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Usual or Nonspecific Interstitial Pneumonia, Interstitial Fibrosis, and the Honeycomb Lung

Philip T. Cagle

Like any other organ, the lung has a limited number of pathologic responses to injury of any type, and fibrosis or scarring is often the final sequela. Whether or not injury results in scarring depends on the nature, severity, and chronicity of such injury. Also, if the injury is localized, it may produce a focal scar, as with healing of an infarct or a localized infection; a diffuse or multifocal injury may eventually result in widespread end-stage fibrosis and honeycombing.[1,2]

Interstitial pneumonia represents a heterogeneous group of often unrelated processes that, to a variable degree, share certain clinical, radiographic, and functional abnormalities. Pathologically, these processes are characterized by widespread cellular infiltration or fibrosis of alveolar walls (*i.e.*, the pulmonary interstitium).[3] They represent the prime example of a restrictive respiratory disorder because they reduce the compliance of the lung parenchyma and the volume of the lung as a whole. Many of them would progress to what is often referred to as honeycomb lung because of obvious radiographic and gross pathologic appearance.

Although interstitial pneumonias may be associated with a specific etiology, most remain idiopathic. Also, despite some basic clinical, radiologic, and functional similarities, they are a histopathologically diverse group of diseases. Clinically, they are acute diseases that rapidly progress over weeks or months, or they may progress slowly over years. The final outcome in most chronic cases is death from respiratory failure due to end-stage interstitial fibrosis.[4–10]

In most cases, the lung biopsy will reveal a random pattern of interstitial chronic inflammation-fibrosis, which is also variable in severity from field to field. This histopathologic pattern was designated "usual interstitial pneumonia" (UIP) by Liebow, because it is the type most often encountered by pathologists.[11,12] Although the random distribution, asynchrony, and active progression of the lesions are distinguishing features of UIP, the individual lesions themselves show the same nonspecific features of most lung scars regardless of their extent or etiology.[1,2,13]

In 80% of patients, UIP is idiopathic; approximately 20% of patients have an associated collagen-vascular disease.[11,14,15] A nonspecific pattern of interstitial fibrosis that resembles idiopathic UIP (*i.e.*, UIP-like interstitial pneumonia-fibrosis) can be seen in a variety of conditions, including radiation pneumonitis and evolving viral pneumonias. Yet the interstitial fibrosis in these latter two categories results from organization of diffuse alveolar damage (DAD; see Chaps. 14 through 16).[1,2,11]

Lung biopsy in rare cases of interstitial pneumonia will disclose a histologic pattern different from that of UIP. Included in this group of chronic interstitial pneumonia with specific histologic features, also originally described by Liebow, are desquamative interstitial pneumonia (DIP), giant cell interstitial pneumonia, and lymphoid interstitial pneumonia; these disorders are discussed in Chapter 32.[11,12]

Other histologic patterns are often included in the interstitial pneumonias. The most notable of these is bronchiolitis obliterans with organizing pneumonia (BOOP) or cryptogenic organizing pneumonia,[16,17] also referred to by Liebow as bronchiolitis obliterans with interstitial pneumonia.[11,12] As discussed later in this chapter, late organizing BOOP may give rise to a UIP-like pattern of pneumonia-fibrosis. BOOP is described in Chapter 33. Finally,

the pneumoconioses, which are also important forms of restrictive lung disease, are conveniently grouped in this section (see Chaps. 34 through 37).

CONCEPTS AND TERMINOLOGY

The use of multiple clinical designations for the same pathologic process has led to considerable confusion in the nomenclature of interstitial lung disease. Some terms are regarded as specific entities, whereas others are used only descriptively. This lack of consensus can be found in both clinical and pathologic literature.

Idiopathic interstitial pulmonary fibrosis (IPF) and diffuse idiopathic interstitial fibrosis (DIF) are generally used synonymously with UIP and refer to interstitial pneumonia-fibrosis of unknown etiology and nonspecific histologic features.[5,6] Cryptogenic fibrosing alveolitis (CFA), a term popular in the United Kingdom, also refers to the same condition.[18,19] The designation "Hamman-Rich syndrome" should be reserved for rapidly progressive intraalveolar and interstitial pulmonary fibrosis, as originally applied.[20,21] Most of the cases reported by Hamman and Rich are now known to be organizing DAD or BOOP.[1,13] Other synonyms include idiopathic accelerated interstitial pneumonia[22] and acute interstitial pneumonia (AIP).[23] The term chronic Hamman-Rich syndrome has also been used for UIP, but this is probably not appropriate.

Some authors use IPF, DIF, CFA, and even Hamman-Rich syndrome to refer specifically to idiopathic UIP, whereas others use the term UIP to encompass all cases of interstitial disease of known or unknown cause, whether acute or chronic, and regardless of the histopathologic findings. In the latter approach, AIP, UIP, DIP, and sometimes other entities are all lumped together, assuming they are variants of the same disease.[18,24–26]

The tendency by some authors, particularly clinicians, to lump all interstitial pneumonias together probably arises, in part, from the following two facts: many of the clinical and radiographic findings are nonspecific and reflect any restrictive interstitial process, and all of these conditions are characterized by interstitial fibrosis and inflammation, which may potentially progress to the honeycomb lung. From a practical viewpoint, however, there are reasons to divide the interstitial pneumonias into different categories on the basis of their pathologic and clinical features, and regardless of any hypothetical relationships among them.

In addition to histopathologic differences between AIP and UIP, the rapid course over weeks of AIP is far different from the protracted course over years of UIP.[23] Aside from histopathologic differences, the clinical course and response to therapy are more favorable in DIP than in UIP.[27] Despite similarities in histopathologic appearance with idiopathic UIP, a UIP-like pattern of fibrosis due to a known cause, such as radiation or drug-induced disease, carries with it specific prognostic, therapeutic, and medicolegal implications.

ACUTE INTERSTITIAL PNEUMONIA

Although AIP can be distinguished from the chronic interstitial pneumonias on both clinical and pathologic grounds, this distinction has not always been made clear in the literature. Hamman and Rich are given credit for the first reports of idiopathic interstitial pneumonia in the modern literature.[20,21] In 1935 and 1944, they described a fulminant and rapidly progressive form of pulmonary fibrosis of unknown etiology that, in retrospect, represents organizing DAD.[1,13,23] Even after it became clear that most cases of interstitial pneumonia were chronic, the acute and chronic diseases were often grouped together under the term IPF, implying that they were variants of the same entity. Even Liebow included some cases of AIP in his category of UIP.[11,12]

In 1986, Katzenstein and colleagues proposed the term AIP for the acute disease to emphasize its clinicopathologic distinction from chronic UIP (Table 31-1).[23] AIP is clinically characterized by sudden onset of fever, cough, and shortness of breath accompanied by the development of bilateral diffuse infiltrates as seen on chest x-ray films. Most patients are relatively young with a mean age of 28 years. Respiratory failure requiring ventilatory support occurs within days, and the mortality rate is high, with death typically occurring in a matter of days or a few weeks. The gross, light microscopic, and ultrastructural features of AIP are those of the organizing phase of DAD and represent a pathologic correlate of the adult respiratory distress syndrome (ARDS; see Chap. 14).[13]

As noted, DAD is a nonspecific reaction to acute lung injury that can be caused by a large number of identifiable agents, including infections, noxious fumes and gases, trauma, drugs, radiation, oxygen toxicity, and ventilatory therapy. An exudative phase characterized by hyaline membranes and inflammation is followed by an organizing phase with active intraalveolar and interstitial fibrosis and type II pneumocyte hyperplasia. If the patient survives and the injury has been severe, residual interstitial fibrosis or even the honeycomb lung results.

Katzenstein and colleagues used the term AIP in reference to cases of unknown etiology, as in the classic Hamman-Rich syndrome.[23] Others use the term to encompass many cases of ARDS of known cause together with the idiopathic cases.

Grossly, the lungs in AIP are heavy, pinkish gray, and uniformly firm (Color Fig. 31-1). Histopathologically, there is diffuse fibrosis consistent with widespread, synchronous injury to the lung. The fibrosis is active with abundant fibroblasts and inflammatory cells in a loose, edematous stroma (Color Figs. 31-2 and 31-3; Fig. 31-1). The septa are lined by enlarged, hyperplastic type

TABLE 31-1
Acute Interstitial Pneumonia (AIP) *versus* Chronic Usual Interstitial Pneumonia (UIP)

	AIP	UIP
CLINICAL FEATURES		
Onset	Sudden	Insidious
Duration	Weeks to months	Years
Fever	Often	Unusual
HISTOPATHOLOGY		
Fibrosis		
Collagen	Immature	Mature
Distribution	Diffuse	Multifocal
Severity	Uniform	Variable
Airway or air space	Obvious	Modest
Hyaline membranes	Often present	Rare

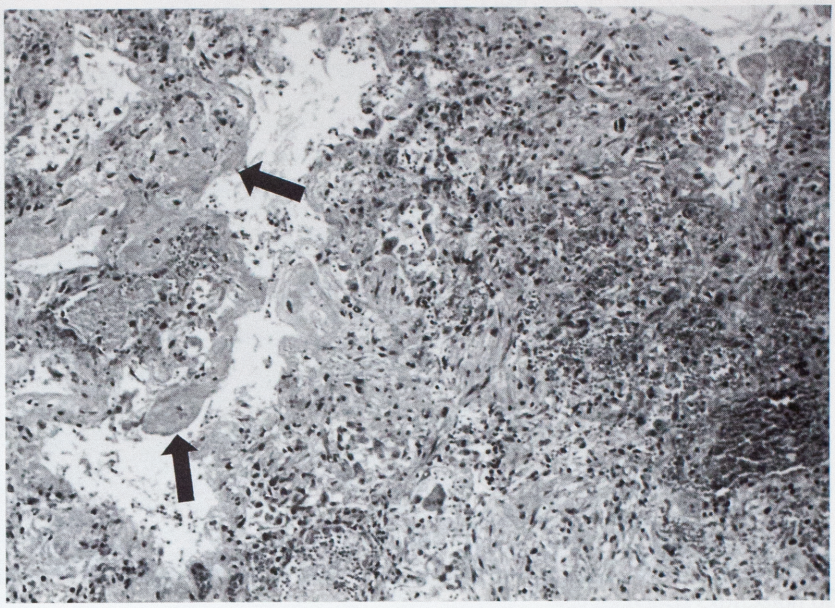

FIGURE 31-1. Acute interstitial pneumonia with residual hyaline membranes (*arrows*) produces abundant fibroblasts with acute and chronic inflammation. (H & E stain; low magnification.)

II pneumocytes sometimes exhibiting striking atypia. Other features include hyaline membranes, thrombi in the small pulmonary arteries, and squamous metaplasia of the bronchiolar epithelium. Later stages of the process show a more distinct interstitial pattern (Figs. 31-2 through 31-4).

Ultrastructural features include fragmentation, denudation and other abnormalities of the epithelial and capillary basement membranes, marked proliferation and atypia of type II pneumocytes and fibroblasts, and numerous inflammatory cells (*i.e.*, lymphocytes, plasma cells, and macrophages, with fewer mast cells and neutrophils).[23]

USUAL INTERSTITIAL PNEUMONIA

Idiopathic UIP is characterized clinically by insidious onset of cough and shortness of breath that slowly progress to respiratory failure. Over months and years, more and more lung parenchyma becomes involved, until end-stage fibrosis and the honeycomb appearance is reached. UIP is characterized not only by the increasing loss over time of functional parenchyma due to scarring but also by the random distribution of the scarring within the lung tissue.[1–13,27]

Although children and young adults may sometimes be affected,[28] most patients with idiopathic UIP are in the 40- to 70-year-old range, with a slight male preponderance.[1–13,27] Rare cases are familial,[28,29] although no human leukocyte antigen has been associated with the disease.[30] The most frequent presenting symptom in patients with UIP is shortness of breath followed by dry cough. Systemic symptoms such as fever are usually absent. Clinical findings include clubbing of the fingers (40%–80%), restrictive defects on pulmonary function tests, and increasing hypoxemia.

Chest x-ray films typically show reduced lung volume and small irregular interstitial densities predominantly in the lower lobes. However, the chest x-ray film may be initially normal in 14% of symptomatic patients with biopsy-proven UIP. Findings of pulmonary hypertension are found in some of the patients. These clinical, radiographic, and functional findings are, however, nonspecific and may be found in patients with other types of interstitial pneumonia.[1–13]

Findings on computed tomography (CT) are comparatively more specific than in conventional radiographs and consist of reticular densities and small cysts that are predominantly subpleural and in the lower lung zones.[31] There is evidence that opacification of air spaces on CT correlates with severe disease activity, identified by inflammation on biopsy.[32] Extent of disease on CT also correlates better with severity of clinical and functional impairment than it does in conventional radiographs.[33]

Idiopathic UIP is almost always a relentlessly progressive disease notorious for its failure to respond significantly to steroids or cytotoxic agents.[1–13,19] Single-lung transplant and bilateral sequential single-lung transplant are the most successful options for treatment.[34] A major association is the increased risk of lung cancer.[35,36]

For the pathologist, because of the haphazard distribution and progressive nature of the scarring, the gross appearance of the

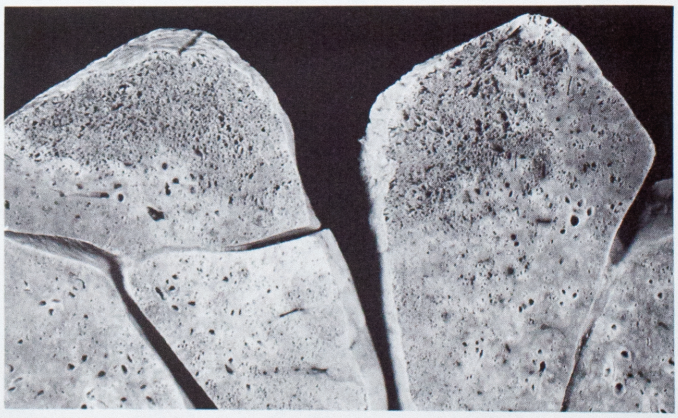

FIGURE 31-2. In lungs of a patient with acute interstitial fibrosis (*i.e.*, Hamman-Rich lung) of 7 weeks' duration, the apices are uninvolved by the process but show fine honeycombing. (Contributed by the editor.)

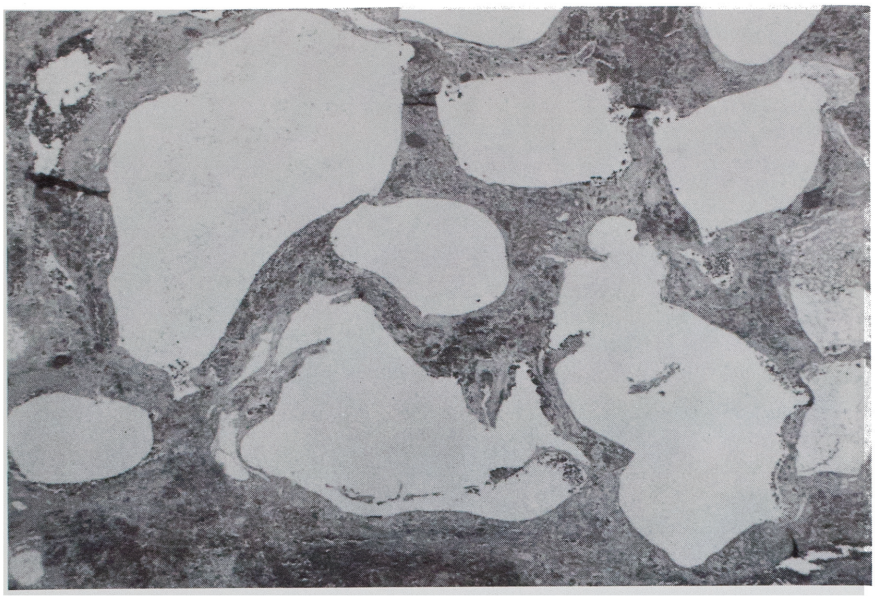

FIGURE 31-3. Simplification of alveolar tissue corresponds to early honeycombing in the same patient as in Figure 31-2. (H & E stain; low magnification; contributed by the editor.)

lung varies with the area examined as well as the overall stage of the disease. Lung tissue may appear grossly normal; it may exhibit areas of stiff, firm parenchyma or focal dense gray scars; or it may be extensively replaced by the honeycomb pattern, with cobblestoning of the overlying pleural surface (Fig. 31-5).

Histopathologically, the random, nonuniform foci of inflammation and fibrosis are consistent with multiple individual and asynchronous injuries to the lung. The foci of interstitial fibrosis are dominated by relatively highly collagenized, mature fibrosis, in contrast to the loose, edematous, and highly fibroblastic immature fibrosis of organizing DAD or BOOP. Foci of varying severity of fibrosis are found adjacent to each other or blending from one to another. There is a progression from normal to mild interstitial fibrosis, in which the basic architectural pattern of the alveoli is still retained, to severe fibrosis with focal honeycombing (Fig. 31-6).

This variation in severity may be found not only from section to area but also from area to area in the same tissue section. The fibrosis is accompanied by type II pneumocyte hyperplasia and patchy focal chronic inflammation, which is variable in intensity and is composed of lymphocytes, plasma cells, and macrophages. Other nonspecific features include epithelial metaplasia, smooth muscle hyperplasia, and blood vessel thickening.

Foci of loose, edematous, fibroblastic fibrous tissue may be found within air spaces, in bronchioles, or in the process of being incorporated into the alveolar septa.[37] This component, as noted above, is much less prominent than in AIP. Variable amounts of proteinaceous exudate and variable numbers of macrophages may be seen in the air spaces in UIP. The former must be differentiated from DAD, and the latter must be differentiated from DIP.

The differential diagnosis of idiopathic UIP includes the other interstitial lung diseases, particularly those that progress slowly to end-stage fibrosis. Because a UIP-like pattern can also be seen in association with known causes, it is important to make such a distinction because of prognostic, therapeutic, or medicolegal implications. Unfortunately, even when a UIP-like pattern has resulted from a specific cause, histopathologic clues to the specific etiology are frequently missing; in such cases, clinical history or systemic findings may be required to pinpoint the etiology.

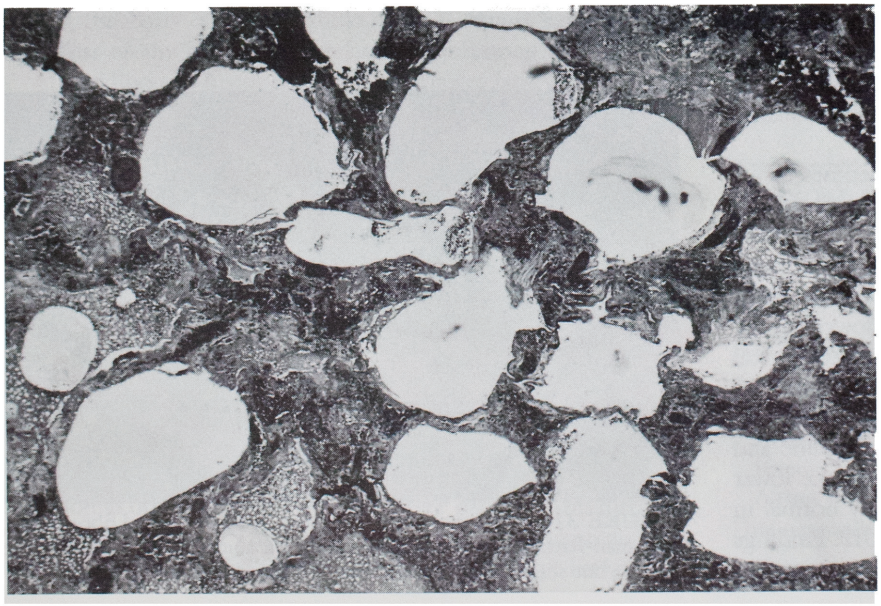

FIGURE 31-4. In the same patient as in Figures 31-2 and 31-3, interstitial fibrosis is darkly stained. (Masson trichrome stain; low magnification; contributed by the editor.)

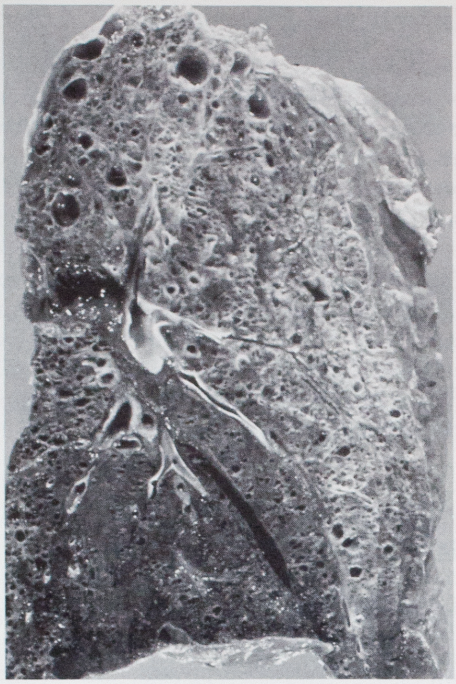

FIGURE 31-5. Honeycomb lung with cobblestoning of the pleura and dense fibrosis with residual cystic spaces that are more prominent in the periphery and upper lobe. (Courtesy of G.T. Hensley, M.D., Miami, FL.)

Pathogenesis

A great deal has been written on the pathogenesis of UIP or idiopathic pulmonary fibrosis. The actual etiologic agent or agents is unknown, but the histopathologic pattern and clinical course indicate that there are repeated multifocal episodes of injury throughout the lungs resulting in an ever-growing accumulation of minute interstitial scars over months and years. This is in sharp contradistinction to those forms of interstitial fibrosis in which the injury is acute and diffuse with a relatively synchronous development of fibrosis, as in AIP or the UIP-like patterns associated with organizing DAD and BOOP. However, at the cellular and subcellular level, similar anatomic and biochemical mechanisms probably apply regardless of the etiology.

Inflammatory cells and mediators, growth factors, and damage to the epithelium and epithelial basement membrane seem to be necessary components in the injury and repair that lead to interstitial fibrosis.[2] Immunologic factors probably have a role in initiating the injury. A wide variety of immune complexes have been described in idiopathic UIP, but their exact relationship to the development of fibrosis is unclear.[5,7]

Alveolitis precedes the development of fibrosis. Epithelial injury, damage to the basement membrane, and exudation are associated with activation of inflammatory cells.[2,38] Early studies emphasized increased numbers of neutrophils in the bronchoalveolar lavage fluid (BAL) of patients with IPF.[39] Other studies by BAL and histology have emphasized an increase in other cells, including eosinophils, lymphocytes, macrophages, Langerhans cells, and mast cells.[40–43]

BAL from IPF patients has also shown inflammatory mediators and growth factors, such as leukotriene B_4,[44] increased expression of CD2 molecules on T lymphocytes,[45] and increased expression of PDGF*B* (*i.e.*, c-*sis* gene) in macrophages.[46,47] The production and complex interactions of these and other inflammatory mediators and growth factors (*e.g.*, TGF-*B* tumor necrosis factor) lead to fibroblast proliferation and activation.

In addition to a direct increase in interstitial connective tissue, there is incorporation of intraalveolar fibrous tissue into the interstitium followed by reepithelialization. Alveolar collapse with fibrous adhesions between alveolar septa contributes to their thickening.[48] Fibrous contraction further adds to the distortion of parenchymal architecture.[49] The severity of the acute injury basically dictates the severity of the scarring.[50]

As noted, the UIP pattern of pulmonary fibrosis is characterized by the overall random distribution of fibrosis in which the individual constituents do not have unique diagnostic features. This process slowly progresses to end-stage fibrosis as the result of accumulation of the multifocal, asynchronous scars over months and years. Many authors limit the use of the term UIP to

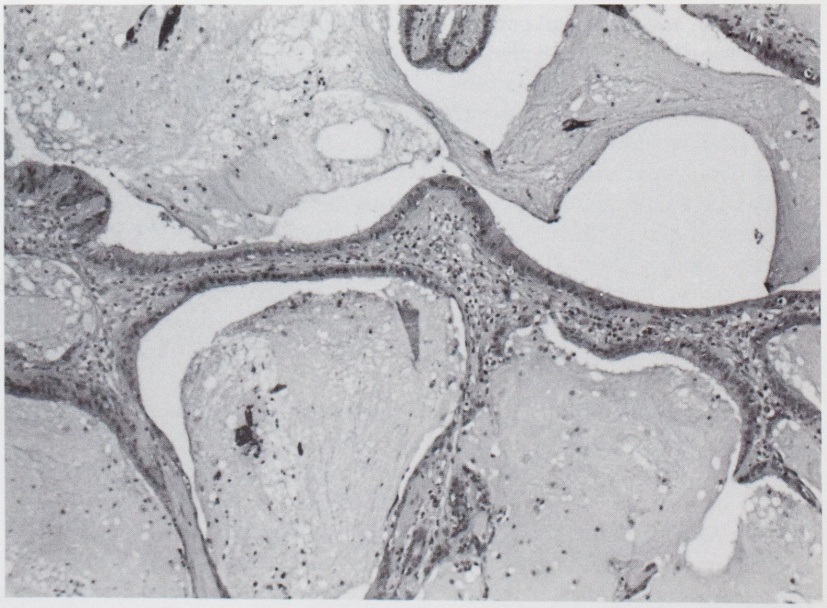

FIGURE 31-6. Honeycomb lung shows variably sized cystic spaces with fibrous walls lined by metaplastic bronchiolar epithelium. Mucus is present within the cystic spaces. (H & E stain; low magnification.)

this particular disease,[13] but some believe that collagen-vascular diseases[11,14,15] and asbestosis[51] may exhibit a pattern of interstitial fibrosis that is histopathologically indistinguishable from idiopathic UIP.

Usual Interstitial Pneumonia in Collagen-Vascular Diseases

Approximately 20% of patients with UIP have an associated collagen-vascular disease.[11,14,15] The relationship of the collagen-vascular disease to the development of UIP has not yet been elucidated, although both are presumably related to altered immune mechanisms. The background pattern of UIP in these diseases is histopathologically, clinically, and radiographically indistinguishable from idiopathic UIP and follows a similar clinical course.[52] Additional findings such as BOOP or rheumatoid nodules in rheumatoid arthritis may be associated with, or superimposed on, the UIP pattern.[52]

UIP associated with collagen-vascular diseases accounts for about 2% of deaths from all respiratory diseases.[15] Other types of pleuropulmonary lesions are generally more common in collagen-vascular diseases. The reported incidence of UIP in the various collagen-vascular diseases depends on the type of diagnosis (*e.g.*, function studies, chest x-ray, biopsy) as well as the patient population studied. Selection of patients with severe manifestations of collagen-vascular disease, especially hospitalized patients, apparently occurs in some studies.[14,15] It is not surprising, therefore, that these patients have a higher incidence of UIP than patients with milder collagen-vascular disease.

Reported incidences of UIP in rheumatoid arthritis have been as low as 1.6% to as high as 30% to 40%.[14,53] In patients with rheumatoid arthritis and active lung disease, Yousem and colleagues found UIP to be the dominant pattern of lung disease in 5 (12.5%) of 40 open lung biopsy specimens.[52] Although pleuropulmonary diseases are reported in 50% to 70% of patients with systemic lupus erythematosus, UIP is much less common and is reported in less than 1% to 6% of patients.[14,15]

Recurrent episodes of acute lupus pneumonitis, including vasculitis, hemorrhage, and interstitial pneumonitis, may cause residual interstitial pulmonary fibrosis. UIP leading to honeycomb lung is a characteristic feature of progressive systemic sclerosis (PSS), and almost all patients with clinically evident disease have some degree of restrictive lung disease.[14,15,54] UIP has also been reported in Sjogren syndrome,[55] polymyositis, dermatomyositis,[56,57] and mixed connective tissue disease (see Chap. 67).[58]

Pulmonary fibrosis resulting from gold or penicillamine therapy of rheumatoid arthritis most likely represents organizing DAD, BOOP, or an allergic alveolitis. Separating the histopathologic changes induced by therapy from those caused by the rheumatoid arthritis itself is generally not possible unless there is a clear temporal relationship to the drug therapy.[52,59] As with idiopathic UIP, UIP associated with collagen-vascular disease may be present on a lung biopsy specimen even when the chest x-ray film appears normal.

The prognosis of UIP in collagen-vascular diseases is generally poor, although there are reports, mostly anecdotal in nature, of response to steroids or cytotoxic agents. Lung transplant is an option in patients with advanced, life-threatening pulmonary fibrosis. As with idiopathic UIP, UIP in collagen-vascular diseases is associated with an increased risk of lung carcinoma. This is particularly true in PSS, in which the risk of lung carcinoma is reported to be 16.5 times higher than in the overall population.[60]

Usual Interstitial Pneumonia in Asbestosis

Asbestosis is discussed in detail in Chapter 36, but a few comments are warranted here. Asbestosis is diffuse pulmonary interstitial fibrosis due to inhalation of large numbers of asbestos fibers. The pattern of interstitial fibrosis is usually that of UIP and develops over many years. It does not become clinically manifest until after a long latency period. It may sometimes progress to end-stage fibrosis, even after exposure to asbestos has ceased. The histopathologic evidence for the etiology consists of asbestos bodies that are found in the tissue sections or by digestion of lung tissue.[51] Individuals who have a history of asbestos exposure may also develop idiopathic UIP, as noted in recent studies by Gaensler and colleagues[61] and Roggli,[62] and this should be distinguished from asbestosis on the basis of the number of asbestos bodies (Fig. 31-7).

THE USUAL INTERSTITIAL PNEUMONIA–LIKE PATTERN

Nonspecific pulmonary fibrosis with a UIP-like pattern may result from any of a large number of identifiable causes, including viral pneumonias,[1,2,11,12] *Mycoplasma* pneumonia,[63] extrinsic allergic alveolitis,[1,11] radiation pneumonitis,[64,65] iatrogenic drug reactions, beryllium, inhalation of toxic gases and fumes,[1,11] bone marrow transplant,[66] chronic aspiration of gastric acid,[67] cocaine abuse,[68] and so forth. In many of these cases, the fibrosis actually represents late organized DAD or BOOP.

In rarer cases, a diffuse, relatively uniform interstitial lymphoplasmacytic infiltrate with interstitial fibrosis may be present initially that lacks the temporally and spatially random pattern of typical UIP. The terms cellular interstitial pneumonia and, simply,

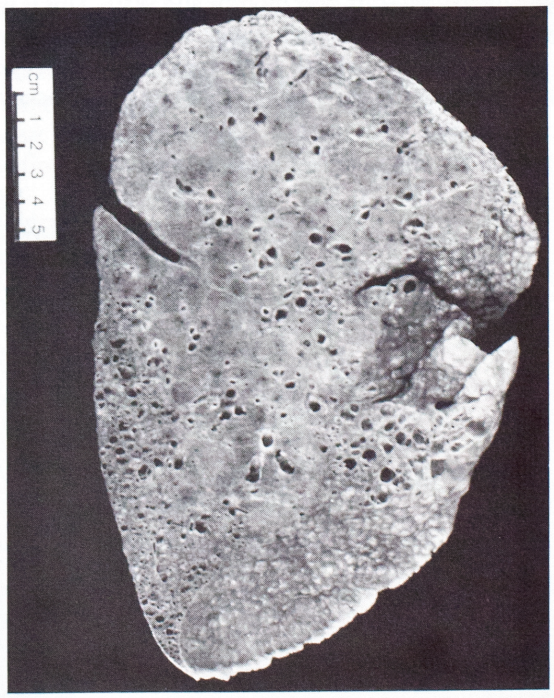

FIGURE 31-7. Usual interstitial pneumonia with honeycombing is present in an adult patient exposed to asbestos for many years in the automotive brake–lining industry. In spite of the patient's history, no significant amounts of asbestos bodies were seen in histologic sections or recovered by tissue digestion. (Contributed by the editor.)

TABLE 31-2
Causes and Identifying Features of Usual Interstitial Pneumonia (UIP) and UIP-Like Patterns

Etiology or Association	Additional Findings
UIP	
Idiopathic UIP	
UIP in collagen-vascular disease (e.g., rheumatoid arthritis)	Rheumatoid nodules, BOOP, pleuritis, prominent interstitial germinal centers, vasculitis
UIP in asbestosis	Asbestos bodies, pleural fibrosis, pleural plaques, airway lesions
UIP-LIKE PATTERNS	
Organizing DAD or BOOP	Bronchiolocentric fibrosis, residual hyaline membranes, viral inclusions as a result of viral pneumonia, vessel thickening and endothelial vacuolization as a result of radiation pneumonitis, bizarre or atypical cells as a result of radiation or drugs, especially antineoplastic agents
Extrinsic allergic alveolitis	Granulomas, BOOP, intense lymphoplasmacytic infiltrates
Sarcoidosis	Granulomas, Schaumann bodies, granulomatous vasculitis, basket-weave hyalinization

BOOP, bronchiolitis obliterans organizing pneumonia; DAD, diffuse alveolar damage.

interstitial pneumonia have been applied to this latter category of lesions.[1,13]

Cases of the UIP-like pattern differ from cases of idiopathic UIP in that the etiology or precipitating event is potentially identifiable; patients typically present with an acute, often single, episode of injury rather than a slow, insidious process; in the early stages the process may resolve or respond favorably to steroids; and even when scarring is permanent, it may not progress.

Microscopically, the inflammation and fibrosis are temporally more uniform and lack the varying age of lesions seen in idiopathic UIP (see Fig. 31-3). Regardless of the terminology used, these UIP-like forms of lung injury produce nonspecific interstitial inflammation and can progress to the honeycomb lung; for this reason they enter into the differential diagnosis of idiopathic UIP. Also, they should be distinguished from idiopathic UIP because of a better prognosis and a frequent favorable response to therapy.

Not all of these UIP-like cases have an acute phase. Radiation fibrosis, for example, may occasionally present as chronic fibrosis without a recognizable phase of DAD or acute radiation pneumonitis.[64,65] Recurrent, small aspirations of gastric acid may produce over time insidious, progressive fibrosis and honeycombing.

Some findings may be suggestive of a particular etiology (Table 31-2). Bronchiolar scarring tends to be a more prominent feature of fibrosis following organizing DAD or BOOP.[1] Vessel thickening and endothelial vacuolization may suggest radiation pneumonitis, although these changes are not pathognomonic (Figs. 31-8 and 31-9).[64] Viral inclusions may suggest a viral pneumonia as the cause of the process (see Chap. 42). In most cases, however, histopathologic clues to the etiology will be absent.[4,69] Clinical history may be important in eliciting a specific reason for a UIP-like pattern on biopsy. Further details can be found in the chapters on acute lung injury (see Chaps. 14 through 17).

SPECIAL STUDIES

UIP and honeycomb lung are diagnosed on the basis of the clinical, radiographic, gross, and routine histopathologic findings. Special diagnostic studies are usually of limited practical value. However, asbestos bodies are more readily identifiable on iron stain and particularly following digestion of lung tissue and quantitation of asbestos bodies (see Chap. 36). Immunohistochemistry or electron microscopy may disclose a virus in an interstitial pneumonia. Trichrome and elastic tissue stains may be useful in identifying obliterated airways or vessels and hypertrophic muscle.

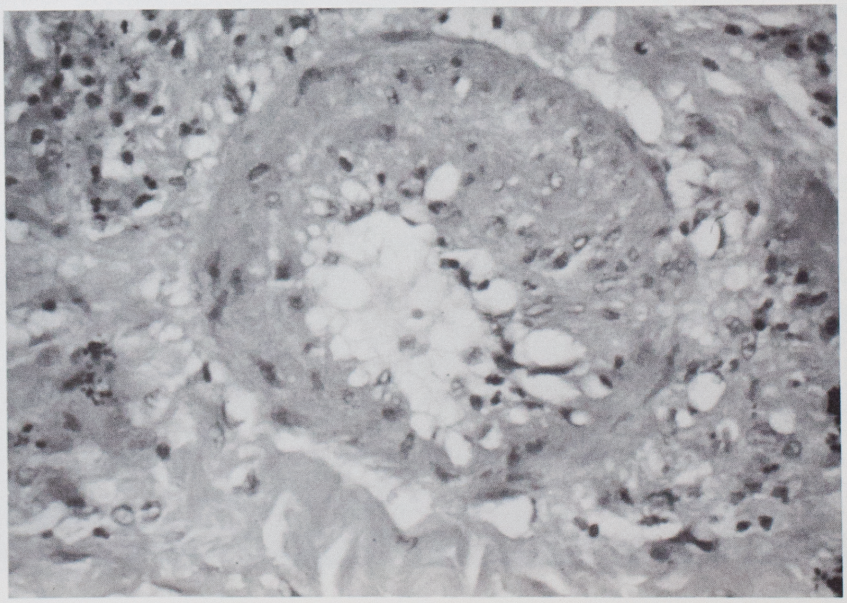

FIGURE 31-8. Endothelial vacuolization and vessel thickening occur in radiation fibrosis. (H & E stain; low magnification.)

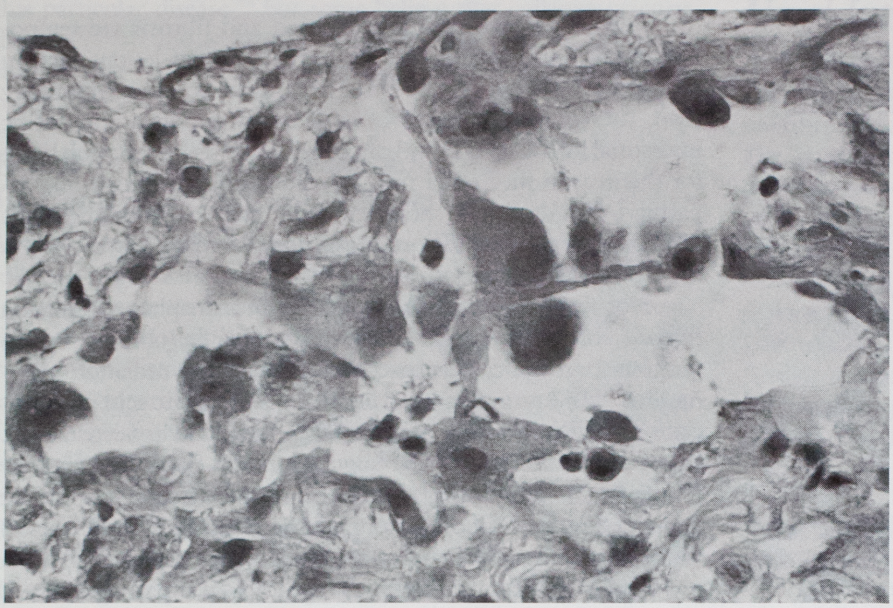

FIGURE 31-9. Marked alveolar cell atypia is present in another patient with radiation fibrosis. (H & E stain; intermediate magnification; contributed by the editor.)

TRANSBRONCHIAL VERSUS *OPEN LUNG BIOPSY*

Although transbronchial biopsy is fairly reliable in the diagnosis of carcinoma or sarcoidosis,[70,71] it is unsuitable for the diagnosis of interstitial pneumonia-fibrosis. Comparison of transbronchial biopsies with subsequent open biopsies has shown that the transbronchial biopsy is much less dependable.[72] This shortcoming is related to several factors:

- The biopsy specimens are small and there is a limited selection of biopsy sites.
- The small size of the biopsy specimens prevents recognition of the pattern and distribution of lesions.
- Fibrosis and inflammation are commonly seen around airways in unrelated conditions such as chronic bronchitis. Forceps often push together the alveolar walls, creating an artifact that may be overinterpreted as pneumonitis or fibrosis. Bronchial anchoring collagen fibers should not be misinterpreted as fibrosis.

Because of the larger sampling size, open lung biopsy permits examination of the pattern and distribution of fibrosis. Nevertheless, it is important that the open lung biopsy be representative of the process, a fact to be ascertained with frozen section before closing the patient's chest.[72,73] An attempt should be made to obtain the biopsy specimen from an area of active disease, because advanced scarring will often show only nonspecific changes. Thoracoscopy to obtain an open biopsy specimen avoids much of the morbidity of thoracotomy.

Many surgeons will automatically biopsy the lingula because of the ease of obtaining this particular tissue.[74] However, because of its unique anatomy, the lingula may be more subject to fibrosis and inflammation than other lung sites; therefore, it must be avoided.[75]

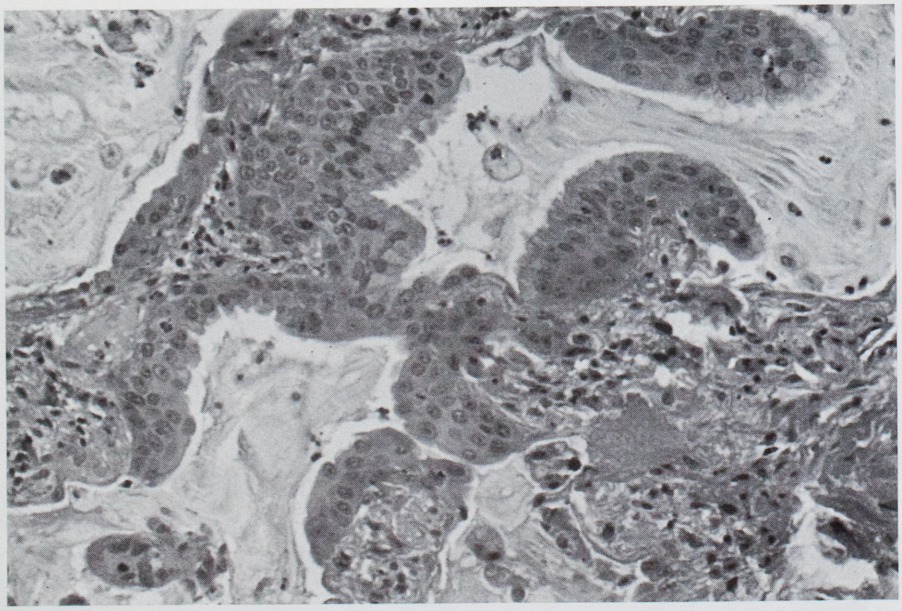

FIGURE 31-10. Metaplastic bronchiolar epithelium lines fibrotic alveoli in a patient with end-stage interstitial fibrosis. (H & E stain; intermediate magnification; contributed by the editor.)

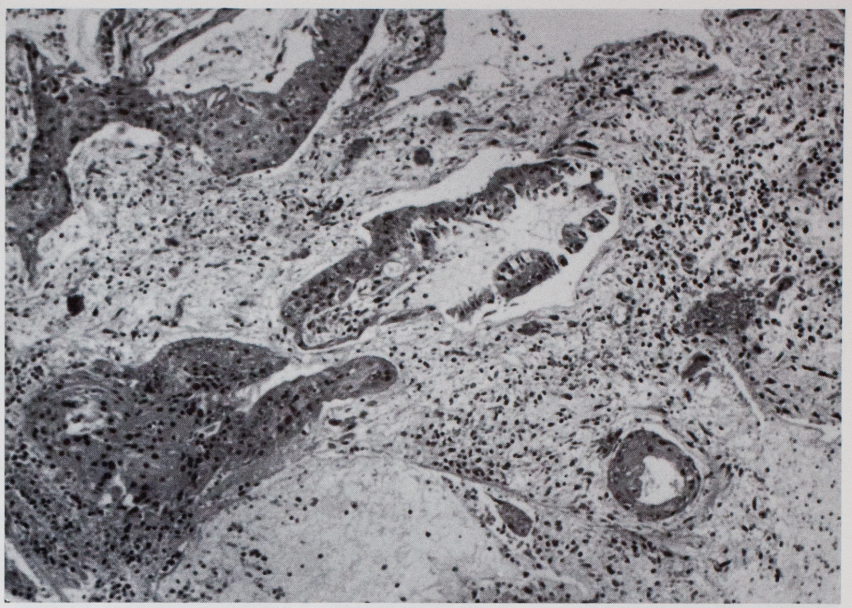

FIGURE 31-11. Metaplastic squamous epithelium lines residual air spaces and airways in a case of fibrosis due to diffuse alveolar damage. (H & E stain; low magnification.)

NONSPECIFIC FEATURES OF PULMONARY SCARRING

In interstitial lung disease, the fibrosis itself may be active and immature, characterized by fibroblastic proliferation and loose, edematous stroma, or more mature and less active and characterized by dense collagen and far fewer fibroblasts. With time, the active fibrosis of, for example, organizing DAD may progress to a residual scar. More active fibrosis may be admixed with less active established fibrosis. The distribution of the fibrosis (*i.e.*, airway-centered in BOOP *versus* random in UIP) may suggest a particular diagnosis.[1,2]

Reactive type II pneumocytes often line fibrotic alveolar septa. These cells are cuboidal to columnar with enlarged, hyperchromatic nuclei and occasional small intranuclear inclusions, and they exhibit reactive cytologic atypia that may be striking. This observation is noteworthy for two reasons: benign atypias that are common in scars should not be misdiagnosed as malignancies, and these atypias are suspected of being precursors to carcinomas that may arise in scars.[21,36] In addition to type II pneumocyte hyperplasia, metaplastic squamous epithelium can be seen in bronchioli (Fig. 31-10) and residual air spaces (Fig. 31-11).

Blood vessels in the areas of fibrosis, particularly small arteries, often display intimal fibrosis and medial hypertrophy and may even be obliterated (Fig. 31-12). Smooth muscle proliferation within the areas of scarring is common (Fig. 31-13) and occasionally striking and must be distinguished from a smooth muscle neoplasm, such as leiomyoma, by the comparatively random, un-

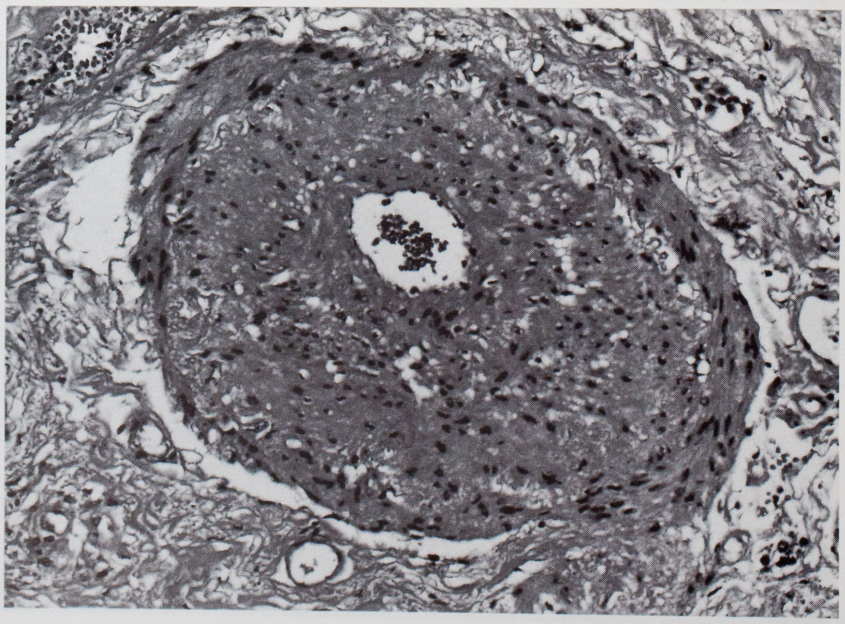

FIGURE 31-12. A markedly thickened blood vessel with severely narrowed lumen is seen in end-stage fibrosis. (H & E stain; low magnification.)

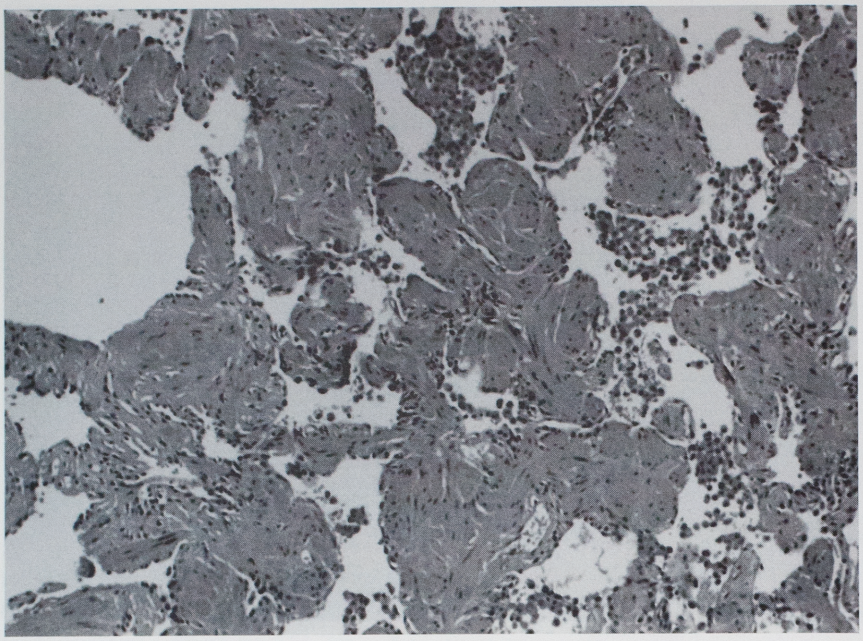

FIGURE 31-13. The thickened alveolar septae in this scar are composed almost entirely of smooth muscle. Note the intraalveolar collections of macrophages. This picture enters into the differential diagnosis of lymphangiomyomatosis (see Chap. 32). (H & E stain; low magnification.)

circumscribed arrangement of the fibers. Varying degrees of dystrophic calcification or ossification may sometimes be present within scars.

Tumorlets are small proliferations of cells that have features of microscopic carcinoid tumors (Figs. 31-14 and 31-15), and meningothelial-like bodies, which were called chemodectomas in the past, are occasionally present in scars (Figs. 31-16 through 31-18).[1] They are benign, incidental findings that are primarily curiosities. Intraalveolar collections of macrophages may be present in and around scars, causing a pseudo-DIP reaction that should be distinguished from true DIP (see Chap. 32).[76]

An advanced, highly collagenized scar is irreversible. Steroid therapy may be successful when there is a predominance of active inflammation over fibrosis, as in DAD or BOOP. Treatment with steroids is much more likely to be successful when an interstitial pneumonia has a significant component of active inflammation and fibroblasts relative to the amount of mature, inactive, fibrous connective tissue.

THE HONEYCOMB LUNG

Honeycombing is usually the common end stage of multiple fibrotic processes in the lungs, including those discussed in this and subsequent chapters (Display 31-1). Honeycombing may be focal and the result of a localized inflammatory process, or it may be bilateral, multifocal, or diffuse because of extensive disease. The term honeycomb lung is often used in the latter circumstance, but focal honeycombing may arise on localized scar.[1,2,10,13]

In areas of honeycombing, the lung architecture is completely and irreversibly effaced and replaced by nonfunctional cystic spaces with densely fibrotic walls. Grossly, the covering pleural surface has a nodular, cobblestone appearance as a result of fibrosis and retraction of the interlobular septa (see Fig. 31-6). On cut surface, the lung parenchyma is replaced by firm, dense, gray, fibrous tissue filled with cystic spaces of variable size. The multiple cystic spaces somewhat resemble the multiple cells or holes of a honeycomb.

Histopathologically, the cystic spaces may be lined by bron-

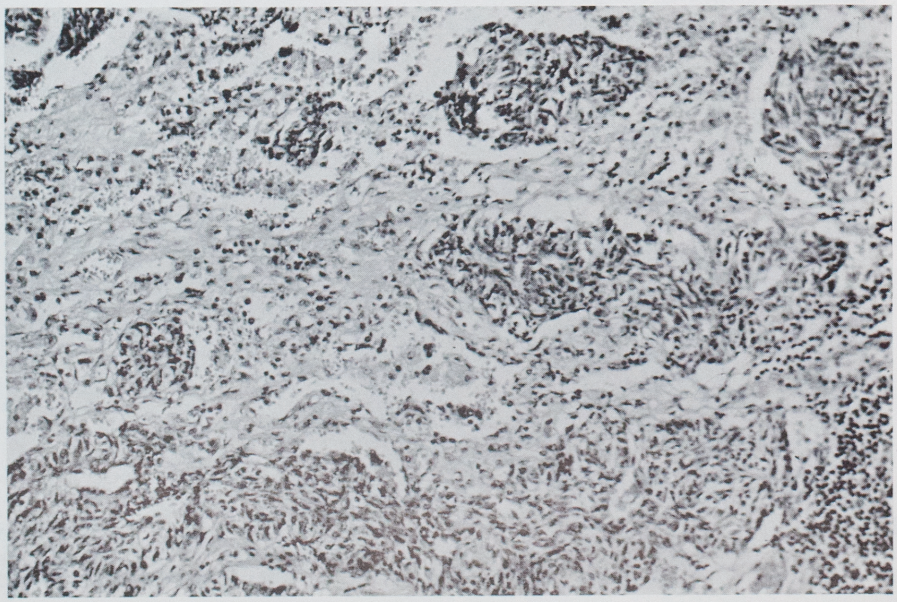

FIGURE 31-14. Multiple tumorlets are present in a patient with severe interstitial fibrosis. (H & E stain; low magnification; contributed by the editor.)

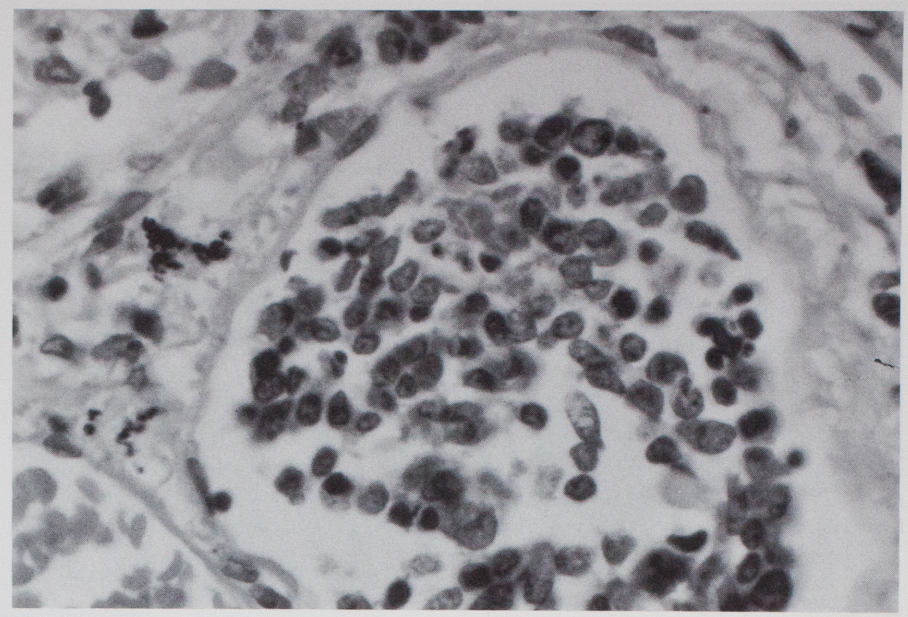

FIGURE 31-15. Higher magnification of Figure 31-14 shows a tumorlet composed of small cells with neuroendocrine features. (H & E stain; intermediate magnification; contributed by the editor.)

chiolar- or squamous-type epithelium and filled with variable amounts of mucus, macrophages, or neutrophils (see Fig. 31-6). Variable numbers of lymphocytes and plasma cells may infiltrate the fibrous tissue. Smooth muscle proliferation and vascular changes may be striking. Lung tissue adjacent to the honeycombing may be relatively normal and may provide clues as to the original pathologic process that led to the honeycombing.

Honeycombing has the same basic gross and histopathologic appearance regardless of the cause,[4] but its distribution may be characteristic in some diseases. For example, honeycombing in asbestosis is more prominent in the lower lobes. Unless residual areas of active disease are present or there are specific clues to the etiology, such as asbestos bodies in asbestosis, usually histopathologic examination does not disclose the cause of the honeycombing.

FOCAL SCARS AND OTHER COMMON FORMS OF LUNG FIBROSIS

Most focal scars are not of great clinical significance because they do not alter respiratory function. However, focal scars can have any of the histopathologic features seen on a wider scale in UIP or honeycomb lung, including type II pneumocyte hyperplasia, epithelial metaplasia, smooth muscle proliferation, and so on. Thus, a focal scar must be differentiated from a diffuse process when seen on a limited biopsy specimen, usually on the basis of the radiologic findings in the patient.

Focal scars result from a localized injury (*e.g.*, infection, trauma, infarct, aspiration), but in many cases the cause is not apparent. They may range in size from trivial microscopic foci to larger areas that may be detectable as coin lesions on chest x-ray films and

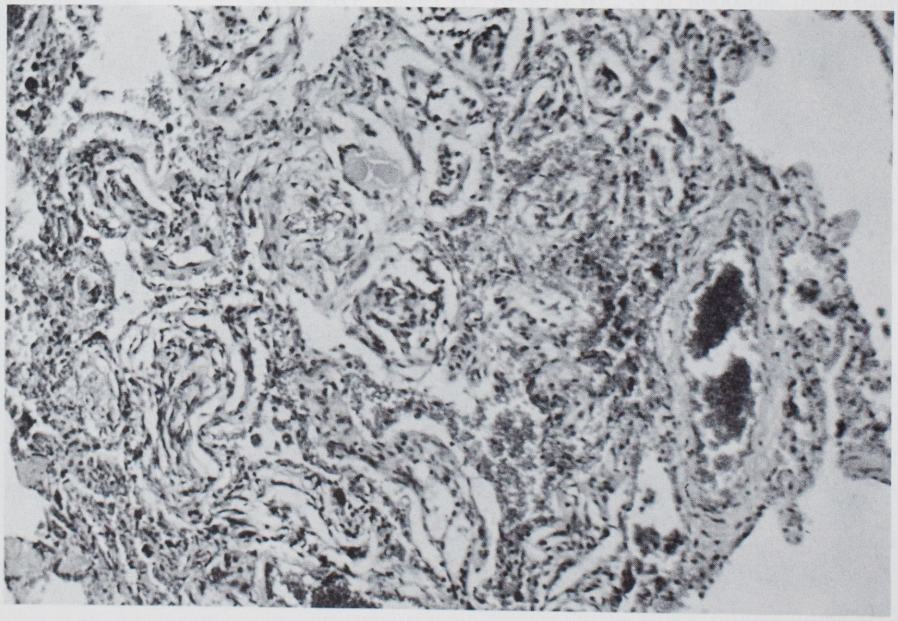

FIGURE 31-16. Microscopic view of a meningothelial-like body. The elongated cells are distributed in clusters around blood vessels. (H & E stain; low magnification; contributed by the editor.)

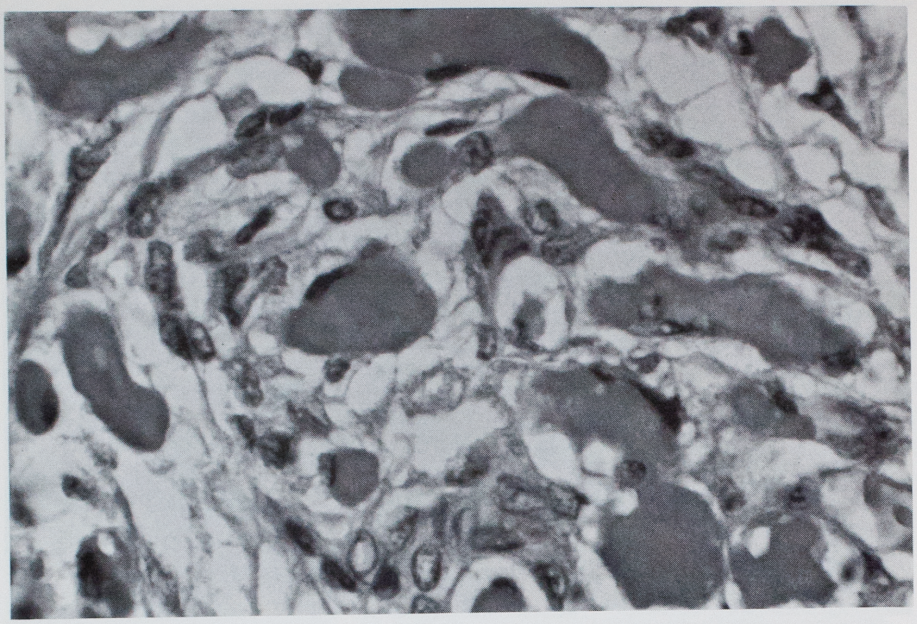

FIGURE 31-17. Detail of a meningothelial-like body shows congestion of the capillaries and intervening cells. (H & E stain; high magnification; contributed by the editor.)

perhaps excised if clinically suspicious for malignancy. Insignificant scars are often found when lung sections are examined in an autopsy. More extensive injury may result in scarring of considerable areas of lung tissue. When scarring is extensive, a specific history of a severe infection or major trauma is likely to be obtained.

Subpleural scarring may be associated with pleural fibrosis secondary to pleuritis or pleural effusions caused by infection, trauma, surgery, or collagen-vascular diseases, or it may be iatrogenic (Figs. 31-20 and 31-21).[2] A variety of inflammatory conditions, such as infection or allergic reactions, may produce scarring around airways and lungs of smokers, frequently with mild peribronchiolar fibrosis.[77] Centrilobular emphysema is, of course, not a form of interstitial fibrosis, but the residual dust-laden fibrovascular connective tissue, particularly in large subpleural bullae, may be misinterpreted as interstitial fibrosis or honeycombing.

PULMONARY FIBROSIS AND LUNG CANCER

Focal scars, interstitial fibrosis, and honeycomb lung may all potentially predispose to the development of lung carcinoma.[35, 36, 78] Most of the fibrosis seen in association with lung tumors represents a desmoplastic response similar to that seen in carcinomas elsewhere in the body. However, in a few cases, lung carcinomas do arise in a preexisting focal scar for which a cause, such as granulomatous inflammation, is evident.[78] Most of these are peripheral adenocarcinomas, particularly the bronchioloalveolar type (see Chap. 47). The percentage of focal scars that give rise to carcinoma must be relatively low given the sheer number of focal scars in the general population.

An increased risk for lung cancer is associated with extensive fibrosis like that seen in UIP. Approximately 10% of patients with idiopathic pulmonary fibrosis developed lung cancer in one series

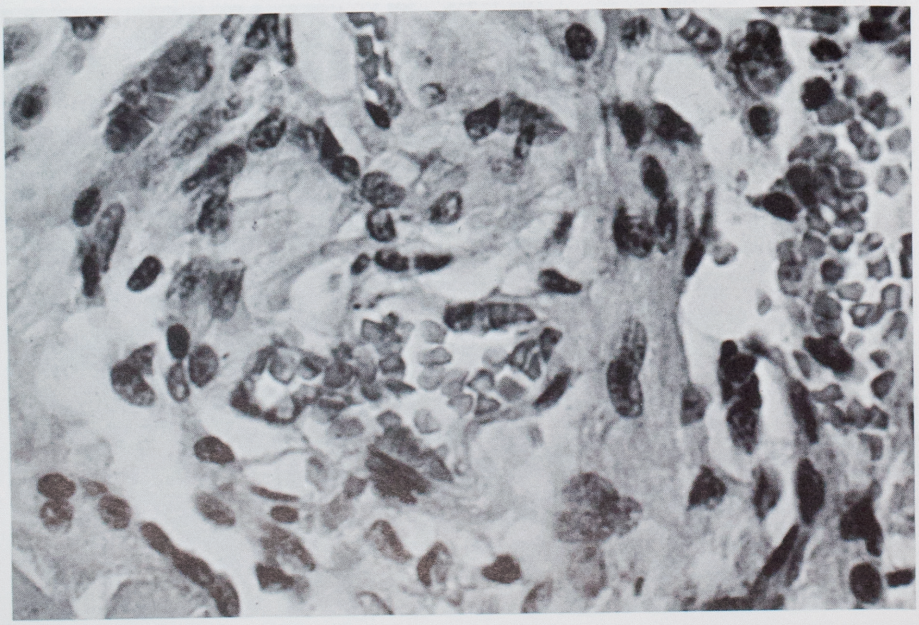

FIGURE 31-18. A meningothelial-like body is composed of bland spindle cells arranged in a Zellballen pattern around blood vessels. (H & E stain; intermediate magnification; contributed by the editor.)

DISPLAY 31-1. ANTECEDENTS OF HONEYCOMBING

Bilateral or Diffuse

Usual interstitial pneumonia
- Idiopathic
- Secondary to collagen-vascular disease

Organizing diffuse alveolar damage
- Idiopathic (*i.e.*, acute interstitial pneumonia)
- As a result of conditions such as infections, noxious fumes, and noxious gases
- Radiation pneumonitis, which may occur without an acute phase

Bronchiolitis obliterans with organizing pneumonia

Interstitial pneumonias with specific histopathologic features
- Desquamative interstitial pneumonia
- Giant cell interstitial pneumonia
- Lymphocytic interstitial pneumonia

Pneumoconioses (*e.g.*, asbestosis, berylliosis)

Sarcoidosis

Eosinophilic granuloma

Extrinsic allergic alveolitis

Infections (*e.g.*, healed granulomatous disease)

Recurrent aspiration

Focal

Focal inflammatory lesion
- Infection
- Trauma
- Infarct
- Aspiration
- Focal subpleural honeycombing with pneumothorax

of 205 patients.[36] The proportions of cell types were not different from those in lung carcinomas unassociated with preexisting fibrosis. Although most of these patients were also smokers, the ratio of the number of observed lung cancers to the number of expected lung cancers was increased even when smoking history was accounted for (14.2 for male smokers and 6.7 for female smokers).

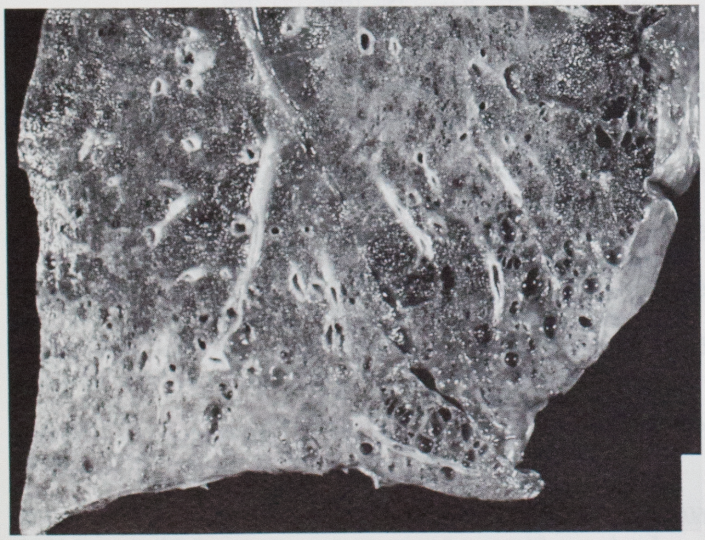

FIGURE 31-19. The left lung in a 65-year-old chronic alcoholic shows localized fibrosis and fine honeycombing at the base. These changes probably resulted from chronic aspiration. (Contributed by the editor.)

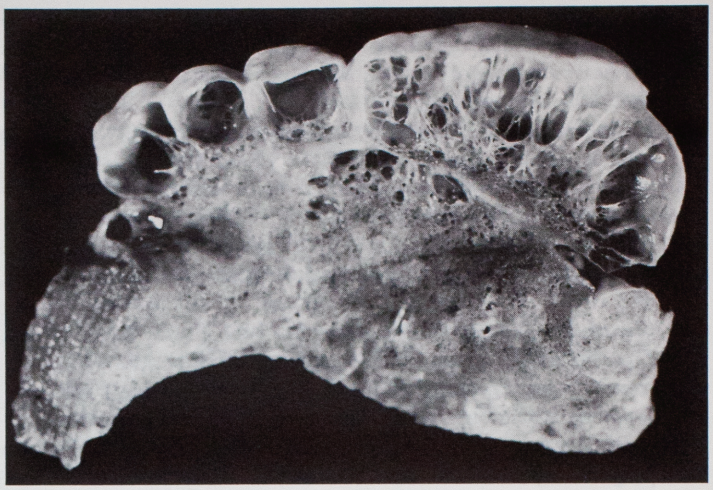

FIGURE 31-20. Subpleural honeycombing and fibrosis are present in a young male drug addict with a history of pneumothorax. (Contributed by the editor.)

The risk for lung cancer is also increased in UIP associated with collagen-vascular disease[60] and with asbestosis.[51] The reason scarring might predispose to a carcinoma is not known, but the atypical hyperplastic epithelium that often lines fibrotic interstitium is thought to be a potential precursor to malignant epithelium (see Figs. 31-10 and 3-11).[35] Perhaps the same growth factors and oncogenes that have stimulated fibroblast growth in these diseases also stimulate epithelial cell growth.[79]

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