in IPF, but it must be admitted that the pathogenesis of IPF is complex and poorly understood. For example, it is unknown precisely how alveolar epithelial cell damage translates into interstitial fibrosis. One model holds that the injured epithelial cells are the source of profibrogenic factors such as TGF-β, whereas a second, nonmutually exclusive model proposes that innate and adaptive immune cells produce such factors as part of the host response to epithelial cell damage. Other work has described abnormalities in the fibroblasts themselves that involve changes in intracellular signaling and features reminiscent of epithelial mesenchymal transition (Chapter 7), but a causal link to fibrosis has not been established.

MORPHOLOGY

Grossly, the pleural surfaces of the lung are cobblestoned as a result of the retraction of scars along the interlobular septa. The cut surface shows firm, rubbery white areas of fibrosis, which occurs preferentially in the lower lobes, the **subpleural regions**, and along the **interlobular septa**. Microscopically, the hallmark is **patchy interstitial fibrosis**, which varies in intensity (Fig. 15-14) and age. The earliest lesions contain exuberant fibroblastic proliferation **(fibroblastic foci)**. With time these areas become more collagenous and less cellular. Quite typical is the coexistence of both early and late lesions (Fig. 15-15). The dense fibrosis causes the destruction of alveolar architecture and formation of cystic spaces lined by hyperplastic type II pneumocytes or bronchiolar epithelium (**honeycomb fibrosis**). With adequate sampling, these diagnostic histologic changes (i.e., areas of dense collagenous fibrosis with relatively normal lung and fibroblastic foci) can be identified even in advanced IPF. There is mild to moderate inflammation within the fibrotic areas, consisting of mostly lymphocytes admixed with a few plasma cells, neutrophils, eosinophils, and mast cells. Foci of squamous metaplasia and smooth muscle hyperplasia may be present, along with pulmonary arterial hypertensive changes (intimal fibrosis and medial thickening). In acute exacerbations diffuse alveolar damage may be superimposed on these chronic changes.

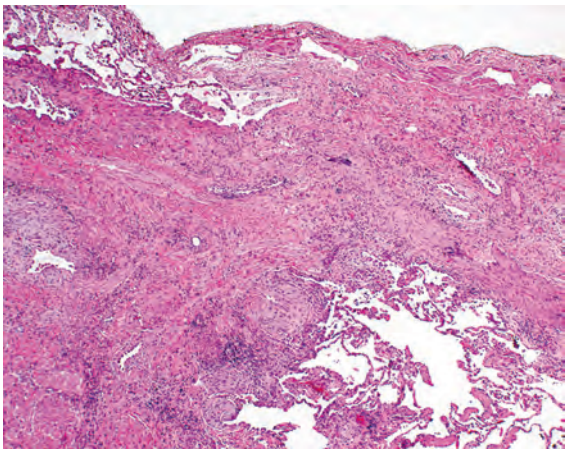

Figure 15-14 Usual interstitial pneumonia. The fibrosis is more pronounced in the subpleural region. (Courtesy Dr. Nicole Cipriani, Department of Pathology, University of Chicago, Chicago, Ill.)

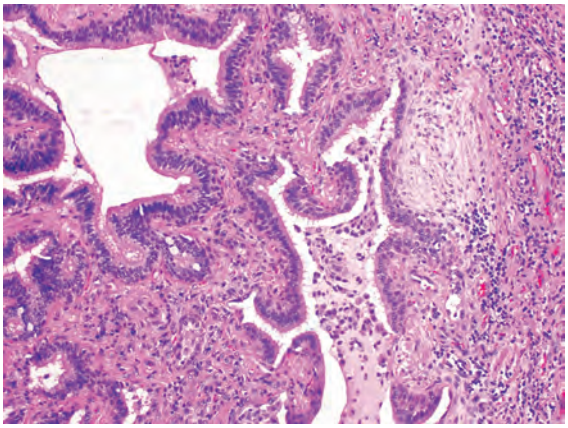

Figure 15-15 Usual interstitial pneumonia. Fibroblastic focus with fibers running parallel to surface and bluish myxoid extracellular matrix. Honeycombing is present on the left.

Clinical Course. IPF begins insidiously with gradually increasing *dyspnea on exertion* and dry cough. Most patients are 55 to 75 years old at presentation. Hypoxemia, *cyanosis*, and clubbing occur late in the course. The progression in an individual patient is unpredictable. Usually there is a gradual deterioration in pulmonary status despite medical treatment with immunosuppressive drugs such as steroids, cyclophosphamide, or azathioprine. Other IPF patients have acute exacerbations of the underlying disease and follow a rapid downhill clinical course. The median survival is about 3 years after diagnosis. Lung transplantation is the only definitive therapy.

Nonspecific Interstitial Pneumonia

The concept of nonspecific interstitial pneumonia emerged when it was realized that there is a group of patients with diffuse interstitial lung disease whose lung biopsies lack the diagnostic features of any of the other well-characterized interstitial diseases. Despite its "nonspecific" name, this entity is important to recognize, since these patients have a much better prognosis than do those with usual interstitial pneumonia. Nonspecific interstitial pneumonia may be idiopathic or associated with connective tissue disease.

MORPHOLOGY

On the basis of its histology, nonspecific interstitial pneumonia is divided into cellular and fibrosing patterns. The cellular pattern consists primarily of mild to moderate chronic interstitial inflammation, containing lymphocytes and a few plasma cells, in a uniform or patchy distribution. The fibrosing pattern consists of diffuse or patchy interstitial fibrotic lesions of roughly the same stage of development, an important distinction from usual interstitial pneumonia. Fibroblastic foci, honeycombing, hyaline membranes and granulomas are absent.

Clinical Course. Patients present with dyspnea and cough of several months' duration. They are more likely to be female nonsmokers in their sixth decade of life. Key features on high-resolution computed tomography are bilateral, symmetric, predominantly lower lobe reticular opacities. Those having the cellular pattern are somewhat younger than those with the fibrosing pattern and have a better prognosis.