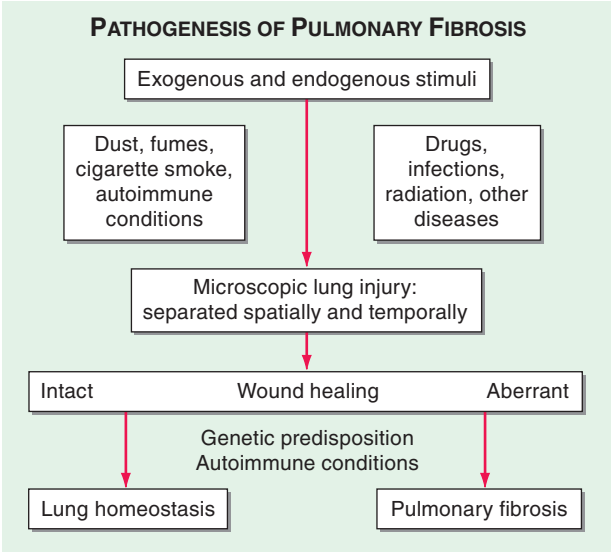

FIGURE 315-1 Proposed mechanism for the pathogenesis of pulmonary fibrosis. The lung is naturally exposed to repetitive injury from a variety of exogenous and endogenous stimuli. Several local and systemic factors (e.g., fibroblasts, circulating fibrocytes, chemokines, growth factors, and clotting factors) contribute to tissue healing and functional recovery. Dysregulation of this intricate network through genetic predisposition, autoimmune conditions, or superimposed diseases can lead to aberrant wound healing, with the result of pulmonary fibrosis. Alternatively, excessive injury to the lung may overwhelm even intact reparative mechanisms and lead to pulmonary fibrosis. *(From S Garantziotis et al: J Clin Invest 114:319, 2004.)*

HISTORY

Duration of Illness *Acute presentation* (days to weeks), although unusual, occurs with allergy (drugs, fungi, helminths), acute interstitial pneumonia (AIP), eosinophilic pneumonia, and hypersensitivity pneumonitis. These conditions may be confused with atypical pneumonias because of diffuse alveolar opacities on chest x-ray. *Subacute presentation* (weeks to months) may occur in all ILDs but is seen especially in sarcoidosis, drug-induced ILDs, the alveolar hemorrhage syndromes, cryptogenic organizing pneumonia (COP), and the acute immunologic pneumonia that complicates systemic lupus erythematosus (SLE) or polymyositis. In most ILDs, the symptoms and signs form a *chronic presentation* (months to years). Examples include IPF, sarcoidosis, pulmonary Langerhans cell histiocytosis (PLCH), pneumoconioses, and CTDs. *Episodic presentations* are unusual and include eosinophilic pneumonia, hypersensitivity pneumonitis, COP, vasculitides, pulmonary hemorrhage, and Churg-Strauss syndrome.

Age Most patients with sarcoidosis, ILD associated with CTD, lymphangioleiomyomatosis (LAM), PLCH, and inherited forms of ILD (familial IPF, Gaucher disease, Hermansky-Pudlak syndrome) present between the ages of 20 and 40 years. Most patients with IPF are older than 60 years.

Gender LAM and pulmonary involvement in tuberous sclerosis occur exclusively in premenopausal women. In addition, ILD in Hermansky-Pudlak syndrome and in the CTDs is more common in women; an exception is ILD in rheumatoid arthritis (RA), which is more common in men. IPF is more common in men. Because of occupational exposures, pneumoconioses also occur more frequently in men.

Family History Familial lung fibrosis has been associated with mutations in the surfactant protein C gene, the surfactant protein A2 gene, telomerase reverse transcriptase (*TERT*), telomerase RNA component (*TERC*), and the promoter of a mucin gene (*MUC5B*). Familial lung fibrosis is characterized by several patterns of interstitial pneumonia, including nonspecific interstitial pneumonia, desquamative interstitial pneumonia, and UIP. Older age, male sex, and a history of cigarette smoking have been identified as risk factors for familial lung fibrosis. Family associations (with an autosomal dominant pattern) have been identified in tuberous sclerosis and neurofibromatosis. Familial clustering has been identified increasingly in sarcoidosis. The genes responsible for several rare ILDs have been identified, i.e., alveolar microlithiasis, Gaucher disease, Hermansky-Pudlak syndrome, and Niemann-Pick disease, along with the genes for surfactant homeostasis in pulmonary alveolar proteinosis and for control of cell growth and differentiation in LAM.

Smoking History Two-thirds to 75% of patients with IPF and familial lung fibrosis have a history of smoking. Patients with PLCH, respiratory bronchiolitis/desquamative interstitial pneumonia (DIP), Goodpasture syndrome, respiratory bronchiolitis, and pulmonary alveolar proteinosis are usually current or former smokers.

Occupational and Environmental History A strict chronologic listing of the patient's lifelong employment must be sought, including specific duties and known exposures. In hypersensitivity pneumonitis (see Fig. 310-1), respiratory symptoms, fever, chills, and an abnormal chest roentgenogram are often temporally related to a hobby (pigeon breeder's disease) or to the workplace (farmer's lung) (Chap. 310). Symptoms may diminish or disappear after the patient leaves the site of exposure for several days; similarly, symptoms may reappear when the patient returns to the exposure site.

Other Important Past History Parasitic infections may cause pulmonary eosinophilia, and therefore a travel history should be taken in patients with known or suspected ILD. History of risk factors for HIV infection should be elicited because several processes may occur at the time of initial presentation or during the clinical course, e.g., HIV infection, organizing pneumonia, AIP, lymphocytic interstitial pneumonitis, and diffuse alveolar hemorrhage.

Respiratory Symptoms and Signs Dyspnea is a common and prominent complaint in patients with ILD, especially the idiopathic interstitial pneumonias, hypersensitivity pneumonitis, COP, sarcoidosis, eosinophilic pneumonias, and PLCH. Some patients, especially those with sarcoidosis, silicosis, PLCH, hypersensitivity pneumonitis, lipoid pneumonia, or lymphangitis carcinomatosis, may have extensive parenchymal lung disease on chest imaging studies without significant dyspnea, especially early in the course of the illness. Wheezing is an uncommon manifestation of ILD but has been described in patients with chronic eosinophilic pneumonia, Churg-Strauss syndrome, respiratory bronchiolitis, and sarcoidosis. Clinically significant chest pain is uncommon in most ILDs. However, substernal discomfort is common in sarcoidosis. Sudden worsening of dyspnea, especially if associated with acute chest pain, may indicate a spontaneous pneumothorax, which occurs in PLCH, tuberous sclerosis, LAM, and neurofibromatosis. Frank hemoptysis and blood-streaked sputum are rarely presenting manifestations of ILD but can be seen in the diffuse alveolar hemorrhage (DAH) syndromes, LAM, tuberous sclerosis, and the granulomatous vasculitides. Fatigue and weight loss are common in all ILDs.

PHYSICAL EXAMINATION

The findings are usually not specific. Most commonly, physical examination reveals tachypnea and bibasilar end-inspiratory dry crackles, which are common in most forms of ILD associated with inflammation but are less likely to be heard in the granulomatous lung diseases. Crackles may be present in the absence of radiographic abnormalities on the chest radiograph. Scattered late inspiratory high-pitched rhonchi—so-called inspiratory squeaks—are heard in patients with bronchiolitis. The cardiac examination is usually normal except in the middle or late stages of the disease, when findings of pulmonary hypertension and cor pulmonale may become evident (Chap. 304). Cyanosis and clubbing of the digits occur in some patients with advanced disease.

LABORATORY

Antinuclear antibodies and anti-immunoglobulin antibodies (rheumatoid factors) are identified in some patients, even in the absence