is characterized by a triad of chronic pulmonary disease, pancreatic insufficiency, and increased concentration of sweat electrolytes.[31] CF is the most common severe autosomal recessive disease in Caucasian populations (*i.e.*, 1 in 2500 live births).[32,33] Lopez-Corella and colleagues reported a surprisingly high frequency of CF in Mexico.[34] The dominant clinical manifestations of this disorder involve the respiratory tract (Fig. 11-10). They account for 98% of deaths from CF, although the gastrointestinal tract and liver share in the general morbidity.[30,34] With current methods of treatment, a median survival of 25 to 30 years of age is achieved. Occasionally, CF occurs in elderly patients, as proven by van Biezen and colleagues, who reported the case of a 70-year-old patient with confirmed heterozygous F508 mutation.[35]

Bronchiectases are the landmark of CF lung changes. They can be detected as early as 2 months of age, and their prevalence increases in older patients, reaching 100% after 2 years of age.[36,37] Hyperplasia and obstruction of tracheal and bronchial submucosal glands are among the earliest observable changes. Bronchial mucus plugging facilitates colonization of the respiratory ducts with microorganisms. Repetitive pulmonary infections lead to bronchiolitis, mucus impaction, and bronchiectasis (Color Fig. 11-3). These changes are more prominent in the upper lobes, and a high proportion of patients develop subpleural cysts (*i.e.*, bronchiectatic cysts) that may communicate with the pleural space with production of pneumothorax. Other changes include stenotic obliteration of bronchi, interstitial fibrosis, and alveolar simplification.[30] The bronchial mucosa often develops squamous metaplasia and goblet cell hyperplasia.[37] Although air trapping as a result of hyperventilation is commonly observed, true emphysema is not a frequent finding; if present, it is usually mild and occurs in patients in the third decade of life.[38]

The cilia of CF patients exhibit normal morphology. Normal ciliogenesis in isolated CF cells has been demonstrated, but altered ciliary morphology represented by compound cilia is a common secondary finding. Structural abnormalities of intercellular tight junctions have been described, but these are probably nonspecific and related to cell injury. Scanning electron microscopy studies have failed to disclose a specific lesion of CF.

Additional pathologic alterations are caused by specific colonizing microorganisms. Three bacteria are chiefly associated with CF of the lungs: *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*.[36] Although there have been suggestions of defects in host defense mechanisms, no definitive evidence has been advanced in support of this contention.

One of the most important advances in the modern era of

FIGURE 11-10. Dilated bronchial glands with thick secretions are present in the bronchial wall of a patient with cystic fibrosis of the pancreas. (H & E stain; intermediate magnification.)

genetic research is the discovery of the CF gene (*CFTR*), which now complements other procedures such as microvillar intestinal enzyme determination in the prenatal diagnosis of this disease.[39–42]

The movement of water across biologic membranes depends on solute transport, specifically inorganic ions. An appropriate ionic absorption-secretion equilibrium is a crucial factor for the mobilization of secretions in the respiratory tract and in all exocrine glands. In the lungs, the ciliary action clears the secretory products, bacteria, dust, and other particulate matter. Diminished permeability to ionized chloride (Cl^-) has been demonstrated in the secretory epithelia of CF patients.[40] This relative impermeability to chloride ions hampers adequate hydration and maintenance of the sol phase of periciliary fluid through increased sodium and fluid reabsorption. The Cl^- membrane transport is normally mediated by a protein with 1480 amino acids called cystic fibrosis transmembrane regulator (CFTR), and encoded by the *CFTR* gene located in the long arm of chromosome 7, where it is flanked by the met protooncogene (*MET*) and the gene marker D758.[41] CFTR is an integral membrane protein, similar to other transport proteins such as P-glycoprotein, which is also encoded in chromosome 7 and is involved in the phenomenon of antineoplastic multidrug resistance.

The most common specific alteration in the CF gene, accounting for 70% of cases, is a deletion of three base pairs in exon 10. As a result of this genomic alteration, a defective protein is produced lacking the amino acid phenylalanine at residue 508 (F508) in the first ATP-binding domain.[42] Unfortunately, the genetic mechanisms underlying CF are far from simple or uniform. Many other less frequent mutations have been reported, among which homozygosity for F508 seems to correlate with pancreatic disease but not with the severity of lung disease. Even though the normal function of the CFTR protein remains largely speculative, it has been hypothesized that the high frequency of the CF gene confers a selective advantage to its carriers, in particular an increased resistance to chloride-secreting diarrhea.[43]

Reports have described successful attempts of transfection of the *CFTR* gene to the airway epithelium, using a replication deficient recombinant adenovirus vector containing the normal human *CFTR* cDNA.[44] These exciting developments portend the possibility of devising a truly effective therapy for the pulmonary manifestations of CF in the near future. This technology together with measures such as population screening and comprehensive programs of education and genetic counselling are reasons for hope for the control of the disease in the near future.

PRIMARY CILIARY DYSKINESIA

PCD is a group of several disorders whose common denominator is an abnormality affecting the cilia with consequent impairment of mucociliary clearance in the respiratory tract and the development of recurrent infections. Its incidence has been estimated to be 1 in 20,000, and about 50% of these patients have situs inversus. This is one of the three main genetic causes of chronic lung disease in humans; CF and α_1-antitrypsin deficiency are the other two. CF has already been discussed, and although α_1-antitrypsin deficiency is an inherited disorder, it usually produces pulmonary lesions only in adults (see Chap. 26).

The original description by Kartagener in 1933 included four patients with bronchiectasis, chronic rhinosinusitis, and situs inversus totalis.[45] Since then, this triad has been referred to as Kartagener syndrome (KS). In 1976, Afzelius expanded the concept to include cases without situs inversus in which the basic abnormality resides in the cilia and the spermatozoan flagella, leading to the same clinical picture.[46] Afzelius proposed that situs inversus can be explained on the basis of dysmotility of embryonic cilia, because this is required for normal levorotation of the viscera. Without normal ciliary function, visceral orientation is random, and situs inversus occurs in 50% of cases that qualify as KS. The association of polysplenia, situs inversus, and extrahepatic biliary atresia with confirmed ciliary abnormalities has been reported.[46,47]

Because the abnormality in these patients was thought to be a lack of ciliary movement, the disease was named immotile cilia syndrome.[48] However, in view of the description of inefficient but still motile cilia in patients with the same clinical presentation, the term PCD has been proposed and gained favor in recent years.[49]

Cilia are hairlike projections 6- to 7-μm long that line the free surface of the respiratory epithelium and other structures such as paranasal sinuses, eustachian tubes, fallopian tubes, and efferent

ducts of the testes and ependymal epithelium. Retinal rods, vestibular hair cells, and olfactory cells also have cilia. The spermatozoa's flagellum is a modified cilium. In the respiratory tract, one cell has at least 200 cilia immersed in a periciliary fluid, which underlies the mucus cover. An orderly metachronous beating displaces the mucus to the pharynx, where it is swallowed or expectorated. The beating rate of cilia in the human trachea is around 12 cycles per second at 37°C or 1000 times per minute.[50,51]

The basic components of a cilium are the microtubules, which are arranged in 9 peripheral pairs or doublets and two central individual units or singlets, the 9 + 2 pattern. This arrangement constitutes the axoneme. Each doublet is composed of two asymmetric microtubules that share part of their walls, made of tubulin molecules arranged in a closed spiral. The outer microtubule (i.e., subunit A) has 13 tubulin molecules per circumference, and the inner microtubule (i.e., subunit B) has only 11. Attached to the outer microtubule, there are two arms composed of dynein, an ATPase protein included in a superfamily of intracellular motor proteins involved in cell movement and cytoplasmic transport. Other structural components are nexin, which forms links between each doublet, and radial spokes, which connect each doublet with a central sheath of protein located around the central singlets (Fig. 11-11). At the neck of the cilium, a unique intramembranous structure called ciliary necklace has been shown using the freeze-etch technique. This is composed of strands of intramembrane particles and is thought to represent a feature of specific membrane differentiation.[52]

More than 200 different polypeptides participate in the cilium structure, and this biochemical heterogeneity allows many different defects to appear. Among the many reported structural anomalies are absence of dynein arms, which can be complete or partial; defective radial spokes; transposition of peripheral microtubules to a central position; absence of axonemal structure within the ciliary shaft; supernumerary microtubular doublets; defects on the basal bodies; abnormal length of cilia; abnormalities of the ciliary necklace; random ciliary orientation; and defective central microtubules.[52,53]

It is important to differentiate primary from secondary ciliary abnormalities. Several acquired ultrastructural changes, such as formation of compound cilia (i.e., cilia having more than one axoneme), rearrangement of the 9 + 2 microtubular pattern (Fig. 11-12), altered orientation in the central singlet units, abnormalities of the ciliary necklace, the basal bodies, or the rootlets, and functional changes, have been associated with respiratory tract bacteria, viruses, and air pollutants. The dynein arms and radial spoke defects are usually present in genetically determined diseases, but the microtubular defects are more commonly seen in acquired conditions.[51,54] However, there are reports of patients with KS in whom the cilia or spermatozoa were ultrastructurally normal.[54] The incidence of ultrastructural abnormalities in cilia of healthy persons ranges from 1% to 5%.[55]

In addition to PCD, which includes KS, ultrastructural abnormalities mainly affecting dynein arms and radial spokes have been described in Polynesian bronchiectasis, chronic bronchitis,
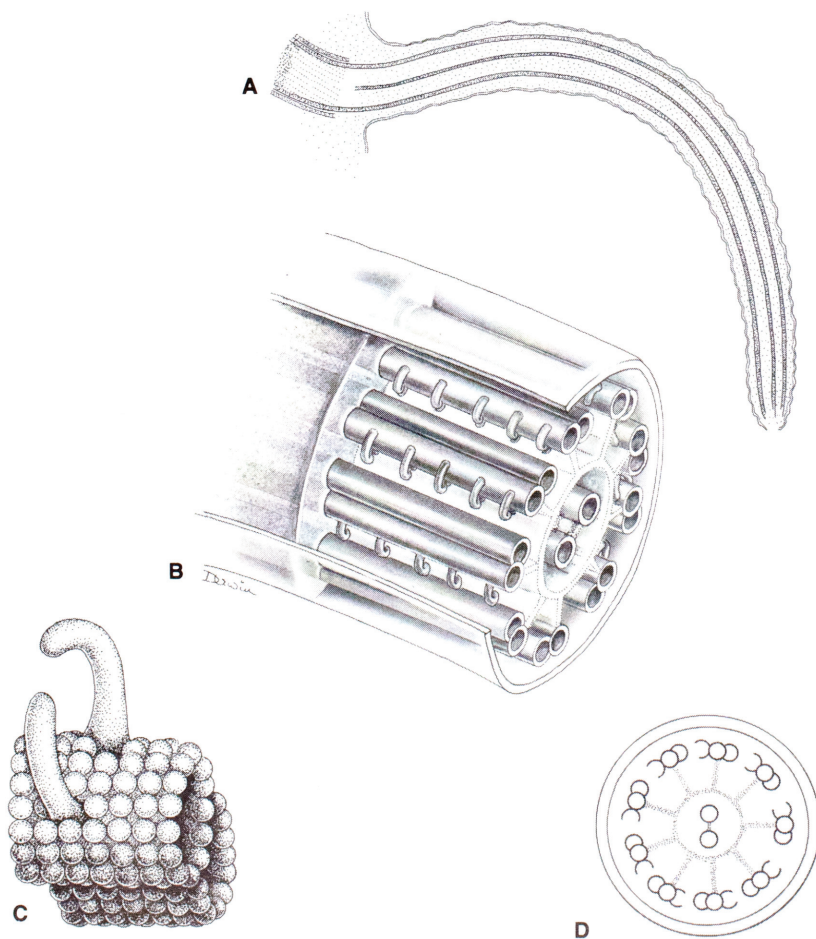

FIGURE 11-11. (**A**) Longitudinal view of a cilium. (*right*) (**B**) The cilium with its cell membrane partly removed reveals the inner ultrastructure of the axoneme. The microtubular doublets are linked to each other by the protein nexin, and radial spokes connect them with the protein sheath surrounding the central singlets. (**C**) An individual doublet is composed of globular molecules of tubuline with the dynein arms projecting from the outer microtubule. (**D**) Cross section (*lower right*) of a cilium. (From Sturgess JM, Turner JAP. Ultrastructural pathology of cilia in the immotile cilia syndrome. Perspect Pediatr Pathol 1984;8:133.)
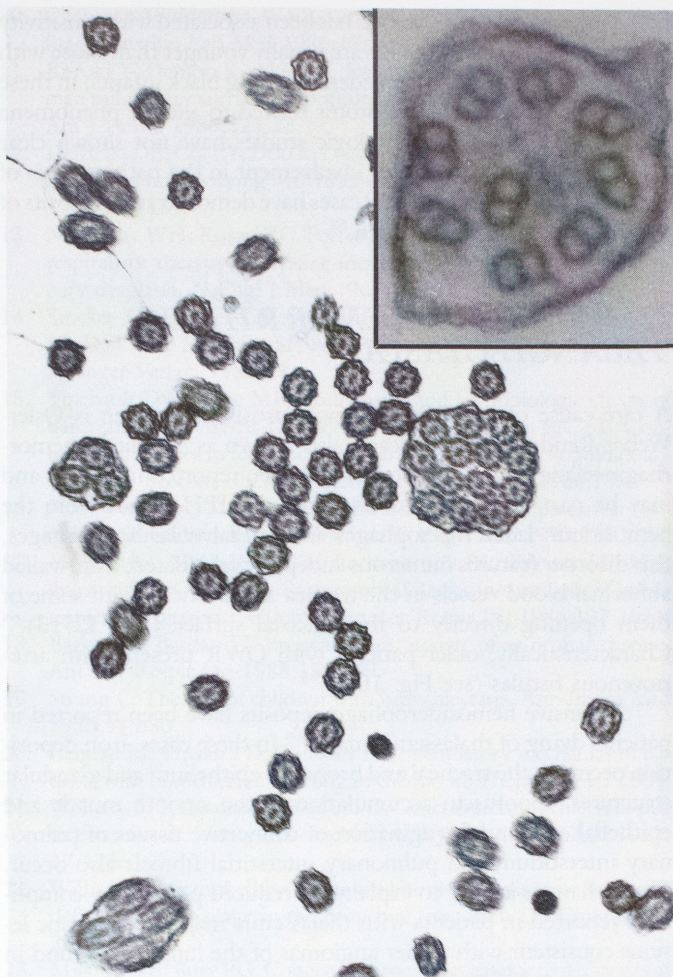
FIGURE 11-12. In abnormal cilia, compound cilia show more than one axoneme. A higher magnification (*inset*) reveals an absence of the central singlets and displacement of one of the peripheral doublets toward the center, with disruption of the normal 9 + 2 microtubular pattern (see Fig. 1-3 for comparison).

retinitis pigmentosa, Laurence-Moon-Biedl syndrome, Cockayne syndrome, and nasal acilia syndrome.[51]

A strict approach is necessary to make the diagnosis of PCD. An evaluation of at least 200 cilia has to be made before a definite opinion is rendered, and three factors must be considered: a history of sinusitis and bronchiectasis, even in cases with situs solitus; mucociliary clearance studies, such as the saccharin test; and the ultrastructure of the cilia.[56] An early diagnosis allows opportune treatment and reduces the chances of complications such as bronchiectasis.

Sampling of nasal septum or tracheobronchial epithelium is commonly used to evaluate ciliary ultrastructure. The biopsy specimen should be examined by light microscopy to confirm the presence of ciliated cells and ciliary motion. The sample is fixed in 2.5% glutaraldehyde for 2 hours and processed for routine electron microscopy. For a better image definition, the tissue can alternatively be fixed in a mixture of 1% tannic acid and 1% glutaraldehyde in phosphate buffer solution, which increases the quality of the obtained images. For samples that were initially fixed in 2.5% glutaraldehyde, postfixation in the mixture of tannic acid

and glutaraldehyde is also recommended, because this produces better results than glutaraldehyde alone.

YOUNG SYNDROME

The association of recurrent sinopulmonary infection and obstructive azoospermia was first described by Young in 1970.[57] Patients with this condition usually present with bronchiectasis and mild pulmonary dysfunction, although many cases are diagnosed during the clinical study of infertility. Even though the clinical picture can suggest CF, the late clinical presentation, normal iontophoresis test, and normal pancreatic function excludes this diagnosis. Mucociliary clearance is abnormal in these patients, but with the exception of one study describing minor axonemal defects, no ultrastructural ciliary abnormalities have been demonstrated in the respiratory tract or the sperm of affected men.[58] De Iongh and associates found increased twisting close to the tips of respiratory cilia in patients affected with this disorder, probably secondary to abnormal rheologic properties of the secreted mucus.[59] Some reports have described patients with associated nasal polyposis as part of this constellation.

IDIOPATHIC PULMONARY HEMOSIDEROSIS

There is a group of disorders characterized by the presence of alveolar hemosiderophages (*i.e.*, hemosiderin-laden macrophages). Many conditions, such as neoplasia, infectious and inflammatory diseases, cardiovascular and hematologic disorders, and virtually any state accompanied by bleeding in the airways or lungs, may have some degree of pulmonary hemosiderosis at some time in the course of their evolution. In such cases, pulmonary hemosiderosis is a nonspecific finding, secondary to the hemorrhagic phenomenon and usually of no great significance.

There is a select group of entities that present with hemoptysis, dyspnea, pulmonary infiltrates, and iron deficiency anemia. These diseases typically affect the lungs, course with multiple or occasionally single episodes of bleeding, and constitute the pulmonary hemorrhagic syndrome (see Chap. 62). In this group are included Goodpasture syndrome, idiopathic pulmonary hemosiderosis (IPH), and vasculitis-associated hemorrhage. Diffuse pulmonary hemorrhage falls into two categories: primary idiopathic hemorrhage and secondary pulmonary hemorrhage. In the first category, all attempts to reveal an underlying cause are negative; the second is usually associated with immunologic derangements that also affect the kidney and blood vessels.

IPH, also known as Ceelen disease, usually affects patients in the first decade of life.[60] Typically, patients present with a chronic, nonproductive cough and dyspnea; laboratory examination reveals microcytic hypochromic anemia; and hemosiderophages are present on cytologic examination of sputum. Roentgenographic pulmonary changes include diffuse or patchy infiltrates and a pattern of diffuse interstitial disease.[61]

Pathologically, IPH is a diagnosis of exclusion after ruling out all other causes of diffuse pulmonary hemorrhage. In a series of seven patients with IPH described by Cutz, the lungs exhibited consolidated areas due to hemosiderophagic cells accumulating in alveoli, interstitial fibrosis, variable degrees of recent hemorrhage,

alveolar edema, and hyperplasia of type II pneumocytes.[62] Perls Prussian blue iron staining was positive in alveolar hemosiderin-laden macrophages and in septal macrophages. Some free deposits were found in the elastic fibers of vessels and interalveolar septa in the connective tissue, which were associated with calcium deposits. A remarkable finding was a prominent increase in mast cells in the vicinity of blood vessels. Immunofluorescence staining was negative for immunoglobulins and complement. Ultrastructurally, membrane-bound inclusions of hemosiderin were found in macrophages, which also contained lamellar bodies produced by type II pneumocytes. Type I cells showed irregular microvilli with deep cytoplasmic invaginations.

Because the cause of IPH is unknown, its pathogenesis remains speculative. A structural defect with secondary weakness of the pulmonary vessels has been proposed, but no convincing evidence has been found to support this theory. Conflicting results have reported intact alveolar capillary walls and capillary basement membrane anomalies such as splitting, thickening, and reduplication.[63]
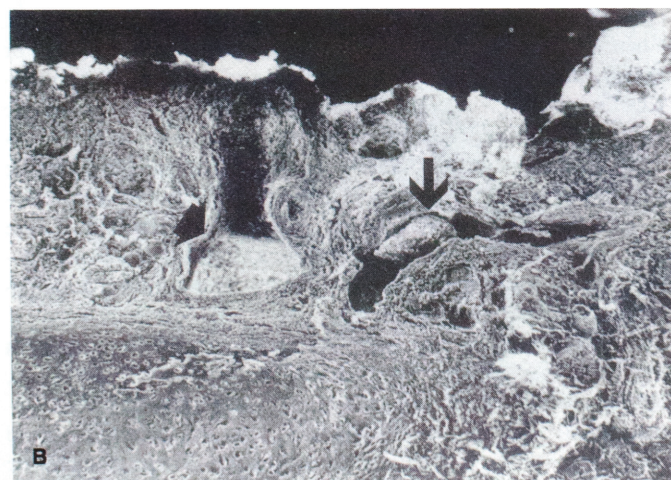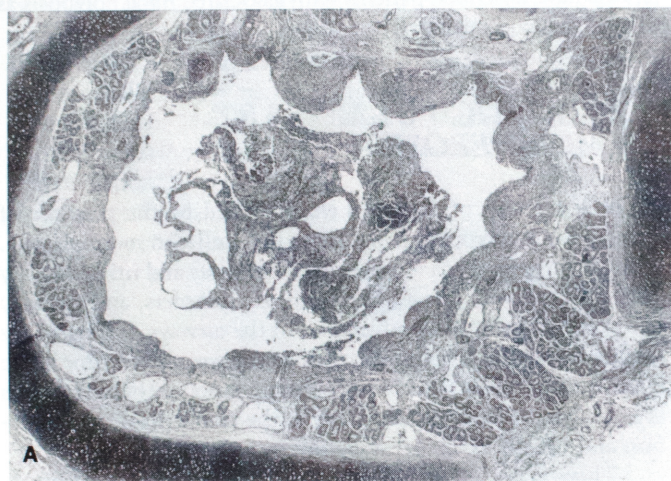

FIGURE 11-13. (**A**) In an infant with Osler-Weber-Rendu disease, there are multiple abnormally dilated vessels in the bronchial lamina propria, and some of them are occluded by thrombi. (H & E stain; panoramic view.) (**B**) A scanning electron micrograph of the respiratory mucosa shows two abnormal vessels: one is open to the surface, and the other is occluded by thrombus (*arrows*). (From Reyes-Mujica M, López-Corella E, Pérez-Fernández L, Cuevas-Schacht F, Carrillo-Farga J. Osler-Weber-Rendu disease in an infant. Hum Pathol 1988;19:1243.)

Pulmonary hemosiderosis has been associated with sensitivity to cow milk. Affected patients are usually younger than those with IPH, and there is a higher incidence among black infants; in these cases, other respiratory symptoms related to allergic phenomena are usually present. Immunologic studies have not shown clear evidence of immunoglobulin involvement in the pathogenesis of the disease, but some reported cases have demonstrated deposits of IgG, IgA, C3, and fibrinogen.[62]

HEREDITARY HEMORRHAGIC TELANGIECTASIA

A rare cause of pulmonary hemosiderosis in children is Osler-Weber-Rendu (OWR) disease, also known as hereditary hemorrhagic telangiectasia, which has also been reported in infants and may be part of a spectrum that includes IPH. Apart from the hemosiderin-laden macrophages and intraalveolar hemorrhages, this disorder features numerous subepithelial, dilated, thin-walled abnormal blood vessels in the trachea and bronchi, with some of them opening directly to the mucosal surface (Fig. 11-13).[64] Characteristically, older patients with OWR present with arteriovenous fistulas (see Fig. 10-1).[65]

Extensive hemosiderophage deposits have been reported in patients dying of thalassemia major.[66] In these cases, iron deposition occurs in the tracheal and bronchial epithelium and glandular structures. Lipofuscin accumulation in the smooth muscle and epithelial cells and ferrugination of connective tissues of pulmonary interstitium and pulmonary interstitial fibrosis also occur. These changes appear to explain the reduced pulmonary compliance reported in patients with thalassemia major. Angiectatic lesions consistent with spider angiomas of the lung were found in these patients.[66] Other reported changes associated with thalassemia are extensive bronchopneumonia and chronic pulmonary thromboembolism.[67]

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