surfactant lipids, are involved in the reduction of surface tension at the air-liquid barrier in the alveoli of the lung. With reduced surface tension in the alveoli, less pressure is required to keep them patent and hence aerated. The importance of surfactant proteins in normal lung function can be gauged by the occurrence of severe respiratory failure in neonates with congenital deficiency of surfactant caused by mutations in the *SFTPB* or *SFTBC* genes.

Surfactant production by type II alveolar cells is accelerated after the thirty-fifth week of gestation in the fetus. At birth, the first breath of life requires high inspiratory pressures to expand the lungs. With normal levels of surfactant, the lungs retain up to 40% of the residual air volume after the first breath; thus, subsequent breaths require far lower inspiratory pressures. With a deficiency of surfactant, the lungs collapse with each successive breath, and so infants must work as hard with each successive breath as they did with the first. The problem of *stiff* atelectatic lungs is compounded by the *soft* thoracic wall that is pulled in as the diaphragm descends. Progressive atelectasis and reduced lung compliance then lead to a train of events as depicted in Figure 10-6, resulting in protein-rich, fibrin-rich exudation into the alveolar spaces with the formation of hyaline membranes. The fibrin-hyaline membranes are barriers to gas exchange, leading to carbon dioxide retention and hypoxemia. The hypoxemia itself further impairs surfactant synthesis, and a vicious cycle ensues.

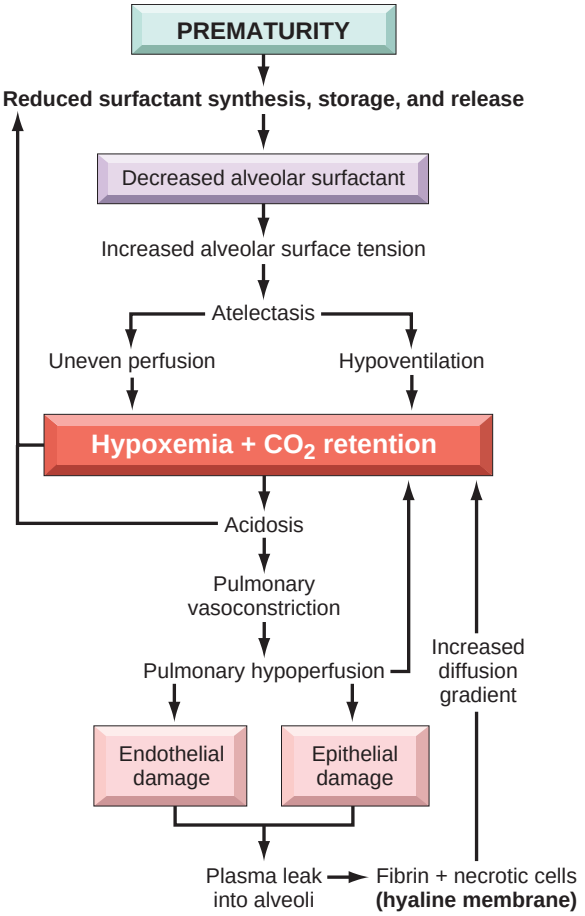

Figure 10-6 Schematic outline of the pathophysiology of respiratory distress syndrome (see text).

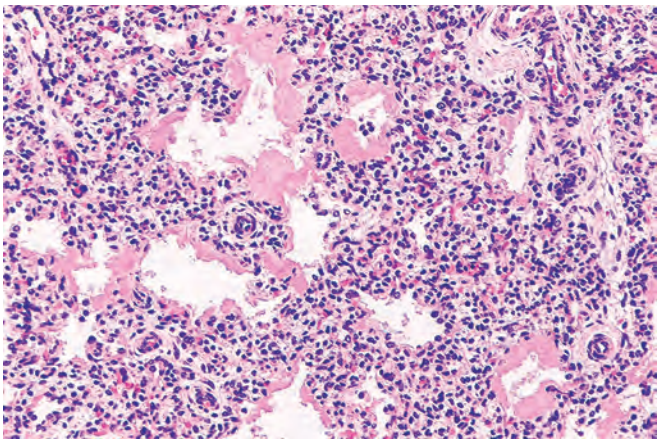

Figure 10-7 Hyaline membrane disease. There is alternating atelectasis and dilation of the alveoli. Note the eosinophilic thick hyaline membranes lining the dilated alveoli.

Surfactant synthesis is modulated by a variety of hormones and growth factors, including cortisol, insulin, prolactin, thyroxine, and TGF-β. *The role of glucocorticoids is particularly important.* Conditions associated with intrauterine stress and FGR that increase corticosteroid release lower the risk of developing RDS. Surfactant synthesis can be suppressed by the compensatory high blood levels of insulin in infants of diabetic mothers, which counteracts the effects of steroids. This may explain, in part, why infants of diabetic mothers have a higher risk of developing RDS. Labor is known to increase surfactant synthesis; hence, cesarean section before the onset of labor may increase the risk of RDS.

MORPHOLOGY

The lungs are distinctive on gross examination. Though of normal size, they are solid, airless, and reddish purple, similar to the color of the liver, and they usually sink in water. Microscopically, alveoli are poorly developed, and those that are present are collapsed (Fig. 10-7). When the infant dies early in the course of the disease, necrotic cellular debris can be seen in the terminal bronchioles and alveolar ducts. The necrotic material becomes incorporated within **eosinophilic hyaline membranes** lining the respiratory bronchioles, alveolar ducts, and alveoli. The membranes are largely made up of fibrin admixed with cell debris derived chiefly from necrotic type II pneumocytes. The sequence of events that leads to the formation of hyaline membranes is depicted in Figure 10-6. There is a remarkable paucity of neutrophilic inflammatory reaction associated with these membranes. The lesions of hyaline membrane disease are never seen in stillborn infants.

In infants who survive more than 48 hours, reparative changes occur in the lungs. The alveolar epithelium proliferates under the surface of the membrane, and may detach into the airspace where it undergoes partial digestion or phagocytosis by macrophages.

Clinical Features. The classic clinical presentation before the era of treatment with exogenous surfactant was described earlier. Currently, the actual clinical course and prognosis for neonatal RDS vary, depending on the maturity and birth weight of the infant and the promptness