Idiopathic Pulmonary Fibrosis, Nonspecific Interstitial Pneumonia/Fibrosis, and Sarcoidosis

Joseph P. Lynch III, MD, FCCP

Objectives:

1. To describe the salient epidemiologic, clinical, physiologic, and radiographic features of idiopathic pulmonary fibrosis, nonspecific interstitial pneumonia / fibrosis, and sarcoidosis.
2. To discuss the salient features on high-resolution CT scans and their impact on prognosis.
3. To review the characteristic histopathologic features of each of these disorders and the role of transbronchial or surgical (open or thoracoscopic) lung biopsies.
4. To discuss the clinical role (if any) of ancillary studies such as radionuclide scanning or BAL to stage or follow up these disorders.
5. To review therapeutic strategies.

Key words: idiopathic pulmonary fibrosis; usual interstitial pneumonia; cryptogenic fibrosing alveolitis; nonspecific interstitial pneumonia; sarcoidosis

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF), also known as cryptogenic fibrosing alveolitis (CFA), is the prototype of chronic interstitial lung disorders.[1-4] Cardinal features include progressive cough, dyspnea, bilateral interstitial infiltrates on chest radiographs, a restrictive ventilatory defect on pulmonary function tests, and progressive fibrosis and destruction of the lung parenchyma.[1, 2] The features are nonspecific and may be observed with myriad other interstitial lung disorders. Pulmonary fibrosis may occur as a complication of collagen vascular diseases,[5] radiation therapy, inhalation injury, pharmacologic agents, or cytotoxic and illicit drugs, and as a sequelae of diverse infectious and inflammatory lung disorders.[2-4] This discussion is restricted to the idiopathic form. As will be discussed in detail later, the term IPF should be restricted to patients with the appropriate clinical features and the histological lesion usual interstitial pneumonia (UIP).[2, 4, 6] Other histological patterns (eg, desquamative interstitial pneumonia (DIP); respiratory bronchiolitis interstitial lung disease (RBILD); nonspecific interstitial pneumonia (NSIP); acute interstitial pneumonia (AIP); lymphoid interstitial pneumonia (LIP); and cryptogenic organizing pneumonia) are distinct entities, with differing clinical expression and prognoses.[2, 4, 6] A definitive diagnosis of UIP requires surgical lung biopsy,[6] but the diagnosis of UIP can be affirmed with confidence by high-resolution thin-section CT (HRCT) scans in some patients.[6-8] IPF is one of the most frustrating disorders to manage, since treatment is largely ineffective.[1, 9-14]

Epidemiology

The prevalence of IPF has been estimated at three to eight cases per 100,000 persons,[3, 15, 16] but one study suggested a prevalence as high as 28 per 100,000.[17] The disease is rare in children, and typically affects older adults, with peak onset after the sixth decade of life.[2, 17] The prevalence in adults aged 35 to 44 years old is 2.7 per 100,000.[17] By contrast, prevalence exceeds 175 per 100,000 in adults >75 years.[17] IPF is more common in men and in smokers.[14, 17, 18] Despite its rarity, IPF accounts for >30,000 hospitalizations and >5,000 deaths annually in the United States.[19] The etiology of IPF has not been elucidated, but exposure to or inhalation of minerals, dusts, organic solvents, urban pollution, or cigarette smoke has been associated with an increased risk.[15, 16, 20-22] Chronic aspiration secondary to GI reflux was implicated in the development of pulmonary fibrosis in one study,[23] but this remains controversial. No clear genetic basis has been found in IPF. Familial IPF / UIP, which accounts for 0.5 to 3% of cases of IPF, is indistinguishable from nonfamilial forms, except patients tend to be younger in the familial variant.[24] The mode of transmission of familial IPF is not known, but is believed to be autosomal dominant with variable penetrance in two thirds of patients.[2] Associations between IPF and α_1-antitrypsin inhibitor (Pi) alleles on chromosome 14 have been described.[25] Genetic polymorphisms for interleukin-1 receptor antagonist (IL-1ra) or tumor necrosis factor- α (TNF-α) may be important in determining risk.[26] IPF occurs in whites or in nonwhites; to my knowledge, prevalence among different ethnic groups has not been studied.

Clinical Features

Initial symptoms of IPF/CFA are cough (typically nonproductive) and dyspnea. Over time, the cough may become paroxysmal and debilitating. The onset of the disease is usually indolent, but it progresses relentlessly, resulting in respiratory failure within 3 to 8 years after onset of symptoms.[27, 28] In the late phases of the disorder, cyanosis and cor pulmonale intervene. Spontaneous remissions do not occur.[1, 2] However, the conditions of a subset of patients stabilize after an initial period of decline.[1, 27] Extrapulmonary involvement does not occur. Fever, sweats, or chills suggest intercurrent infection. Physical examination reveals end-inspiratory rales (often with a "Velcro" quality) in >85% of patients with IPF.[7, 12, 14, 28] Clubbing is noted in 25 to 93% of patients.[7, 12, 14, 28] Unfortunately, as will be discussed in detail later, responsiveness to therapy for IPF is poor. The disease progresses in most patients irrespective of therapy, and sustained or complete remission is rarely achieved.[1, 9-11, 13, 14, 29] Mean survival from the onset of symptoms approximates 3 to 5 years.[7, 9, 11, 12, 14, 27, 29-31] Fewer than 15% of patients survive 10 years from the onset of symptoms.[7,9,11,12,14,27,29,30] Factors associated with worse prognosis include the following: older age[14,27,32]; more severe impairments in pulmonary function or chest radiographs[14,27,32,33]; and a history of never smoking.[14, 34] The reasons for the apparent protective effect of smoking are not clear, but could reflect inhibitory effects of cigarette smoke on lung fibroblast proliferation and chemotaxis.[35] In some studies, mortality was higher in men,[32, 34, 36] but others found no influence of gender on survival.[14] The major cause of death is respiratory failure; other causes include pulmonary embolism, cardiac failure, and cerebrovascular accidents (primarily in the elderly).[31, 37] Acute respiratory failure (ARF) requiring mechanical ventilation (MV) may complicate IPF/UIP, either from infection or an acute exacerbation of the underlying disease process.[38-40] In this context, mortality is high (> 90%). For this reason, MV is usually ill-advised in patients with severe UIP. Lung cancer occurs in 4 to 13% of patients with IPF.[41, 42] In a study of 890 patients with CFA in the United Kingdom, 39 (4.4%) developed lung cancer, compared to an incidence of only 0.9% in control subjects with miscellaneous lung diseases.[41] Although the incidence of lung cancer was increased in current smokers with CFA/IPF (8.9%) compared to nonsmokers (3.1%) or ex-smokers (3.1%), the heightened risk of lung cancer was not solely due to the effects of cigarette smoking.

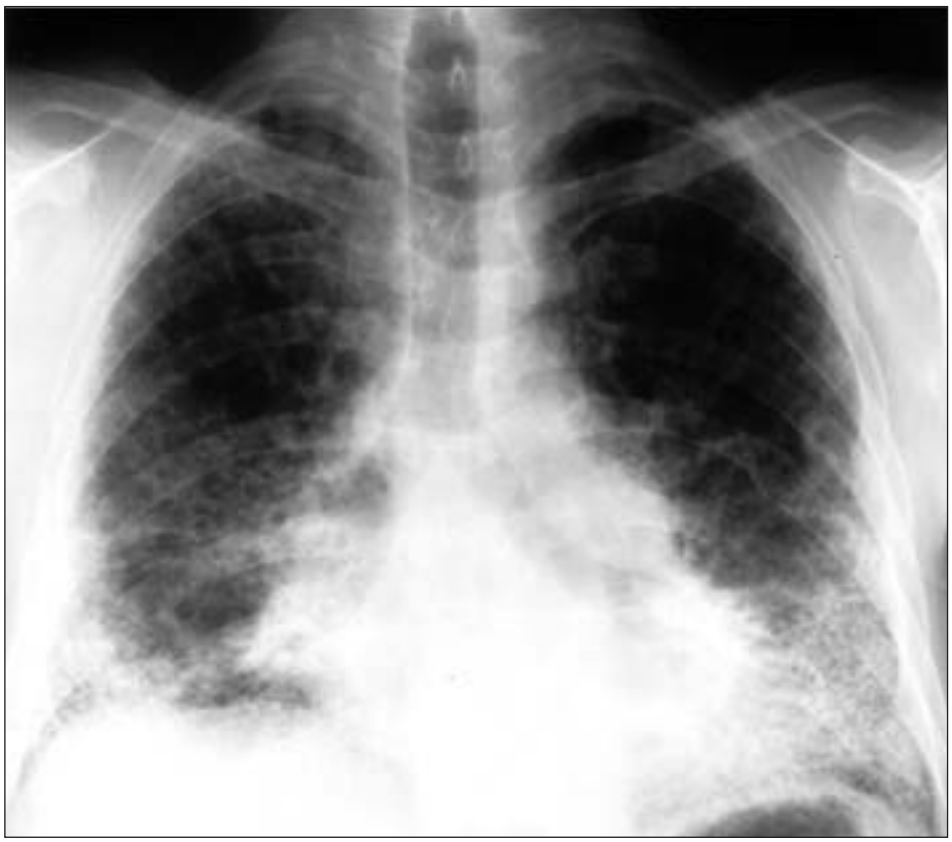


Figure 1. IPF/UIP. Posteroanterior chest radiograph from a 61-year-old man with IPF/UIP demonstrates extensive reticulonodular infiltrates with a bibasilar predominance. A mixed alveolar and interstitial pattern is evident in the lower lobes.

Laboratory Tests

Laboratory test results are nonspecific. Circulating antinuclear antibodies or rheumatoid factor have been found in 10 to 20% of patients with IPF; the erythrocyte sedimentation rate is elevated in 60 to 94% of patients.[1] Serologic studies do not correlate with the extent or activity of the disease, and do not predict therapeutic responsiveness.[1, 2] However, one retrospective study of 52 patients with IPF noted that serum levels of surfactant protein (SP)-A and SP-D correlated with the extent of alveolitis, and levels were higher in nonsurvivors.[43] Additional studies are required to assess the value (if any) of these parameters.

Chest Radiographic Findings

Abnormalities on chest radiographs are present in >95% of patients with IPF.[1, 14, 44] In the early phases of the illness, bilateral basilar shadows, with a predilection for the peripheral regions of the lung, are evident (Fig 1). The proclivity for peripheral (subpleural) lung zones is best demonstrated by HRCT scans.[44, 45] The disease is usually symmetrical. Interstitial, reticulonodular, alveolar, or mixed interstitial and alveolar infiltrates may be seen. With disease progression, all lung fields are affected and lung volumes decline. Similar radiographic features may be observed in asbestosis and collagen vascular disease-associated pulmonary fibrosis.[45-47] Pulmonary hypertension and cor pulmonale may be seen in far-advanced cases. Intrathoracic lymphadenopathy and pleural thickening are not features on plain chest radiographs, but may be noted on CT scans.[45] Pneumothoraces (secondary to rupture of honeycomb cysts) occur in 5 to 10% of patients.[1, 44] Chest radiographs have limited prognostic value, but serial radiographs (including old films) may gauge the pace and evolution of the disease.[1, 48]

High-Resolution Thin-Section CT Scans

HRCT Features and Value in the Differential Diagnosis: HRCT scans, using thin (1 to 2 mm) sections without the use of contrast, are far more accurate than conventional chest radiographs in assessing the extent and nature of the disease.[10, 48] HRCT has diagnostic[45, 48-50] and prognostic[10, 34, 51-53] value, and should be part of the initial evaluation of suspected interstitial lung disease (ILD).[46] The HRCT features of IPF/UIP are stereotypic and predictable and include the following: a patchy, heterogeneous distribution with a predilection for the peripheral (subpleural) and basilar regions of the lungs; small cystic radiolucencies (*ie*, honeycomb change); coarse reticular or linear opacities (intralobular and interlobular septal lines); ragged pleural surfaces; irregular or thickened bronchial walls or pulmonary vessels; bronchiectasis and bronchioloectasis (Figs2-6).[48,54,55] Air bronchograms (1 to 2 mm in diameter) reflect dilated peripheral airways surrounded by fibrotic lung tissue. Focal ground-glass opacities (*ie*, hazy zones of increased alveolar attenuation) may be present in UIP, but are not a dominant feature[7, 12, 48, 54-56]; predominant or extensive ground-glass opacities suggest an alternative diagnosis such as DIP,[57] hypersensitivity pneumonia (HP),[4] or nonspecific interstitial pneumonia/fibrosis (NSIP).[4, 7, 12] Honeycomb change is a cardinal feature of UIP,[48, 54, 55] but is absent in AIP and DIP.[4, 7, 12] Honeycombing is not a prominent feature in NSIP, but focal honeycomb change may be seen in fibrotic variants of NSIP.[8, 12, 58] In severe cases of IPF/UIP, severe volume loss, anatomic distortion, and dilated pulmonary arteries are observed. Zones of emphysema (particularly in the upper lobes) may be present concomitantly in smokers.[54, 59, 60]

HRCT may obviate the need for surgical lung biopsy, provided the CT features are *classical* for UIP.[7, 8, 34, 50, 58] The accuracy of a "confident diagnosis" of UIP by a trained observer is >90%.[8, 49, 50, 61] However, fewer than two thirds of patients with histologically confirmed UIP exhibit classical features of UIP by HRCT ("confident diagnosis" by CT).[7, 8, 50, 58] Interobserver and intraobserver variability may be problematic for inexperienced radiologists; consensus is usually reached when extensive honeycomb change and subpleural predominance are present.[1, 8, 62] However, CT patterns overlap between UIP and fibrotic NSIP.[58] Subpleural predominance, reticulation, and honeycomb change may be found in some patients with fibrotic NSIP and focal ground-glass opacities are sometimes found in UIP.[58] *Predominant* ground-glass opacities make UIP unlikely, however.[12, 58] In one recent study of patients with a *clinical syndrome consistent with* IPF, HRCT accurately discriminated UIP from NSIP in 66% of cases.[58] However, when a "confident" diagnosis of either UIP or NSIP was made, accuracy improved to 72%; when all four radiologists agreed, accuracy was 83%.[58]

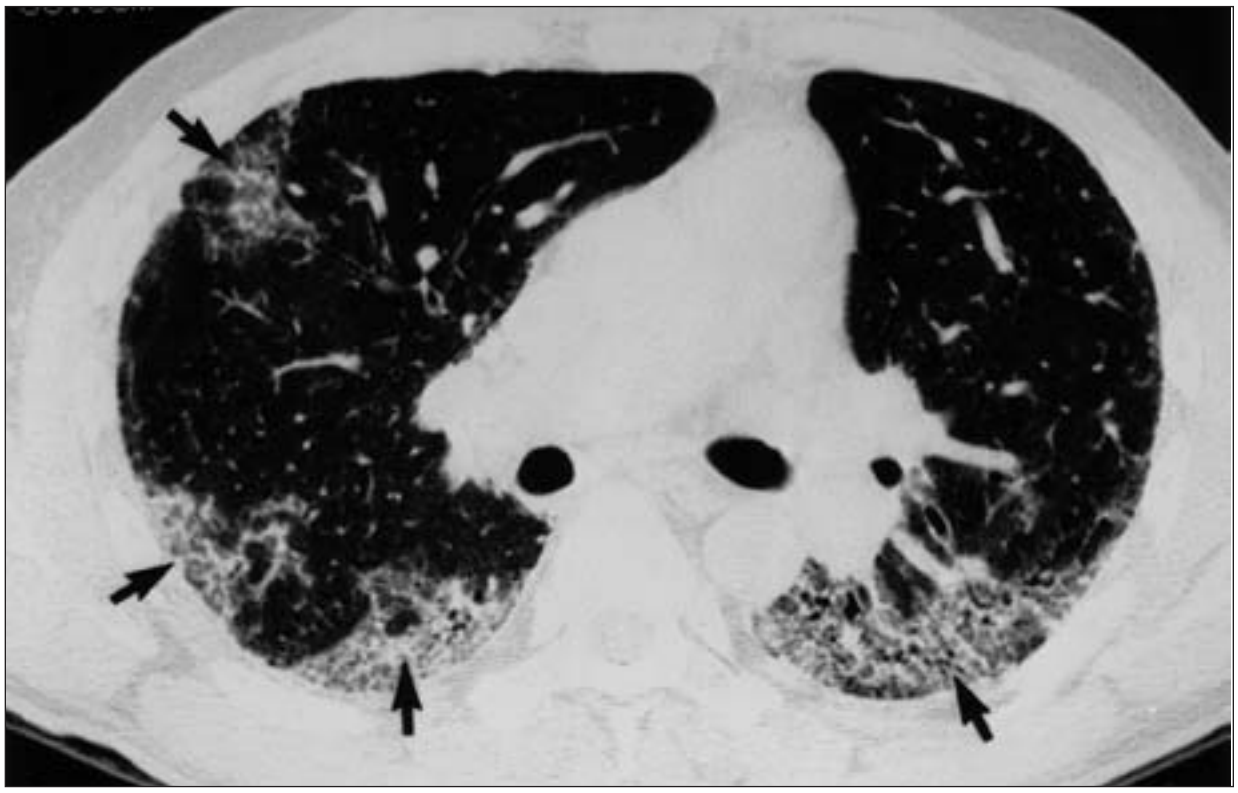


Figure 2. UIP. HRCT demonstrates foci of ground-glass opacities in the subpleural regions of the lower lobes (arrows). A few small honeycomb cysts are also present. The central portions of the lung are relatively spared.

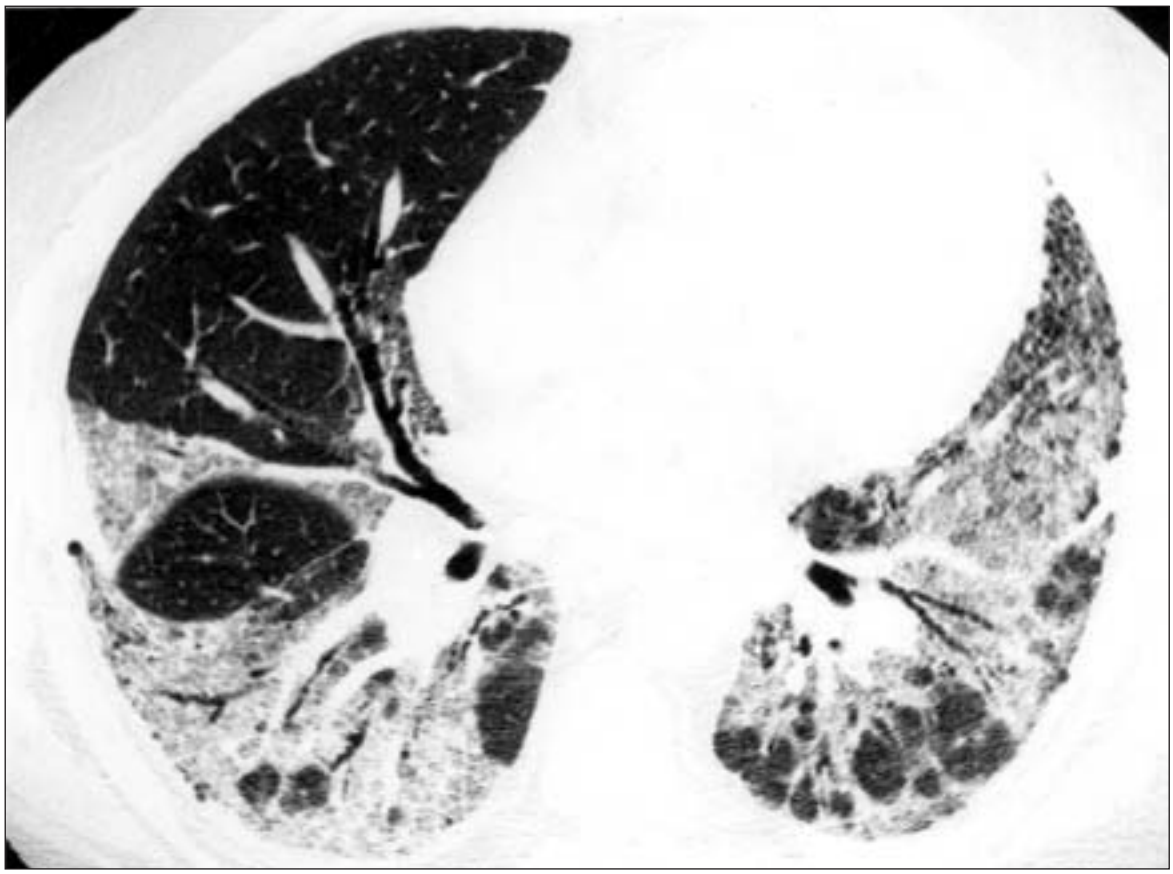


Figure 3. HRCT from a 53-year-old man with UIP confirmed on open lung biopsy specimen. Note extensive areas of ground-glass opacities with air-bronchograms in the lower lobes. Despite extensive involvement of the posterior regions of both lower lobes, the anterior portion of the left lower lobe is relatively normal, emphasizing the patchy nature of the disease.

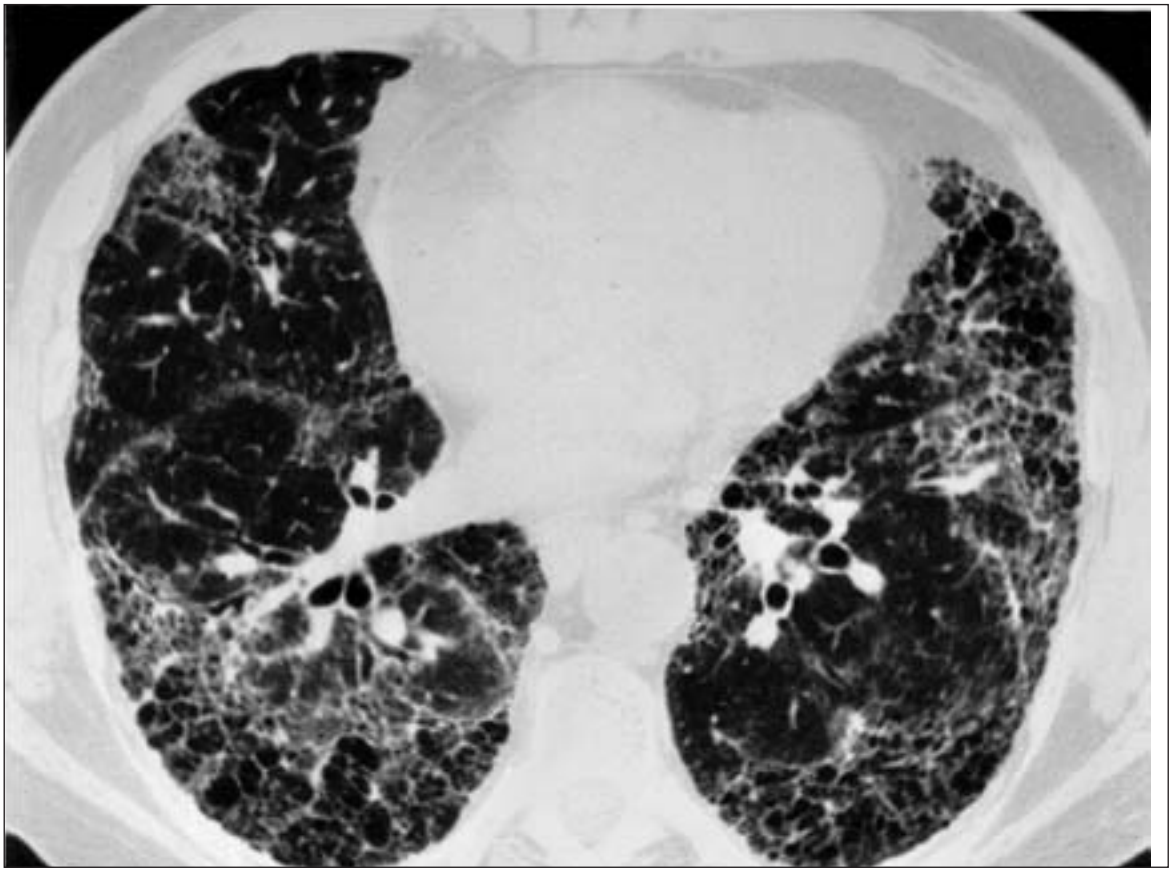


Figure 4. HRCT from a 63-year-old woman with UIP confirmed on open lung biopsy specimen. Honeycomb change is evident, particularly in the peripheral (subpleural) regions. Dilated bronchi, indicating traction bronchiectasis, are also present. There are no ground-glass opacities.

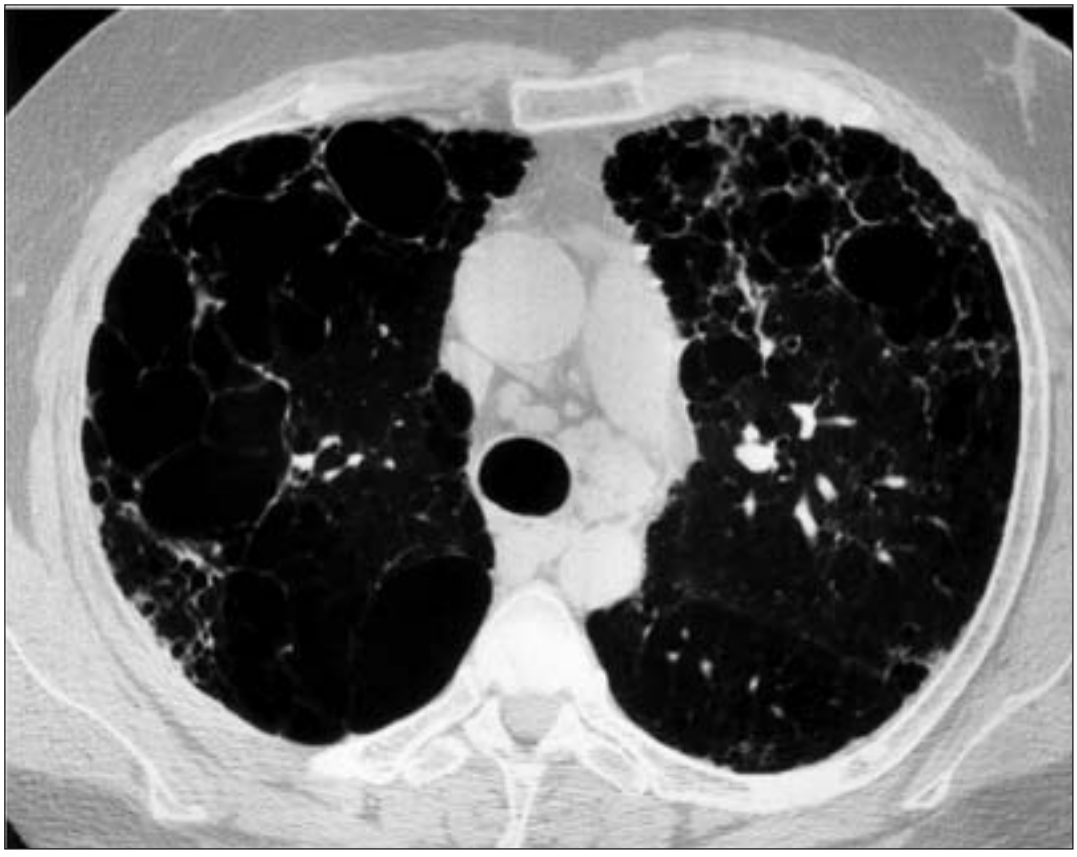


Figure 5. HRCT from a 44-year-old man with severe UIP on open lung biopsy specimen. Note the marked cystic radiolucencies (some cysts exceed 3 cm in diameter) and honeycombing involving both lungs. Although most of the lung parenchyma has been destroyed, note the accentuation of the cystic disease process in the peripheral (subpleural) regions.

Quantitative CT scans may enhance diagnostic accuracy. Using a semiquantitative CT scoring system, we found that a mean CT fibrotic score ≥ 2.0 in any lobe (indicating the presence of HC in ≥25% of the lobe)[63] was highly specific (86%) and sensitive (90%) for UIP.[34] When CT fibrotic scores exceeded 2.0 in *all* lobes, specificity for UIP improved to 93% but sensitivity was only 46%.[34] Thus, when HRCT features are "typical" (classical) for UIP, surgical lung biopsy is not necessary. However, unless specific contraindications exist, surgical biopsies should be performed when CT scans are nondiagnostic or atypical.[34]

Prognostic Value of HRCT in IPF: The prognosis of IPF can be inferred from the extent and nature (*ie*, predominant pattern) of HRCT abnormalities.[10, 48, 52, 53, 56, 64, 65] Although a combination of abnormalities (*eg*, ground glass opacities, reticulation, honeycomb change) are usually present in individual patients, early reports noted that "predominant ground-glass opacity pattern" in patients with IPF correlated with higher rates of response to corticosteroid therapy (33 to 44% improvement) and higher survival compared with reticular or honeycomb change patterns.[29, 48, 51, 63, 64] However, it is likely that steroid-responsive patients with extensive ground-glass opacities had histological patterns distinct from UIP (*eg*, DIP,[57] NSIP,[7, 12, 33, 66] or HP[2, 4]). A reticular pattern, characterized by intersecting fine or coarse lines, or honeycomb changes denote fibrosis within alveolar septae, ducts, and airspaces.[48, 56, 65] Reticular patterns or honeycomb changes never regress and may worsen over time (with or without therapy).[10, 48, 53, 54, 56] However, mixed patterns are common, and exceptions to these generalizations exist. Ground-glass opacities are not uniformly associated with therapeutic responsiveness, and may evolve to honeycomb change or reticular lines.[48, 51, 64, 65] Given the potential for fibrosis to evolve over time, the value of CT in predicting long-term prognosis is modest.[1, 8]

The *extent* of disease on HRCT correlates roughly with severity of functional impairment (*ie*, FVC and carbon monoxide diffusing capacity [DLCO])[54, 55]; the *pattern* of HRCT does not.[55] When emphysema coexists, lung volumes (FVC and total lung capacity [TLC]) are preserved, and DLCO is disproportionately reduced.[55] Changes

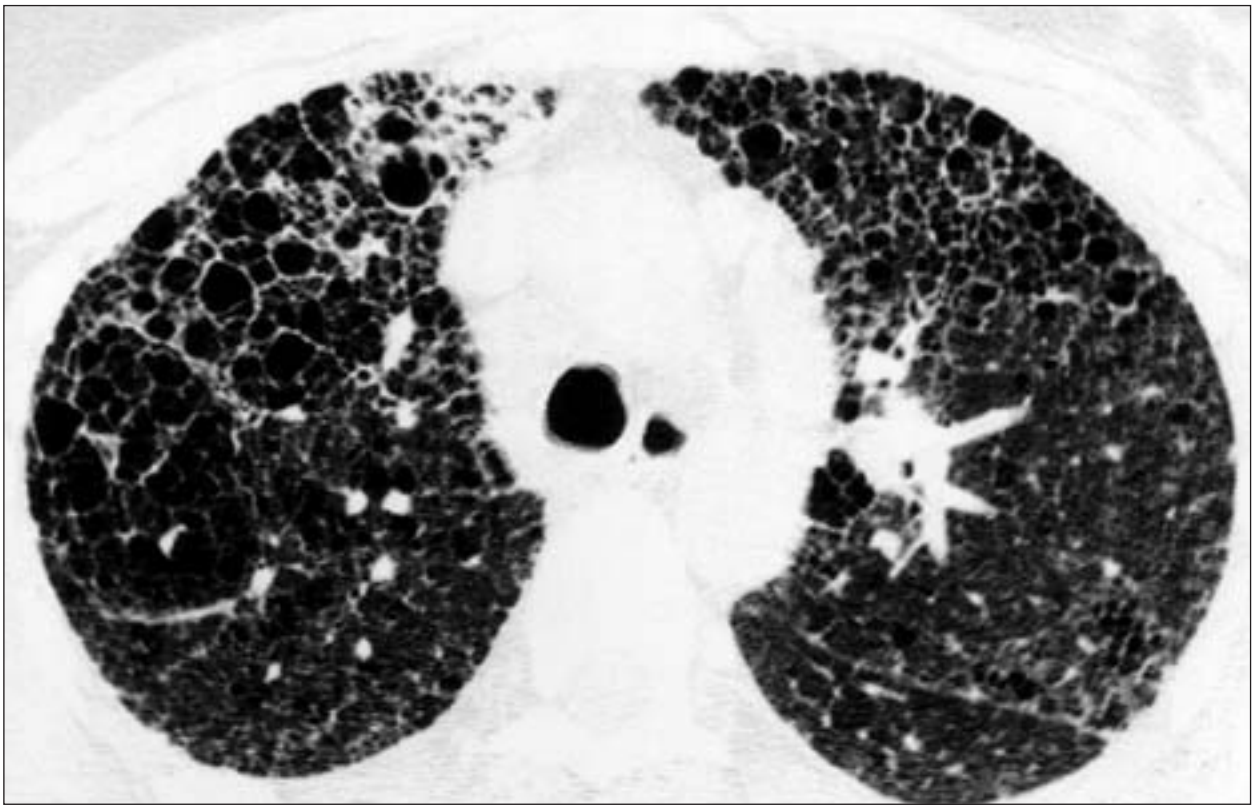


Figure 6. HRCT from a 48-year-old woman with UIP. Extensive cystic radiolucencies (honeycomb cysts) scattered throughout the lung parenchyma. Despite treatment with corticosteroids, AZA, and CP, she died of progressive respiratory failure.

in FVC and DLCO are usually concordant with changes in HRCT.[51, 54] Pulmonary function test results improve only when ground-glass opacities regress on HRCT.[48, 51, 54] Extensive fibrosis or honeycomb change on HRCT predicts a poor response to therapy.[10, 48, 51] Semiquantitative HRCT scoring systems have prognostic value.[10, 34, 53] In one prospective study of 38 patients with IPF (all of whom were treated with corticosteroids), we assessed the relative amounts of ground-glass opacities (alveolar) or reticular (fibrotic) infiltrates on pretreatment CT scans.[10] CT parameters correlated with the extent of alveolar inflammation or fibrosis on surgical lung biopsy specimens. Importantly, pretreatment CT alveolar and CT fibrotic scores predicted short-term response (at 3 months) to therapy and long-term mortality.[10] Consistent with earlier reports, responders to corticosteroids had higher CT alveolar scores and lower CT fibrotic scores compared with nonresponders or patients in stable condition. Long-term survival was higher in patients with lower pretherapy CT fibrotic scores. Severe fibrosis on pretreatment CT (*ie*, CT fibrotic score >2.0) predicted mortality with 80% sensitivity and 85% specificity. The addition of physiological data did not improve the ability of HRCT to predict survival.[10] In a recent study, British investigators arrived at similar conclusions in a cohort of 115 patients with UIP awaiting lung transplantation.[53] Twelve pretreatment variables correlated with 2-year survival on the waiting list. However, by multivariate stepwise regression analysis, only DLCO percent predicted and HRCT fibrotic scores independently predicted survival. Receiver operating curve analysis gave the best fit (predictive value) using a combination of DLCO and HRCT fibrotic scores. The optimal points on the receiver operating curves discriminating survivors from nonsurvivors corresponded to a DLCO of 39% predicted and HRCT fibrotic scores >2.25.[53] The curve resulting from a model combining these two parameters yielded a specificity and sensitivity of 84% and 82%, respectively, for discriminating survivors from nonsurvivors. These data are remarkably similar to our own data.[10] We recently extended our experience in a cohort of 106 patients with UIP,[34] which confirmed that a CT fibrotic score ≥2.0 was a significant predictor of mortality.[34] A mean CT fibrotic score ≥2.0 in *any* lobe was associated with increased mortality (risk ratio of 3.35) compared to patients with a CT fibrotic score < 2 in all lobes. A similar finding was noted when patients were segregated by mean CT fibrotic score ≥2 for all lobes (risk ratio of 2.5) (p=0.002). However, when the histological diagnosis was incorporated into the model, the diagnosis of UIP was the most powerful predictor of mortality, and overshadowed the predictive ability of the CT fibrotic score.[34] Other investigators noted worse survival in patients with CT scans "typical of IPF" compared to HRCT "not typical of IPF.[7, 8] More complex HRCT scoring systems (using stereological methods) correlate well with open lung biopsy,[67] but are logistically difficult and of limited clinical utility. In summary, extensive honeycomb change or reticulation on HRCT and no or minimal ground-glass opacities suggest a low likelihood of response to medical therapy and high mortality.[10, 34, 53] Unless contraindications exist, these patients should be listed for lung transplantation.[53,68,69] In contrast, response rates to therapy (*eg*, corticosteroids or immunosuppressive/cytotoxic agents) are higher when significant ground-glass opacities and no honeycomb changes are present. Additional studies are required to further define the predictive value of HRCT on long-term outcome.

Physiology

Characteristic physiologic aberrations in IPF/UIP include reduced lung volumes (FVC and TLC) consistent with a restrictive defect, impaired oxygenation, and impaired gas exchange.[1, 14, 30, 55, 59, 70-72] The DLCO is reduced, often disproportionately to other aberrations.[30, 55, 59, 70, 73] The DLCO is an indirect reflection of the pulmonary vasculature; reductions reflect destruction or loss of alveolar walls or capillaries. In nonsmokers with IPF/UIP, expiratory flow rates are preserved and the FEV_1/FVC ratio is increased. When emphysema coexists, lung volumes may be normal.[54, 59] However, in this context, DLCO and oxygenation are disproportionately affected. Measurement of the DLCO is complex, and varies even among individual patients. Normalizing the DLCO by the lung volume (VA), yielding the DLCO/VA ratio, does not improve the predictive value of DLCO and is not necessary.[74] Reduced compliance and alterations in pressure-volume

curves are characteristic of IPF,[1, 14] but these sophisticated studies require an esophageal balloon and lack practical clinical value. Impaired oxygenation, which is accentuated with exercise, is a cardinal feature of IPF.[1, 14, 71] Early in the course of the disease, arterial PaO_2 may be preserved at rest, but invariably worsens with exercise. As the disease advances, hypoxemia at rest is a nearly universal feature; most patients require continuous supplemental oxygen. Cardiopulmonary exercise tests reveal hypoxemia or widened alveolar-arterial oxygen difference [$P(A\text{-}a)O_2$], reduced oxygen consumption ($V0_2$), increased dead space (V_D/V_T), increased minute ventilation for the level of V_{O_2}, high frequency, low tidal volume breathing pattern, and low O_2 pulse.[14, 71, 75]

Not surprisingly, severe derangements in pulmonary function test results or oxygenation predict a worse prognosis and lower survival rates.[1, 30, 70, 72, 74, 76] Survival is worse in patients with severe impairments in vital capacity (VC) or DLCO. The 3-year mortality rate exceeds 50% when VC falls below 60% of predicted or DLCO falls below 45% of predicted.[36, 70, 73, 74] Changes in TLC are less predictive of survival.[37, 73] However, the prognostic value of physiological parameters *at a single time point* is limited. Composite scoring systems incorporating clinical, physiological, and radiographic parameters predict survival better than physiological or radiographic features *alone*.[14] King et al[14] prospectively applied a comprehensive clinical, physical, and radiographic score (obtained at the time of initial visit) to predict survival in a cohort of 183 patients with UIP. Parameters included age, finger clubbing, smoking history, the extent of profusion of interstitial opacities and pulmonary hypertension on chest radiographs, percent predicted TLC, and PaO_2 during maximal exercise. An abbreviated clinical, physical, and radiographic score, which excluded PaO_2 during maximal exercise, was applied to 228 patients. Although the comprehensive clinical, physical, and radiographic score was superior to the abbreviated clinical, physical, and radiographic score, both scoring systems had excellent prognostic value. Although HRCT data were not included in that study, it is likely that incorporating HRCT data in place of chest radiographs would enhance the predictive value of such systems. Further, it can be argued that other parameters (*eg*, FVC or DLCO) could be substituted in place of TLC.

Sequential physiological studies are critical to assess the evolution of the disease and response to therapy. I obtain serial measurements of FVC, DLCO, and O_2 saturation at 3-month intervals to follow the course of the disease.[1] The FVC is logistically easy to perform, relatively inexpensive, and less variable than TLC or DLCO. Thus, FVC is an ideal parameter to follow individual patients.[1] Because of inherent variability, serial changes in DLCO are less reliable.[1] Formal cardiopulmonary exercise tests with arterial cannulation are inconvenient, expensive, and are of limited practical value.[1] Serial 6-min walk tests with oximetry[77] are more convenient and cost-effective to monitor the course of the disease and assess the need for supplemental oxygen. Although optimal parameters to assess response to therapy have not been validated, the American Thoracic Society defined improvement as $\geq$ 10 % increase in FVC or TLC; $\geq$ 15% increase in DLCO; $\geq$ 4% increase in O_2 saturation or $\geq$ 4 mm increase in Pa02 during exercise.[2] Improvement or stability in VC or DLCO with corticosteroid therapy is associated with improved prognosis.[10, 30, 66] Conversely, deterioration in VC or DLCO at 3 months, [66] 1 year,[30] or later time points[78] predicts a higher mortality.

Histologic Features

The histologic pattern of UIP is observed in IPF[2, 6] but can be found in other etiologies (*eg*, connective tissue disorders, asbestosis, diverse occupational, environmental, or drug exposures).[2, 3] Historically, UIP was considered to occur in a subset of patients with IPF,[79, 80] but current recommendations restrict the term IPF to patients with *idiopathic* UIP.[2, 4] UIP is the most common of the idiopathic interstitial pneumonias, comprising 47 to 71% of cases.[7, 12, 27, 34, 81, 82] Other idiopathic interstitial pneumonias share features in common with UIP, but are distinct and separate disorders (*eg*, DIP; RBILD; NSIP; and AIP).[6] The literature is confusing, however, as these variants were often included in series of IPF, even though clinical, radiographic, and prognostic features are disparate. Each of these entities is briefly discussed below.

Usual Interstitial Pneumonia: The cardinal features of UIP that distinguish this entity from other idiopathic interstitial pneumonias are temporal heterogeneity, profusion of fibroblastic

foci, and honeycomb change.[6] UIP exhibits both *geographic* and *temporal* heterogeneity. The lesions are bilateral but patchy, and exhibit a striking predilection for the basilar and peripheral (subpleural) regions of the lung. This nonuniform distribution can be appreciated at low power magnification (Fig 7, top). In addition to "geographic" heterogeneity, the lesions also exhibit *temporal* nonuniformity. Areas of active injury, inflammation, and fibroblastic proliferation coexist with areas of dense (old) fibrosis. Even within the same lobe, alternating zones of interstitial inflammation, fibrosis, honeycomb change, and normal lung can be observed. Alveolar walls are thickened by excessive collagen, extracellular matrix, patchy mononuclear cell infiltrates (*eg*, lymphocytes, plasma cells), and fibroblasts.[2, 6] Intra-alveolar macrophages may be observed, but they are not conspicuous. Scattered neutrophils or eosinophils may be present. These inflammatory changes are not prominent, and are usually confined to areas of collagen deposition or honeycomb change.[6]. The variability of UIP is also evident when the nature of the fibrosis is examined. Zones of "old," relatively acellular, collagen bundles are interspersed with aggregates of actively proliferating myofibroblasts and fibroblasts. These aggregates, termed "fibroblastic foci," develop in areas of prior lung injury and are associated with active collagen synthesis. Fibroblastic foci are not pathognomonic, but are necessary for the diagnosis of UIP (Fig 7, bottom).[6] Small cystic radiolucencies (termed honeycomb cysts) within the subpleural regions reflect irreversible scarring and architectural remodeling.[6] Honeycomb change is an essential and often prominent feature of UIP, but is not specific as honeycomb change may be a sequela of severe lung injury due to diverse causes.[4] In late phases of UIP, the lung architecture is destroyed and replaced by large cystic airspaces (remnants of previous alveoli) and dense scar. Such cases are termed end-stage fibrosis or honeycomb lung (Fig 8). Secondary features

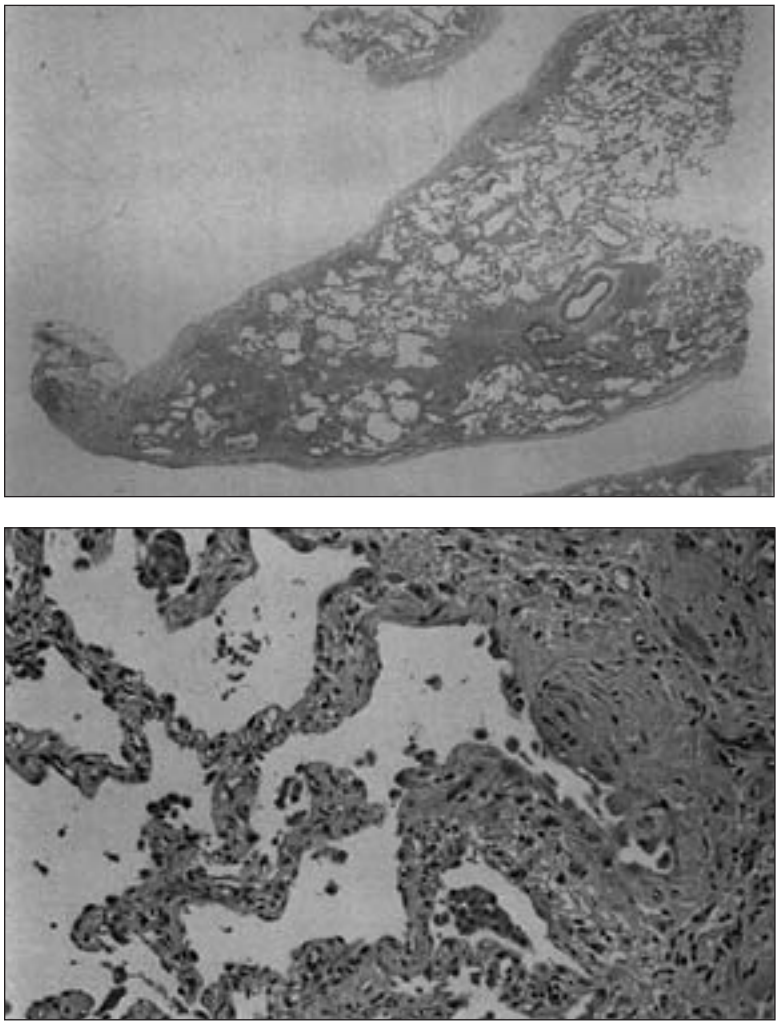


Figure 7. *Top*, photomicrograph of UIP. Open lung biopsy specimen. Patchy subpleural fibrosis with dense scarring cause remodeling of lung architecture. Note the marked heterogeneity. (hematoxylin-eosin) (reproduced with permission: Lynch et al, J Respir Dis 2000; 21;197-214). *Bottom*, photomicrograph of UIP. Open lung biopsy specimen. Fibrosis shows heterogeneity with dense eosinophilic collagen and a loose fibroblastic focus. The adjacent lung is relatively unaffected. These findings are consistent with UIP (hematoxylin-eosin) (reproduced with permission: Lynch et al, J Respir Dis 2000; 21;197-214).

include pulmonary hypertensive changes, smooth-muscle hypertrophy and hyperplasia, type II pneumocyte proliferation and hyperplasia, bronchioloectasis, and traction bronchiectasis. Subpleural fat and metaplastic bone reflect severe disease.[81] Focal emphysematous blebs may be present in smokers.

Desquamative Interstitial Pneumonia: DIP is a histologic syndrome characterized by dense collections of alveolar macrophages within airspaces (Fig 9), a homogeneous pattern, preserved alveolar architecture, and minimal or absent fibrosis or honeycombing.[6, 79] A significant interstitial component is lacking and is overshadowed by the intra-alveolar component. The striking heterogeneity and peripheral distribution characteristic of UIP are lacking in DIP. The uniformity of the lung lesion in DIP suggests a reaction to an inhaled stimulus, rather than persistent alveolar injury characteristic of UIP. More than 90% of patients with DIP are smokers, suggesting that constituents of tobacco play a contributory role.[6, 83] Chest radiographs typically demonstrate reduced lung volumes and nonspecific linear or reticulonodular interstitial infiltrates; in one quarter of patients, bibasilar, hazy ground-glass opacities are present.[83] HRCT scans demonstrate diffuse ground-glass opacities, often with a bibasilar or subpleural predominance; honeycomb change is absent.[52, 57] The average age of onset of symptoms for patients with DIP is approximately 40 years.[5, 6] Pulmonary function tests demonstrate a restrictive defect, with reduced D_{LCO}.[5] Prognosis is generally good, with long-term survival exceeding 90% at 5 years.[6, 27, 34, 64, 81] Although most patients are treated with corticosteroids, spontaneous improvement may occur.[79] Cessation of cigarette smoking is mandatory. The conditions of most patients improve or stabilize with corticosteroid therapy,[55, 64, 83] but progressive, even fatal, respiratory failure can ensue. To my knowledge, the role of cytotoxic and other immunosuppressive agents has not been studied.[5]

Respiratory Bronchiolitis Interstitial Lung Disease: Another histologic variant, termed

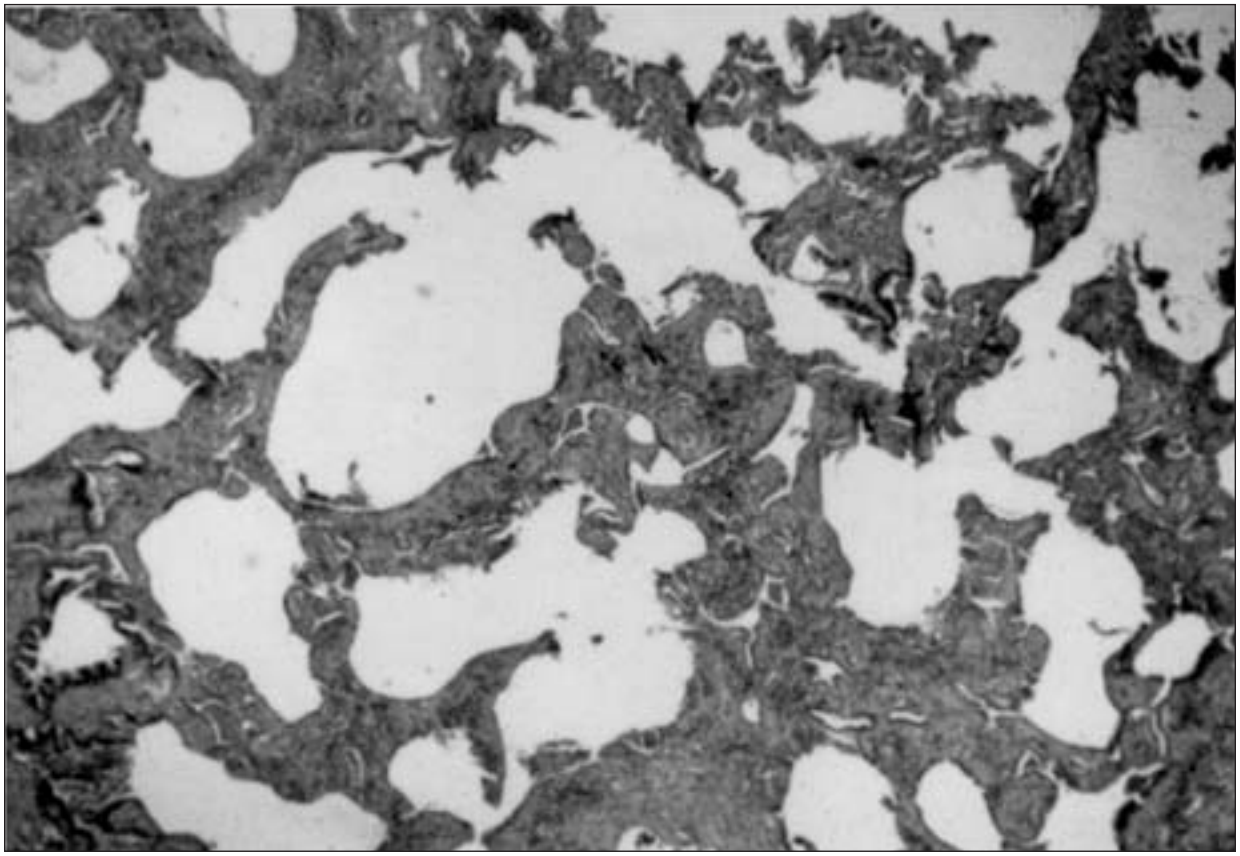
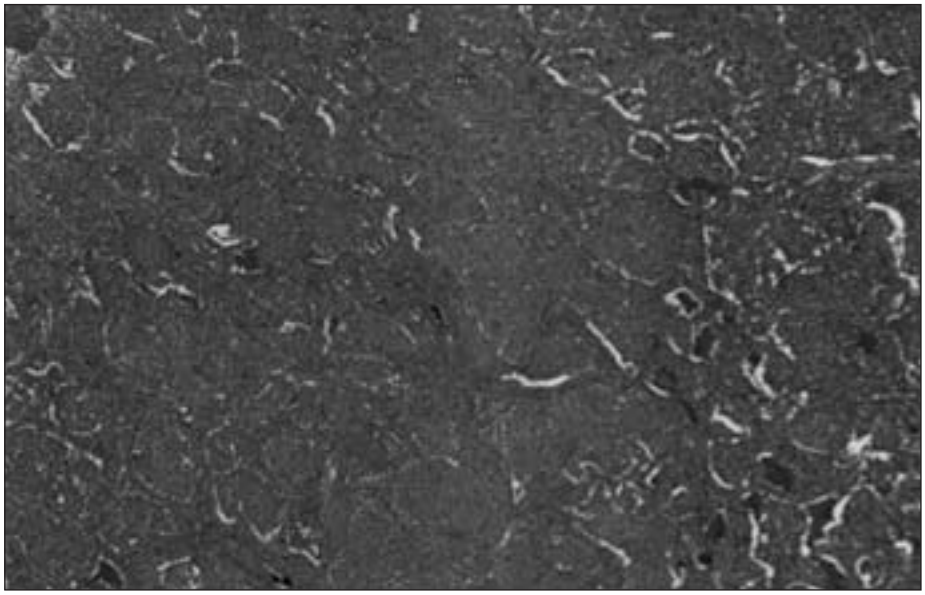
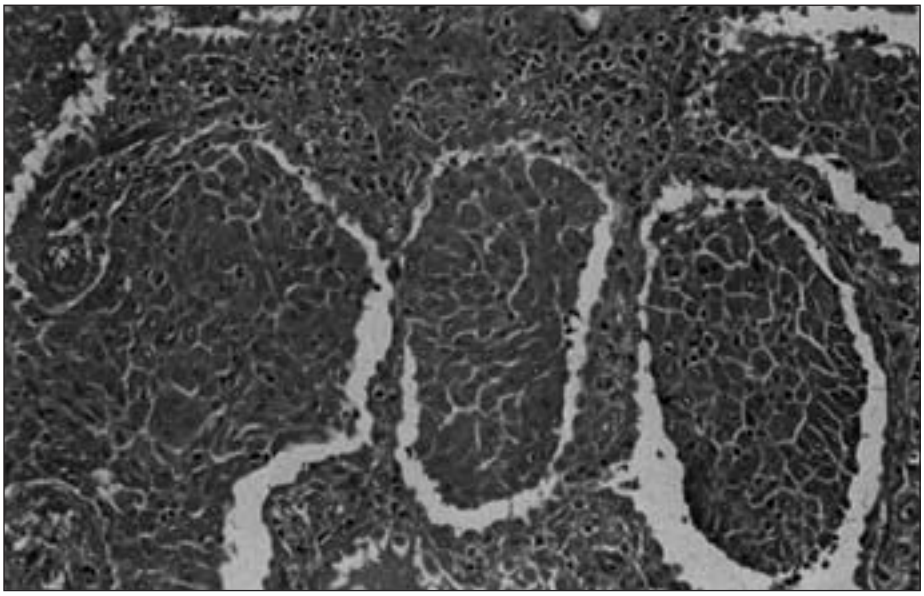


Figure 8. Photomicrograph of IPF. Open lung biopsy specimen reveals end-stage honeycomb lung. The large cystic airspaces represent destroyed and coalescent alveolar septae. Minimal inflammatory cells are present at this late phase . Reproduced with permission, from: Lynch JP III, Strieter RM. In: Internal Medicine for the Specialist. Montvale, NJ: Medical Economics, 1988; 61-84.





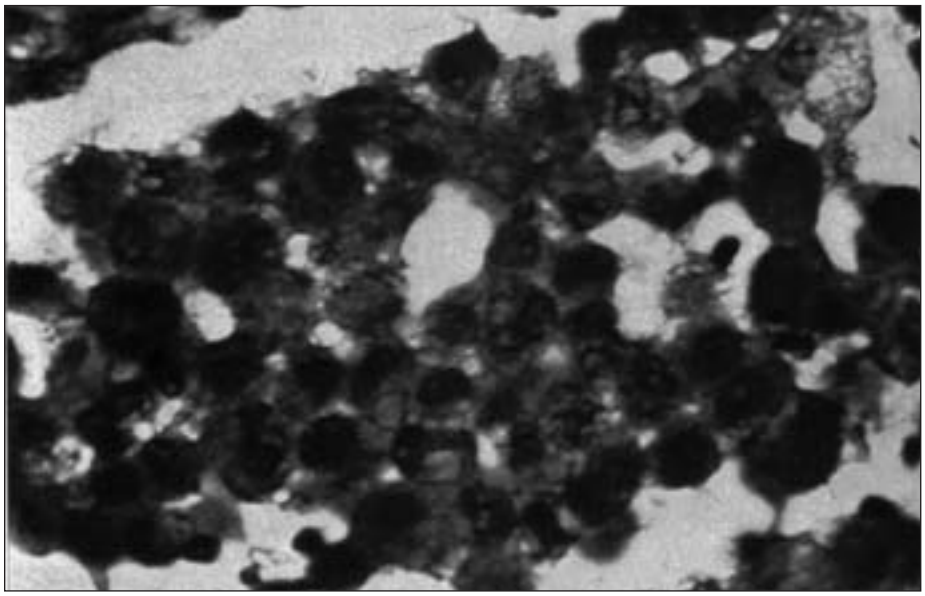
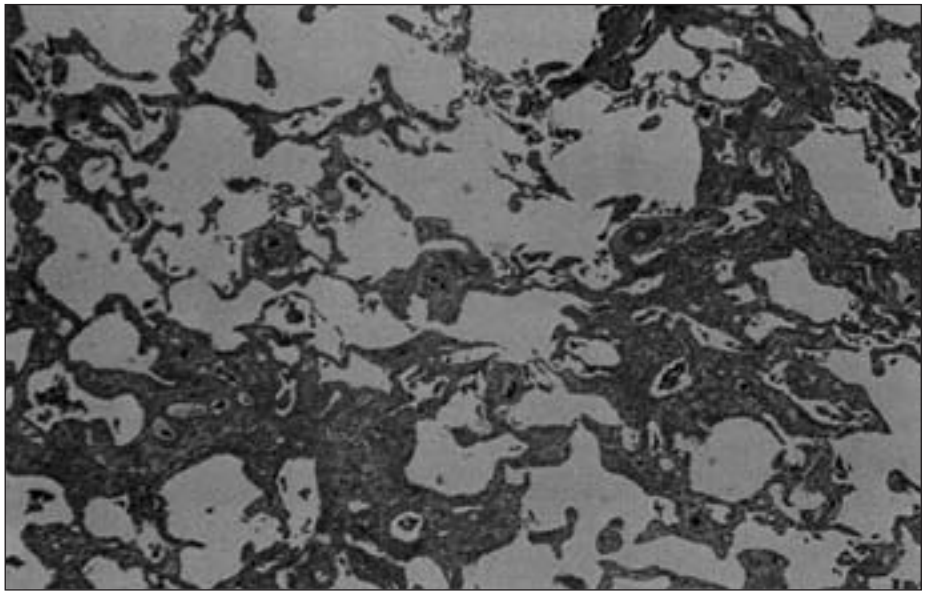
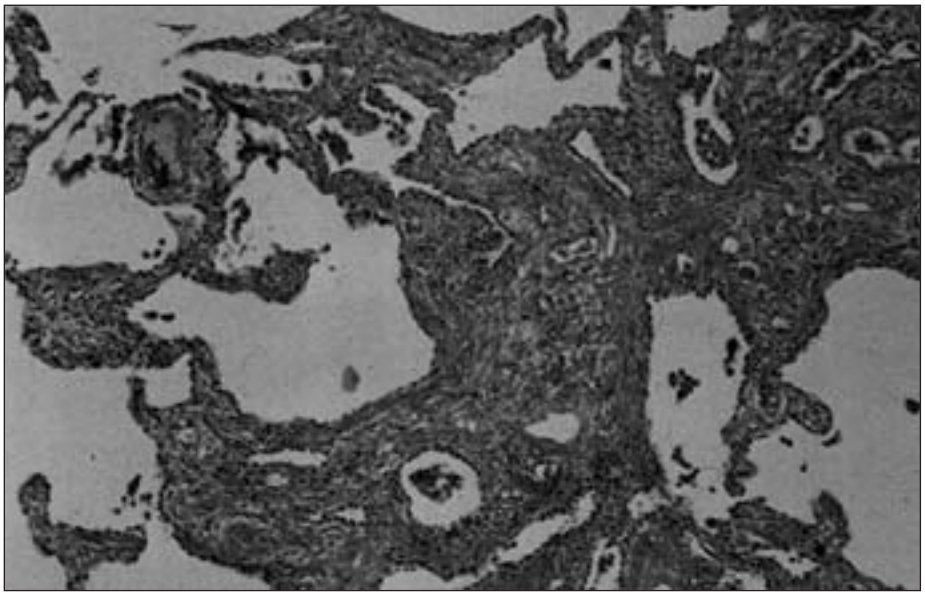


Figure 9. *Top*, photomicrograph of DIP. Open lung biopsy specimen demonstrates extensive and diffuse filling of the alveolar spaces with alveolar macrophages. A single lymphoid aggregate is present. The alveolar architecture is preserved (reproduced with permission: Lynch et al, J Respir Dis 2000; 21;197-214). *Center*, DIP. Photomicrograph (high power) showing dense aggregates of alveolar macrophages filling the alveolar spaces. The alveolar walls are thickened, but the alveolar architecture is preserved. Fibrosis or honeycomb cysts are absent (reproduced with permission: Lynch et al, J Respir Dis 2000; 21;197-214). *Bottom*, DIP. Dense aggregates of alveolar macrophages fill alveolar spaces (hematoxylin-eosin) (reproduced with permission: Lynch et al, J Respir Dis 2000; 21;197-214).





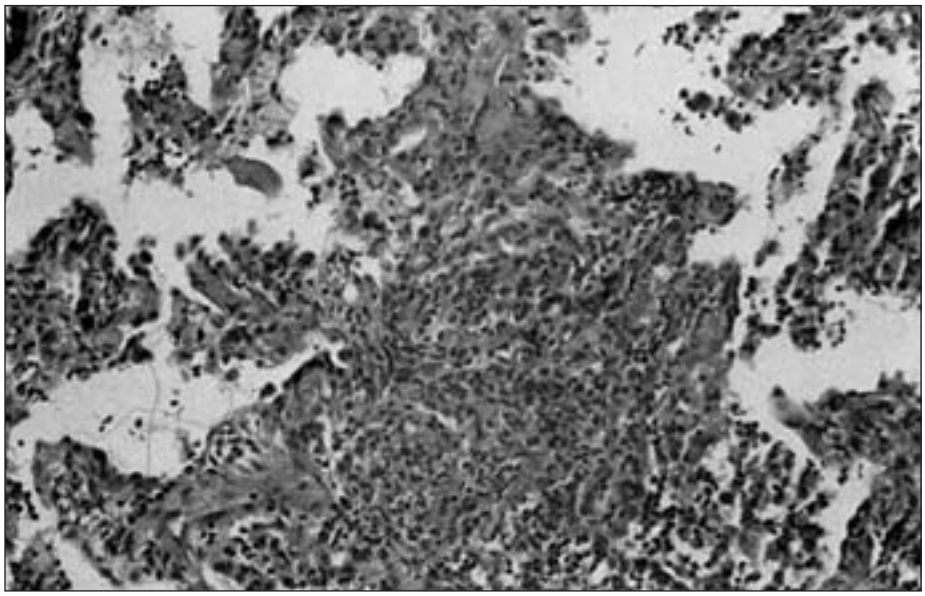


Figure 10. *Top*, photomicrograph of NSIP. Open lung biopsy specimen shows patchy interstitial fibrosis that lacks the subpleural distribution and temporal heterogeneity of UIP (reproduced with permission: Lynch et al, J Respir Dis 2000; 21;197-214). *Center*, photomicograph of NSIP. Open lung biopsy specimen. The alveolar septae are thickened by fibrosis and interstitial chronic inflammation (hematoxylin-eosin) (reproduced with permission: Lynch et al, J Respir Dis 2000; 21;197-214). *Bottom*, photomicrograph of NSIP. Open lung biopsy specimen. Prominent interstitial inflammation without dense scarring is evident. Some pneumocytes are hyperplastic. These inflammatory features are consistent with the cellular form of NSIP (reproduced with permission: Lynch et al, J Respir Dis 2000; 21;197-214).

respiratory bronchiolitis interstitial lung disease (RBILD), is characterized by dense collections of pigmented alveolar macrophages within respiratory bronchioles but sparing the distal lung parenchyma.[6] Honeycombing or severe fibrosis is not found. The pathologic lesion respiratory bronchiolitis was originally described in an autopsy series of young cigarette smokers who died of nonpulmonary causes.[84] The lesions were subsequently termed "small airways disease" or "smoker's bronchiolitis." Histologic features overlap with DIP, but DIP is more uniform and extensive than RBILD and exhibits a striking intra-alveolar component.[6] DIP and RBILD share common histopathologic features and occur almost exclusively in smokers,[6, 83, 85-87] suggesting a common pathogenesis. Patients with RBILD are generally young (<45 years) and present with mild symptoms of cough, dyspnea, or sputum production.[5, 6, 85, 86] Chest radiographs demonstrate small irregular opacities ("dirty lungs") or reticular or reticulonodular infiltrates, but are normal in up to 28% of patients.[6, 83, 85-87] HRCT scans reveal numerous 2- to 3-mm irregular peribronchiolar nodules; ground-glass opacities or emphysema may also be present.[83, 87, 88] Pulmonary function tests reveal reduced D_{LCO} and mild airflow obstruction; lung volumes are variable.[83, 87] The course of RBILD is indolent or stable, and prognosis is generally excellent. However, data are limited. Cessation of cigarette smoking is essential.[6, 85, 86] Improvement and even complete resolution often occur following cessation of cigarette smoking.[5, 6, 85, 86] Corticosteroids are required in a minority of patients. Late fibrosis or fatalities are rare. However, British investigators identified 10 patients with RBILD from 1980 to 1998, of whom 7 were treated with prednisolone (combined with azathioprine [AZA] or cyclophosphamide [CP] in 6).[87] Despite cessation of smoking and aggressive therapy, three had deteriorating conditions. Thus, the spectrum of RBILD is broader than the original descriptions.[85, 86]

Acute Interstitial Pneumonia (Hamman-Rich Syndrome): AIP (originally described by Hamman and Rich in 1944) is a syndrome characterized by rapidly progressive respiratory failure (often within a few days) and histologic features of diffuse alveolar damage on lung biopsy specimen.[89-91] This entity is distinct from IPF/UIP. Clinical features of AIP include the following: bilateral alveolar infiltrates; an acute and rapid course; hypoxemic respiratory failure requiring MV support; extensive ground-glass opacities on HRCT; high mortality rate (>50%); and potential responsiveness to high-dose corticosteroid therapy.[39,40,89-92] An acute viral-like prodrome usually precedes the onset of AIP; fever is present in up to 50% of patients.[89-92]. Chest radiographs reveal diffuse, ground-glass, alveolar opacities (consistent with ARDS).[39, 40] Histologic features include hyaline membranes, fibrinous exudate, epithelial cell necrosis, and interstitial and intra-alveolar edema.[92] As the process organizes and undergoes repair, type II cells proliferate along alveolar walls, hyaline membranes and airspace exudates resorb, and fibroblasts proliferate within the alveolar interstitium and spaces.[6,89,92] The histologic features of AIP are nonspecific and are found with myriad disorders, including ARDS, inhalation or drug-induced injury, collagen vascular diseases, or infections.[6] Mortality rates with idiopathic AIP range from 50 to 88%.[89-92] Although data are limited, sustained and complete remissions have been achieved with high-dose corticosteroid therapy.[39,40,89-92 92] Patients surviving the initial episode may heal with no sequelae or with variable degrees of fibrosis.[90, 91] Recurrent, even fatal episodes, of AIP may occur months or years after the initial episode.[90] Although AIP is distinct from IPF/UIP, a subset of patients with IPF/UIP develop an accelerated course, diffuse or multifocal parenchymal infiltrates on HRCT scan, and histopathologic features of AIP on lung biopsy specimens or necropsy.[39, 40] In this context, aggressive treatment with high-dose IV corticosteroids is warranted.

Nonspecific Interstitial Pneumonia/Fibrosis: In 1994, Katzenstein and Fiorelli[93] proposed the term nonspecific interstitial pneumonia/fibrosis to describe lung biopsy specimens from immunocompetent patients with clinical syndromes resembling IPF but with histologic features distinct from UIP, DIP, or AIP.[6] An inciting cause was not identified in most patients, but some had underlying connective tissue diseases, drug reactions, or HP.[93] NSIP likely represents a stereotypic response to diverse injuries or toxins. The term NSIP is confusing, as this term was initially applied to nonspecific histologic lesions in immunocompromised hosts (*eg*, HIV-infected

patients or bone marrow transplant recipients). Salient histologic features of idiopathic NSIP included varying degrees of inflammation and fibrosis which is temporally uniform (occurring over a single time span) (Fig 10). Scattered foci of bronchiolitis obliterans organizing pneumonia (BOOP) are noted in nearly 50% of patients; prominent accumulation of intra-alveolar macrophages (mimicking DIP), in one third.[93] The key histologic feature distinguishing NSIP from UIP is its temporal uniformity.[6] In NSIP, the lesions appear to be of similar age whereas in UIP, both recent and old lesions are present concomitantly.[6] Varying degrees of fibrosis and inflammation are observed in NSIP and UIP, but honeycombing, a prominent feature of UIP, is rarely seen in NSIP.[7, 12, 27, 81, 94] UIP is characterized by heterogeneity, greater destruction of the alveolar architecture, extensive fibrosis, and minimal intra-alveolar inflammation.[6] The temporal uniformity in NSIP suggests a response to a single insult. Clinical manifestations of NSIP are similar to IPF/UIP, with bibasilar crackles, cough, dyspnea, interstitial infiltrates, reduced DLCO, and a restrictive defect on pumonary function test results.[7, 12] Since clinical and radiographic features overlap with UIP, it is highly likely that examples of NSIP were included in historical series of IPF. However, several difference between NSIP and UIP have been noted. The onset of NSIP is subacute (evolving over a few weeks) but is chronic and insidious with IPF (evolving over > 1 to 2 years). Fever, noted in one third of patients with NSIP, is not found in UIP. Clubbing is found in 10 to 40% of patients with NSIP, but in 66 to 93% of patients with UIP.[7, 12] Compared to patients with UIP, patients with NSIP are younger and there is a slight female predominance in NSIP.[7, 12] BAL lymphocytosis is common in NSIP, but rare with UIP.[12] Recent studies using HRCT highlighted differences between NSIP and UIP. [7, 12, 95] Bilateral ground-glass opacities are characteristic in NSIP, but rare in UIP.[58] Honeycomb cysts, a cardinal feature of UIP, are absent or sparse in NSIP.[7, 12, 95] Most importantly, the prognosis of NSIP is much better than UIP. The conditions of most patients with NSIP improve either spontaneously or in response to corticosteroid therapy. In striking contrast, improvement is rare in UIP (<10%), even with aggressive therapy.[10, 12, 27, 64] Five-year survival with NSIP exceeds 70% compared to < 30% with UIP.[7, 12, 27, 29, 81] It is highly likely that many patients with presumed IPF and ground-glass opacities on HRCT, BAL lymphocytosis, or "steroid-responsiveness" in fact represented NSIP.[29, 31, 51, 96, 97] Recent studies suggest that the designation NSIP is excessively broad.[12,81] Segregation by histopathologic features into cellular interstitial pneumonia or fibrotic forms of NSIP identifies patient subsets with differing prognoses.[12, 81] Patients with the cellular form have more ground-glass opacities and less honeycombing on HRCT, a higher rate of steroid responsiveness, and lower mortality rates.[12, 81] Additional studies are required to further elucidate the clinical features and outcomes associated with NSIP and histologic subsets (*eg*, cellular or fibrotic forms).

Surgical Lung Biopsy (Open or Thoracoscopic)

The optimal staging and role of lung biopsies in IPF are controversial. Surgical (open or thoracoscopic) lung biopsies are required to establish the diagnosis of UIP unequivocally, but many clinicians are reluctant to subject patients to the morbidity of surgery, particularly when therapeutic options for IPF are of limited value.[53] Clinical surveys have found that surgical biopsies are performed in fewer than one third of patients with IPF.[3, 53, 98] Within the past few years, HRCT has increasingly been used in lieu of surgical biopsy to diagnose UIP/IPF.[7, 32, 53] However, surgical lung biopsy remains the gold standard for the diagnosis of UIP and assessment of prognosis.[6] The role of surgical lung biopsies in clinical practice is threefold: (1) to rule out other etiologies; (2) to better define the *pattern* of IIP (primarily UIP vs NSIP); and (3) to better define prognosis. Video-assisted thoracoscopic lung biopsy (VATS) is less invasive than open lung biopsies[99] and provides adequate histologic material.[33, 100] VATS can often be performed in the outpatient setting with minimal morbidity. Tissue should be obtained from at least two sites (*eg*, upper and lower lobes of the same lung); "representative" areas should be sampled (*ie*, avoid normal or very fibrotic areas).[33, 34, 100] Specific histologic features or subtypes of idiopathic interstitial pneumonias have prognostic value.[6, 12, 34, 100] Establishing the histologic diagnosis of UIP is a strong predictor of increased mortality and poor response to therapy when

compared to other idiopathic interstitial pneumonias.[6, 27, 32-34] In one recent prospective study, long-term survival was worse in patients with greater degrees of fibroblastic foci, whereas the degree of alveolar cellularity or alveolar wall fibrosis did not affect survival.[100] However, variation in histopathologic features in individual patients limit the prognostic accuracy of even surgical lung biopsies.[10, 33, 80, 97] While surgical biopsy is touted as a gold standard, a minute fraction of the lung parenchyma is sampled. Evaluation of surgical lung biopsy specimens is subject to interobserver and intralobar variation, even by expert pulmonary pathologists.[33, 82] Further, discriminating UIP from fibrotic NSIP is difficult.[81, 82] More importantly, foci of UIP and NSIP may be found within the *same lobe* in individual patients.[1, 33] A confident diagnosis of UIP or NSIP may be difficult to make, particularly by pathologists lacking expertise in pulmonary histopathology. Importantly, HRCT may corroborate the diagnosis of UIP, *provided that radiographic features are classic.*[7, 12, 50, 101] Further, the extent and pattern of changes on HRCT have prognostic value.[10, 29, 55] Although the decision to perform VATS lung biopsy should be individualized, we favor VATS biopsy (if no contraindications exist) in patients with recent onset of interstitial lung disease (ILD) of unknown cause, when findings from transbronchial lung biopsies (TBBs) are nondiagnostic.[46] However, VATS biopsy is not warranted in patients with a prolonged course (> 2 years) and clinical, physiological, and HRCT features that are characteristic of IPF/UIP.[2, 7, 50] Further, the risk of VATS lung biopsy is excessive in elderly (>70 years old) or debilitated patients, particularly when clinical and HRCT features strongly suggest UIP. In such patients, HRCT is sufficient to determine an approach to therapy. Bronchoscopy with TBBs is most useful to diagnose *alternative* causes of ILD (*eg*, sarcoidosis, Langerhans cell granulomatosis, pulmonary alveolar proteinosis, lymphangitic carcinomatosis, BOOP, etc). Because of the small sample size (2 to 5 mm), TBBs cannot substantiate the diagnosis of UIP, DIP, or NSIP and cannot be used to assess the extent of inflammation or fibrosis.

Bronchoalveolar Lavage

BAL is useful to exclude alternative etiologies that may mimic IPF (*eg*, specific infections such as *Pneumocystis carinii*, Mycobacteria, and fungi; pulmonary alveolar proteinosis; and Langerhans cell granulomatosis), but its clinical utility in assessing prognosis in IPF is limited.[2, 3] Increased numbers and percentages of neutrophils are present in 67 to 90% of patients with IPF but do not predict therapeutic responsiveness.[2, 96, 97, 102] Increased eosinophils may also be found in BAL fluid, but the prognostic significance is controversial.[1, 96, 97] Although BAL lymphocytosis has been associated with a more cellular biopsy specimen, less honeycombing, and a greater rate of corticosteroid responsiveness,[96, 97] it is an uncommon finding.[2] BAL has yielded significant insights into the pathogenic mechanisms responsible for IPF, but BAL is of doubtful clinical value in assessing the extent or activity of IPF.[2, 3, 53, 102]

Radionuclide Scans

Gallium 67 citrate scanning has been used as a surrogate marker of alveolar inflammation (alveolitis) in IPF and other inflammatory pulmonary disorders. Increased intrapulmonary uptake of ^{67}Ga was associated with a more cellular biopsy specimen in some studies. However, even with careful quantification, ^{67}Ga scans fail to predict responsiveness to therapy.[1, 103] ^{67}Ga scans are expensive and inconvenient, as scanning is performed 48 h after injection. Despite initial enthusiasm for its application, gallium scanning is of no practical value. Clearance of ^{99}Tc-diethylenetriamine penta-acetate (DTPA) aerosol is accelerated in IPF and is a marker of increased lung permeability.[53, 104] British investigators found that normal DTPA clearance in IPF was associated with stable lung function; survival was not analyzed and patients with progressive systemic sclerosis were included in that cohort.[104] By contrast, accelerated clearance of the fast component (*ie*, reduced $t_{0.5}$F) was an independent predictor of mortality in patients with idiopathic UIP.[53] In that study, age and D_{LCO} were the most important predictors of survival, followed by percent predicted TLC and $t_{0.5}$F.[53] Thus, the incremental *practical* value of $t_{0.5}$F

appears to be small. Further, increased clearance of DTPA occurs in smokers and those with other inflammatory lung disorders; its prognostic value is debatable.[3] Clearance of inhaled pertechnegas (an aerosol of ^{99}Tc-labeled carbon particles) is increased in IPF, HP, and collagen vascular disease-associated pulmonary fibrosis, but not sarcoidosis when compared to normal controls,[105] consistent with increased alveolar capillary permeability. Changes in pulmonary vascular permeability have also been noted on positron emission tomography (PET) scans in patients with IPF,[106] but a clinical role for these expensive and complex techniques has not been established.[3] At present, radionuclide imaging studies have no role in the staging or management of IPF.

Pathogenesis

The cause and pathogenetic mechanisms responsible for IPF have not been elucidated. The fibrotic/inflammatory process in UIP has been likened to "abnormal wound healing,"[107] with a vigorous fibroblastic response to alveolar epithelial cell injury. Injury of alveolar epithelial cells and destruction of the subepithelial basement membranes lead to local recruitment, differentiation, and proliferation of fibroblasts.[1, 107] Excessive deposition of collagen and extracellular matrix contributes to the fibrotic process. A complex interplay between inflammatory and mesenchymal cell populations amplifies and perpetuates the fibrotic response.[1, 107] Early theories of pathogenesis suggested that a heightened inflammatory response led to injury and fibrosis. Current theories suggest a primary role for fibroblast dysregulation; inflammatory cells may play a contributory, albeit minor, role.[107] Soluble mediators (cytokines) produced by fibroblasts and alveolar epithelial cells amplify and perpetuate the fibrotic response. Transforming growth factor-β (TGF-β) likely plays a critical role in UIP.[1, 107] Other cytokines that appear to be involved in the pathogenesis include tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8), and CXC chemokines.[1] Other possible mediators of the fibrotic process in UIP include integrin-mediated intercellular adhesion molecules (ICAM), surfactant proteins, proteases, leukotrienes, oxygen radicals, and myriad soluble mediators.[1, 107] Relative deficiency of gamma-interferon (γ-IFN), a cytokine that inhibits collagen synthesis and fibrosis, may contribute to the fibroproliferative process.[1, 107] The signals responsible for initiating and perpetuating this process are not known. As will be discussed below, therapeutic strategies designed to ablate inflammatory responses have had *little or no impact* on the outcome of IPF/UIP. In light of this, novel therapies targeted against fibroblast proliferation or other profibrotic mediators, are currently being investigated (discussed later).

Therapy

Corticosteroids were the mainstay of therapy for IPF for more than three decades.[9-13] However, to my knowledge, randomized, placebo-controlled trials assessing therapy have not been done, and the value of corticosteroids is controversial.[108] Recent consensus statements conclude that existing therapies are of unproven benefit.[2, 109, 110] Several large retrospective studies failed to document survival benefit with *any* form of therapy.[9, 32, 100, 111] Several early studies cited response rates of 10 to 30% with corticosteroids, but these older studies included a mix of histologic entities (*eg*, UIP, DIP/RBILD, NSIP, HP), and cannot be extrapolated to UIP.[1, 97] More recent studies that included patients with UIP cited response rates of 0 to 17%.[7, 12, 13, 27, 82] Importantly, a survival benefit with corticosteroid therapy has *not* been demonstrated.[9, 11, 100, 108] Optimal dose or duration of therapy has not been studied (to my knowledge). Historically, high doses of prednisone or prednisolone (*eg*, ≥ 1 mg/kg/d or equivalent for 4 to 6 weeks, with a gradual taper were advocated.[36, 97, 112] Given the significant toxic reactions associated with such regimens,[13, 66] recent expert consensus statements advocate lower doses (for patients in whom corticosteroid therapy is being considered).[2, 3] Given the lack of proven benefit, corticosteroids should *not* be used in patients at high risk for corticosteroid adverse effects (discussed below). Further, when corticosteroids are used, treatment should be discontinued within 3 months, *if objective benefit* has not been substantiated. Patients failing to respond or experiencing adverse effects from corticosteroids may be offered treatment with AZA or CP (discussed below). Patients exhibiting unequivocal response

to corticosteroids at the 3-month follow-up receive maintenance prednisone therapy, which is gradually tapered over several months. The rate of taper needs to be individualized, based on clinical response and presence or absence of adverse effects. I try to taper to 10 mg daily (or 20 mg on alternate days) within 6 to12 months. Since IPF is a chronic disease, prolonged (sometimes indefinite) maintenance therapy with low-dose alternate-day prednisone (*eg,* 10 to 20 mg qod) may reduce the chance of recrudescent disease. Unfortunately, corticosteroids are associated with a plethora of adverse effects, particularly in elderly or debilitated patients.[1, 13] Mood changes, irritability, neuropsychiatric effects, weight gain, opportunistic infections, reactivation of *Herpes zoster* (shingles), glucose intolerance, peptic ulcer disease, cataracts, compression fractures, aseptic vascular necrosis, etc, are potential complications. Extreme age (>75 years), insulin-dependent diabetes mellitus, poorly controlled hypertension, peptic ulcer disease, osteoporosis, neuropsychiatric disorders, or obesity are relative contraindications to high-dose corticosteroids. Most clinicians are reluctant to treat elderly patients with high-dose corticosteroids. In one clinical survey, 61% of IPF patients <70 years were treated with corticosteroids, compared to only 28% of patients >70 years.[11] We believe the risk of high-dose corticosteroids in elderly patients (>70 years) with IPF outweighs potential benefits. In elderly patients, we prefer AZA.

Immunosuppressive or Cytotoxic Agents: AZA (a purine antagonist) and CP (an alkylating agent) have inhibitory effects on diverse cell-mediated and humoral immune functions.[113] These agents have been used to treat IPF patients failing to respond or experiencing side effects from corticosteroids, or with contraindications to corticosteroids. However, a survival benefit with these agents has not been established.[1, 9, 32, 100]

Cyclophosphamide (Cytoxan): Oral CP (1 to 2 mg/kg/d) has been associated with anecdotal responses in IPF (including corticosteroid-recalcitrant patients, but data confirming efficacy are lacking. To my knowledge, only two randomized trials compared CP with prednisone. Investigators at the National Institutes of Health randomized 28 patients with mid-course IPF to treatment with prednisone alone, CP (1.5 mg/kg/d) alone, or CP *plus* prednisone.[114] Among CP-treated patients, BAL neutrophil counts declined at 3 and 6 months (suggesting a suppressive effect on neutrophilic alveolitis) but pulmonary function test results did not improve at the end of 6 months. The clinical benefit of CP was uncertain. British investigators randomized 43 untreated patients with IPF to treatment with oral CP (100 to 125 mg/d) *plus* low-dose prednisolone (20 mg every other day) *or* high-dose prednisolone *alone* (60 mg daily for 1 month, with subsequent taper).[115] End points were clinical scores, chest radiographs, and pulmonary function test results. Patients exhibiting >10% improvement in pulmonary function test results were considered responders. Patients failing to respond to either arm of therapy could be crossed over to the alternate arm at the discretion of the investigators. The overall benefit was modest with either arm. Among 21 patients receiving CP, pulmonary function tests results improved in five patients at 1-year follow-up. However, improvement was maintained above pretreatment baseline in only one patient at 3-year follow-up; seven were in stable condition, and the rest had worsened conditions. Mortality at 3 years was lower with CP (3 of 21) than with prednisolone (10 of 22), but data were skewed by differences in severity of disease between the two groups at the time of randomization. Nine of 12 patients with an initial TLC below 60% of predicted were randomized to the prednisolone arm; only 3 were randomized to CP. All 12 in this cohort failed to respond to therapy. Any apparent benefit associated with CP may reflect differences in extent and severity of disease at the initial presentation. Furthermore, responses were rarely achieved among patients in whom prior therapy failed. Only one of eight patients in whom CP failed responded to salvage therapy with high-dose prednisolone. Among 16 patients in whom prednisolone therapy failed, only three responded to subsequent therapy with CP. A recent retrospective study from England found that the use of CP or corticosteroids was associated with worse survival in a cohort of patients with IPF.[9] This likely reflects selection bias, since patients with severe or rapidly progressive disease most likely received more aggressive therapy. Other large retrospective studies found no survival benefit with CP.[32, 100] Our experience with CP has been disappointing. Among 19 corticosteroid-refractory IPF patients treated with oral CP (2 mg/

kg/d for 6 months), only 1 (5%) had an improved condition; 11 had deteriorating conditions (58%); and 7 (37%) remained in stable condition.[116] These dismal results cannot be extrapolated to previously *untreated* IPF patients, but suggest that CP is of marginal value in patients failing to respond to high-dose corticosteroids. Other investigators cited low rates of response to CP among corticosteroid-recalcitrant patients with IPF.[117, 118] High-dose IV "pulse" CP has been used to treat patients with corticosteroid-recalcitrant IPF, but results are unimpressive.[119, 120] In one study, Kolb and colleagues[121] treated 18 IPF patients failing to respond to corticosteroids with once monthly pulse CP *plus* oral prednisolone. At 1 year, VC improved by > 10% above baseline in only three patients. Responders had higher BAL lymphocyte counts (mean of 34%) compared to nonresponders, were younger, and had shorter duration of disease. Since open lung biopsies were not performed, these "responders" could have had NSIP, which is more responsive to therapy than UIP. These various studies are inadequate to assess the role or efficacy of CP (either oral or pulse) for IPF. To my knowledge, no studies have compared IV pulse vs oral CP. In summary, CP may be used as primary or salvage therapy for IPF, but its long-term efficacy is unproven. Myriad toxic reactions associated with CP include hemorrhagic cystitis, bone marrow suppression, stomatitis, GI symptoms, infertility, alopecia, and (rarely) interstitial pneumonitis.[113] CP is oncogenic. Bladder carcinomas have been cited in 2 to 7% of treated patients; malignant lymphoproliferative disorders have bee cited in 1 to 3% of patients.[113] The potential for serious late complications relegates CP to a secondary role in treating IPF. Because CP has potential bone marrow toxicity, serial CBC counts and platelet counts should be monitored every 2 weeks for the first 6 weeks, and monthly thereafter. Urinalyses should be performed every 3 to 6 months to monitor for microscopic hematuria, a precursor lesion of bladder carcinoma. Development of hemorrhagic cystitis mandates cessation of therapy.

Azathioprine (Imuran): Oral AZA (2 to 3 mg/kg/d), usually combined with corticosteroids, has been used for more than two decades as therapy for IPF, [80, 112] but efficacy is debatable. AZA may be used as initial primary therapy, as adjunctive therapy (to achieve a steroid-sparing effect), or for patients failing to respond or experiencing adverse effects from corticosteroids. Data are limited to a few uncontrolled and two prospective trials (only one of which was randomized). In the first study, 20 patients with progressive IPF were initially treated with high-dose prednisone, which was tapered to a maintenance dose by 3 months.[80] At 3 months, AZA was *added*. Twelve of 20 (60%) responded, but the *independent* effect of AZA was impossible to assess, since all patients received concomitant corticosteroids. AZA was judged to be beneficial in at least eight patients. In a subsequent trial, 27 patients with previously untreated IPF were randomized to treatment with either high-dose prednisone *plus* AZA (n=14) or high-dose prednisone *alone* (n=13).[112] End points were pulmonary function at 1 year and mortality. AZA improved pulmonary function slightly, but effects were modest. At 1 year, mean VC and D_{LCO} increased by 6.5% and 7.3% among AZA-treated patients, compared to increments of only 1.7% and 0.9%, respectively, among patients receiving corticosteroids alone. The impact on mortality was inconclusive. Within 1 year, four patients in each group had died. Late mortality (mean follow-up of 9 years) was lower (43%) among patients treated with AZA plus corticosteroids than among those receiving corticosteroids alone (77%), but the difference was not statistically significant. To my knowledge, no studies have compared AZA *alone* to corticosteroids *alone*. Despite a paucity of therapeutic trials, a recent consensus report from the British Thoracic Society recommends combining AZA (2 to 3 mg/kg/d) with prednisolone (0.5 mg/kg/d) as initial therapy for IPF.[3] For patients failing to respond or intolerant of corticosteroids, they recommended AZA *alone*.[3] They reserve oral CP (dose of 1 to 2 mg/kg/d) for IPF patients failing to respond or unable to tolerate AZA (or AZA plus prednisone).

AZA, in a daily dose of 100 to 200 mg orally, is usually well tolerated; <5% of patients cease therapy due to side effects.[113] Potential toxic reactions include the following: bone marrow suppression; GI symptoms (primarily nausea, vomiting, or diarrhea); stomatitis; rash; and heightened susceptibility to infections.[113] Severe hepatotoxicity occurs in 0.3%. Idiosyncratic febrile reactions with arthralgias and chills

occur in 1 to 2% of patients. AZA does not cause bladder injury or bladder carcinomas and has less oncogenic potential than CP. Because of its suppressive effects on marrow marrow, CBC and platelet counts should be obtained every 2 weeks for the first 2 months, and every 4 to 6 weeks thereafter. Significant anemia, leukopenia (<3,500 mm^3), or thrombocytopenia (<120,000/mm^3) warrants dose reduction. AZA should be used with caution in patients taking allopurinol, and the dose should be reduced for at least 50%. After 6 months, efficacy should be examined. A more prolonged course of AZA is reserved for patients showing objective responses.

Cyclosporine: Cyclosporine, which exerts potent suppressive effects on T-helper lymphocyte function in proliferation, is rarely used in IPF. Favorable responses were cited in anecdotal cases and small retrospective series.[122-125] Cyclosporine is very expensive and causes a plethora of adverse effects (*eg*, neurological, renal, GI, hypertrichosis, induction of hematologic malignancies).[113] The role of cyclosporine as therapy for IPF appears limited, but additional studies are required to determine efficacy.

Other Immunosuppressive/Cytotoxic Agents

Methotrexate (MTX) is useful as a steroid-sparing agent in sarcoidosis and diverse immune-mediated disorders, but published studies employing methotrexate in IPF are lacking. Mycophenolate mofetil, a purine antagonist with potent immunosuppressive properties, has not been studied in IPF (to my knowledge).

Antifibrotic Agents (Colchicine, D-Penicillamine, γ-Interferon

D-penicillamine: D-penicillamine, a chelating agent that interferes with collagen cross linking *in vitro* and reduces collagen deposition in animal models of pulmonary fibrosis, has been used to treat collagen vascular–associated fibrosis and IPF,[3, 111] but data supporting its efficacy are lacking. Side effects are substantial (particularly loss of taste, rash, nausea, vomiting, and nephrotoxicity) and outweigh potential benefits.

Colchicine: Colchicine, an antimitotic agent that suppresses fibroblast growth factors *in vitro* and inhibits collagen deposition in animal models, has been used to treat IPF, but efficacy is doubtful. Data from one prospective but nonrandomized study[111] and one randomized trial[13] found no benefit with colchicine (dose of 0.6 mg once or twice daily). A large retrospective study from the Mayo Clinic identified 238 patients who had been treated with colchicine, either alone or combined with prednisone.[32] By multivariate analysis, there was no evidence that colchicine (or any pharmacologic therapy) influenced survival. Although data are limited, I see no role for colchicine as therapy for UIP/IPF.

Expert Consensus Statements and Recommendations for Therapy

Two recent consensus statements[2, 3] emphasized that no therapy for UIP was of proven benefit. Both statements advocated an *individualized* approach to therapy. Given the potential toxicities associated with corticosteroid and immunosuppressive therapy, not all patients with IPF should be treated. However, treatment is advised for patients with a deteriorating course, significant symptoms, or surrogate markers consistent with an inflammatory component (*eg*, ground-glass opacities on HRCT). The risks of any treatment protocol should be balanced by potential benefits. For patients requiring treatment, the British Thoracic Society Committee advocated the *combination* of oral prednisolone (0.5 mg/kg/d) plus AZA (2 to 3 mg/kg/d) as *initial* therapy.[3] The American Thoracic Society statement recommends combining prednisone (0.5 mg/kg/d for 4 weeks, with subsequent taper) with oral AZA (2 to 3 mg/kg/d) or oral CP (2 mg/kg/d).[2] Both statements recommend using AZA or CP *alone* for patients unable to take corticosteroids. Although these recommendations were endorsed by a panel of experts, these regimens have not been studied in scientific trials (to my knowledge).

Novel and Future Therapies

Anti-inflammatory strategies are of unproven efficacy in UIP. Major advances await the development of novel therapies that prevent fibroproliferation and enhance alveolar re-epithelialization.[107] Agents that have been tested in pilot studies include interferons, N-acetylcysteine (NAC), and pirfenidone.

γ-*Interferon:* γ-Interferon (γ-IFN) nhibits collagen synthesis by fibroblasts *in vitro* and attenuates fibrosis in animal models.[1] Recently, investigators from Austria cited beneficial responses to interferon γ-1b (γ-IFN-1b) plus low-dose corticosteroids in an open, randomized trial of 18 patients with IPF who had failed to respond to prior therapy with corticosteroids or immunosuppressive agents.[126] Patients were randomized to treatment with prednisolone *alone* (7.5 mg/d, which could be increased up to 50 mg if necessary) or combination therapy with γ-IFN plus prednisone (7.5 mg daily). At 12 months, lung function deteriorated in all nine patients receiving prednisolone alone. In contrast, pulmonary function test results improved in nine patients treated with γ-IFN-1b (200 μg subcutaneously three times weekly) *plus* low dose prednisolone.[126] Further, levels of transcription of genes for TGF-β1 and connective-tissue growth factor decreased significantly only in the group receiving γ-IFN plus prednisolone. Reduced levels of γ-IFN and increased levels of TGF-β1 and connective-tissue growth factor appear to be important in the pathogenesis of UIP/IPF. These data[126] are promising, but additional studies are required to determine if γ-IFN has a role to treat IPF. A multicenter, randomized, placebo-controlled trial is in progress to evaluate recombinant γ-IFN1-b for corticosteroid-recalcitrant UIP (Inter-mune Pharmaceuticals Inc; Burlingame, CA), but data are not yet available. Given its expense (>$50,000 annually), and the lack of proven efficacy, additional data are warranted before γ-IFN1-b can be advocated as therapy for UIP.

A multicenter, placebo-controlled trial assessing β-interferon 1-a (IFN-β1-a) (AVONEX, Biogen, Cambridge, MA) for IPF refractory to conventional therapy (*ie*, corticosteroids or immunosuppressive therapy) showed no benefit.[1]

N-acetylcysteine: NAC, which stimulates glutathione synthesis, has been used as an antioxidant in IPF,[127] but efficacy is unproven. Currently, a randomized, double-blind, placebo-controlled trial is underway in Europe to assess the possible role of NAC in UIP.[128] In this study, oral NAC (1,800 mg/d) or placebo will be added

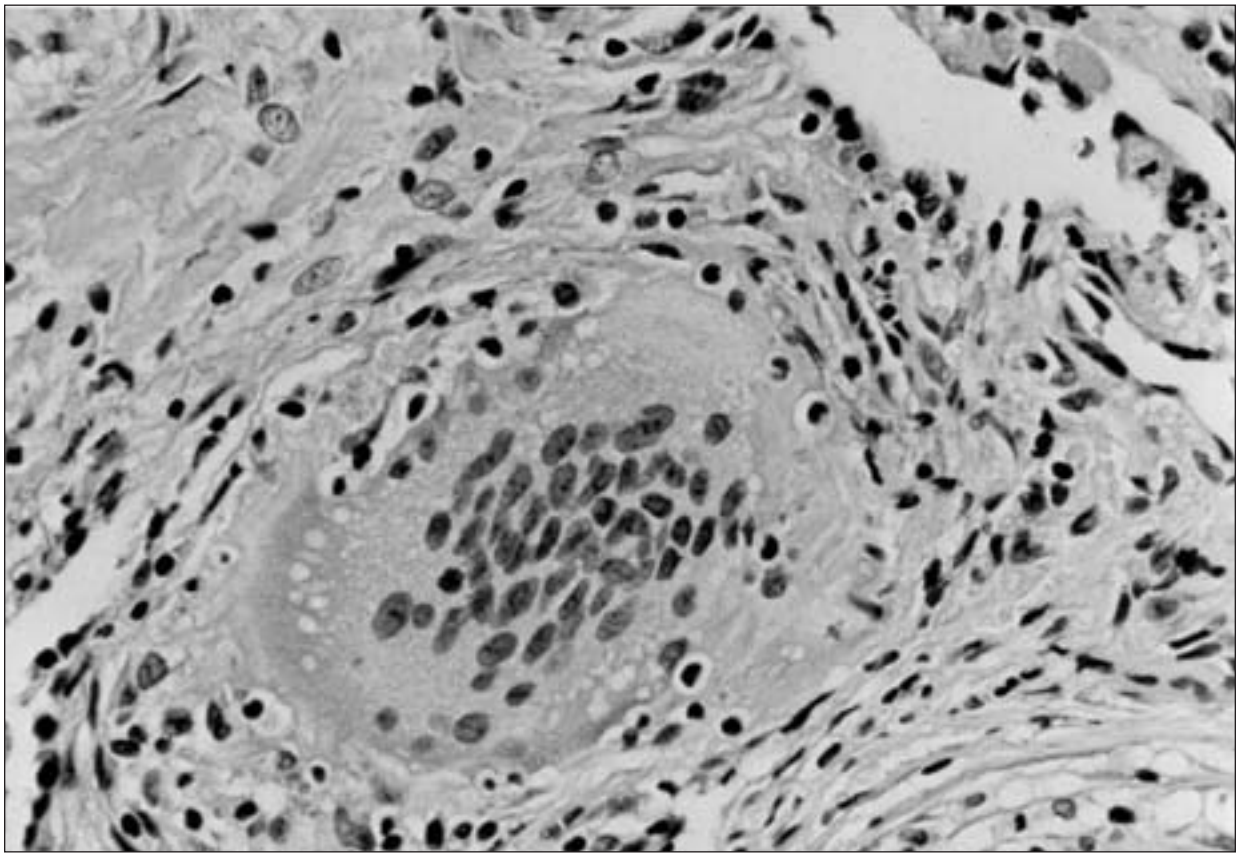


Figure 11. Sarcoidosis. Photomicrograph of TBB specimen. Multinucleated giant-cell in the center of a granuloma, surrounded by lymphocytes and mononuclear cells in the periphery (hematoxylin-eosin stain). (From Lynch JP III, Strieter RM. In: Internal medicine for the specialist. Montvale, NJ: Medical Economics, 1994; 38-62.)

to conventional therapy with prednisone (0.5 mg/kg/d) plus AZA (2 mg/kg/d).

Pirfenidone: Pirfenidone (5-methyl-1-phenyl-2-{1H}-pyridone) attenuates pulmonary fibrosis in animal models, reduces synthesis of collagen I and III and TNF-α, inhibits TGF-β-stimulated collagen synthesis, decreases extracellular matrix, and blocks the mitogenic effect of profibrotic cytokines.[1] In a phase II open-label trial, 54 consecutive IPF patients were treated with pirfenidone.[129] Forty-six had failed to respond to conventional therapy; and 8 were untreated. With pirfenidone, 1- and 2-year survival rates were 78% and 63%, respectively. These data are insufficient to assess efficacy.

Novel (Future) Agents

Unfortunately, current therapies for IPF are only marginally effective. Possible future therapies include the following: proline inhibitors[109, 130]; antioxidants[131]; inhibitors of 5-lipoxygenase[132]; cysteinyl-leukotriene receptor antagonists[133]; platelet-activating factor receptors antagonists; inhibitors of leukocyte integrins, cytokines, or proteases,[109, 110] keratinocyte growth factors, relaxin, and lovastatin.[1]

Single Lung Transplantation: Single lung transplantation is the best option for patients with severe IPF refractory to medical therapy.[134, 135] Early listing for transplantation is urged in patients with progressive IPF in whom corticosteroid therapy fails, because the waiting time for procuring donor organs may exceed 2 years.[136] Patients with severe functional impairment (*eg*, FVC <60% predicted, D_{LCO} < 40% predicted), oxygen dependency, and a deteriorating course refractory to medical therapy should be listed promptly for transplantation. Unfortunately, many patients with severe IPF die while awaiting organs.[68] Two- and 5-year survival rates following single lung transplantation approximate 70% and 50%, respectively.[134, 135]

Adjunctive Therapy: Supplemental oxygen is critical to optimize quality of life and enhance exercise capacity. Continuous oxygen ameliorates

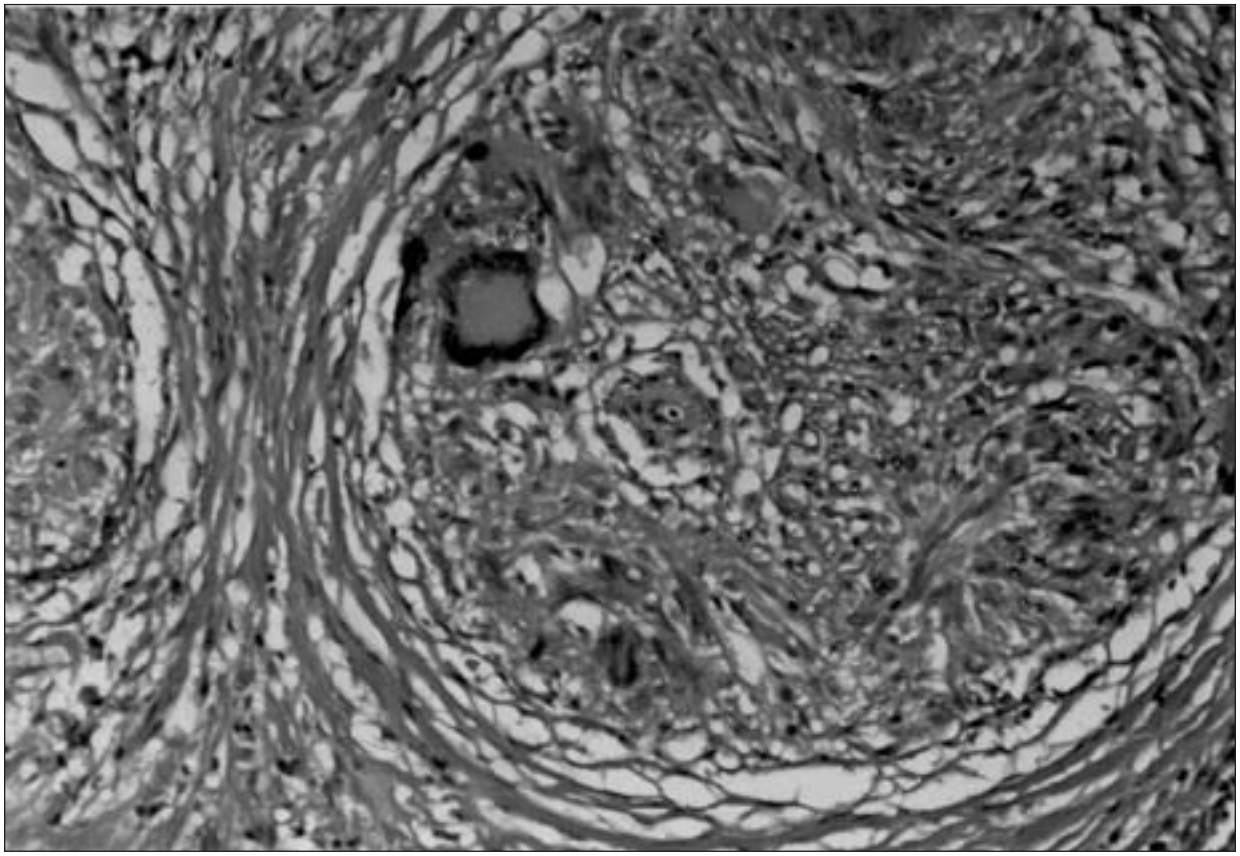


Figure 12. Sarcoidosis. Photomicrograph of TBB specimen. "Burned out" granuloma demonstrating nonnecrotizing granuloma containing multinucleated giant cells and epithelioid cells in the center. In the periphery, no significant inflammatory cells are present, but concentric rings of collagen encircle the granuloma (hematoxylin-eosin stain). (From Lynch JP III, Strieter RM. In: Internal medicine for the specialist. Montvale, NJ: Medical Economics, 1994; 38-62.)

pulmonary vasoconstriction and may delay the clinical development of cor pulmonale. Judicious use of diuretics may be necessary to control peripheral edema in patients with cor pulmonale. The role of vasodilators in patients with secondary pulmonary hypertension is controversial.[137]

Sarcoidosis

Sarcoidosis is a poorly understood granulomatous disease that involves the lung and intrathoracic lymph nodes in >90% of patients.[138-141] However, virtually any organ can be affected. Skin involvement, peripheral lymphadenopathy, and eye involvement each occur in 20 to 30% of patients.[139,142] Clinically significant involvement of spleen, liver, myocardium, CNS, or bone occurs in 2 to 6% of patients.[139] The clinical expression and course are heterogeneous. One third or more of patients are asymptomatic, with incidental findings of hilar lymphadenopathy on chest radiographs. Symptoms are protean, reflecting the site of organ involvement.[142] The natural history is usually favorable. Spontaneous remissions occur in nearly two thirds of patients, and a waxing and waning course is common.[138, 140] Fever, erythema nodosum, polyarthritis, and bilateral hilar lymphadenopathy (Lofgren's syndrome) are common early features and have been associated with an excellent prognosis.[143] Factors associated with poor prognosis and more aggressive disease include black race, osseous involvement, lupus pernio (disfiguring nasolabial cutaneous lesions), chronic hypercalcemia, and chronic pulmonary sarcoidosis.[138-141] In 10 to 15% of patients with sarcoidosis, the course is chronic and progressive, resulting in permanent damage and fibrosis of affected organs. Fatalities occur in 1 to 6% of patients.[138-140] Lower mortality rates (0 to 0.5%) have been cited in nonreferral settings, when the diagnosis was made as part of routine radiographic screening.[144,145]

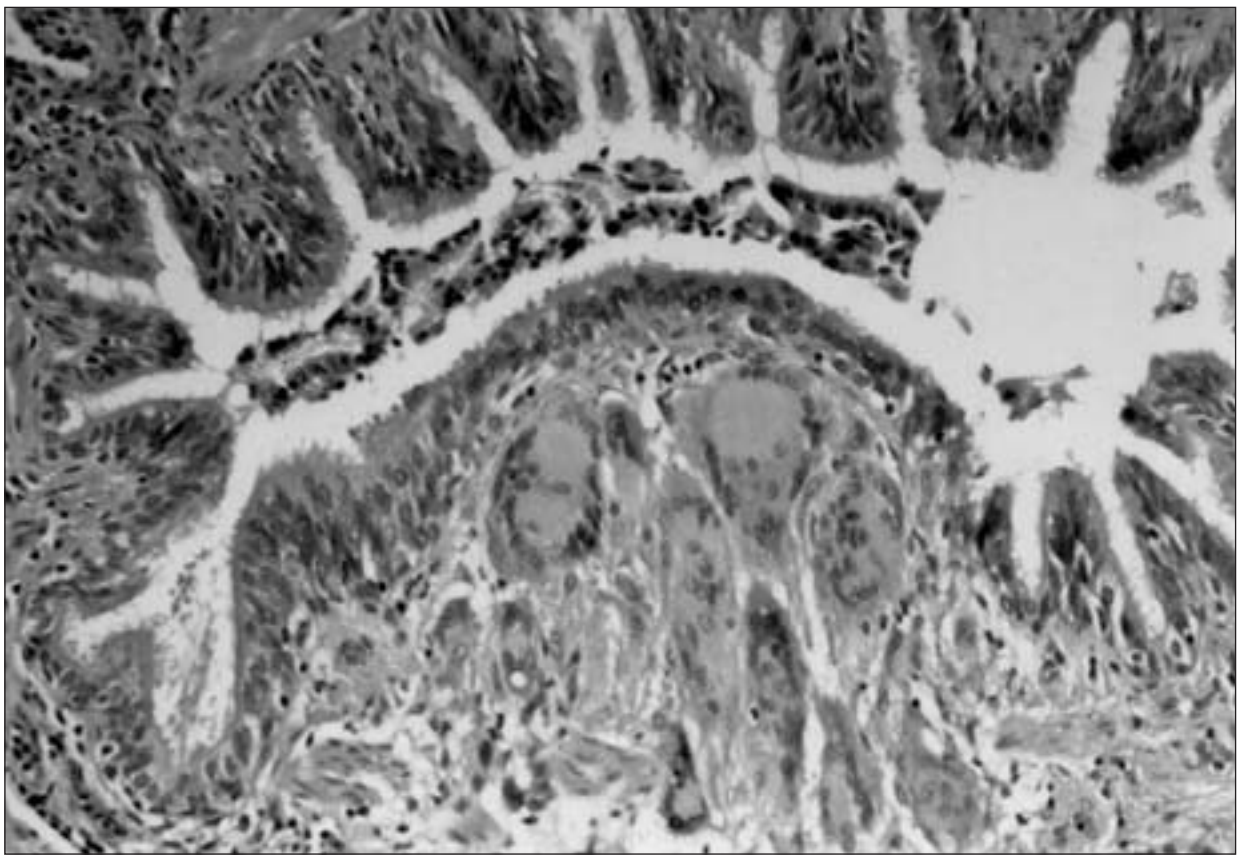


Figure 13. Sarcoidosis. Photomicrograph of endobronchial lung biopsy specimen. Prominent multinucleated giant cells within the submucosa underlying the bronchioles (hematoxylin-eosin stain). (From Lynch JP III, Strieter RM. In: Immunologically mediated pulmonary disease. Philadelphia: Lippincott-Williams and Wilkins, 1991; 189-216.)

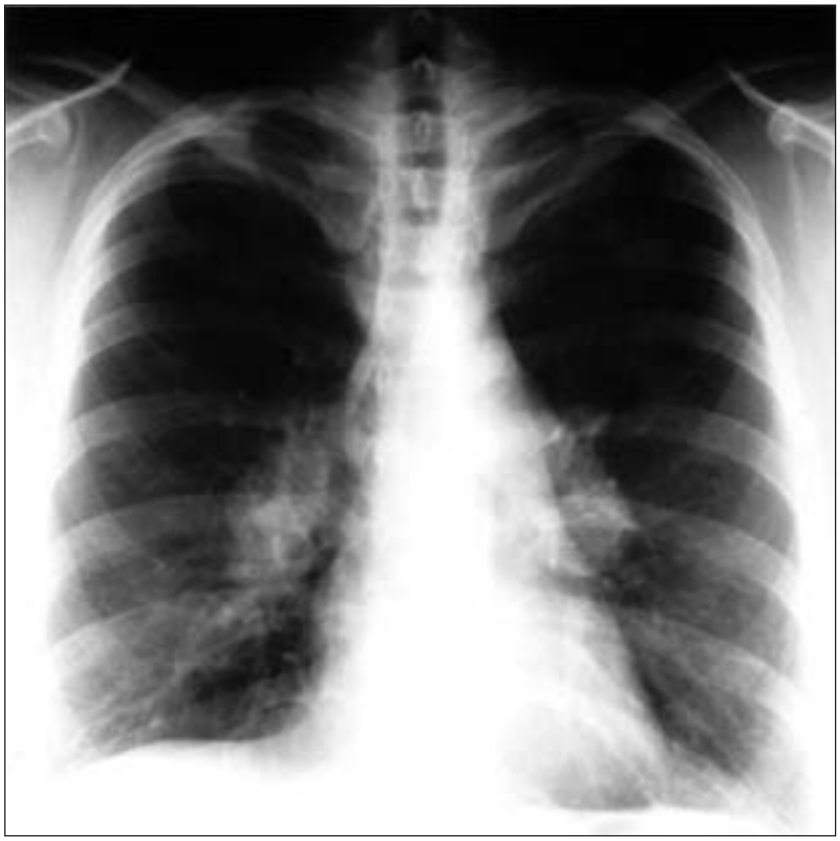


Figure 14. Sarcoidosis (stage I). Chest radiograph demonstrating extensive bilateral hilar and right paratracheal lymphadenopathy.

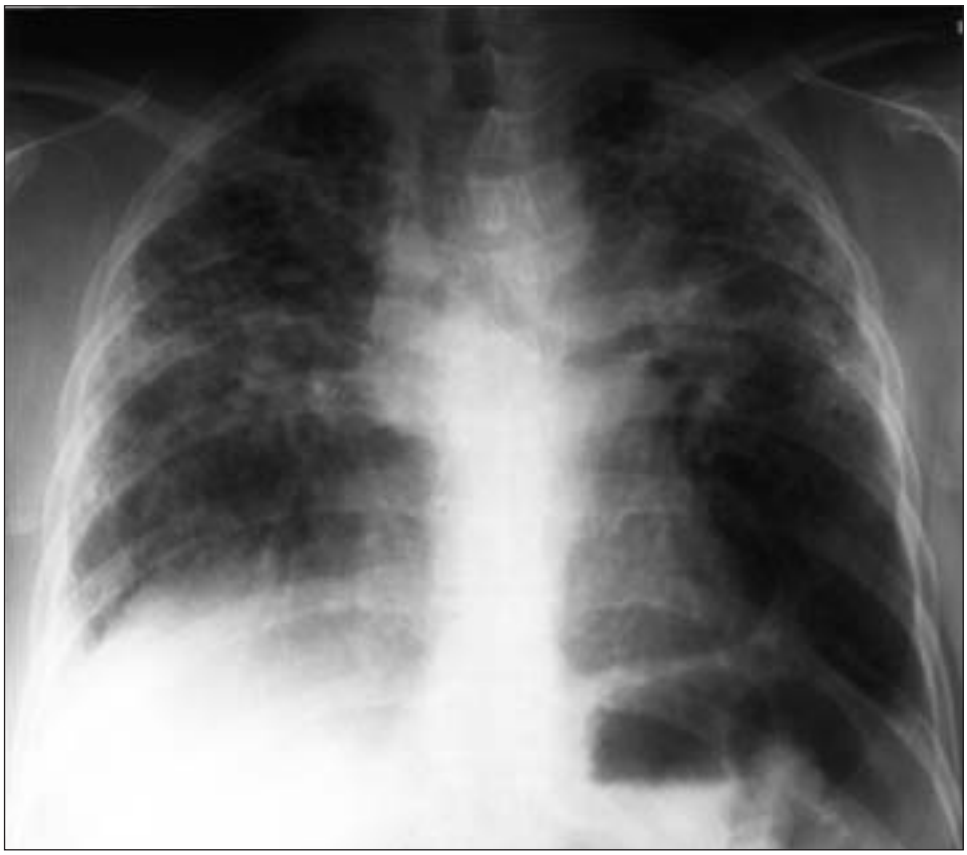


Figure 15. Stage II sarcoidosis. Chest radiograph demonstrating extensive cystic radiolucencies (honeycombing) and fibrosis preferentially affecting upper lobes of both lungs. Linear fibrotic strands and volume loss are noted throughout. In addition BHL is present.

Epidemiology

Sarcoidosis is worldwide in distribution, but the prevalence varies according to racial and geographic factors. Sarcoidosis is 4 to 8 times more common in blacks than in whites.[146] In North America and Europe, prevalence rates of 10 to 20 cases per 100,000 persons have been cited.[146, 147] In Scandinavia and certain parts of the British Isles, prevalence rates exceed 80 cases per 100,000.[147, 148] The incidence is much lower (<2 per 100,000) in southern Europe.[147, 149] Sarcoidosis has infrequently been reported in Central or South America or Africa, but whether this represents underrecognition or reduced prevalence of the disease is not known. More than two thirds of patients present between ages 20 and 40 years.[150] There is a slight female predominance.[140, 146] Sporadic cases within families are well recognized.[150] Familial sarcoidosis (defined as having first- or second-degree relatives with sarcoidosis) occurs in 17% of African-American patients with sarcoidosis compared to 6% among white patients.[146] Data from the multicenter ACCESS study noted that the familial relative risk of sarcoidosis was highest among siblings, followed by grandparents, and then parents.[151] A specific genetic defect has not been identified, but genes of the major histocompatibility locus on chromosome 6p are believed to be involved.[152] The inheritance pattern is likely complex, with heterogeneous alleles, polymorphisms, and linkages.[153,154] The cause of sarcoidosis remains elusive, but genetic, environmental, and infectious causes have been suggested.[141]

Histopathology

The histologic hallmark of sarcoidosis is the noncaseating (nonnecrotizing) granuloma composed of epithelioid cells and multinucleated giant cells, surrounded by a cuff of lymphocytes and plasma cells[140] (Fig 11). Fibrosis is present in varying degrees (Fig 12). Disruption and destruction of parenchyma may be prominent. Since mycobacterial and fungal granulomas can cause nonnecrotizing granulomas, special stains for acid-fast bacilli and fungi should be performed to exclude these infectious etiologies. In the respiratory tract, sarcoid granulomas are often situated in the submucosa of bronchioles and along bronchovascular bundles[140] (Fig 13). Coalescent granulomata may give rise to

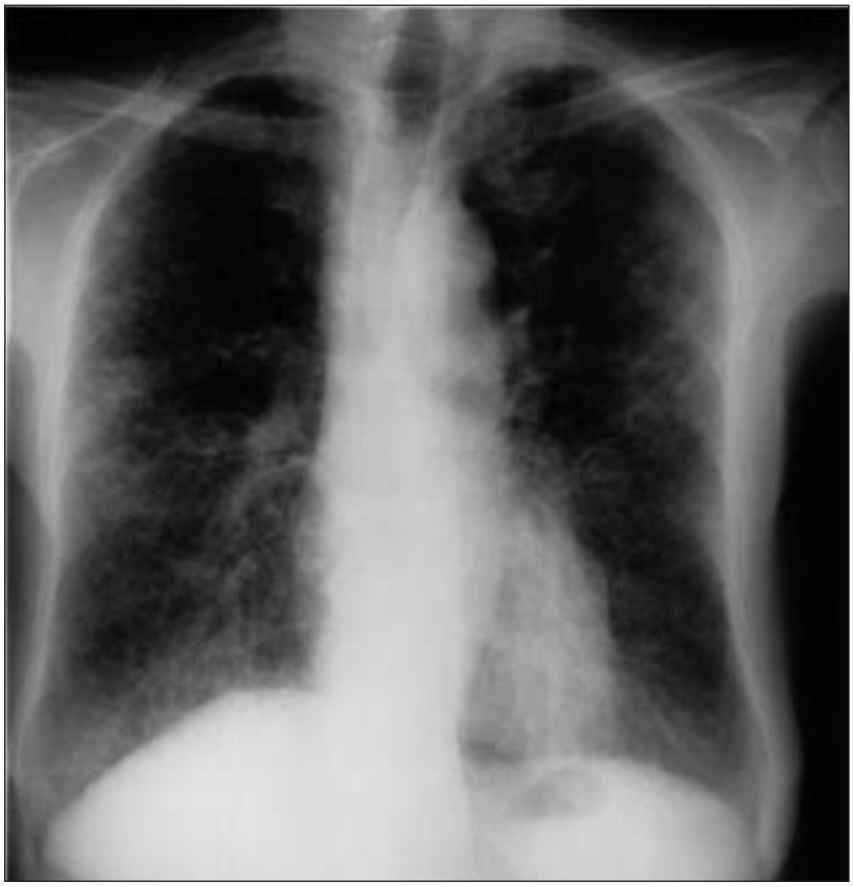


Figure 16. Stage III sarcoidosis. Chest radiograph demonstrates patchy reticulonodular densities throughout both lung fields. Lung volumes are well preserved. There is no definite lymphadenopathy.

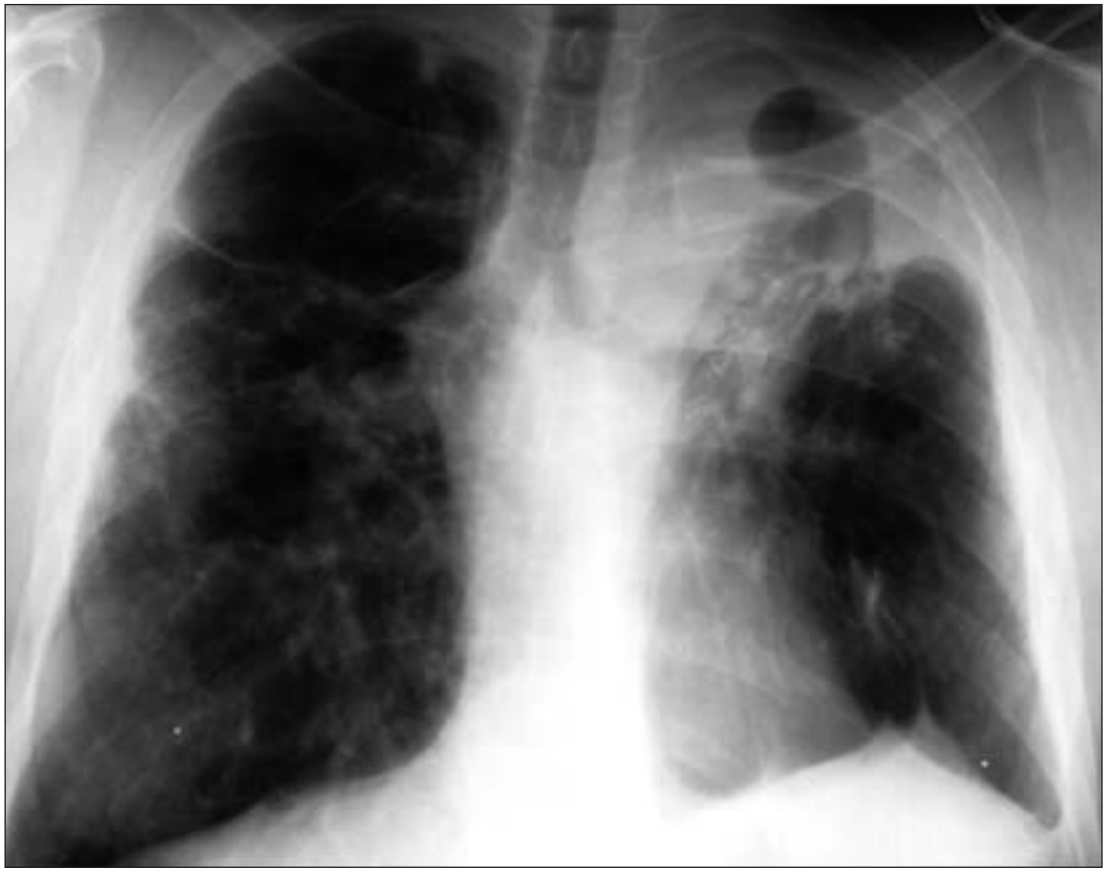
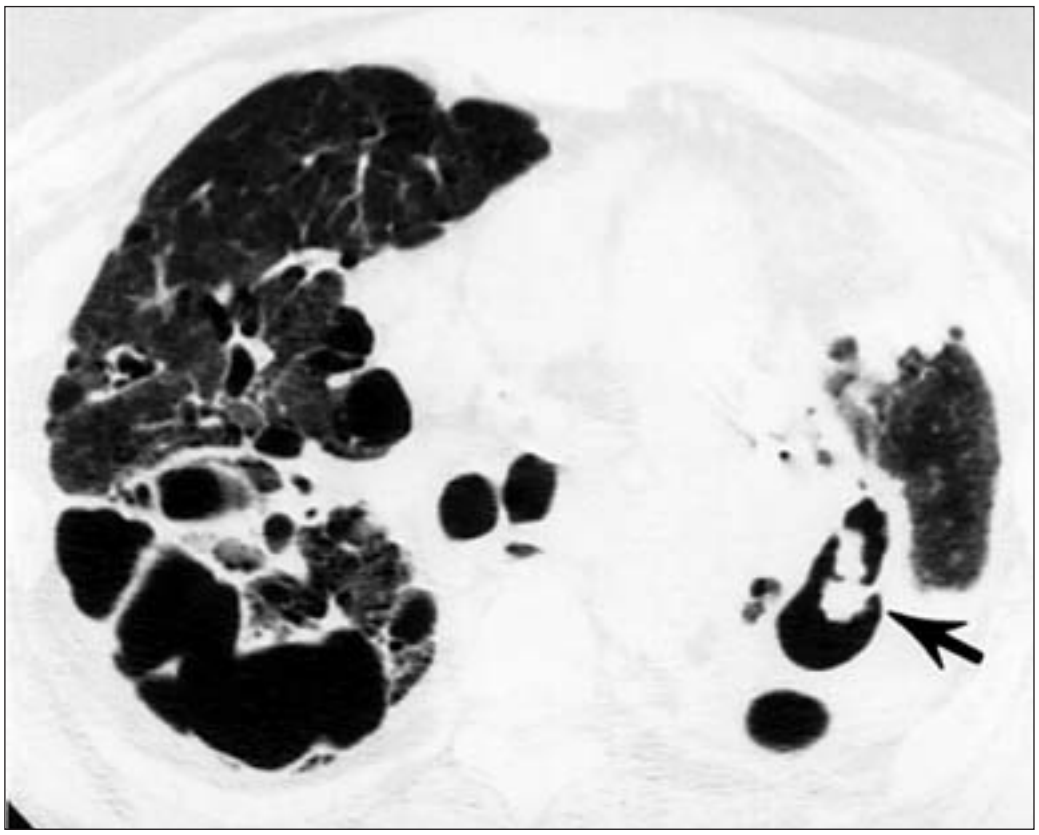


Figure 17a. *Top*, stage IV sarcoidosis. Posteroanterior chest radiograph demonstrates extensive cystic, bullous, and fibrotic changes; upward retraction of the hilum; and extensive pleural thickening in the left apex. Note surgical clips on the left lung from a previous left upper lobe lobectomy for a mycetoma. *Bottom*, HRCT demonstrating a mycetoma (arrow) in the superior segment of the left lower lobe in the same patient as in Fig 17, top, 8 months after resection a left upper lobe mycetoma. Note the bullae and cystic changes in the remaining lung parenchyma.



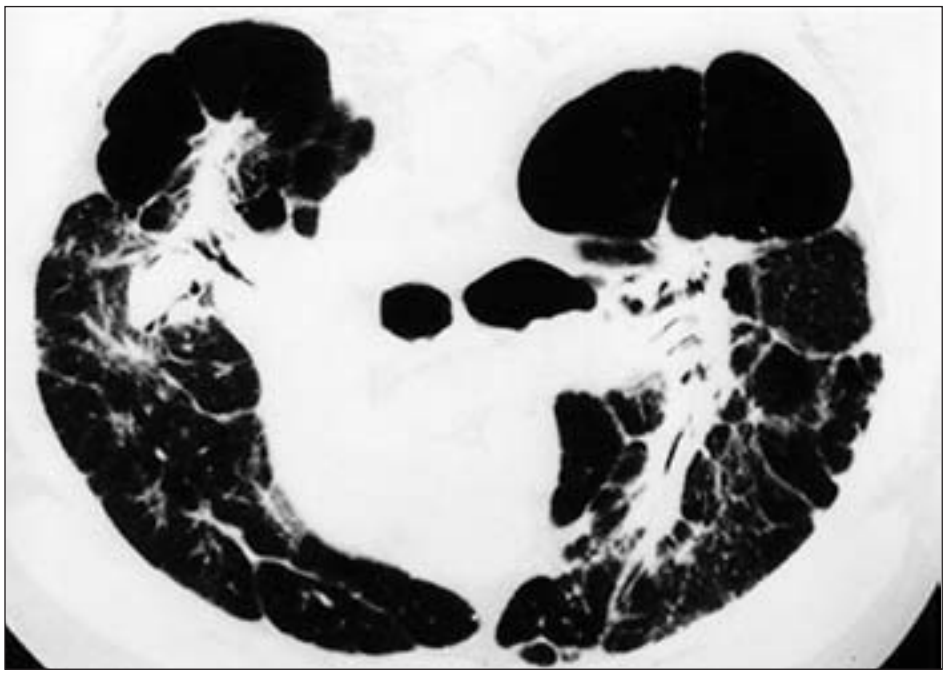


Figure 18. HRCT scan from a 48-year-old man with severe, chronic pulmonary sarcoidosis. Cuts at the level of the main carina show areas of bronchial thickening and consolidation centrally, in an axial distribution. Large cystic, bullous changes are evident in the posterior lung fields. The lung architecture is distorted.

confluent mass lesions, nodules, or consolidation of lung parenchyma.[138] Exuberant granulomatous inflammation may infiltrate and destroy affected organs, leading to significant and irreparable loss of function. In the lung, progression to end-stage fibrosis (honeycomb lung) can occur. Fiberoptic bronchoscopy with TBBs is the preferred diagnostic procedure to diagnose pulmonary sarcoidosis. Diagnostic yields are 60 to 95%.[138] To avoid sampling error, I take several biopsy specimens from both the upper and lower lobes at the time of initial diagnostic bronchoscopy. When TBB specimens are nondiagnostic, mediastinoscopic lymph node biopsy specimens may substantiate the diagnosis, provided enlarged mediastinal lymph nodes are present. However, mediastinoscopy as a routine, initial diagnostic procedure for hilar lymphadenopathy is not cost-effective and has potential morbidity.[155] In one study of 19 patients with suspected sarcoidosis, endosonography-guided fine-needle aspiration of enlarged mediastinal lymph nodes demonstrated nonnecrotizing granulomas in 100%; 1 patient had tuberculosis (sensitivity and specificity rates of 100% and 94%, respectively).[156] Experience with this technique is limited. Surgical lung biopsy (*ie*, VATS or open) is rarely necessary to diagnosis sarcoidosis. Biopsy of extrapulmonary sites may be appropriate when specific lesions or abnormalities are identified (*eg*, lymphadenopathy, skin lesions, abnormal liver enzyme levels).[139]

Laboratory Features

Laboratory features are nonspecific. Hypercalcemia occurs in 1 to 4% of patients, and hypercalciuria in 15 to 40%.[138-140, 142] These derangements in calcium metabolism reflect enhanced production of 1,2-dihydroxycalciferol by mononuclear phagocytes from sarcoid granulomas.[139] Polyclonal hypergammaglobulinemia occurs in 30 to 80% of patients with chronic disease.[139, 140, 157] Serum angiotensin-converting enzyme (ACE) levels are elevated in 30 to 80% of patients with sarcoidosis.[138, 140] False-positives are uncommon (<10%), but increased serum ACE levels can occur in active histoplasmosis and other granulomatous processes. The use of serum ACE as a surrogate marker of disease activity is discussed later.

Chest Radiographs

Abnormalities are present on chest radiographs in >90% of patients with sarcoidosis.[113] Bilateral hilar lymphadenopathy (BHL), often associated with enlargement of right paratracheal lymph nodes, is the classic radiographic feature, observed in more than two thirds of patients (Fig 14).[158] Pulmonary parenchymal infiltrates are present in 25 to 50% of patients.[113] Pulmonary parenchymal infiltrates are typically bilateral and patchy, with a predilection

for the mid and upper lung zones (Fig 15). Multiple focal nodular or alveolar opacities in the upper lobes may mimic tuberculosis and fungal pneumonia. Other disorders that preferentially involve the upper lobes include Langerhans' cell granulomatosis, cystic fibrosis, silicosis, and chronic eosinophilic pneumonia. Cavitation is not a feature of sarcoidosis. Pleural effusions occur in <2% of patients.[113] Pleural thickening on plain chest radiographs is rare, and usually reflects longstanding chronic disease. Diffuse reticulonodular or miliary infiltrates may be indistinguishable from other chronic interstitial lung disorders (*eg*, IPF, pneumoconiosis, pulmonary alveolar proteinosis, lymphangitic carcinomatosis) (Fig 16). Progression of the lung lesion results in distortion and destruction of the lung architecture, with upward retraction of the hilae, broad coarse septal bands, bullae, and end-stage honeycomb lung (Fig 17, top). With far-advanced disease, mycetomas, bullous emphysema, and pulmonary hypertension may be observed (Fig 17, bottom). Calcification of hilar or mediastinal nodes may be seen in longstanding sarcoidosis.

Radiographic Classification System

The radiographic staging system developed more than four decades ago continues to be useful prognostically. This schema applies the following criteria on plain chest radiographs: stage 0, normal; stage I, BHL without parenchymal infiltrates; stage II, BHL plus parenchymal infiltrates; and stage III, parenchymal infiltrates without intrathoracic lymphadenopathy.[113,158] Some investigators advocate defining patients with extensive destruction, fibrosis, and volume loss as having stage IV disease. This radiographic staging system may be useful as a prognostic guide, although significant variability exists. Spontaneous remissions occur in 60 to 90% of patients with stage I disease, in 40 to 70% with stage II disease, and in 10 to 20% with stage III disease.[113, 159] Serious sequelae are rare with stage I sarcoidosis, but may be appreciable in other stages. Virtually all fatalities due to pulmonary sarcoidosis occur in patients with radiographic stage II, III, or IV disease.[113] The course of the disease is usually dictated within the first 18 to 24 months of onset.[113] Spontaneous remissions occur in up to 40% within the first 6 months[159, 160]; >80% of spontaneous remissions occur within the first 2 years.[161] Persistence of radiographic infiltrates beyond 2 years suggests that spontaneous remissions are unlikely to occur, and strongly warrants consideration of corticosteroid therapy.[161] In some patients, the course is chronic, with multiple exacerbations or disease progression over years.[113, 159]

Chest CT

Chest CT is far more sensitive than conventional chest radiography in delineating parenchymal details or detecting the extent of intrathoracic lymphadenopathy[162, 163] In addition to hilar lymphadenopathy, enlarged lymph nodes in the paratracheal, pretracheal, para-aortic, internal mammary, subcarinal regions, and axillary regions are often noted on CT scans.[162, 163] This additional information is rarely of clinical value. Routine CT scanning is not required to diagnose or stage sarcoidosis and is not cost-effective.[162] However, CT may be helpful in patients with atypical manifestations or with normal chest radiographs but with clinical suspicion of disease.[162, 163] HRCT scans, using 1- to 2-mm slices, are superior to conventional CT in depicting parenchymal lesions and discriminating alveolitis from fibrosis.[48, 163-165] Characteristic HRCT features of sarcoidosis include the following: nodular opacities and micronodules (<3 mm in diameter) along bronchovascular bundles; central bronchovascular thickening and nodularity; confluent nodular opacities with air-bronchograms; ground-glass opacities; crowding and central retraction of bronchi and vessels near the hilae; and pleural or subpleural nodules.[158] Progression of the sarcoid lung lesion may form conglomerate masses, architectural distortion, and cystic destruction (Fig 18). Other nonspecific features include irregular interfaces, thickened alveolar septae or pleural surfaces, traction bronchiectasis, and distortion or displacement of vessels, bronchi, or interlobar fissues. The preferential distribution of parenchymal lesions in sarcoidosis along bronchovascular bundles and lymphatics, with an upper lobe predominance, contrasts sharply with IPF/UIP, which has a predilection for the basilar and subpleural (peripheral) regions of the lungs.[158]

Specific CT features have prognostic significance. Focal nodular, alveolar, or ground-glass opacities suggest an active inflammatory component. In contrast, distortion of lung parenchyma, volume loss, linear bands, bronchiectasis, cystic radiolucencies, and bullae are characteristic of end-stage fibrosis.[165] Because of its expense, I do not advocate *routine* HRCT in the diagnosis or staging of sarcoidosis. However, HRCT has a role in *selected* patients in assessing prognosis and determining the likelihood of response to therapy. Patients with extensive fibrosis, honeycombing, and lung distortion are not likely to respond to therapy with corticosteroids or immunosuppressive agents. By contrast, patients with large focal alveolar opacities and a ground-glass pattern are better candidates for therapy.

Pulmonary Function Tests

Restrictive ventilatory defects are observed in 30 to 60% of patients with pulmonary sarcoidosis.[113] Airways obstruction, with reduced FEV_1 and expiratory flow rates, occurs in 20 to 40% of patients.[166] Airflow obstruction may reflect submucosal or endobronchial inflammation, parenchymal distortion, bronchostenosis, or exaggerated bronchial reactivity.[113] Bronchial hyperactivity may be linked to endobronchial granulomatous inflammation.[167] In a recent study of patients with pulmonary sarcoidosis, reductions in maximal inspiratory mouth pressure and maximal expiratory mouth pressure correlated better than lung volumes or in DLCO with degree of dyspnea.[168] Reductions in DLCO are common in sarcoidosis, but are less severe than in patients with IPF.[72,73] Hypoxemia is unusual, but may be present in patients with advanced disease. Cardiopulmonary exercise test results are abnormal in up to 50% of patients with sarcoidosis, even when static pulmonary function test results are normal.[169] In one recent study, significant associations were noted between chest radiographic stage and TLC, DLCO, A-a O_2 gradient, and PO^2 with exercise.[170] However, cardiopulmonary exercise tests are logistically cumbersome and have limited practical value. Pulmonary function tests at a single time point cannot discriminate active from inactive disease and do not correlate with histopathology. Serial pulmonary function tests are important to objectively follow the course of the disease. I perform initial baseline studies to include spirometry, lung volumes, and DLCO. Spirometry is usually adequate to longitudinally monitor the course of the disease, as FVC is the most sensitive indicator of disease progression (or resolution). Spirometry should be repeated at 6-month intervals for the first 2 years, even in patients with minimal or no pulmonary symptoms. Patients with pulmonary symptoms or derangements in pulmonary function require more frequent studies. Deteriorating pulmonary function or persistence of severe derangements warrants a trial of corticosteroid therapy, irrespective of whether radiographic abnormalities are present.

Ancillary Studies

Serum ACE levels, radionuclide scans, and BAL cell profiles have been used to more accurately determine the extent and activity of the disease, but their role remains controversial. Serum ACE levels, ^{67}Ga scans, and BAL may reflect different stages or components of the disease process. Further, serum ACE levels and ^{67}Ga scans may reflect the macrophage component, which may not necessarily correlate with BAL lymphocytosis or lymphokine release.

Angiotensin-Converting Enzyme

ACE, an enzyme normally produced by endothelial cells, is produced in exaggerated amounts by sarcoid granuloma macrophages.[113] Serum ACE levels may reflect total body granuloma burden, but are not sensitive to active localized disease. Changes in serum ACE level often parallel the course of the disease and may be used to guide treatment decisions, provided clinical information is taken into account. Isolated elevations of serum ACE levels in the absence of clinical symptoms do not require therapy. Further, normal serum ACE levels in patients with progressive signs or symptoms do not exclude active disease. I obtain a baseline serum ACE level in patients with sarcoidosis and obtain serial levels in *selected* patients when clinical criteria are inadequate to judge disease activity.

Gallium 67 Citrate Scans

^{67}Ga citrate scans have been used as a surrogate marker of disease activity in sarcoidosis and other inflammatory pulmonary disorders. ^{67}Ga is taken up avidly by activated alveolar macrophages, and intrapulmonary uptake of ^{67}Ga may be a marker of active alveolar inflammation (alveolitis). Characteristic patterns of uptake have been noted in sarcoidosis (*eg*, increased uptake in lacrimal, salivary, and parotid glands and hilar and mediastinal lymph nodes). [171] Gallium^{67} scans are expensive, inconvenient, and difficult to quantitate, and do not reliably predict prognosis or response to therapy.[143] I see no role for ^{67}Ga scanning in either the initial staging or longitudinal follow-up of patients with sarcoidosis.

Bronchoalveolar Lavage

BAL reveals increased numbers of activated T lymphocytes (predominantly CD4+) and activated macrophages, with reduced T-suppressor cells (CD8+), in patients with active pulmonary sarcoidosis.[172-174] Early studies suggested that BAL CD4+ counts or CD4+/CD8+ ratios had prognostic value, but most subsequent investigations failed to find correlations between BAL cell profiles and subsequent outcome.[113, 140] High levels of T lymphocytes or lymphokines may reflect active alveolitis, but do not imply that deterioration will inevitably occur. Because of the waxing and waning nature of sarcoidosis, BAL has limited prognostic value. Marked increases in CD4+ lymphocytes, consistent with an intensive alveolitis, are characteristic of Lofgren's syndrome, yet spontaneous remissions occur in >90% of patients in this setting. In contrast, persistent elevation of BAL lymphocytes at 1 year has been associated with a low rate of spontaneous resolution. Serial bronchoscopy is invasive, expensive, and impractical for sequential evaluation of sarcoidosis.

Pathogenesis

The inciting signals responsible for the exuberant granulomatous response, and its subsequent progression to fibrosis (or resolution), have not been identified. Interactions between activated mononuclear phagocytes (*eg*, monocytes and macrophages) and activated T-helper/inducer lymphocytes are responsible for the induction and evolution of the granulomatous process.[174] At sites of active disease, striking increases in helper/inducer (CD4+) lymphocytes and increased CD4+/CD8+ ratios[173] and increased release of diverse lymphokines (consistent with a Th1 response), monokines, and biochemical markers have been noted.[174,175] Early in the course, Th1 cytokines (*eg*, IFN-γ and interleukin-2 (IL-2) predominate at sites of disease activity; this compartmentalization of the immune response (with a Th1 cytokine bias) may abate as the disease remits.[175] Lung T cells from patients with active pulmonary sarcoidosis release several cytokines that contribute to the induction of the immune response and facilitate T-cell replication and mononuclear phagocyte activation.[173, 176] Alveolar macrophages from patients with pulmonary sarcoidosis are activated, enhance antigen presentation, express receptors for IL-2, and release growth factors that promote fibroblast recruitment and proliferation.[173, 174, 176] Macrophages play a dual role in orchestrating the sarcoid lung lesion, by producing monokines that may either amplify or down-regulate the inflammatory process.

Therapy

Corticosteroids are the mainstay of therapy and may produce dramatic remissions in patients with severe or progressive sarcoidosis.[177] Favorable responses to corticosteroids are achieved in 60 to 90% of patients with symptomatic sarcoidosis, but relapses occur in 16 to 74% of patients following cessation of therapy.[113, 160, 177, 178] Long-term efficacy is less clear. Because of the potential for spontaneous resolution and toxic reactions associated with corticosteroids, indications for treatment are controversial. Several prospective studies performed in the 1970s failed to show a favorable effect on long-term prognosis. Although several studies suggested short-term improvement with steroid therapy, relapses often occurred following cessation of therapy. The lack of efficacy may reflect the study designs, as patients with stage I disease, minimal or no symptoms, and normal lung function were often entered into treatment trials. In most of these studies, high rates of improvement or

stabilization were noted in both treated and untreated patients. The long-term impact of corticosteroids was difficult to assess, owing to the high rate of spontaneous remissions as well as inclusion of patients with irreversible disease. These data cannot be extrapolated to patients with severe or progressive pulmonary disease, who are the best candidates for therapy. A multicenter, randomized trial of stage II or III sarcoidosis sponsored by the British Thoracic Society found that treatment with corticosteroids in patients with persistent radiographic infiltrates after an initial 6-month observation period was associated with improved lung function, chest radiographs, and symptoms compared with untreated control subjects.[159] Among 149 patients with stage II or III pulmonary sarcoidosis eligible for the study, 33 patients required immediate steroid therapy for control of symptoms and were excluded. In addition, 58 patients whose chest radiographs improved spontaneously within 6 months of entry served as an untreated observation group. The remaining 58 untreated patients with persistent radiographic infiltrates after 6 months were randomized to receive routine corticosteroids for 18 months (n=27) or selective therapy only (to control symptoms or deteriorating pulmonary symptoms; (n=31). No placebo group was included. The dose of steroid in the treated group was modest (*ie*, prednisolone 30 mg daily for 1 month, tapered to 10 mg by 4 months; maintenance therapy with 10 mg daily was continued for 9 months). Incremental doses were permitted as necessary to maximize radiographic improvement. The results affirmed the benefit of regular treatment with corticosteroids in patients with radiographic stage II or III disease who failed to have spontaneous remission during the 6-month period of observation. These data support the use of corticosteroids for patients with stage II or III disease whose conditions fail to improve spontaneously within a reasonable period. The optimal observation period prior to deciding on therapy has not been determined. A period of no more than 6 to 18 months is appropriate, as spontaneous remission beyond this point is unlikely. More immediate institution of therapy is warranted for patients with severe or deteriorating symptoms or pulmonary dysfunction.

Corticosteroids have potential toxicity, and routine therapy for patients with mild or no symptoms is inappropriate. Indications for therapy should be circumscribed and focused. Despite the lack of consensus regarding efficacy of therapy, there is little doubt that corticosteroids dramatically suppress or reverse the disease in some cases. Corticosteroids are warranted for myocardial, CNS, or ophthalmologic (*eg*, uveitis) complications of sarcoidosis.[139] Corticosteroids are also indicated for chronic hypercalcemia (to avert late complications of nephrocalcinosis and nephrolithiasis) and for severe or progressive pulmonary or extrapulmonary dysfunction. Dose and duration of therapy need to be individualized. Chronic disease of mild-to-moderate severity can be treated with modest dosages (*eg*, 40 mg every other day for 3 to 4 months, with subsequent taper). Higher doses (*eg*, prednisone 1 mg/kg per day for 4 weeks, with a gradual taper) are appropriate for myocardial or CNS manifestations. The duration of therapy, and rate of taper, need to be individualized according to clinical response and presence or absence of adverse effects. A 3-month trial of corticosteroid therapy is usually adequate to judge efficacy. If no objective response has been shown within this time, corticosteroid dosages can be tapered and discontinued. In contrast, among responders, corticosteroid therapy should be continued, albeit in a tapering regimen, for 12 to 18 months. Relapses may occur as the steroid dosage is reduced or discontinued. In such cases, escalation of the dose may be efficacious. Long-term corticosteroid therapy is indicated only for patients who have shown unequivocal response to therapy.

Inhaled Corticosteroids: Inhaled corticosteroids have been associated with anecdotal responses in patients with mild pulmonary sarcoidosis. Firm data supporting their efficacy are lacking. One recent double-blind, placebo-controlled trial in Finland randomized 189 patients with pulmonary sarcoidosis (stage I, II, or III) to treatment with either oral prednisone for 3 months followed by inhaled budesonide or placebo.[179] Among patients with stage II disease, chest radiographs did not differ between between groups. Differences in pulmonary function test results (FVC, D_{LCO}) between groups were minimal. A trend toward improvement in D_{LCO} was noted in corticosteroid-treated patients with stage II disease. These differences were

small and did not achieve statistical significance. Changes in FVC over time were similar between groups. In another double-blind trial, British investigators randomized 44 adults with stage II or III pulmonary sarcoidosis to treatment with inhaled fluticasone (1,000 μg bid) or placebo for 6 months.[180] Approximately 75% were receiving oral corticosteroids at the start of the study. No significant differences in pulmonary function test results, mean dose of oral corticosteroids, or chest radiographs were detected at any time point. Long-term follow-up up from the Finnish study, which randomized patients with stage I and II newly diagnosed (<3 months) sarcoidosis to *immediate* treatment with placebo or prednisolone for 3 months, followed by inhaled budesonide for 15 months, was recently published.[181] No initial differences were noted in treated or placebo groups in chest radiographs at 1 year. However, at 5 years, patients in the placebo cohort had lower mean FVC and DLCO and worse chest radiographs compared to treated patients.[181] Differences between groups were small, and the significance of these observations is not clear. These studies [79-181] suggest that inhaled corticosteroids have minimal value as *primary* therapy for pulmonary sarcoidosis. However, given their low toxicity, a trial of inhaled corticosteroid therapy is reasonable in patients with significant endobronchial inflammation, cough, or persistent pulmonary symptoms.

Immunosuppressive or Cytotoxic Agents: Immunosuppressive or cytotoxic agents (*eg,* MTX, AZA, cyclosporine, chlorambucil, and CP) have been used, with anecdotal successes, in patients failing to respond to therapy or experiencing side effects from corticosteroids. However, randomized trials evaluating these agents are lacking, and the best agent has not been determined.

Immunosuppressive Agents: Both AZA and MTX may be useful for sarcoidosis refractory to corticosteroids or as steroid-sparing agents in patients requiring high-dose corticosteroids for control of the disease.

Azathioprine

AZA (dose of 2 to 3 mg/kg/d), alone or combined with corticosteroids, has been associated with anecdotal successes in sarcoidosis, even in patients failing to respond to corticosteroid therapy. However, randomized trials have not been performed. Further, studies directly comparing AZA with alternative agents for sarcoidosis are lacking. In two early studies, 10 of 20 patients failing to respond to corticosteroid therapy responded to AZA therapy.[182, 183] In another retrospective study, 8 of 14 patients with neurosarcoidosis responded to AZA therapy.[184] Diab et al[185] treated seven patients with a combination of prednisone and AZA; the conditions of all seven improved. In contrast, investigators from South Africa found AZA to be of marginal benefit in a retrospective study of 10 patients with pulmonary sarcoidosis.[186] All had shown only partial (n=6) or no (n=4) response to corticosteroid therapy. The addition of AZA (100 to 150 mg/d) *plus* low-dose corticosteroids was associated with significant and sustained improvement in lung function in only two patients; two additional patients had transient improvement and a steroid-sparing effect. Two patients failing to respond to AZA treatment subsequently responded to treatment with cyclosporine and high-dose corticosteroids. No patient who failed to respond to high-dose corticosteroid therapy responded to AZA therapy. German investigators treated 11 patients with chronic sarcoidosis with AZA *plus* prednisolone.[187] All had symptomatic improvement; chest radiographs improved in nine; pulmonary function test results improved in seven. Late relapses (8 to 22 months) occurred in three patients.[187] Although these data are limited, I believe AZA may be useful as a steroid-sparing agent or in selected patients with severe or progressive sarcoidosis refractory to corticosteroid therapy. Extensive clinical experience with AZA in organ transplant recipients and other immune disorders suggests that late sequelae associated with long-term AZA use are uncommon.[113]

Methotrexate

MTX, a folic acid antagonist with both immunosuppressive and anti-inflammatory effects, has been efficacious for both pulmonary and extrapulmonary sarcoidosis.[188] MTX can be given parenterally (IM) or orally as a pulse once weekly. Dosages ranging from 10 to 25 mg weekly have been used. In three uncontrolled studies by investigators from the University of

Cincinnati comprising more than 230 patients, favorable responses to MTX were cited in 52 to 66% of patients.[189-190] Relapses were frequent with cessation of therapy, but usually responded to reinstitution of MTX therapy These investigators recently published a double-blind, randomized study of 24 patients with new-onset, symptomatic sarcoidosis.[192] Following initial treatment with prednisone for 4 weeks, patients were randomized to treatment with MTX or placebo for 6 months. Prednisone dosage was tapered according to a predetermined schedule. Among patients receiving >6 months of MTX, a steroid-sparing effect was suggested.[192] While these studies are not definitive, MTX has a role as a steroid-sparing agent in sarcoidosis. Because of potential toxicities, MTX should be restricted to patients requiring unacceptably high doses of steroids (>20 mg/d) or experiencing serious side effects from steroids. In this context, a 4- to 6-month trial of methotrexate therapy is reasonable. I initiate therapy with 7.5 mg once weekly, and escalate the dose by 2.5-mg increments weekly (to a maximal dose of 15 mg) until a clinical response or toxicity has occurred. Serious adverse effects are rare (<1% of patients), but side effects requiring cessation of therapy occur in 3 to 15% of cases.[113] Adverse effects of MTX are dose dependent and may be minimized by addition of folic acid (1 mg/d). Adverse effects associated with MTX include GI effects (*eg*, nausea, vomiting, and diarrhea), stomatitis (*eg*, mucosal or oral ulcers), and rash. Less common complications, each occurring in 1 to 4% of patients, include megaloblastic anemia, leukopenia, or thrombocytopenia; opportunistic infections; and interstitial pneumonitis.[113] In contrast to the alkylating agents, MTX is not carcinogenic. MTX is teratogenic and cannot be used in patients at risk of conception. The most worrisome side effect is hepatic cirrhosis, which may occur in up to 2% of patients with long-term use (>2 years). To my knowledge, the risk of permanent liver disease with long-term use of MTX (>2 years) has not been defined in a cohort of patients with sarcoidosis. Contraindications to MTX include ethanol abuse, concomitant liver disease, history of hepatitis, unreliable patient, renal failure, active infection, anemia, and leukopenia. Serial transaminase levels, CBC counts, and platelet counts should be monitored every 4 to 8 weeks in patients receiving MTX. Persistent or progressive rises in hepatic enzyme levels, thrombocytopenia, or leukopenia warrant discontinuation of therapy or reduction of the dose. Given its potential for late, irreversible, hepatotoxicity, MTX therapy should be continued beyond 6 months only in patients demonstrating unequivocal objective improvement. Enthusiasm for its use needs to be tempered by the high relapse rate noted on cessation of therapy. I prefer AZA for patients with chronic progressive sarcoidosis requiring long-term treatment (>1 year).

Cyclosporine

Cyclosporine, a fungal decapeptide that exhibits relatively selective inhibitory effects on T-cell activation, proliferation, and lymphokine release, would be expected to be an ideal agent for treating sarcoidosis. However, despite anecdotal responses in some corticosteroid-resistant patients,[186] cyclosporine has been disappointing as therapy for pulmonary sarcoidosis. In a study from the National Institutes of Health, eight patients with symptomatic pulmonary sarcoidosis received oral cyclosporine (10 mg/kg/d) for 6 months.[193] Despite inhibitory effects on T-cell proliferation and cytokine release *in vitro*, pulmonary function or BAL results did not change. In one study, six patients with steroid-refractory CNS sarcoidosis were treated with cyclosporine plus corticosteroids for 6 months.[194] No patient achieved complete remission, but a steroid-sparing effect was suggested. A subsequent study by these investigators cited favorable responses in 11 of 14 patients with neurosarcoidosis treated with cyclosporine.[184] A randomized controlled trial by Wyser and coworkers [195] showed no benefit with oral cyclosporine (5 to 7 mg/kg/d) *combined* with prednisone as compared to prednisone *alone* in a cohort of 37 patients with pulmonary sarcoidosis. Adverse effects (particularly renal insufficiency and infections) and relapses were higher in the patients receiving combined therapy.[195] Cyclosporine is very expensive (>$500 per month) and is associated with numerous toxic reactions (*eg*, hypertension, renal insufficiency, hirsuitism, neuropathies, disorders in lipid levels, heightened susceptibilities to infections, and lymphoproliferative disorders).[113] In light of the myriad complications associated with its use, and the lack of demonstrated efficacy, cyclosporine has at best a marginal role as salvage therapy

for patients with severe, progressive sarcoidosis refractory to corticosteroid therapy.

Alkylating Agents: Published data regarding alkylating agents (*eg*, CP, chlorambucil) for the treatment of sarcoidosis are limited to sporadic case reports and small retrospective series. Chlorambucil, an alkylating agent of the nitrogen mustard class, was associated with favorable responses in 12 of 18 patients in whom corticosteroid therapy previously failed in two nonrandomized studies.[196, 197] Israel and McComb[198] reported clinical responses in 20 of 31 patients (64%) treated with chlorambucil. Only five had *failed* to respond to corticosteroid therapy; the remaining patients required unacceptably high doses of corticosteroids. Adverse effects associated with chlorambucil include GI, mucosal, and bone marrow toxicity; increased susceptibility to infections; alopecia; and induction of malignancies (particularly leukemias).[113] Because of its oncogenicity, I do not believe chlorambucil has a role in the therapy of corticosteroid-recalcitrant sarcoidosis.

Oral CP (1 to 2 mg/kg/d) has only rarely been used to treat sarcoidosis. Anecdotal responses have been noted, but data are limited to a few case reports.[177] Lower and colleagues[190] cited favorable responses in 8 of 10 patients treated with IV pulse CP for neurosarcoidosis, 8 of whom had concomitant lung involvement. Prior therapy included corticosteroids in all 10; MTX in 8. Thus, CP has a role for severe sarcoidosis refractory to treatment with corticosteroids or other immunosuppressive agents. However, in light of its oncogenic potential, particularly in relatively young patients, I reserve CP for severe sarcoidosis refractory to treatment with corticosteroids and AZA or MTX.

Other Anti-inflammatory and Immunomodulatory Agents: Nonsteroidal anti-inflammatory agents (*eg*, indomethacin and phenylbutazone) have been used to treat the acute articular manifestations of sarcoidosis, but have no role in treating more severe cases of pulmonary or extrapulmonary sarcoidosis.

Antimalarial Drugs

Antimalarial drugs (*eg*, chloroquine and hydroxychloroquine) have immunomodulating properties and are efficacious in treating rheumatoid arthritis, systemic lupus erythematosus, and diverse immune-mediated diseases. Antimalarials concentrate in cells of the reticuloendothelial system and melanin-containing tissues (*eg*, skin, spleen, leukocytes, kidney) and are preferentially concentrated in epithelioid, mononuclear, and giant cells comprising sarcoid granulomata. Anecdotal responses have been noted with the antimalarials for cutaneous,[199] osseous,[177] and neurologic[200] sarcoidosis and sarcoid-induced hypercalcemia.[201] The role of antimalarials in treating pulmonary sarcoidosis is less well established. However, a randomized trial of 23 patients with symptomatic pulmonary sarcoidosis (radiographic stage II or III) suggested benefit with chloroquine.[202] Sixteen of the 23 patients had previously been treated with high-dose corticosteroids, without sustained improvement. All 23 patients were treated with high-dose chloroquine (750 mg/d) for 6 months. Five patients withdrew from the study before the 6-month acute phase (three because of intolerable side effects). After 6 months, the dose of chloroquine was tapered by 250 mg every 2 months. Eighteen patients were then randomized to a maintenance group (chloroquine, 250 mg/d) (n=10) or observation group (no chloroquine) (n=8). After the initial 6-month treatment with high-dose chloroquine, symptoms, pulmonary function test results, serum ACE, and gallium scans improved. Following randomization, the rate of decline in pulmonary function test results was slower and there were fewer relapses in patients receiving maintenance chloroquine compared to no chloroquine therapy. To my knowledge, studies comparing chloroquine with corticosteroid therapy have not been done. The major toxicity of antimalarials is ocular (particularly chloroquine); dizzyness and nausea may also occur.[202] Unfortunately, prolonged administration of chloroquine can lead to irreversible retinopathy and blindness. Given the potential serious ocular toxicity associated with chloroquine, hydroxychloroquine (*Plaquenil*), which is less toxic, is preferred. The dose of hydroxychloroquine is 200 mg once or twice daily for a 6-month trial. Long-term maintenance therapy (dose of 100 to 400 mg daily) is reserved for patients manifesting unequivocal responses. Slit-lamp examinations by an ophthalmologist every 6 to 9 months should be done to rule out ocular

toxicity. The combination of hydroxychloroquine with corticosteroids or immunosuppressive agents may enhance immunomodulatory effects compared to any of these agents alone.

Alternative Therapies

Anecdotal responses have been cited with thalidomide,[177, 203] a sedative with teratogenic properties, melatonin,[140] and pentoxifylline[204] in patients with sarcoidosis, but the value of these agents is unproven. Responses to IV infusions of infliximab (Remicade), a chimeric human-murine anti-human TNF-α monoclonal antibody, were cited in four of four patients in two small series.[205,206] However, treatment with infliximab is very expensive and has been associated with a heightened risk of tuberculosis[207] and other opportunistic infections, increased autoantibody production, [208,209] and other adverse effects.[209] Currently, infliximab or other TNF-α inhibitors (*eg*, entanercept [Enbrel][210] or adalimumab [not yet released])[207] are of unproven value for sarcoidosis and should be reserved for research investigations.

Pulmonary Hypertension

Pulmonary hypertension is a rare complication of sarcoidosis, but may occur in patients with advanced radiographic stages.[138] Although data are limited, favorable responses to short- and long-term vasodilators have been cited (*eg*, inhaled nitric oxide, IV epoprostenol, and oral calcium channel blockers).[211] Supplemental oxygen should be administered for patients with hypoxemia.[138]

Lung Transplantation

Single or bilateral lung transplantation has been successfully accomplished in patients with severe pulmonary sarcoidosis refractory to aggressive medical therapy. [135,212-214] Recurrence of sarcoid granulomas within the lung allografts is common, but rarely causes clinical symptoms.[214,215] Lung transplantation is a viable option for patients with end-stage pulmonary sarcoidosis and limited life expectancy.[214,216] Survival rates following single or double lung transplantation are similar, approximating 50 to 70% at 3 years.[214,216,217] Criteria for listing for transplantation are not well defined. However, waiting time for organs can be prolonged, and up to 53% of patients with end-stage pulmonary sarcoidosis die while awaiting transplantation.[214,217] Factors associated with increased mortality on the waiting list include the following: $PaO_2 \leq 60$ mm Hg; pulmonary artery pressure ≥ 35 mm Hg: cardiac index ≤ 2 L/min/m^2; right atrial pressure ≥ 15 mm Hg.[217] Invasive aspergillosis may complicate lung transplantation among sarcoid patients with preexisting mycetomas.[217]

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Notes

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