The idiopathic interstitial pneumonias are part of the wide spectrum of diffuse parenchymal lung diseases (Fig. 19.1). While recognition of diffuse interstitial pulmonary fibrosis can be traced back to studies by Hamman and Rich in the 1930s and 1940s, they were first classified as a set of histopathologic patterns in the 1960s by Liebow and Carrington into usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP), bronchiolitis obliterans with interstitial pneumonia (BIP), giant cell interstitial pneumonia (GIP) and lymphoid interstitial pneumonia (LIP). At about the same time, Scadding in the United Kingdom proposed the term fibrosing alveolitis, suggesting (incorrectly) that DIP and UIP were early and late phases of a single disorder. There has subsequently been much discussion and controversy over what patterns should be included in such a classification system, in terms of both histology and what these patterns represent regarding clinical disease. As a result, some patterns have now been categorized according to their recognized causes; for example, GIP has been reclassified as a pneumoconiosis, the cause being exposure to cobalt during the production of hard metals or during diamond polishing (see Chapter 26). Other patterns such as LIP were reclassified as preneoplastic disorders in the context of lymphoproliferative disease during the 1980s and 1990s (see Chapter 32), but with greater understanding of the pathogenesis of pulmonary lymphomas through proteomics and genomics, cases are again treated more as interstitial pneumonias.

In addition to this greater understanding of pathogenesis in relation to the five initial histopathologic patterns, new histopathologic patterns have been described, such as respiratory bronchiolitis-associated interstitial lung disease (RBILD) and nonspecific interstitial pneumonia (NSIP), as well as new clinicopathologic entities such as acute interstitial pneumonia (AIP), leading to proposed revisions (Table 19.1).

However, the usage of both new and old terminology was not without problems. First, terms were being used in different ways by clinicians and pathologists, some as purely histopathologic patterns, some as clinical diseases, and some as both. For example, in the 1980s and 1990s, idiopathic pulmonary fibrosis (IPF) and cryptogenic fibrosing alveolitis (CFA) described the same well-defined clinical entity, but had different histopathologic equivalents; IPF was said to show only a pattern of UIP, while CFA encompassed a wider range of patterns, including UIP and DIP. Second, some terms were not histogenetically accurate; for example, DIP is neither desquamative nor predominantly interstitial. Third, more recently described patterns such as NSIP were poorly characterized in terms of their clinical correlates. Yet, despite these shortcomings, evidence accumulated from around the world that recognition of these histopathologic patterns provides significant prognostic data.

The 1990s also saw a meteoric rise in the importance of the high-resolution computed tomography (HRCT) for diagnosing any diffuse parenchymal lung disease, especially interstitial pneumonias, and all these factors, therefore, led to the creation of an American Thoracic Society/European Respiratory Society-sponsored committee comprising clinicians, radiologists, and pathologists, who then developed and proposed a consensus classification system for idiopathic interstitial pneumonias (Table 19.2) and an algorithm for its usage (Fig. 19.3). This classification, based on seven histopathologic patterns, has become the cornerstone for interpreting surgical lung biopsies in this setting, although it is not without its critics and is already undergoing refinement in relation to smoking-related disease and new patterns of disease described since 2002.

**When and What to Biopsy**

The diagnostic accuracy of HRCT in identifying patients with a UIP pattern in IPF/CFA is now such that patients seldom come to biopsy. Indeed in the United Kingdom,
Diffuse parenchymal lung disease

- DPLD of known cause, e.g., drugs or association, e.g., collagen vascular disease
- Idiopathic interstitial pneumonias (IIP)
  - Idiopathic pulmonary fibrosis (IPF)
  - IIPs other than IPF
    - Desquamative interstitial pneumonia
    - Respiratory bronchiolitis-associated interstitial lung disease
    - Acute interstitial pneumonia
    - Cryptogenic organizing pneumonia
    - Nonspecific interstitial pneumonia (provisional)
    - Lymphoid interstitial pneumonia
- Granulomatous DPLD, e.g., sarcoidosis
- Other forms of DPLD, e.g., LAM or HX

**Figure 19.1.** Spectrum of diffuse parenchymal lung disease (DPLDs). HX, histiocytosis X; LAM, lymphangioleiomyomatosis. (Adapted from American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias, with permission. Copyright © 2002, American Thoracic Society.)

**Table 19.1.** Proposed classifications of interstitial pneumonias

| Liebow and Carrington (1969) | Katzenstein and Myers (1998) | American Thoracic Society/European Respiratory Society Consensus (2002) |
|-----------------------------|-----------------------------|-----------------------------------------------------------------------|
| Usual interstitial pneumonia | Usual interstitial pneumonia | Usual interstitial pneumonia |
| Desquamative interstitial pneumonia | Desquamative interstitial pneumonia/respiratory bronchiolitis interstitial lung disease | Desquamative interstitial pneumonia |
| Bronchiolitis obliterans interstitial pneumonia | Acute interstitial pneumonia | Respiratory bronchiolitis |
| Lymphoid interstitial pneumonia | Nonspecific interstitial pneumonia | Organizing pneumonia |
| Giant cell pneumonia | | Diffuse alveolar damage |

**Figure 19.2.** Survival graphs from the United States (A) and from the United Kingdom (B), show variations in prognosis associated with histologic patterns of interstitial pneumonia. NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia. (A and B reprinted with permission from, respectively, Bjoraker et al., with permission; and Nicholson et al., with permission. Copyright © 2000, American Thoracic Society.)
TABLE 19.2. Histologic patterns of interstitial pneumonias and clinicopathologic counterparts in an idiopathic setting

| Histopathologic pattern                  | Clinicopathologic diagnosis                                    |
|-----------------------------------------|-----------------------------------------------------------------|
| Usual interstitial pneumonia (UIP)       | Cryptogenic fibrosing alveolitis (CFA)/idiopathic pulmonary fibrosis (IPF) |
| Nonspecific interstitial pneumonia (NSIP)| Nonspecific interstitial pneumonia*                             |
| Organizing pneumonia (OP)                | Cryptogenic organizing pneumonia                                 |
| Diffuse alveolar damage (DAD)            | Acute interstitial pneumonia                                    |
| Desquamative interstitial pneumonia (DIP)| Desquamative interstitial pneumonia                               |
| Respiratory bronchiolitis (RB)          | Respiratory bronchiolitis-associated interstitial lung disease (RBILD) |
| Lymphoid interstitial pneumonia (LIP)    | Lymphoid interstitial pneumonia                                  |

*Provisional term for clinicopathologic diagnosis.

Source: American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias,24 with permission. Copyright © 2002, American Thoracic Society.

only 40% of patients with IPF/CFA undergo any form of biopsy: 28% have a transbronchial biopsy and 12% a surgical lung biopsy.25 Indeed it is often the atypical cases (Fig. 19.3), in relation to either presenting signs and HRCT data, or unusual longitudinal behavior, that generally lead to sampling of tissue.26

When tissue is sampled, a surgical biopsy is nearly always required to determine the pattern of interstitial pneumonia, and is now usually obtained at video-assisted thoracoscopy. Typically, the physician, radiologist, and surgeon discuss the case prior to operation, to determine the area(s) where disease activity is thought to be best

**Figure 19.3.** The diagnostic process in diffuse parenchymal lung diseases (DPLDs) begins with a clinical evaluation that includes a history, physical examination, chest radiograph, and lung function tests. On the basis of the information, patients may be divided into two groups: those who do not have idiopathic interstitial pneumonia (IIP) and those who could have IIP. Patients in the latter category are further evaluated with high-resolution computed tomography (HRCT). This generally results in four categories of patients: (1) those with distinctive features that enable a confident diagnosis of idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP), (2) those with atypical clinical or HRCT features of IPF, (3) those with features diagnostic of another DPLD, and (4) those with suspected other forms of DPLD. Although some patients go directly to surgical lung biopsy, others undergo only transbronchial biopsy or bronchoalveolar lavage (BAL). If these findings are nondiagnostic, a surgical lung biopsy may then be necessary to separate the various IIPs from non-IIP DPLD. DAD, diffuse alveolar damage; DIP, desquamative interstitial pneumonia; LIP, lymphoid interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; PLCH, pulmonary Langerhans’ cell histiocytosis; RB, respiratory bronchiolitis; TBB, transbronchial biopsy. (From American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias,24 with permission. Copyright © 2002, American Thoracic Society.)
represented, so that the biopsy is most likely to provide diagnostic tissue. Studies suggest that taking biopsies from multiple sites also reduces sampling error and provides more valuable prognostic data. It is also especially important to avoid areas of end-stage lung (fortunately the days of receiving solely the tip of the right middle lobe or lingula are largely over) (see Chapter 1). Historically, such cases have always been reported as being “consistent with IPF/CFA,” and it is true that most cases of end-stage lung are the result of UIP. However, studies looking at the ability to differentiate end-stage UIP from other end-stage disorders such as NSIP have shown poor interobserver reproducibility, and it is preferable to classify these changes as no more than end-stage lung or honeycomb lung rather than assign a histopathologic pattern. As stated above, such areas can be avoided by preoperative discussion in order to select the ideal site for biopsy, otherwise HRCT data are usually of more value than the biopsy.

Opinion is divided as to whether biopsies should be inflated with formalin upon receipt in the laboratory, in that this process improves morphology and fixation, but runs the risk of both washing out diagnostic features such as accumulation of macrophages and distorting the architecture if undertaken in too zealous a fashion. My approach is to undertake very gentle injection of formalin only. Sampling of fresh frozen tissue and for electron microscopy is also recommended in case other rare forms of diffuse parenchymal lung disease are unexpectedly found on microscopy and further investigations are required, although this tissue is not processed in the majority of cases.

Transbronchial biopsy may establish an alternative diagnosis, but will not provide tissue for the diagnosis of UIP or NSIP. However, it may be of value in confirming organizing pneumonia (OP) and, in the last few years, has provided sufficient data in classic cases of RBILD to provide a diagnosis without recourse to surgical lung biopsy, an example of how advances in translational research between pathogenesis and investigative modalities such as HRCT have influenced management (see Chapter 1).

Usual Interstitial Pneumonia and Idiopathic Pulmonary Fibrosis

Usual interstitial pneumonia is the most common histopathologic pattern seen in cases of idiopathic interstitial pneumonia, and in most cases it correlates clinically with IPF, also known as CFA (see below).

Histopathologic Features

Usual interstitial pneumonia is characterized primarily by progressive chronic fibrosis of the parenchyma that is more marked at the periphery of the lungs and in the lower lobes, both macroscopically (Fig. 19.4) and microscopically. At an acinar level, the changes are characteristically subpleural or paraseptal in distribution, typically being sharply demarcated from areas of normal or nearly normal alveolar lung (Fig. 19.5). This low power distribution is one of the cardinal features of UIP. The other cardinal feature is localized areas of fibroplastic proliferation termed fibroblastic foci that abut the areas of established fibrosis. The fibroblastic foci comprise an abundance of plump spindle cells and little intervening collagen, compared to the poorly cellular hyalinized collagen seen in a lung in idiopathic pulmonary fibrosis shows extensive peripheral honeycombing.
areas of established fibrosis (Fig. 19.6). This variation in the age of fibrosis is termed by some as “temporal heterogeneity,” and the patchy distribution as “spatial heterogeneity.” These fibroblastic foci are thought to represent the sites of repeated and continued lung damage, not least because the extent of these foci is associated with mortality and an increased rate of disease progression. However, although there have been significant advances in understanding the pathogenesis of IPF/CFA, the exact cause remains unknown.

In association with the fibrosis, there is a chronic inflammatory cell infiltrate of usually mild and no more than moderate intensity, mainly comprising small lymphocytes with occasional plasma cells. Aggregates of B lymphocytes may also be present, although these are not usually prominent in idiopathic disease. Small aggregates of inflammation and vascularity may be seen immediately beneath the fibroblastic foci (Fig. 19.6). As the disease becomes more advanced, alveolar architecture is increasingly lost with the eventual formation of cysts separated by bands of fibrosis, so-called end-stage lung or honeycombing. These dilated air spaces show varying degrees of bronchiolization and, less commonly, goblet cell hyperplasia. Features such as smooth muscle hypertrophy, type 2 cell hyperplasia, endarteritis obliterans, osseous metaplasia, and squamous metaplasia are also found in UIP, but these are likely to be secondary phenomena and are not specific to this pattern (Fig. 19.7). Occasionally, eosinophilic pneumonia-like areas may be seen in UIP. These patients are described as slightly younger at presentation, although prognosis appears similar to cases without such
Figure 19.7. Examples of the more commonly seen secondary changes in usual interstitial pneumonia: A. Smooth muscle hypertrophy. B. Type 2 cell hyperplasia. C. Endarteritis. D. Squamous metaplasia. E. Osseous metaplasia.
areas. How these cases relate to levels of eosinophils in bronchoalveolar lavage (BAL) is also unknown.\(^3\) The histopathologic features of UIP are summarized in Table 19.3.

### Clinicopathologic Correlation

Idiopathic pulmonary fibrosis (IPF)/CFA is the clinical correlate for a histopathologic pattern of UIP in the vast majority of patients. However, a minority of patients have other disorders, such as chronic hypersensitivity pneumonia (see Chapter 17) and drug toxicity (see Chapter 22). A pattern of UIP is also described in association with collagen vascular diseases (see Chapter 20), asbestosis (see Chapter 27), and Hermansky-Pudlak syndrome (see Chapter 16). Because these latter disorders are discussed in other chapters, only IPF/CFA is discussed here.

#### Idiopathic Pulmonary Fibrosis

**Clinical Presentation**

Patients with IPF/CFA have chronically progressive disease with a mean survival from the onset of dyspnea of 2 to 3 years (Fig. 19.2).\(^3\)\(^,\)\(^4\)\(^,\)\(^14\)\(^,\)\(^20\)\(^,\)\(^26\)\(^,\)\(^41\) Most patients present over the age of 50 years and the disease is twice as common in males. Early studies have suggested smoking as a risk factor, although more recent data argue against this.\(^42\) There is no geographic or ethnic predilection. Rarely, the disease may be familial.\(^43\) Symptoms include dyspnea, dry cough, and loss of weight. Inspiratory bilateral basal crackles are heard, and there is often clubbing of the fingers. Lung function tests show restrictive abnormalities. In terms of imaging, chest x-rays typically show small lung fields and irregular reticulonodular or nodular shadows at the periphery and bases of the lungs. In advanced disease, honeycomb shadows and features of pulmonary hypertension may also be seen. However, the chest x-ray has been largely superseded by HRCT since the early 1990s, and the features are virtually pathognomonic in classic cases of IPF; these being bilateral coarse irregular reticular changes that predominate in a subpleural and peripheral distribution (Fig. 19.8). Traction bronchiectasias and honeycomb change are also frequently seen. A ground-glass pattern may also be present.\(^24\) Serologic investigations may show a raised erythrocyte sedimentation rate, and there may also be antinuclear antibodies or rheumatoid factor present in about one third of patients, although the titers are usually low compared to those patients with pulmonary fibrosis associated with connective tissue disorders abnormalities. Bronchoalveolar lavage is a further investigative tool that has had impact on research and to a lesser degree management of these patients, via assessing the differential cell count within fluid injected into and then aspirated from the peripheral lung.\(^44\)\(^,\)\(^45\) In a typical patient with IPF, there is an increase in the overall cell count with excess neutrophils and, to a lesser extent, eosinophils (Fig. 19.9). The presence of increased neutrophils and eosinophils has been associated with a worse prognosis in patients classified as CFA,\(^46\) and more recent studies looking specifically at UIP support the earlier data,\(^47\) although neutrophils may merely reflect severity whereas eosinophils may reflect future disease progression.\(^48\) A lymphocytosis is comparatively rare and warrants investigation of other causes of pulmonary fibrosis, particularly chronic hypersensitivity pneumonia.\(^44\)\(^,\)\(^47\)

**Treatment and Prognosis**

There is no standard or optimal treatment for IPF, but the consensus view is that first-line treatment should consist of low-dose prednisolone together with immuno-suppression using drugs such as azathioprine or cyclophosphamide.\(^13\) There are also several potential drugs
that are undergoing clinical evaluation at present that target various cytokines related to the development of fibrosis. Of these recent trials, data suggest that interferon-γ and N-acetylcysteine may provide additional benefit to the patient, but these drugs are yet to be fully evaluated. Transplantation, often of a single lung, is an alternative treatment option, although this is clearly dependent on constraints of organ availability.

Prognosis is poor, with more recent studies showing 50% survival of less than 3 years. Death is usually due to respiratory failure, either chronically progressive or due to an acute exacerbation (see Diffuse Alveolar Damage and Acute Interstitial Pneumonia, below), cardiac failure, or lung cancer. Idiopathic pulmonary fibrosis was found to have a 14-fold increased risk of carcinoma of the lung in patients matched for age and smoking (see Chapter 34). The tumors may be of any histopathologic type, more commonly non–small-cell carcinomas. These carcinomas may be resectable during life, but operative mortality is higher. Various clinical and pathologic features are related to prognosis, although some (for example, cellular versus fibrotic phases) may reflect other histopathologic patterns that were historically included in cohorts of patients with cryptogenic fibrosing alveolitis. Clinical parameters associated with a longer survival include younger age (<50 years), female sex, shorter symptomatic period (<1 year) with less dyspnea and relatively preserved lung function, the presence of ground-glass and reticular opacities on HRCT, an increased proportion of lymphocytes on BAL fluid, a beneficial response or stable disease 3 to 6 months after corticosteroid therapy, and current cigarette smoking. Lung function data in the form of a composite physiologic index and longitudinal behavior also helpful regarding the prognosis. In addition, the extent of fibroblastic foci is associated with disease progression and mortality, a finding that dovetails with the increasingly held view that IPF is related to epithelial damage and dysregulation of repair.
Pathogenesis

The histopathologic features of IPF suggest that the disease results from repeated episodes of focal damage to the alveolar epithelium. However, the injurious agent or agents are not known, with viruses, occupational agents, gastric reflux, and drugs all being putative candidates. However, no single agent appears to play a causative role. There are also features in common with pulmonary fibrosis seen in association with connective tissue disorders, with serologic investigations not infrequently showing hyperglobulinemia and the presence of autoantibodies such as rheumatoid factor. Other studies have shown antibodies directed against the alveolar epithelium. Therefore, IPF/CFA may represent a form of autoimmune disease with the alveolar epithelium as the target tissue. Genetic susceptibility may also play a role, with functional polymorphisms for various cytokines associated with increased incidence of IPF and familial cases being associated with mutations related to the surfactant protein-C gene.

Considerable research effort is now concentrated on the alveolar epithelial cells as the site of initial injury. The hyperplastic pneumocytes express numerous profibrotic cytokines, including transforming growth factor-β (TGF-β), as well as other cytokines that may inhibit cell migration and therefore repair of damaged alveoli. This lack of reepithelialization in part may also be due to increased pneumocyte apoptosis and cell death, perhaps promoted by cytokines the epithelial cells and myofibroblasts secrete, such as TGF-β. The loss of epithelium, with apposition of basement membranes and subsequent collapse likely contributes to the remodeling process, and this dysregulation of repair may also drive sustained fibroblastic proliferation in the underlying stroma. As stated earlier, the extent of these fibroblastic foci correlates with the rate of disease progression and mortality. The fibroblasts show an altered typically myofibroblastic phenotype that reflects activation with regard to production of extracellular matrix proteins. Persistence of this activated phenotype likely contributes to development of chronic fibrosis and remodeling, along with a reduced capacity for degradation of extracellular matrix proteins, through imbalances between matrix metalloproteinases and their tissue inhibitors. A detailed review of the various cytokines has recently been published by Thannickal et al. (Fig. 19.10).

However, although emphasis has shifted away from IPF’s being a disease driven by inflammation, inflammatory cells still likely play significant roles in modulating disease. Lymphocytes are the predominant interstitial inflammatory cell in IPF, largely comprising T lymphocytes, particularly of the suppressor/cytotoxic (T8) variety. The alveolar epithelial cells show aberrant expression of human leukocyte antigen (HLA)-DR, suggesting that the epithelium may be recognized as autoantigenic by the cytotoxic T8 cells. However T-helper lymphocytes are also found, and a shift from type I (generally antifibrotic) to type II (generally profibrotic) cytokine profiles may also contribute to fibrosis. Other inflammatory cells such as macrophages, mast cells, eosinophils, and neutrophils, also likely contribute to overall disease activity.

Angiogenesis also likely plays a role, with new vessel formation being well characterized in normal tissue repair. However, there are conflicting data with regard to various proangiogenic factors in UIP/IPF; for example, there is increased IL-8 in the tissue of patients with IPF, but while vascular endothelial growth factor (VEGF) is expressed in fibroblastic foci in UIP, its levels are reduced in BAL fluid. It has also been shown that the granulation tissue of OP is of greater vascularity than that within fibroblastic foci of UIP/IPF, and also expresses VEGF to a greater degree. Conversely, foci of increased vascularity can be seen at the bases of fibroblastic foci if correctly oriented, while others describe decreasing vascularity as fibrosis increases within the interstitium. Therefore, exactly how and if remodeling of architecture relates to angiogenesis currently remains uncertain.
The most problematic area is the distinction of UIP from fibrotic NSIP, with diagnostic confidence often low in this situation in interobserver studies. Key distinguishing features are a relatively diffuse pattern of interstitial fibrosis and an absence or scarcity of fibroblastic foci in NSIP. Indeed, some cases of IPF show a pattern of fibrotic NSIP in part explaining this potential overlap. In these difficult cases, consideration of the clinical and imaging features may be of great help in deciding whether the patient truly has IPF or whether the histology represents some other clinicopathologic entity. There are also occasions when multiple biopsies show UIP at one site and fibrotic NSIP at another, so-called discordant UIP. In this instance, the prognosis is driven by the pattern of UIP. Discordance between radiologic and histopathologic diagnoses of UIP and fibrotic NSIP also indicate that the presence of UIP is the adverse prognostic factor in either modality.

Organizing pneumonia may progress to interstitial fibrosis, and when foci of intraalveolar organization are closely applied to the interstitium, presumably as they become incorporated, they can look identical to the fibroblastic foci of UIP. However, the presence of more typical areas of organizing pneumonia elsewhere in the biopsy, plus clinical and radiologic correlation, usually allows distinction from IPF/CFA.

Sometimes there are abundant macrophages, resulting in a DIP-like pattern, but if there is an underlying pattern of patchy subpleural fibrosis with fibroblastic foci, then the biopsy should be classified as UIP. Interstitial fibrosis, when present in DIP, is usually mild and diffuse. There may also rarely be a superimposed pattern of diffuse alveolar damage (DAD) superimposed on background UIP in patients with an acute exacerbation (see Diffuse Alveolar Damage and Acute Interstitial Pneumonia, below), although DAD itself is easily distinguished by the characteristic hyaline membranes or diffuse intraalveolar organization (see Chapter 4).

The absence of asbestos bodies excludes asbestosis and, although Langerhans cells may not always be present in burned-out Langerhans cells granulomatosis, the stellate and more bronchocentric distribution of fibrosis and especially HRCT data usually exclude IPF/CFA. Drug reactions should also be excluded especially in the presence of focal eosinophilic-pneumonia-like areas. Chronic hypersensitivity pneumonia may show small granulomas, be more bronchocentric in its distribution of fibrosis, and have a greater extent of chronic inflammation than UIP in IPF/CFA, but this is not always the case and again emphasizes the need for clinical and imaging correlation in order to avoid misdiagnosis.

### Nonspecific Interstitial Pneumonia

The term nonspecific interstitial pneumonia (NSIP) was first used in relation to a pattern of inflammation seen in association with HIV infection, but it was the seminal paper in 1994 by Katzenstein and Fiorelli that first used NSIP in the context of interstitial pneumonias. Nonspecific interstitial pneumonia has subsequently evolved into a recognized pattern of idiopathic interstitial pneumonitis with defined characteristics on histology and HRCT, although its clinical correlate remains less well defined and the term nonspecific interstitial pneumonia is regarded as provisional in the consensus classification system (Table 19.1).

### Histopathologic Features

Histologically, NSIP has a temporally uniform pattern, characterized by expansion of the interstitium, a variable extent of chronic inflammation and fibrosis. The inflammatory cell infiltrate comprises mainly small lymphocytes with some plasma cells and macrophages, while the fibrosis can be collagenous or fibroblastic in nature, or even both. However, the overall age of the fibrosis, when present, appears relatively constant within the affected areas. Although initially subdivided into grades 1 to 3, dependent on the degrees of fibrosis and inflammation, later studies showed that the survival for the mixed (grade 2) and fibrotic (grade 3) patterns were similar, while those with no fibrosis (grade 1) had a much better prognosis.

Therefore, the consensus classification recommended usage of only two subtypes: cellular NSIP (Fig. 19.11) and fibrotic NSIP (Fig. 19.12). The other main feature in the diagnosis of fibrotic NSIP is a lack or scarcity of fibroblastic foci, primarily distinguishing it from UIP. There is also relative preservation of architecture in NSIP compared to UIP. The minor features of cellular NSIP are listed in Table 19.4 and of fibrotic NSIP in Table 19.5. For fibrotic NSIP, these are not dissimilar to those seen in UIP, although they are of lesser intensity.

### Clinicopathologic Correlation

#### Clinical Presentation

Because of continued uncertainty over what NSIP clinically represents, its incidence and prevalence remain to be defined, with variations in published series likely reflecting bias within individual cohorts. In time, subsets of NSIP in relation to pathogenesis (as discussed below in this section) may evolve, but current data reflect populations of NSIP based on histology alone. With this in mind, patients generally present at around 50 years of age, being slightly younger than those with IPF/CFA and UIP. Those with cellular NSIP are younger still, averaging
FIGURE 19.11. **A.** A case of cellular nonspecific interstitial pneumonia shows a mild diffuse interstitial infiltrate of chronic inflammatory cells with no interstitial fibrosis. **B.** At high power, mild type 2 cell hyperplasia is also seen.

FIGURE 19.12. **A.** A case of fibrotic nonspecific interstitial pneumonia at low power shows interstitial fibrosis that has a more diffuse distribution than usual interstitial pneumonia. **B, C.** At high power, there are varying degrees of inflammation associated with the interstitial fibrosis, but fibroblastic foci are either absent or scarce.
### Table 19.4. Histologic features of cellular nonspecific interstitial pneumonia

| Major features                                      | Minor (or secondary) changes | Pertinent negative features |
|-----------------------------------------------------|------------------------------|----------------------------|
| Mild to moderate interstitial chronic inflammation  | Mild alveolar macrophage accumulation | Dense interstitial fibrosis |
| Diffuse involvement of affected parenchyma          | Follicular hyperplasia       | Lack of inorganic dusts (e.g., asbestos) |
| Preservation of alveolar architecture               | Organizing pneumonia         | Lack of granulomas          |
|                                                     | Peribronchiolar fibrosis     | Lack or paucity of eosinophils |
|                                                     | Mild chronic pleuritis       | Lack of organisms (e.g., viral inclusions) |
|                                                     | Type 2 pneumocyte hyperplasia|                            |
|                                                     | Focal alveolar fibrin        |                            |

*Features less intense than in UIP.

### Pathogenesis

A noticeable feature of the consensus classification was that, although the histopathologic and radiologic features of NSIP were well characterized, there was uncertainty as to its clinical correlate. The term *nonspecific interstitial pneumonia* was therefore left as provisional (Table 19.2), and subsequent studies have focused on addressing this issue. Currently, it seems likely that there is more than one etiology and if one returns to the original paper by Katzenstein and Fiorelli, it is interesting to note that they were particular in stating that there were several clinical associations with this histopathologic pattern (collagen vascular diseases, exposure to environmental allergens, history of acute lung injury), many of which reflect more recent conclusions as to the causes of this pattern (Fig. 19.14).

### Treatment and Prognosis

Nonspecific interstitial pneumonia appears to be responsive to corticosteroid therapy, especially cellular NSIP, but is often treated in addition with immunosuppressive therapy, either azathioprine or cyclophosphamide. In one series, survival for fibrotic NSIP is significantly better than that seen in UIP (90% versus 43%) but the difference is considerably less in one study that followed the patients to 10 years (35% versus 15%). Five-year survival for cellular NSIP approaches 100%.

There is now good evidence that fibrotic NSIP can occur in a setting of IPF/CFA, as both patterns can be seen in the same patient and even in the same lobe. However, whether these cases of NSIP represent early or inactive...
19. Interstitial Pneumonias

**FIGURE 19.13.** An HRCT of fibrotic nonspecific interstitial pneumonia shows coarse reticular shadowing and traction bronchiectasis, but no honeycombing.

Phases of IPF remains unclear. The prevalence of such cases in individual cohorts of patients with a histopathologic pattern of NSIP may be part of the cause of variations in prognosis for this pattern seen between different institutions, and the fact that some series of fibrotic NSIP describe a mortality at 10 years closer to that of UIP than a comparison at 5 years.

Nonspecific Interstitial Pneumonia in Hypersensitivity Pneumonia

Some cases of fibrotic NSIP are likely due to chronic hypersensitivity, in which the granulomas are absent and there is a relative or absolute lack of bronchocentricity to the inflammation and fibrosis that points toward an airway-centered disease. Occasional fibroblastic foci may further confuse the picture. However, although bronchocentricity may be absent on biopsy, it may be more easily apparent on HRCT with the advantage therein of assessing the whole lung. A similar lack of bronchocentricity and granulomas may cause less chronic cases to be preferentially classified as cellular NSIP. In both instances, undertaking biopsies from different sites obviates what is often a sampling error, and good clinical correlation will often identify other salient features, on clinical questioning, bronchoalveolar lavage, or via serologic investigations.

Nonspecific Interstitial Pneumonia in Relation to Smoking

It is well established that histopathologic patterns of DIP and RB are mainly caused by injury due to cigarette smoking (see Respiratory Bronchiolitis and Respiratory Bronchiolitis-Associated Interstitial Lung Disease, below, and Desquamative Interstitial Pneumonia, below), but there may be a further cohort of patients who show a pattern of fibrotic NSIP due to a similar injury, often in association with microscopic evidence of emphysema. In these putative cases, there is typically very little chronic inflammation, and the fibrosis appears distinctly hyaline. However, there is little conclusive data as yet to confirm this hypothesis.

Nonspecific Interstitial Pneumonia in Relation to Acute Lung Injury

In Katzenstein and Fiorelli’s original paper, a few long-term survivors of diffuse alveolar damage were noted to have a pattern of NSIP in areas of residual lung fibrosis. These should be easily identified by obtaining a clinical history of a previous episode of acute respiratory failure. In addition to this, there is also a cohort of patients with organizing pneumonia who progress to fibrosis, and they

**FIGURE 19.14.** Nonspecific interstitial pneumonia (NSIP): overlap with interstitial diseases. NSIP has some degree of overlap with a variety of interstitial diseases. UIP, usual interstitial pneumonia; HP, hypersensitivity pneumonia; OP, organizing pneumonia; DIP, desquamative interstitial pneumonia; EP, eosinophilic pneumonia; LIP, lymphocytic interstitial pneumonia; DAD, diffuse alveolar damage. (From Travis WD, ed., Armed Forces Institute of Pathology. Non-neoplastic disorders of the lower respiratory tract. In: Atlas of nontumor pathology. Washington, DC: American Registry of Pathology, 2002, with permission.)
Nonspecific Interstitial Pneumonia in the Context of Collagen Vascular Disease

Collagen vascular diseases (CVDs) are a heterogeneous group of diseases that includes rheumatoid arthritis, systemic sclerosis, polymyositis/dermatomyositis (PM/DM), systemic lupus erythematosus (SLE), Sjögren’s syndrome, and mixed connective tissue disorders (MCTDs). Series published after recognition of NSIP show this pattern to be prevalent in systemic sclerosis, poliomyositis, Sjögren’s syndrome, and rheumatoid arthritis, although there are subtle variations in the prevalence of other patterns or overlapping features when viewed collectively. These are discussed in greater detail in Chapter 20.

Idiopathic Nonspecific Interstitial Pneumonia

When a pathologist first makes a histopathologic diagnosis of NSIP, it should be regarded as a “holding pattern” from which the clinician can then return to the patient to look for the clinical associations described above, rather than as a final “wastebasket” diagnosis. As such, many cases will be given a clinicopathologic diagnosis that relates to the above discussion (Fig. 19.14), but there remain a minority of cases that are truly idiopathic. Some of these may be patients presenting with pulmonary manifestations of a CVD, as it is known that these can precede other systemic manifestations. Others may represent as yet undiscovered gene mutations or environmental insults.

Differential Diagnosis

Many of the differential diagnoses of a histopathologic pattern of NSIP are reflected in the above discussion on pathogenesis. However, clinical correlation notwithstanding, it is the opinion of the pathologist that there is a lack or absence of fibroblastic foci and patchy subpleural distribution (as in UIP), bronchocentric inflammation, fibrosis and granulomas (as in hypersensitivity pneumonia), intraalveolar organization (as in OP), alveolar macrophage accumulation (as in DIP), hyaline membranes (as in DAD), and density of interstitial chronic inflammation (as in LIP) that leads to the eventual histopathologic classification as NSIP. Another approach when viewing such biopsies is that, in the context of interstitial fibrosis and inflammation, none of the above histopathologic features predominates, and this relative lack of cardinal diagnostic features for other patterns leads to classification as NSIP.

Respiratory Bronchiolitis and Respiratory Bronchiolitis-Associated Interstitial Lung Disease

Respiratory bronchiolitis is a common incidental histopathologic finding in heavy smokers, and is seen in most resections for lung cancer in the parenchyma removed at anatomic resection. However, these changes were not known to cause symptoms in terms of diffuse parenchymal lung disease until Myers et al. described six patients in 1987, all heavy smokers, who had clinical, radiologic, and physiologic evidence of chronic interstitial lung disease but only respiratory bronchiolitis on surgical lung biopsy. The term respiratory bronchiolitis-associated interstitial lung disease (RBILD) was later coined in a further series that clarified the histopathologic differences among the incidental changes of smoking, RBILD, and DIP.

Histopathologic Features

Respiratory bronchiolitis is characterized by an accumulation of alveolar macrophages within respiratory bronchioles spilling into neighboring alveoli. Their accumulation may be associated with peribronchiolar alveolar septal thickening by fibroblasts and collagen deposition, characteristically radiating from the bronchiole (Fig. 19.15). There is usually an accompanying chronic inflammatory cell infiltrate in the walls of the bronchioles and the surrounding alveolar interstitium. The alveolar parenchyma at the periphery of acini is either mildly affected or normal. No honeycomb changes have been described, although there may be varying amounts of centrilobular emphysema (Table 19.6).

Clinicopathologic Correlation

Clinical Presentation

The most important consideration when assessing a patient whose biopsy shows RB is to determine whether the patient truly has RB-ILD or if the biopsy features are a sampling error in a smoker with a different disease process. Almost all patients with RBILD are cigarette smokers, and they are aged between 22 and 53 years with an equal sex distribution. The commonest presenting features are a gradual onset of shortness of breath and a prominent cough. Other symptoms include chest pain, weight loss, and rarely fever and hemoptysis. Clubbing is extremely rare. A normal chest radiograph is found in approximately 20% of patients with RBILD. High-resolution CT scans show varying degrees of patchy ground-glass opacity and centrilobular nodules.
FIGURE 19.15. A–C. A case of respiratory bronchiolitis-associated interstitial lung disease (RBILD) shows a milder and more centrilobular distribution of the macrophages when compared to desquamative interstitial pneumonia in Figure 19.17. 

(Fig. 19.16), and, as expected, several series have noted considerable overlap in the HRCT appearances of RBILD and DIP, supporting the idea that they represent different degrees of reaction to cigarette smoke. Indeed, similar but less extensive findings are also seen in asymptomatic smokers. Lung function tests show both restrictive and obstructive abnormalities, despite the centriacinar nature of RBILD, although most frequently there is a mixed, predominantly restrictive ventilatory defect, usually associated with a mild to moderate reduction in the carbon monoxide diffusing capacity (DL\textsubscript{CO}). Airflow obstruction is usually mild. Bronchoalveolar lavage studies show an increase in pigmented alveolar macrophages with serial data suggesting that, on average, BAL macrophage percentages in ex-smokers fall to lifelong nonsmoking levels in 3 years. 

TABLE 19.6. Histologic features of respiratory bronchiolitis

| Major features                                      | Minor (or secondary) changes                   | Pertinent negative features                                      |
|-----------------------------------------------------|------------------------------------------------|-------------------------------------------------------------------|
| Bronchocentric accumulation of macrophages          | Coexistent centrilobular emphysema            | Lack of diffuse involvement of pulmonary acini                    |
| Mild bronchiolar fibrosis and chronic inflammation  |                                                | No honeycomb change                                               |
| Light brown cytoplasmic pigmentation within macropophages |                                              | No evidence of other airway damaging agents                       |

Source: Adapted from American Thoracic Society. Copyright © 2000, American Thoracic Society.
FIGURE 19.16. An HRCT of respiratory bronchiolitis shows randomly distributed, poorly defined, low attenuation centrilobular nodules.

Treatment and Prognosis

Cessation of smoking has led to the improvement of symptoms in some patients, and there have also been reported responses to corticosteroid therapy. Five-year survival approaches 100% for these patients, although there are some reports of deterioration of symptoms.97

Pathogenesis

Epidemiologic evidence in published series shows that smoking plays a prime role in the development of RB in nearly all patients who are either current or ex-smokers.8,9,97,98 Rare patients have given history of other inhalational exposures.97 The level of cytoplasmic pigmentation of macrophages and the presence of peribronchial fibrosis correlated with the pack-year smoking history in one study.98 Although there are no studies that address why only certain patients become symptomatic, there are interesting follow-up HRCT studies on smokers with presumed RB who develop evidence of emphysema at these sites over time, providing data in relation to the pathogenetic role of macrophages in the development of emphysema.103

Differential Diagnosis

Respiratory bronchiolitis (RB) is easily distinguishable from UIP, NSIP, OP, LIP, and DAD, as a significant accumulation of macrophages is not seen and other diagnostic histopathologic features (marked established fibrosis, fibroblastic foci, intraalveolar organization, dense lymphoid interstitial infiltrate, and hyaline membranes) are absent. If any of these features are present, even in one of multiple biopsies, it should raise the possibility of the respiratory bronchiolitis being incidental to a second pathology. Indeed, in terms of diagnosis, confirmation through a clinicopathologic review that RB is the cause of symptoms and not an incidental finding is as important as its identification. Distinction from DIP is discussed below in the context of smoking-related interstitial lung disease.

Desquamative Interstitial Pneumonia

Desquamative interstitial pneumonia (DIP) is mainly an alveolar filling defect, first described by Liebow in 1965, in which alveoli are expanded by macrophages, although these were initially thought to be desquamated pneumocytes, hence the name. Historically, some groups viewed DIP as an early cellular phase of cryptogenic fibrosing alveolitis, although this is now known not to be the case from data on prognosis and studies on disease progression using HRCT.105 Most cases are more closely associated with RBILD and a history of smoking. An alternative term, alveolar macrophage pneumonia, has been proposed, given that it is neither desquamative nor predominantly interstitial, but the consensus view is to continue with the term DIP.24

Histopathologic Features

The major feature is the presence of large numbers of macrophages within alveoli, with a diffuse distribution throughout pulmonary acini. These macrophages characteristically have abundant eosinophilic cytoplasm, which may have a glassy appearance and often contain a finely granular light brown pigment that stains variably for fine granular hemosiderin. The alveolar architecture is generally well maintained, although there is usually a mild chronic inflammatory cell infiltrate within the interstitium. Lymphoid follicles are also not infrequently present. Moderate numbers of eosinophils may also be seen, both within the interstitium and admixed with the alveolar macrophages (Fig. 19.17). Interstitial fibrosis is rarely more than mild in intensity and it lacks the fibroblastic foci characteristic of UIP.107 Although there may be loss of architecture and cystic air-space formation, the changes appear closer to emphysema than the honeycomb change seen in UIP, with the remodeling of architecture and bronchiolization of honeycomb change being exceptional (Table 19.7).

Clinicopathologic Correlation

Clinical Presentation

Patients usually present in the fourth or fifth decade, complaining of a gradual increase in shortness of breath in association with a dry cough. Fever, fatigue, and loss of
**Figure 19.17.** A. A case of desquamative interstitial pneumonia shows uniform distribution of alveolar macrophage accumulation. B,C. The macrophages have abundant glassy eosinophilic cytoplasm, sometimes with light brown pigmentation that shows variable staining for hemosiderin (D). At high power, the macrophages responsible for desquamative interstitial pneumonia and RBILD appear identical (cf. Figure 19.15C).

| Major features                                      | Minor (or secondary) changes                                      | Pertinent negative features                                      |
|-----------------------------------------------------|------------------------------------------------------------------|------------------------------------------------------------------|
| Uniform involvement of lung parenchyma              | Mild to moderate interstitial fibrosis                            | No honeycomb change                                              |
| Marked accumulation of macrophages                  | Mild interstitial chronic inflammation                           | Lack of fibroblastic foci typical of UIP                         |
| Light brown cytoplasmic pigmentation within macrophages | Mild follicular hyperplasia                                      | No eosinophilic microabscesses                                   |
|                                                     | Often a mildly increased numbers of eosinophils                  | Lack of inorganic dusts (e.g., asbestos)                         |
|                                                     | Concomitant centrilobular emphysema                              | Lack of granulomas                                                |

*Source: Adapted from American Thoracic Society.*\(^{13}\) Copyright © 2000, American Thoracic Society; and Craig et al.\(^{107}\)
FIGURE 19.18. An HRCT of desquamative interstitial pneumonia shows widespread ground-glass opacification.

Weight may occur, although clubbing is rare. Bilateral basal inspiratory crackles are frequently found on auscultation. The HRCT findings of DIP are documented in several studies, with ground-glass opacities the most common feature (Fig. 19.18). Pulmonary function tests are consistently restrictive with the reduction in DLCO a useful guide to the underlying severity of disease. Hypoxia only appears to supervene in advanced disease. There are few studies on BAL, but it is said to show an increase in cell numbers, particularly macrophages, and occasionally increased eosinophils.

Treatment and Prognosis

Cessation of smoking plays a prime role in treatment, and may in itself lead to symptomatic improvement. However, the disease is typically treated with corticosteroids with or without immunosuppressive agents, often with a good response to treatment. It is likely that in occasional cases, a poor response to corticosteroids or immunosuppressive agents is indicative of significant underlying fibrosis, especially in long-standing disease. Also, some patients do progress with a poor prognosis.

Desquamative interstitial pneumonia has a better outcome than UIP and fibrotic NSIP, with poor outcome only in a minority of cases. In recent studies, 5-year survival approaches 100%. In adults, there is no difference in prognosis between smokers and non-smokers. Prognosis is worse in children, especially those with familial disease, likely reflecting a different etiology such as an inborn error of metabolism.

Pathogenesis

Epidemiologic studies suggest that DIP is a pathologic response to a variety of pulmonary insults rather than a specific disease. In adults, there is a history of smoking in about 90% of cases, and in these individuals DIP may be regarded as an excessive macrophage response to the smoke. However, although RBILD is almost exclusively a disease of smokers, there are several other agents that are rarely reported as causing a DIP-like reaction such as dust inhalation, drug reactions, and inborn errors of metabolism. There is also a small group of patients, who are never smokers and have no evidence of any other causative association and are therefore regarded as having idiopathic disease.

The Concept of Smoking-Related Interstitial Lung Disease

Smoking related-interstitial lung disease (SRILD) has been proposed as a term to encompass DIP, RBILD, and Langerhans’ cell granulomatosis (LCG), with RB and DIP-like changes frequently seen in the lung adjacent to LCG. Small stellate scars that are likely foci of burned-out Langerhans’ cell granulomatosis may also be seen in biopsies from patients with RB and DIP. However, defining SRILD is not that straightforward, as interstitial changes are complicated by emphysema of varying degree, and there may be some cases that histopathologically are closer to NSIP (see Nonspecific Interstitial Pneumonia, above). These areas of research notwithstanding, it is reasonable to group cases with RB, DIP, or LCG as SRILD, but only in the context of a history of smoking and appropriate radiology, and it is often useful to ascribe this term when features overlap among the various patterns in surgical lung biopsies and there is a history of smoking. However, the individual terms should be maintained within this heading, as there remain important differences between the entities therein. For example, histopathologically there are differences in severity between the RB and DIP, with an increased extent of fibrosis, lymphoid hyperplasia, and eosinophil numbers in DIP. Epidemiologically, nearly all cases of RB are related to inhalation of smoke, while about 10% of DIP may be due to other causes. Clinical presentation and courses also differ, with DIP being more aggressive than RBILD and with no evidence that progression from RBILD to DIP occurs. The BAL profiles of the two diseases are also dissimilar.

On HRCT, the micronodular abnormalities of RBILD are not seen in DIP, and although HRCT follow-up data are rare, there is evidence that DIP may progress to a fine fibrosis akin to fibrotic NSIP, while the only follow-up data on RB suggest it may progress to centrilobular emphysema. Finally, the indications for corticosteroid treatment are often
19. Interstitial Pneumonias

marginal in RBILD, whereas treatment is usually more active in DIP. Therefore, DIP and RBILD should continue to be regarded as separate entities, and the term smoking related-interstitial lung disease should be used with caution outside of DIP, RBILD, and LCG in patients with a smoking history until the relevance of coexistent emphysema and interstitial fibrosis are better clarified.

Differential Diagnosis

In DIP, severe fibrosis and honeycombing are exceptional features, and UIP should be thoroughly excluded in these instances. Also, UIP will usually show fibroblastic foci and does not typically have an abundance of macrophages. In cases where there is doubt over the histopathologic pattern, correlation with clinical and imaging data helps in distinguishing IPF/CFA from DIP. With regard to other histopathologic patterns, DIP should be easily distinguishable from OP, LIP, and DAD, as a significant accumulation of macrophages is not seen and other diagnostic histopathologic features (intraalveolar organization, dense lymphoid interstitial infiltrate, and hyaline membranes) are absent. In relation to NSIP, there may occasionally be an overlap between these patterns, as the volume of macrophages is not consistently present throughout all lung fields. However, correlation with the clinical and imaging data in these situations usually leads to the correct clinicopathologic diagnosis. The overlap among DIP, NSIP, and smoking is discussed in the previous section. Occasionally eosinophils may be notably prominent in DIP, raising the differential diagnosis of eosinophilic pneumonia. However, clinical presentation and HRCT patterns differ, and eosinophilic microabscesses are not seen in DIP.

Diffuse Alveolar Damage and Acute Interstitial Pneumonia

Diffuse alveolar damage is the histopathologic pattern seen most commonly in the acute respiratory distress syndrome (ARDS), which is discussed in detail in Chapter 4. It may also be seen in the context of an acute exacerbation of patients with IPF/CFA and even more rarely, in an idiopathic setting.

Histopathologic Features

Diffuse alveolar damage is characterized by marked expansion of the interstitium by a predominantly fibroblastic proliferation with an accompanying mixed inflammatory cell infiltrate of variable intensity. There is hyperplasia of type 2 pneumocytes that may show sufficient cytologic atypia to enter the differential diagnosis of malignancy in cytologic specimens. The bronchiolar epithelium may also show squamous metaplasia. In the exudative phase, hyaline membranes are nearly always present (Fig. 19.19), while organizing pneumonia by definition predominates in the organizing phase. Thrombi are not infrequent within small pulmonary arteries (Table 19.8).

### Table 19.8. Histologic features of diffuse alveolar damage/acute interstitial pneumonia

| Major features                                      | Minor features                        | Pertinent negative features                                      |
|-----------------------------------------------------|---------------------------------------|------------------------------------------------------------------|
| Diffuse distribution                                | A background of UIP in acute exacerbations | Lack of granulomas, abscess or necrosis                          |
| Uniform temporal appearance                        |                                       | No evidence of infection (viral inclusions, special stains, culture, etc.) |
| Diffuse alveolar septal thickening, either          |                                       | No marked increase in eosinophils                                |
| cellular or fibroblastic                            |                                       |                                                                  |
| Hyaline membranes (exudative phase)                 |                                       |                                                                  |
| Organizing pneumonia (organizing phase)             |                                       |                                                                  |

Source: American Thoracic Society. Copyright © 2000, American Thoracic Society; and Rice et al.
CFA, the features of DAD will be superimposed on a background of UIP and very rarely fibrotic NSIP.124

Clinicopathologic Correlation

Clinical Presentation

Acute Interstitial Pneumonia

Although far more commonly seen in the setting of ARDS, DAD may also rarely occur in an idiopathic setting, in which situation the disorder is termed acute interstitial pneumonia (AIP). As opposed to the other clinicopathologic disorders in the consensus classification, AIP has an acute presentation and rapid clinical progression,11 considered in some cases to be synonymous with Hamman-Rich disease.2 There is a wide age range, and patients have no underlying disease or predisposing factors for acute respiratory failure.11,125 Clinical presentation begins with a flu-like episode, which is succeeded by rapidly progressive severe dyspnea usually leading to death from respiratory failure. High-resolution CT shows bilateral ground-glass opacities, bronchial dilatation, and dependent consolidation.

Acute Exacerbation of Idiopathic Pulmonary Fibrosis/Cryptogenic Fibrosing Alveolitis

Although the clinical course of IPF/CFA is usually chronic and slowly progressive, some patients experience rapid deterioration during the course of their illness. This phenomenon has been termed acute exacerbation of IPF/CFA and until recently has been considered very rare, although series are increasingly being reported, most often in the radiology literature.124,126-129 Criteria for acute exacerbation vary between publications, and there is likely a spectrum of severity of these changes within a subpopulation of patients with IPF/CFA.126,127 For example, Kondoh et al.126 define acute exacerbation as exacerbation of dyspnea within 1 month, new diffuse pulmonary opacities on chest radiography, a decrease in arterial oxygen tension (PaO₂) of more than 10 mm Hg under similar conditions, and absence of apparent infectious agents and heart failure. The age range mirrors approximately that for IPF/CFA. High-resolution CT shows features of DAD superimposed on those of UIP.

Treatment and Prognosis

Most patients with AIP die of their disease, with mortality reported as up to 70%.11,125 However, a minority shows complete recovery or survival with residual fibrosis. Some may have repeated episodes of AIP and develop chronic progressive fibrosis.130 Most patients with acute exacerbations of IPF/CFA also die of their disease (Fig. 19.20).124 Some survive initially, only to succumb to further episodes. Quantification of HRCT features may provide prognostic information in both AIP131 and acute exacerbations of IPF.127

Pathogenesis

The pathogenesis remains unknown for AIP in terms of the precipitating event, although the biologic progression of AIP likely reflects that seen in ARDS (see Chapter 4). The etiology of acute exacerbations is also unknown, but oxygen toxicity and triggering infection are unlikely causes.124 Some cases of acute exacerbation have been precipitated by BAL132 or surgical lung biopsy,133 and others by surgical resection of lung cancers associated with IPF/CFA.57

Differential Diagnosis

In terms of differential diagnosis, UIP should be distinguishable through an absence of temporal heterogeneity and the presence of hyaline membranes, excluding the
acute exacerbations discussed above.126,127 If patients survive the acute episode in AIP, which comprises histopathologically the exudative and organizing phases, the residual fibrosis can show a pattern of fibrotic NSIP10 and the clinical presentation is then essential in making the diagnosis in such cases.11,125 In similar fashion, the organizing phase of DAD may be indistinguishable from organizing pneumonia due to other chronic causes, although cryptogenic organizing pneumonia (COP) often has a more patchy and peribronchial distribution with less prominent interstitial changes.134 Nevertheless, a review of the clinical and imaging data is again required for accurate clinicopathologic diagnosis.135

Organizing Pneumonia and Cryptogenic Organizing Pneumonia

Organizing pneumonia (OP) is a nonspecific pattern of repair seen in response to injury. Although not strictly an interstitial process, it often enters the differential diagnosis of the interstitial pneumonias. It may be classified as primary (or idiopathic when it is termed cryptogenic organizing pneumonia [COP])136-138 or secondary (with a recognized cause/association). Organizing pneumonia and its clinical correlates are discussed in detail in Chapter 4 in relation to acute lung injury.

Lymphoid Interstitial Pneumonia

Although LIP was part of Liebow and Carrington’s3 original classification, it was subsequently reclassified as a lymphoproliferative disease due to the largely erroneous view that it was a preneoplastic condition. However, although it is discussed in detail in Chapter 32, as diagnostic difficulties more often reflect distinction from lymphoma than other patterns of interstitial pneumonia, it is currently included in the consensus classification, as it is now viewed as a reactive pulmonary lymphoid hyperplasia that predominantly involves the interstitium. In reality, idiopathic LIP is exceptionally rare, as most cases are associated with Epstein-Barr virus infection, immunosuppression, or a connective tissue disorder.139-145

Idiopathic Bronchiolocentric Interstitial Pneumonia or Airway-Centered Interstitial Fibrosis

Since the consensus classification, there have been two publications describing a pattern of small airway-centered interstitial fibrosis, which was initially termed idiopathic bronchiolocentric interstitial pneumonia.146,147 In both papers, there is a female predominance (about 75%), the age range being 28 and 69, and averaging about 40 years. Clinically, patients presented with chronic cough, progressive dyspnea, and more rarely wheeze, recurrent pneumonia, and chest pain. Only a minority of patients were smokers or ex-smokers. Eight of 12 patients in one study had a history of possible inhalational exposures, including wood smoke, birds, cotton, pasture, chalk dust, agrochemical compounds, and cocaine use.147 In the other study, two of 10 patients had a previous diagnosis of gastroesophageal reflux.146

Chest radiographs and pulmonary function tests show interstitial and restrictive lung disease, while the histopathologic appearance is that of a centrilobular inflammatory process with small airway fibrosis and inflammation that radiates into the interstitium of the distal acinus in a patchy fashion.146 Chest radiographs have revealed predominantly diffuse reticular and reticulonodular infiltrates, often in the central lung fields, with thickening of the bronchial walls and decreased lung volumes. High-resolution CTs demonstrated peribronchovascular fibrosis and interstitial thickening.147 Bronchoalveolar lavage showed a mild increase in lymphocytes in four patients.147 No patients had serologic evidence of a collagen vascular disease. Pulmonary function tests showed moderate to severe physiologic abnormalities, in most instances indicating a restrictive lung disease with decreased peripheral flow rates.146,147

The histopathologic features are similar to those in chronic hypersensitivity pneumonia, with bronchiolocentric interstitial fibrosis and peribronchiolar metaplasia extending around and often linking fibrotic and sometimes heavily muscularized bronchioles (Fig. 19.21). However, granulomas are not seen.146,147

Prognostic data are limited, but in the earlier study, at a mean follow-up of 4 years, one third of patients died of disease and most of the others had persistent or progressive disease, suggesting a more aggressive course than hypersensitivity pneumonitis and nonspecific interstitial pneumonia, the two major differential diagnoses.146 In the latter study, mortality was similar, although about one third responded to therapy with corticosteroids and bronchodilators.147 However, one further cohort of patients with peribronchiolar metaplasia as the primary histopathology on surgical lung biopsy for investigation of interstitial lung disease had an excellent survival.148

Whether or not the patterns of bronchiolocentric interstitial pneumonia or indeed peribronchiolar metaplasia relate to specific entities, further investigation is warranted into this pattern of bronchiolocentric, yet mainly interstitial, injury to the lung and its overlap with small airways disease.
Interstitial Pneumonias in Children

Most authors have classified pediatric interstitial lung disease according to systems devised for diseases for adults, although there are additional terms such as chronic pneumonitis of infancy and cellular pneumonitis in infants. There is a comparative lack of data on HRCT in children, so tissue sampling is more frequently required and, as in adults, this usually is a surgical lung biopsy for cases with a suspected interstitial pneumonia. A set of guidelines is due to be published by the European Respiratory Society.

In terms of the interstitial pneumonias, there are several series of CFA in children, but most predate recognition of NSIP. Indeed, when the adult histopathologic criteria are applied, UIP is exceptionally rare in children and most reported cases would be classified as other patterns. Most are probably more appropriately classified as NSIP, although this pattern is even less well characterized in children than in adults, and there is increasing evidence that some such cases may represent mutations in relation to surfactant protein genes, particular type C. Lymphoid interstitial pneumonia is also comparatively common in children, and, as in adults, is typically associated with either collagen vascular diseases or congenital and acquired immunodeficiency states.

Desquamative interstitial pneumonia is well described but rare in children. The outcome is worse, especially in infancy and familial disease. Clearly, smoking is not the etiology in children, and some children have been shown to have surfactant B deficiency or Gaucher’s disease. Respiratory bronchiolitis–associated interstitial lung disease appears to be limited to adults.

Diffuse alveolar damage is not infrequently seen in infancy, being the histopathologic pattern seen in both adult and infantile respiratory distress syndromes. However, occasional cases of acute respiratory failure develop in older children with a histopathologic pattern of DAD, and a clinical diagnosis of AIP is appropriate if no underlying causes are identified. Rare cases of OP have also been reported in children.

In addition to these patterns, chronic pneumonitis of infancy and cellular interstitial pneumonitis in infants are also described, although, while chronic pneumonitis of infancy has a distinct histopathologic pattern, cellular interstitial pneumonitis of infants appears similar to NSIP. Histologically, cases of chronic pneumonitis of infancy show extremely florid type 2 cell hyperplasia and diffuse expansion of the interstitium by fibroblastic tissue, with comparatively little interstitial chronic inflammation. Acellular intraalveolar material resembling that seen in alveolar proteinosis is a frequent finding. Some cases may represent surfactant protein B deficiency (see Chapter 6).

Conclusion

This consensus classification provides an appropriate system based on current knowledge, which appears reproducible in terms of the pathologist’s identifying patterns in isolation, and workable in terms of the role of the pathologist in making the final clinicopathologic diagnosis. It also highlights the fact that the gold standard for diagnosis is no longer the biopsy in isolation but more the clinicopathologic conference in which clinical, imaging, and histopathologic data are jointly discussed. Optimally, the conference provides greater consistency in...
diagnosis and also identifies purer cohorts for studies investigating causation. These patterns are also recognizable in the context of collagen vascular diseases (see Chapter 20) and pediatric disease (see Chapters 6 and 7), although clinical data differ and patterns should be interpreted accordingly. Finally, pathologists and physicians alike should be aware that all classifications are dynamic, and this system, in particular, will likely change as new patterns are encountered and discussed (such as idiopathic bronchiolocentric interstitial pneumonia) and new etiologic data come to light, already noted in the context of SRILD.

Acknowledgments. I thank David Hansell, Zelena Aziz, Athol Wells, Roland M. du Bois and Bryan Corrin, all from the Royal Brompton Hospital, London, for their help and advice in preparing this chapter.

References

1. Turner-Warwick M. Interstitial lung disease. Sem Respir Med 1984;6:1-102.
2. Hamman R, Rich A. Acute diffuse interstitial fibrosis of the lung. Bull Johns Hopkins Hosp 1944;74:177.
3. Liebow AA, Carrington CB. The interstitial pneumonias. In: Simon M, Potchen EJ, Lemay E, eds. Frontiers in pulmonary radiology. New York: Grune and Stratton, 1969:102-141.
4. Scadding JG. Fibrosing alveolitis. Br Med J 1964;2:686.
5. Scadding JG, Hinson KFW. Diffuse fibrosing alveolitis (diffuse interstitial fibrosis of the lungs): correlation of histology at biopsy with prognosis. Thorax 1967;22:291-304.
6. Anttila S, Sutinen S, Paananen M et al. Hard metal lung disease: a clinical, histological, ultrastructural and X-ray microanalytical study. Eur J Respir Dis 1986;69:83-94.
7. Demedts M, Gheysens B, Nagels J, et al. Cobalt lung in diamond polishers. Am Rev Respir Dis 1984;130:130-135.
8. Myers JL, Veal CF Jr, Shin MS, Katzenstein AL. Respiratory bronchiolitis causing interstitial lung disease. A clinicopathologic study of six cases. Am Rev Respir Dis 1987;135:880-884.
9. Yousem SA, Colby TV, Gaensler EA. Respiratory bronchiolitis-associated interstitial lung disease and its relationship to desquamative interstitial pneumonia. Mayo Clin Proc 1989;64:1373-1380.
10. Katzenstein AA, Fiorelli RF. Nonspecific interstitial pneumonia/fibrosis. Histologic features and clinical significance. Am J Surg Pathol 1994;18:136-147.
11. Katzenstein AL, Myers JL, Mazur MT. Acute interstitial pneumonia: a clinicopathologic, ultrastructural, and cell kinetic study. Am J Surg Pathol 1986;10(4):256-267.
12. Katzenstein AL, Myers JL. Idiopathic pulmonary fibrosis: Clinical relevance of pathologic classification. Am J Respir Crit Care Med 1998;157:1301-1315.
13. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International Consensus Statement. American Thoracic Society (ATS) and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000;161:646-664.
14. Nicholson AG, Colby TV, du Bois RM, Hansell DM, Wells AU. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med 2000;162:2213-2217.
15. Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathological subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998;157:199-203.
16. Daniil ZD, Gilchrist FC, Nicholson AG, et al. A histologic pattern of nonspecific interstitial pneumonia is associated with a better prognosis than usual interstitial pneumonia in patients with cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med 1999;160:899-905.
17. Nagai S, Kitaichi M, Itoh H, Nishimura K, Izumi T, Colby TV. Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP. Eur Respir J 1998;12:1010-1019.
18. Travis WD, Matsui K, Moss J, Ferrans VJ. Idiopathic nonspecific interstitial pneumonia: prognostic significance of cellular and fibrosing patterns—survival comparison with usual interstitial pneumonia and desquamative interstitial pneumonia. Am J Surg Pathol 2000;24:19-33.
19. Flaherty KR, Travis WD, Colby TV, et al. Histopathologic Variability in Usual and Nonspecific Interstitial Pneumonias. Am J Respir Crit Care Med 2001;164:1722-1727.
20. Flaherty KR, Toews GB, Travis WD, et al. Clinical significance of histological classification of idiopathic interstitial pneumonia. Eur Respir J 2002;19:275-283.
21. Johkoh T, Muller NL, Cartier Y, et al. Idiopathic interstitial pneumonias: diagnostic accuracy of thin-section CT in 129 patients. Radiology 1999;211:555-560.
22. Tung KT, Wells AU, Rubens MB, Kirk JM, du BR, Hansell DM. Accuracy of the typical computed tomographic appearances of fibrosing alveolitis. Thorax 1993;48:334-338.
23. Hansell DM, Wells AU. CT evaluation of fibrosing alveolitis—applications and insights. J Thoracic Imag 1996;11:231-249.
24. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002;165:277-304.
25. Johnston ID, Prescott RJ, Chalmers JC, Rudd RM. British Thoracic Society study of cryptogenic fibrosing alveolitis: current presentation and initial management. Fibrosing Alveolitis Subcommittee of the Research Committee of the British Thoracic Society. Thorax 1997;52:38-44.
26. Hunninghake GW, Zimmerman MB, Schwartz DA, et al. Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2001;164:193-196.
27. Myers JL, NSIP, UIP, and the ABCs of idiopathic interstitial pneumonias. Eur Respir J 1998;12:1003-1004.
28. Primack SL, Hartman TE, Hansell DM, Muller NL. End-stage lung disease: CT findings in 61 patients. Radiology 1993;189:681-686.
29. Carrington CB, Gaensler EA, Coutu RE, Fitzgerald MX, Gupta RG. Natural history and treated course of usual and desquamative interstitial pneumonia. N Engl J Med 1978; 298:801–809.

30. Katzenstein AL, Myers JL, Prophet WD, Corley LS, Shin MS. Bronchiolitis obliterans and usual interstitial pneumonia: A comparative clinicopathologic study. Am J Surg Pathol 1986;10:373–381.

31. Katzenstein A-L, Askin FE. Idiopathic interstitial pneumonia. In: Katzenstein A-L, Askin FB, eds. Surgical pathology of non-neoplastic lung disease. Philadelphia: WB Saunders, 1997:48–80.

32. King TE Jr, Schwarz MI, Brown K, et al. Idiopathic pulmonary fibrosis: relationship between histopathologic features and mortality. Am J Respir Crit Care Med 2001;164:1025–1032.

33. Nicholson AG, Fulford LG, Colby TV, du Bois RM, Hansell DM, Wells AU. The frequency of fibroblastic foci in usual interstitial pneumonia and their relationship to disease progression. Am J Respir Crit Care Med 2002;166:173–177.

34. Britton J, Hubbard R. Recent advances in the aetiology of cryptogenic fibrosing alveolitis. Histopathology 2000;37:387–392.

35. Yousem SA. Eosinophilic pneumonia-like areas in idiopathic usual interstitial pneumonia. Modern Pathol 2000; 13:1280–1284.

36. Stack BH, Choo-Kang YF, Heard BE. The prognosis of cryptogenic fibrosing alveolitis. Thorax 1972;27:535–542.

37. Turner-Warwick M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis: clinical features and their influence on survival. Thorax 1980;35:171–180.

38. Turner-Warwick M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis: response to corticosteroid treatment and its effect on survival. Thorax 1980;35:593–599.

39. Tukiainen P, Taskinen E, Holsti P, Korhola O, Valle M. Prognosis of cryptogenic fibrosing alveolitis. Thorax 1983; 38:349–355.

40. Hubbard R, Johnston I, Britton J. Survival in patients with cryptogenic fibrosing alveolitis: a population-based cohort study. Chest 1998;113:396–400.

41. Johnston IDA, Prescott RJ, Chalmers JC, Rudd RM. British Thoracic Society study of cryptogenic fibrosing alveolitis: current presentation and initial management. Thorax 1997;52:38–44.

42. King TE Jr, Tooze JA, Schwarz MI, Brown KR, Cheriack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J Respir Crit Care Med 2001;164:1171–1181.

43. Marshall RP, Puddicombe A, Cookson WOC, Laurent GJ. Adult familial cryptogenic fibrosing alveolitis in the United Kingdom. Thorax 2000;55:143–146.

44. Turner-Warwick M, Haslam PL. The value of serial bronchoalveolar lavages in assessing the clinical progress of patients with cryptogenic fibrosing alveolitis. Am Rev Respir Dis 1987;135:26–34.

45. Haslam PL, Baughman RP. Report of ERS Task Force: guidelines for measurement of acellular components and standardization of BAL. Eur Respir J 1999;14:245–248.

46. Haslam PL, Turton CW, Lukoszczak A, et al. Bronchoalveolar lavage fluid cell counts in cryptogenic fibrosing alveo-

47. Veearahavan S, Latsi PI, Wells AU, et al. BAL findings in idiopathic nonspecific interstitial pneumonia and usual interstitial pneumonia. Eur Respir J 2003;22:239–244.

48. Wells AU, Hansell DM, Haslam PL, et al. Bronchoalveolar lavage cellularity: lone cryptogenic fibrosing alveolitis compared with the fibrosing alveolitis of systemic sclerosis. Am J Respir Crit Care Med 1998;157:1474–1482.

49. Ziesche R, Hofbauer E, Wittmann K, Petkov V, Block LH. A preliminary study of long-term treatment with interferon gamma-1b and low-dose prednisolone in patients with idiopathic pulmonary fibrosis. N Engl J Med 1999;341:1264–1269.

50. Nathan SD, Barnett SD, Moran B, et al. Interferon gamma-1b as therapy for idiopathic pulmonary fibrosis. An intra-patient analysis. Respiration 2004;71:77–82.

51. Raghu G, Brown KK, Bradford WZ, et al. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. N Engl J Med 2004;350:125–133.

52. Meyer A, Buhl R, Kampf S, Magnusson H. Intravenous N-acetylcysteine and lung glutathione of patients with pulmonary fibrosis and normals. Am J Respir Crit Care Med 1995;152:1055–1060.

53. MacNee W, Rahman I. Oxidants/antioxidants in idiopathic pulmonary fibrosis. Thorax 1995;50(suppl 1):S53–S58.

54. Selman M, Thannickal VJ, Pardo A, Zisman DA, Martinez FJ, Lynch JP, III. Idiopathic pulmonary fibrosis: pathogenesis and therapeutic approaches. Drugs 2004;64:405–430.

55. Thannickal VJ, Toews GB, White ES, Lynch JP III, Martinez FJ. Mechanisms of pulmonary fibrosis. Annu Rev Med 2004;55:395–417.

56. Turner-Warwick M, Lebowitz M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis and lung cancer. Thorax 1980;35:496–499.

57. Kumar P, Goldstraw P, Yamada K, et al. Pulmonary fibrosis and lung cancer: risk and benefit analysis of pulmonary resection. J Thorac Cardiovasc Surg 2003;125:1321–1327.

58. Wells AU, Desai SR, Rubens MB, et al. Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. Am J Respir Crit Care Med 2003;167:962–969.

59. Latsi PI, du Bois RM, Nicholson AG, et al. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. Am J Respir Crit Care Med 2003;168:510–511.

60. Wangoo A, Shaw RJ, Diss TC, Farrell PJ, duBois RM, Nicholson AG. Cryptogenic fibrosing alveolitis: lack of association with Epstein-Barr virus infection. Thorax 1997;52:888–891.

61. Tsukamoto K, Hayakawa H, Sato A, Chida K, Nakamura H, Miura K. Involvement of Epstein-Barr virus latency membrane protein 1 in disease progression in patients with idiopathic pulmonary fibrosis. Thorax 2000;55:958–961.

62. Stewart JP, Egan JJ, Ross AJ et al. The detection of Epstein-Barr virus DNA in lung tissue from patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1999;159:1336–1341.
63. Meliconi R, Andreone P, Fasano L et al. Incidence of hepatitis C virus infection in Italian patients with idiopathic pulmonary fibrosis. Thorax 1996;51:315–317.

64. Hubbard R. Occupational dust exposure and the aetiology of cryptogenic fibrosing alveolitis. Eur Respir J Suppl 2001;32:119s–121s.

65. Tobin RW, Pope CE, Pellegrini CA, Emond MJ, Sillery J, Raghu G. Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998;158:1804–1808.

66. Hubbard R, Venn A, Smith C, Cooper M, Johnston I, Britton J. Exposure to commonly prescribed drugs and the etiology of cryptogenic fibrosing alveolitis: A case-control study. Am J Respir Crit Care Med 1998;157:743–747.

67. Hubbard R, Venn A, Britton J. Exposure to antidepressants and the risk of cryptogenic fibrosing alveolitis: a case-control study. Eur Respir J 2000;16:409–413.

68. Wallace WAH, Howie SEM. Immunoreactive interleukin 4 and interferon-gamma expression by type II alveolar epithelial cells in idiopathic lung disease. J Pathol 1999;187:475–480.

69. Whyte M, Hubbard R, Meliconi R, et al. Increased risk of fibrosing alveolitis associated with interleukin-1 receptor antagonist and tumor necrosis factor-alpha gene polymorphisms. Am J Respir Crit Care Med 2000;162:755–758.

70. Pantelidis P, Fanning GC, Wells AU, Welsh KI, du Bois RM. Analysis of tumor necrosis factor-alpha, lymphoxygenalpha, tumor necrosis factor receptor II, and interleukin-6 polymorphisms in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2001;163:1432–1436.

71. Thomas AQ, Lane K, Phillips J III, et al. Heterozygosity for a surfactant protein C gene mutation associated with usual interstitial pneumonitis and cellular nonspecific interstitial pneumonitis in one kindred. Am J Respir Crit Care Med 2002;165:1322–1328.

72. Kradin RL, Divertie MB, Colvin RB, et al. Usual interstitial pneumonitis is a T-cell alveolitis. Clin Immunol Immunopathol 1986;40:224–235.

73. Wells AU, Lorimer S, Majumdar S, et al. Fibrosing alveolitis in systemic sclerosis: increase in memory T-cells in lung interstitium. Eur Respir J 1995;8:266–271.

74. Wallace WA, Schofield JA, Lamb D, Howie SE. Localisation of a pulmonary autoantigen in cryptogenic fibrosing alveolitis. Thorax 1994;49:1139–1145.

75. Jakubzick C, Choi ES, Carpenter KJ, et al. Human pulmonary fibroblasts exhibit altered interleukin-4 and interleukin-13 receptor subunit expression in idiopathic interstitial pneumonia. Am J Pathol 2004;164:1899–2001.

76. Keane MP, Arenberg DA, Lynch JP III, et al. The CXC chemokines, IL-8 and IP-10, regulate angiogenic activity in idiopathic pulmonary fibrosis. J Immunol 1997;159:1437–1443.

77. Lippi-Blanco E, Soini Y, Kinnula V, Paakko P. VEGF and bFGF are highly expressed in intraluminal fibromyxoid lesions in bronchiolitis obliterans organizing pneumonia. J Pathol 2002;196:220–227.

78. Koyama S, Sato E, Haniu M, Numanami H, Nagai S, Izumi T. Decreased level of vascular endothelial growth factor in bronchoalveolar lavage fluid of normal smokers and patients with pulmonary fibrosis. Am J Respir Crit Care Med 2002;166:382–385.

79. Lippi-Blanco E, Kaarteenaho-Wik R, Soini Y, Risteli J, Paakko P. Intraluminal fibromyxoid lesions in bronchiolitis obliterans organizing pneumonia are highly capillarized. Hum Pathol 1999;30:1192–1196.

80. Ebina M, Shimizu K, Shibata N, et al. Heterogeneous increase in CD34-positive alveolar capillaries in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2004;169:1203–1208.

81. Renzoni EA. Neovascularization in idiopathic pulmonary fibrosis: too much or too little? Am J Respir Crit Care Med 2004;169:1179–1180.

82. Nicholson AG, Gibbs AR, Addis BJ, et al. Interobserver variation in diffuse parenchymal lung disease. Thorax 2004;59:500–505.

83. Monaghan H, Wells AU, Colby TV, du Bois RM, Hansell DM, Nicholson AG. Prognostic implications of histologic patterns in multiple surgical lung biopsies from patients with idiopathic interstitial pneumonias. Chest 2004;125:522–526.

84. Flaherty KR, Thwaite EL, Kazerouni EA, et al. Radiological versus histological diagnosis in UIP and NSIP: survival implications. Thorax 2003;58:143–148.

85. Ognibene FP, Masur H, Rogers P, et al. Nonspecific interstitial pneumonitis without evidence of Pneumocystis carinii in asymptomatic patients infected with human immunodeficiency virus (HIV). Ann Intern Med 1988;109:874–879.

86. MacDonald SL, Rubens MB, Hansell DM, et al. Nonspecific interstitial pneumonia and usual interstitial pneumonia: comparative appearances at and diagnostic accuracy of thin-section CT. Radiology 2001;221:600–605.

87. Hartman TE, Swensen SJ, Hansell DM, et al. Nonspecific interstitial pneumonia: Variable appearance at high-resolution chest CT. Radiology 2000;217:701–705.

88. Akira M, Inoue G, Yamamoto S, Sakatani M. Non-specific interstitial pneumonia: findings on sequential CT scans of nine patients. Thorax 2000;55:854–859.

89. Cottin V, Donsbeck AV, Revel D, Loire R, Cordier JF. Nonspecific interstitial pneumonia. Individualization of a clinicopathologic entity in a series of 12 patients. Am J Respir Crit Care Med 1998;158:1286–1293.

90. Nicholson AG, Wells AU. Nonspecific interstitial pneumonia—nobody said it’s perfect. Am J Respir Crit Care Med 2001;164:1553–1554.

91. Hansell DM, Nicholson AG. Smoking related diffuse parenchymal lung disease: HRCT-pathologic correlation. Sem Respir Crit Care Med 2003;24:377–392.

92. Bourou D, Nicholson AG, Colby TV, et al. Histopathological subsets of fibrosing alveolitis in patients with scleroderma and their relationship to natural history and treated course. Am J Respir Crit Care Med 2002;165:1581–1586.

93. Douglas WW, Tazelaar HD, Hartman TE, et al. Polymysitis-dermatomyositis-associated interstitial lung disease. Am J Respir Crit Care Med 2001;164:1182–1185.

94. Tansey D, Wells AU, Colby TV, et al. Variations in histologic patterns of interstitial pneumonia between connective tissue disorders and their relationship to prognosis. Histopathology 2004;44:585–596.
95. Ito I, Nagai S, Kitaichi M, et al. Pulmonary manifestations of primary Sjogren's syndrome: a clinical, radiologic and pathologic study. Am J Respir Crit Care Med 2005;171:632–638.

96. Niewoehner DE, Kleinerman J, Rice DB. Pathologic changes in the peripheral airways of young cigarette smokers. N Engl J Med 1974;291:755–758.

97. Moon J, du Bois RM, Colby TV, Hansell DM, Nicholson AG. Clinical significance of respiratory bronchiolitis on open lung biopsy and its relationship to smoking related interstitial lung disease. Thorax 1999;54:1009–1014.

98. Fraig M, Shreesha U, Savici D, Katzenstein AL. Respiratory bronchiolitis: a clinicopathologic study in current smokers, ex-smokers, and never-smokers. Am J Surg Pathol 2002;26:647–653.

99. King TE. Respiratory bronchiolitis-associated interstitial lung disease. Clin Chest Med. 1993;14:693–698.

100. Park JS, Brown KK, Tuder RM, Hale VA, King Jr TE, Lynch DA. Respiratory bronchiolitis-associated interstitial lung disease: radiologic features with clinical and pathologic correlation. J Comput Assist Tomogr 2002;26:13–20.

101. Heyneman LE, Ward S, Lynch DA, Remijardin M, Kohkoh T, Muller NL. Respiratory bronchiolitis, respiratory bronchiolitis-associated interstitial lung disease, and desquamative interstitial pneumonia: Different entities or part of the spectrum of the same disease process? Am J Roentgenol 1999;173:1617–1622.

102. Agius RM, Rutman A, Knight RK, Cole PJ. Human pulmonary alveolar macrophages with smokers' inclusions: their relation to the cessation of cigarette smoking. Br J Exp Pathol 1986;67:407–413.

103. Remijardin M, Edme JL, Boulenguez C, Remi J, Mastor I, Sobaszek A. Longitudinal follow-up study of smoker's lung with thin-section CT in correlation with pulmonary function tests. Radiology 2002;222:261–270.

104. Fromm GB, Dunn LJ, Harris JO. Desquamative interstitial pneumonitis. Characterization of free intraalveolar cells. Chest 1980;77:552–554.

105. Hartman TE, Primack SL, Kang EY, et al. Disease progression in usual interstitial pneumonia compared with desquamative interstitial pneumonia. Assessment with serial CT. Chest 1996;110:378–382.

106. Akira M, Yamamoto S, Hara H, Sakatani M, Ueda E. Serial computed tomographic evaluation in desquamative interstitial pneumonia. Thorax 1997;52:333–337.

107. Craig PJ, Wells AU, Doffman S, et al. Desquamative interstitial pneumonia, respiratory bronchiolitis and their relationship to smoking. Histopathology 2004;45:275–282.

108. Hartman TE, Primack SL, Hansell D, McGuinness G, Muller NL. Desquamative interstitial pneumonia: thin-section CT findings in 22 patients. Radiology 1993;187:787–790.

109. Kubo M, Koshino T, Shimizu H, et al. A case of desquamative interstitial pneumonia with increased numbers of eosinophils in the bronchoalveolar lavage fluid. Nihon Kyobu Shikkan Gakkai Zasshi 1997;35:1084–1092.

110. Matsuo K, Tada S, Kataoka M et al. Spontaneous remission of desquamative interstitial pneumonia. Intern Med 1997;36:728–731.

111. Kitaichi M. Desquamative interstitial pneumonia: an idiopathic interstitial pneumonia with a possibility of spontaneous regression. Intern Med 1997;36:672–673.

112. Stillwell P, Norris DG, O’Connell EJ, Rosenow EC, Weiland LH, Harrison EG. Desquamative interstitial pneumonitis in children. Chest 1980;77:165–171.

113. Tal A, Maor E, Bar-Ziv J, Gorodischer R. Fatal desquamative interstitial pneumonia in three infants siblings. J Pediatr 1984;104:873–876.

114. Herbert A, Sterling G, Abraham J, Corrin B. Desquamative interstitial pneumonia in an aluminum welder. Hum Pathol 1982;13:694–699.

115. Corrin B, Dewar A, Rodriguez-Roisin R, Turner-Warwick M. Fine structural changes in cryptogenic fibrosing alveolitis and asbestosis. J Pathol 1985;147:107–119.

116. Freed JA, Miller A, Gordon RE, Fischbein A, Kleinerman J, Langer AM. Desquamative interstitial pneumonia associated with chrysotile asbestos fibres. Br J Ind Med 1991;48:332–337.

117. Hamadeh MA, Atkinson J, Smith LJ. Sulfasalazine-induced pulmonary disease. Chest 1992;101:1033–1037.

118. Amir G, Ron N. Pulmonary pathology in Gaucher's disease. Hum Pathol 1999;30:666–670.

119. Aubry MC, Wright JL, Myers JL. The pathology of smoking-related lung diseases. Clin Chest Med 2000;21:11–35, vii.

120. Nagai S, Hoshino Y, Hayashi M, Ito I. Smoking-related interstitial lung diseases. Curr Opin Pulmon Med 2000;6:415–419.

121. Ryu JH, Colby TV, Hartman TE, Vassallo R. Smoking-related interstitial lung diseases: a concise review. Eur Respir J 2001;17:122–132.

122. Selman M. The spectrum of smoking-related interstitial lung disorders: the never-ending story of smoke and disease. Chest 2003;124:1185–1187.

123. Vassallo R, Jensen EA, Colby TV, et al. The overlap between respiratory bronchiolitis and desquamative interstitial pneumonia in pulmonary Langerhans cell histiocytosis: high-resolution CT, histologic, and functional correlations. Chest 2003;124:1199–1205.

124. Rice AJ, Wells AU, Bouros D, et al. Terminal diffuse alveolar damage in relation to interstitial pneumonias. An autopsy study. Am J Clin Pathol 2003;119:709–714.

125. Olson J, Colby TV, Elliott CG. Hamman-Rich syndrome revisited. Mayo Clin Proc 1990;65:1538–1548.

126. Kondoh Y, Taniguchi H, Kawabata Y, Yukoi T, Suzuku K, Takagi K. Acute exacerbation in idiopathic pulmonary fibrosis. Analysis of clinical and pathologic findings in three cases. Chest 1993;103:1808–1812.

127. Akira M, Hamada H, Sakatani M, Kobayashi C, Nishioka M, Yamamoto S. CT findings during phase of accelerated deterioration in patients with idiopathic pulmonary fibrosis. Am J Roentgenol 1997;168:79–83.

128. Kitaichi M. Pathologic features and the classification of interstitial pneumonitis of unknown etiology. Bull Chest Dis Res Inst Kyoto University 1990;23:1–18.

129. Ambrosini V, Cancellieri A, Chilosi M, et al. Acute exacerbation of idiopathic pulmonary fibrosis: report of a series. Eur Respir J 2003;22:821–826.
130. Vourlekis JS, Brown KK, Cool CD et al. Acute interstitial pneumonitis—case series and review of the literature. Medicine 2000;79:369–378.
131. Ichikado K, Suga M, Muller NL, et al. Acute interstitial pneumonia: comparison of high-resolution computed tomography findings between survivors and nonsurvivors. Am J Respir Crit Care Med 2002;165:1551–1556.
132. Suga T, Sugiyama Y, Ohno S, Kitamura S. Two cases of IIP which developed acute exacerbation after bronchoalveolar lavage. Nihon Kyobu Shikkan Gakkai Zasshi 1994; 32:174–178.
133. Enomoto T, Kawamoto M, Kunugi S, et al. Clinicopathological analysis of patients with idiopathic pulmonary fibrosis which became acutely exacerbated after video-assisted thoracoscopic surgical lung biopsy. Nihon Kokyuki Gakkai Zasshi 2002;40:806–811.
134. Colby TV. Pathologic aspects of bronchiolitis obliterans organizing pneumonia. Chest 1992;102:385–433.
135. Myers JL, Colby TV. Pathologic manifestations of bronchiolitis, constrictive bronchiolitis, cryptogenic organizing pneumonia, and diffuse panbronchiolitis. Clin Chest Med 1993;14:611–622.
136. Davison AG, Heard BE, McCullister WAC, Turner-Warwick MEH. Cryptogenic organising pneumonia. Q J Med 1983; 52:383–394.
137. King TEJ, Mortenson RL. Cryptogenic organizing pneumonia. The North American experience. Chest 1992;102: 85–135.
138. Cordier JF. Organising pneumonia. Thorax 2000;55:318–328.
139. Kramer MR, Saldana MJ, Ramos M, Pitchenik AE. High titres of Epstein-Barr virus antibodies in adult patients with lymphocytic interstitial pneumonitis associated with AIDS. Respir Med 1992;86:49–52.
140. Barbera JA, Hayashi S, Hegele RG, Hogg JC. Detection of Epstein-Barr virus in lymphocytic interstitial pneumonia by in situ hybridisation. Am Rev Respir Dis 1992;145: 940–946.
141. Kaan PM, Hegele RG, Hayashi S, Hogg JC. Expression of bcl-2 and Epstein-Barr virus LMP1 in lymphocytic interstitial pneumonia. Thorax 1997;52:12–16.
142. Andiman WA, Eastman R, Martin K, et al. Opportunistic lymphoproliferations associated with Epstein-Barr viral DNA in infants and children with AIDS. Lancet 1985;2: 1390–1393.
143. Koss MN, Hochholzer L, Langloss JM, Wehunt WD, Lazarus AA. Lymphoid interstitial pneumonia: clinicopathological and immunopathological findings in 18 cases. Pathology 1987;19:178–185.
144. Strimlan CV, Rosenow EC, Weiland LH, Brown LR. Lymphocytic interstitial pneumonitis. Review of 13 cases. Ann Intern Med 1978;88:616–621.
145. Nicholson AG, Wotherspoon AC, Diss TC, et al. Reactive pulmonary lymphoid disorders. Histopathology 1995;25: 405–412.
146. Yousem SA, Dacie S. Idiopathic bronchiolocentric interstitial pneumonia. Mod Pathol 2002;15:1148–1153.
147. Churg A, Myers J, Suarez T, et al. Airway-centered interstitial fibrosis: a distinct form of aggressive diffuse lung disease. Am J Surg Pathol 2004;28:62–68.
148. Fukouka J, Franks TJ, Colby TV, et al. Peribronchiolar metaplasia (PBM): a common incidental histologic lesion and a rare cause of interstitial lung disease (PBM-ILD). Mod Pathol 2004;17:336A.
149. Fan LL, Langston C. Chronic interstitial lung disease in children. Pediatr Pulmonol 1993;16:184–196.
150. Bokulic RE, Hilman BC. Interstitial lung disease in children. Pediatr Clin North Am 1994;41(3):543–567.
151. Katzenstein A-LA, Gordon LP, Oliphant M, Swender PT. Chronic pneumonitis of infancy. A unique form of interstitial lung disease occurring in early childhood. Am J Surg Pathol 1995;19(4):439–447.
152. Schroeder SA, Shannon DC, Mark EJ. Cellular interstitial pneumonitis in infants: a clinicopathologic study. Chest 1992;101:1065–1069.
153. Bush A, du Bois RM. Congenital and pediatric interstitial disease. Curr Opin Pulmon Med 1996;2:347–356.
154. Bush A. Diagnosis of interstitial lung disease. Pediatr Pulmonol 1996;22:81–82.
155. Fan LL. Evaluation and therapy of chronic interstitial pneumonitis in children. Curr Opin Pediatr 1994;6:248–254.
156. Clement A, Allen J, Corrin B, et al. Task force on chronic interstitial lung disease in immunocompetent children. Eur Respir J 2004;24:686–697.
157. Nicholson AG, Kim H, Corrin B, et al. The value of classifying interstitial pneumonitis in childhood according to defined histological patterns. Histopathology 1998;33: 203–211.
158. Katzenstein A-L, Askin FB. Pediatric disorders. In: Katzenstein M, Askin FB, eds. Surgical pathology of non-neoplastic lung disease. Philadelphia: WB Saunders, 1997: 361–382.
159. Fan LL. Pediatric interstitial lung disease. In: Schwartz MI, King TE Jr, eds. Interstitial lung disease. Hamilton: Decker, 1998:103–188.
160. Nogee LM, Dunbar AE, Wert SE, Askin F, Hamvas A, Whitsett JA. A mutation in the surfactant protein C gene associated with familial interstitial lung disease. N Engl J Med 2001;344(8):573–579.
161. Nogee LM. Alterations in SP-B and SP-C expression in neonatal lung disease. Annu Rev Physiol 2004;66: 601–623.
162. Waters KA, Bale P, Isaacs D, Mellis C. Successful chloroquine therapy in a child with lymphoid interstitial pneumonitis. J Pediatr 1991;119:989–991.
163. Sharief N, Crawford OF, Dinwiddie R. Fibrosing alveolitis and desquamative interstitial pneumonitis. Pediatr Pulmonol 1994;17:359–365.