of institution of therapy. *A major thrust in the control of RDS focuses on prevention, either by delaying labor until the fetal lung reaches maturity or by inducing maturation of the lung in the fetus at risk.* Critical to these objectives is the ability to assess fetal lung maturity accurately. Because pulmonary secretions are discharged into the amniotic fluid, analysis of amniotic fluid phospholipids provides a good estimate of the level of surfactant in the alveolar lining. Prophylactic administration of exogenous surfactant at birth to extremely premature infants (gestational age < 28 weeks) has been shown to be very beneficial, such that it is now uncommon for infants to die of acute RDS.

In uncomplicated cases, recovery begins to occur within 3 or 4 days. In affected neonates, oxygen is required. However, high concentration of ventilator-administered oxygen for prolonged periods is associated with two well-known complications: *retrolental fibroplasia* (also called *retinopathy of prematurity*) in the eyes, and *bronchopulmonary dysplasia.* Fortunately, both complications are now infrequent as a result of gentler ventilation techniques, antenatal glucocorticoid therapy, and prophylactic surfactant treatments.

- Retinopathy of prematurity has a two-phase pathogenesis. During the *hyperoxic* phase of RDS therapy (phase I), expression of the proangiogenic vascular endothelial growth factor (VEGF) is markedly decreased, causing endothelial cell apoptosis; VEGF levels rebound after return to relatively hypoxic room air ventilation (phase II), inducing retinal vessel proliferation (*neovascularization*) characteristic of the lesions in the retina.
- *The major abnormality in bronchopulmonary dysplasia is* striking decrease in alveolar septation (manifested as large, simplified alveolar structures) and a dysmorphic capillary configuration. Thus, the current view is that bronchopulmonary dysplasia is caused by a potentially reversible impairment in the development of alveolar septation at the so-called "saccular" stage. Multiple factors—hyperoxemia, hyperventilation, prematurity, inflammatory cytokines, and vascular maldevelopment—contribute to bronchopulmonary dysplasia and probably act additively or synergistically to promote injury. The levels of a variety of proinflammatory cytokines (TNF, interleukin-1β [IL-1β], IL-6, and IL-8) are increased in the alveoli of infants who develop bronchopulmonary dysplasia, suggesting a role for these cytokines in arresting pulmonary development.

Infants who recover from RDS are also at increased risk for developing a variety of other complications associated with preterm birth; most important among these are *patent ductus arteriosus, intraventricular hemorrhage,* and *necrotizing enterocolitis.* Thus, although technologic advances help save the lives of many infants with RDS, it also brings to the surface the exquisite fragility of the immature neonate.

Necrotizing Enterocolitis

Necrotizing enterocolitis is most common in premature infants, with the incidence of the disease being inversely proportional to the gestational age. It occurs in approximately 1 out of 10 very low birth weight infants (<1500 gm). Approximately 2500 cases occur annually in the United States.

The pathogenesis of necrotizing enterocolitis is uncertain, but is in all likelihood multifactorial. In addition to prematurity, most cases are associated with enteral feeding, suggesting that some postnatal insult (such as introduction of bacteria) sets in motion the cascade culminating in tissue destruction. While infectious agents likely play a role in the pathogenesis of necrotizing enterocolitis, no single bacterial pathogen has been linked to the disease. A large number of inflammatory mediators have been associated with necrotizing enterocolitis, and their discussion is beyond the scope of this book. One particular mediator, platelet activating factor (PAF), has been implicated in increasing mucosal permeability by promoting enterocyte apoptosis and compromising intercellular tight junctions, thus adding "fuel to the fire." Stool and serum samples of infants with necrotizing enterocolitis demonstrate higher PAF levels than age-matched controls. Ultimately, breakdown of mucosal barrier functions permits transluminal migration of gut bacteria, leading to a vicious cycle of inflammation, mucosal necrosis, and further bacterial entry, eventually culminating in sepsis and shock (Chapter 4).

The clinical course is fairly typical, with the onset of bloody stools, abdominal distention, and development of circulatory collapse. Abdominal radiographs often demonstrate gas within the intestinal wall *(pneumatosis intestinalis).*

MORPHOLOGY

Necrotizing enterocolitis typically involves the terminal ileum, cecum, and right colon, although any part of the small or large intestines may be involved. The involved segment is distended, friable, and congested, or it can be frankly gangrenous; intestinal perforation with accompanying peritonitis may be seen. Microscopically, mucosal or transmural coagulative necrosis, ulceration, bacterial colonization, and submucosal gas bubbles may be seen (Fig. 10-8). Reparative changes, such as the formation of granulation tissue and fibrosis, may begin shortly after the acute episode. When detected early on, necrotizing enterocolitis can be often managed conservatively, but many cases (20% to 60%) require resection of the necrotic segments of bowel. Necrotizing enterocolitis is associated with high perinatal mortality; those who survive often develop post-necrotizing enterocolitis strictures from fibrosis caused by the healing process.

Perinatal Infections

In general, fetal and perinatal infections are acquired through one of two primary routes—transcervically (also referred to as ascending) or transplacentally (hematologic). Occasionally, infections occur by a combination of the two routes in that an ascending microorganism infects the endometrium and then invades the fetal bloodstream via the chorionic villi.

Transcervical (Ascending) Infections

Most bacterial and a few viral (e.g., herpes simplex II) infections are acquired by the cervicovaginal route. Such infections may be acquired in utero or around the time of