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P.L. Molyneaux, A.G. Nicholson, N. Hirani, and A.U. Wells 18.11.3 Bronchiolitis obliterans and cryptogenic organizing pneumonia 4185 Vasilis Kouranos and A.U. Wells 18.11.4 The lung in autoimmune rheumatic disorders 4191 M.A. Kokosi and A.U. Wells 18.11.5 The lung in vasculitis 4200 G.A. Margaritopoulos and A.U. Wells 18.11.1 Diffuse parenchymal lung disease: An introduction F. Teo and A.U. Wells ESSENTIALS The nomenclature of diffuse parenchymal lung disease (also known as interstitial lung disease) has caused a great deal of confusion, with use of complicated histopathological terms not always corres- ponding to clinico-radiological entities. Five major groupings are now recognized: (1) idiopathic interstitial pneumonias; (2) diseases associated with systemic conditions, including rheumatological disorders; (3) diseases caused by environmental triggers or drugs; (4) granulomatous diseases; and (5) other diffuse lung diseases. Idiopathic interstitial pneumonias Classification is based on recognition of clinical, radiological, and histo- pathological patterns, as opposed to the purely histopathological ter- minology. Diagnosis is complicated by the large number of disorders grouped within the diffuse parenchymal lung diseases. A systematic diagnostic algorithm, based upon careful clinical evaluation and a lo- gical sequence of tests, is essential. Clinical history, clinical examination, chest radiography, pulmonary

function tests, and selective blood tests should be followed by high-resolution CT, bronchoalveolar lavage (in some cases), and lung biopsy (in a few cases). The chronic diffuse parenchymal lung diseases can be broadly subclassified into five patterns of longitudinal disease behaviour, based upon cause, severity, the relative degree of inflammation and fibrosis, and observed change in the short term. Each clinical pattern is associated with a separate approach to management. Reversible and self-limited disease—usually caused by an extrinsic agent and typically responds to withdrawal of an offending agent. Reversible major disease with risk of progression, with or without supervening fibrosis—a feature of drug-induced lung disease and some other conditions; usually treated with high-dose corticoster- oids, with dose reduction to minimum possible once inflammation is controlled. Residual but stable fibrotic disease—most commonly encountered in sarcoidosis, following drug-induced lung disease, and in patients with formerly active rheumatological disorders; treatment is not required. Progressive fibrotic disease—in which stabilization is a realistic goal—frequently seen in sarcoidosis, hypersensitivity pneumonitis, rheumatological conditions, and in many patients with fibrotic non- specific interstitial pneumonia; aggressive initial treatment is usually warranted and long-term therapy is often required. Inexorably progressive fibrotic disease—the hallmark of idiopathic pulmonary fibrosis; long-term treatment may slow disease progres- sion and reduce mortality; early recognition of relentless progression is important when lung transplantation is possible, and to assure provision of effective palliation when it is not. Definition The nomenclature of diffuse parenchymal lung disease has caused confusion over the decades. Contributory factors include non- standardized terminology (e.g. ‘extrinsic allergic alveolitis’ and ‘hypersensitivity pneumonitis’ as alternative terms for the same entity), the inappropriate grouping of otherwise diverse clinico- pathological entities (previous use of the umbrella term ‘crypto- genic fibrosing alveolitis/idiopathic pulmonary fibrosis’ to describe all idiopathic interstitial pneumonias), and the use of similarly 18.11 Diffuse parenchymal lung diseases

18.11.1 Diffuse parenchymal lung disease 4167 worded yet distinct disease definitions (e.g. bronchiolitis obliterans organizing pneumonia and bronchiolitis obliterans syndrome). The terminology has been refined as our understanding of disease mech- anisms, presentations, and prognosis has evolved. Diffuse parenchymal lung disease is synonymous with interstitial lung disease. The former terminology reflects, perhaps more aptly, the fact that disease processes involve the lung parenchyma, but also the airspace components of the acini in many cases. Infective pneumonias, pulmonary oedema, and some malignancies involve the acinar regions of the lung but are not, by convention, grouped with the diffuse parenchymal lung diseases, although they may pre- sent with similar clinical and radiological findings and should be considered in the formulation of a differential diagnosis. However, a decision was made to adopt the term interstitial lung disease in the British Thoracic Society (in collaboration with the Thoracic Society of Australia and New Zealand and Irish Thoracic Society) document to achieve consistency with other international guidelines. Specific disease will be considered in subsequent chapters. In this introduction, a broad approach to the classification of the diffuse lung diseases and their diagnosis and investigation will be discussed. Classification Diffuse parenchymal lung diseases can be subdivided into five major groupings:

1. Idiopathic interstitial pneumonias
2. Systemic disease (including rheumatological) associated inter- stitial lung disease
3. Environmental or drug related interstitial lung disease

4. Granulomatous diseases
5. Other diffuse lung diseases (e.g. histiocytosis and lymphangioleiomyomatosis) In most patients with environmentally and drug-induced lung dis- ease, granulomatous lung disease or systemic disease-associated interstitial lung disease (groups 2–5), the cause and, thus, the diagnosis is immediately apparent or is rapidly disclosed by standard investigations detailed next. By contrast, diagnosis is less straightforward when a cause is not immediately apparent (group 1). By definition, most of these patients can be categorized as having one of the idiopathic interstitial pneumonias, discussed in detail in the remainder of this chapter. Table 18.11.1.1 lists diseases of known and unknown cause within the broad headings given here, and disorders that present more acutely are shown in Table 18.11.1.2. Idiopathic interstitial pneumonias The diseases grouped as the 'idiopathic interstitial pneumo- nias' have given rise to particular confusion, largely because terms used to describe histopathological patterns have been used interchangeably but inaccurately with disease 'labels'. In 1944, Hamman and Rich first described a presentation of rapidly Table 18.11.1.1 Diffuse parenchymal lung disease Associated with systemic diseases Rheumatological: Systemic sclerosis, rheumatoid arthritis, polymyositis/dermatomyositis, systemic lupus erythematosus, Sjögren's syndrome, ankylosing spondylitis Vasculitis: Wegener's granulomatosis, Churg– Strauss granulomatosis, microscopic polyangiitis, pulmonary–renal syndrome (including Goodpasture's syndrome), capillaritis, Behçet's syndrome Vascular: Primary pulmonary hypertension, idiopathic pulmonary haemosiderosis, pulmonary veno-occlusive disease, antiphospholipid syndrome Diseases caused by environmental triggers or drug ingestion Hypersensitivity pneumonitis: fungal, bacterial, avian, chemical Fibrogenic inorganic dusts: asbestosis, silica, hard metal alloyberyllium, coal, aluminium Therapeutic agents,a illicit drugs, radiation, pesticides, oxygen and other inhaled gases Granulomatous diseases Sarcoidosis, hypersensitivity pneumonitis, berylliosis, Langerhans cell histiocytosis, Wegener's granulomatosis, Churg–Strauss syndrome, lymphomatoid granulomatosis, bronchocentric granulomatosis Idiopathic interstitial pneumonias Idiopathic pulmonary fibrosis, nonspecific interstitial pneumonia, desquamative interstitial pneumonia, respiratory bronchiolitis–interstitial lung disease, acute interstitial pneumonia, cryptogenic organizing pneumonia, lymphocytic interstitial pneumonia, idiopathic pleuroparenchymal fibroelastosis Other diffuse lung diseases Inherited disorders: tuberous sclerosis, neurofibromatosis, Hermansky–Pudlak syndrome, lipid storage disorders, familial idiopathic pulmonary fibrosis Pulmonary eosinophilia: known causes (fungi, parasites, drugs), acute idiopathic, chronic idiopathic Lymphangioleiomyomatosis Alveolar proteinosis Alveolar microlithiasis Amyloidosis Chronic aspiration a see www.pneumotox.com for full listing.

section 18 Respiratory disorders 4168 progressive fatal disease, in which the cardinal histological fea- tures were interstitial inflammation and fibrosis. It subsequently became clear that chronic insidiously progressive fibrosing dis- ease was not uncommon. A typical clinical picture was defined, consisting of progressive dyspnoea, bilateral predominantly basal crackles on auscultation, reticulonodular predominantly basal abnormalities on chest radiography, and a restrictive ventilatory defect on lung function testing. This clinical entity was termed 'cryptogenic fibrosing alveolitis (CFA)' or 'idiopathic pulmonary fibrosis (IPF)'. However, it became clear that the outcome asso- ciated with this presentation, hereafter termed the 'CFA clinical syndrome', was highly

heterogeneous. Although most patients progressed inexorably to a fatal outcome, usually within three to four years, a more insidious course was seen in a significant minority, and in 10–15% of cases there was a response to cortico- steroid therapy and, usually, a good long-term outcome. Histological patterns of disease encountered in the CFA clinical syndrome were first classified by Liebow in 1975 as usual inter- stitial pneumonia (UIP), desquamative interstitial pneumonia (DIP), bronchiolitis obliterans with usual interstitial pneumonia (BIP), lymphocytic interstitial pneumonia (LIP), and giant cell interstitial pneumonia. However, it subsequently became clear that these patterns of disease were also present outside an idio- pathic setting. The most frequent, UIP, was occasionally found in connective tissue disease, drug-induced lung disease, and chronic hypersensitivity pneumonitis, and LIP was most commonly as- sociated with rheumatological disease and, more recently, AIDS- related disease. Giant cell interstitial pneumonia was seldom idiopathic but was caused by exposure to hard metals (cobalt, tungsten carbide, titanium salts). It also became apparent that the historical histological pattern of UIP did, in fact, encompass separate patterns of UIP and nonspecific interstitial pneumonia (NSIP), which denoted a better outcome. These considerations led to a revision of Liebow's classifica- tion. The interstitial pneumonias of known cause were removed (although smoking-related disorders were retained). The re- vised classification, in an attempt by a nomenclature committee of the American Thoracic Society and European Respiratory Society in 2001 to integrate clinical, radiological, and histo- pathological patterns as opposed to hitherto purely histo- pathological terminology, included UIP, NSIP, DIP, respiratory bronchiolitis–interstitial lung disease (RB-ILD), diffuse al- veolar damage (DAD), LIP, and cryptogenic organizing pneu- monia (Table 18.11.1.3). The term CFA became synonymous with IPF, requiring an underlying histological pattern of UIP or compatible high-resolution computed tomography (HRCT) appearances, and was distinguished from the nonspecific 'CFA clinical syndrome'. It was also recognized that different histo- logical patterns may be found within the same disease (e.g. NSIP with UIP pattern in idiopathic pulmonary fibrosis), and this underscored the importance of integrating clinical, radio- logical, and pathological information in arriving at a unifying diagnosis. In 2013, the American Thoracic Society and European Respiratory Society further revised the classification of idiopathic intersti- tial pneumonias (IIP). NSIP, hitherto a provisional diagnosis with poorly characterized clinical and radiologic features, became accepted as a distinct major clinical entity, and idiopathic LIP was classified as a rare IIP. Major IIPs were distinguished from rare (idiopathic LIP and pleuroparenchymal fibroelastosis) and unclassifiable IIPs, and subgrouped into chronic fibrosing (IPF and NSIP), smoking-related (RB-ILD and DIP) and acute/sub- acute IIPs (acute interstitial pneumonia and cryptogenic organ- izing pneumonia). (Table 18.11.1.3). Rare histological patterns of acute fibrinous and organizing pneumonia and interstitial pneu- monias with a bronchiolocentric distribution were introduced. Finally, a clinical disease behaviour classification was proposed to capture thought processes of clinicians and serve as a rationale for treatment and monitoring decisions in disease that is difficult to classify. The pattern of UIP and its associated disorder, IPF, and cryptogenic organizing pneumonia are covered separately in Chapter 18.11.2. The other idiopathic interstitial pneumonias are reviewed briefly next. Table 18.11.1.2 Acute presentations of diffuse parenchymal lung disease: differential diagnosis Primary diffuse parenchymal lung disorders Acute interstitial pneumonia Acute exacerbations of idiopathic pulmonary fibrosis Diffuse alveolar haemorrhage due to vasculitis or coagulopathy Fulminant cryptogenic and secondary organizing pneumonia Acute pneumonitis due to rheumatological disease Hypersensitivity pneumonitis Acute pulmonary eosinophilia Drug-induced lung disease Mimics of diffuse parenchymal lung disease Pulmonary oedema due to left ventricular failure, uraemia or other causes Infection, especially opportunistic with Pneumocystis

carinii Extensive, rapidly progressive metastatic malignancy Table 18.11.1.3 American Thoracic Society/European Respiratory Society nomenclature of idiopathic interstitial pneumonias Clinical-radiological diagnosis Pathology pattern Cryptogenic fibrosing alveolitis (idiopathic pulmonary fibrosis) Usual interstitial pneumonia Nonspecific interstitial pneumonia Nonspecific interstitial pneumonia (provisional) Desquamative interstitial pneumonia (alternative name: alveolar macrophage pneumonia) Desquamative interstitial Pneumonia Respiratory bronchiolitis–interstitial lung Disease Respiratory bronchiolitis–interstitial lung disease Acute interstitial pneumonia Diffuse alveolar damage Cryptogenic organizing pneumonia Organizing pneumonia Lymphocytic interstitial pneumonia Lymphocytic interstitial pneumonia Pleuroparenchymal fibroelastosis Pleuroparenchymal fibroelastosis

18.11.1 Diffuse parenchymal lung disease 4169 Major idiopathic interstitial pneumonias Chronic fibrosing interstitial pneumonias Idiopathic pulmonary fibrosis See Chapter 18.11.2. Nonspecific interstitial pneumonia Nonspecific interstitial pneumonia is the least satisfactory entity among the idiopathic interstitial pneumonias. Histologically, there is variable interstitial inflammation and fibrosis but, unlike usual interstitial pneumonia, the pattern with which it is most likely to be confused, disease is uniform throughout biopsy specimens, both in severity and in the age of fibrosis (Fig. 18.11.1.1). Fibroblastic foci, the cardinal finding in usual interstitial pneumonia, are absent or sparse. The radiological and clinical manifestations of NSIP are diverse. Inflammation predominates in a few cases and the treated outcome is uniformly good, but in most patients with fibrotic NSIP, fibrosis is as prominent as, or more prominent than, inflammation. Certain clinico-radiological profiles are increasingly recognized in NSIP:

1. NSIP/IPF: the most prevalent profile in most European countries and the United States, it is clinically and physiologically indistin- guishable from that of IPF, despite major outcome differences. On HRCT, the basal distribution of disease is similar to that of IPF, but unlike IPF, there is prominent ground-glass attenuation and honeycombing is absent or minimal (Fig. 18.11.1.2).
2. NSIP/OP: this profile is typically present in pulmonary fibrosis associated with inflammatory myopathy. In this large subgroup, predominating in reports from South Korea and Japan, the clin- ical and radiological features are those of organizing pneumonia admixed with fibrosis and there is a prominent lymphocytosis on bronchoalveolar lavage.
3. NSIP/HP: this profile arose mainly from reports in France and Mexico, with clinical exposure histories, HRCT and bronchoalveolar lavage (BAL) features closely resembling that of hypersensitivity pneumonitis, despite the absence of granulomas in biopsy tissue. In more recent reports, a subgroup of hyper- sensitivity pneumonitis patients with typical NSIP at biopsy is recognized. The prognosis is variable. Corticosteroid and immunosuppres- sive therapy are often effective in producing regression or sta- bilization of disease, but in a few cases, largely confined to those presenting with clinical and HRCT features overlapping with those of IPF, there is inexorable progression to a fatal outcome despite treatment. Smoking-related interstitial pneumonias Desquamative interstitial pneumonia The cardinal histological feature is diffuse accumulation of macro- phages in alveolar spaces in a uniform pattern, variably associated with minor interstitial inflammation and fibrosis (Fig. 18.11.1.3). DIP is a rare disorder almost exclusively found in smokers in their fourth or fifth decades, with a male to female predominance of 2:1. Typical HRCT appearances comprise extensive ground-glass at- tenuation (Fig. 18.11.1.4).

The disease presents with the features of the CFA clinical syndrome, with finger clubbing present in 50% of patients. Unlike IPF, a response to corticosteroids is seen in at least 70% and the longer-term treated outcome in these patients is often good. Current smokers should be advised to quit. Respiratory bronchiolitis–interstitial lung disease (RB-ILD) As in DIP, the histological features of RB-ILD are dominated by the presence of pigmented macrophages, but unlike DIP, these ac- cumulate around the bronchioles (respiratory bronchiolitis; see Fig. 18.11.1.5), often with associated peribronchiolar inter- stitial inflammation and fibrosis, with preserved pulmonary Fig. 18.11.1.1 A case of fibrotic nonspecific interstitial pneumonia showing established interstitial fibrosis with a moderate degree of associated chronic inflammation. In areas of affected lung, the features appear homogeneous and diffuse, unlike appearances in usual interstitial pneumonia (see Chapter 18.11.2), and fibroblastic foci are not present. Fig. 18.11.1.2 HRCT appearances from the lower lung zone in a patient with biopsy-proven fibrotic NSIP. There is widespread ground-glass attenuation with mild traction bronchiectasis and, in some regions, a subtle admixed reticular element, resulting in a sense of increased texture within abnormal lung.

section 18 Respiratory disorders 4170 parenchyma. Typical HRCT findings include bronchial wall thick- ening, poorly defined centrilobular nodules, and patchy ground- glass attenuation and emphysema. RB-ILD is found only in current or recent former smokers and in many patients, there is overlap in histological features between RB-ILD and DIP. The histological appearances in RB-ILD are identical to those of asymptomatic re- spiratory bronchiolitis, which is always present in current smokers. The distinction between RB-ILD and respiratory bronchiolitis is based upon disease severity, as defined by symptoms, the se- verity of lung function impairment and the extent of disease on HRCT. RB-ILD is diagnosed when a clinically significant diffuse lung disease is considered to be present. It is increasingly recog- nized that RB-ILD may be diagnosed without surgical lung bi- opsy in smokers with the aforementioned HRCT features and a macrophage-predominance in bronchoalveolar lavage. The dis- order usually has a good outcome and often regresses with smoking cessation but based on limited data, corticosteroid therapy is seldom efficacious. Acute/subacute interstitial pneumonias Acute interstitial pneumonia Acute interstitial pneumonia, also known as the Hamman-Rich syndrome (or idiopathic adult respiratory distress syndrome), is characterized by a histological pattern of diffuse alveolar damage, with hyaline membranes lining damaged alveoli (Fig. 18.11.1.6) and buds of organization in the alveoli of those acini that have been damaged and are undergoing the healing process. Presentation is most commonly reported in the fifth or sixth decade, with no gender predilection. Symptoms are typically heralded by a viral prodrome, with progressive dyspnoea over days to weeks. There is widespread ground-glass consolidation, often with trac- tion bronchiectasis, and dependent consolidation on HRCT. Outcome is fatal in 80–90% of cases. Although high dose cortico- steroid therapy and immunosuppressive agents are commonly given, there is no evidence that treatment influences outcome in most cases. Fig. 18.11.1.3 A case of DIP with typical appearances of macrophage filling of alveolar spaces diffusely within pulmonary acini. There is also mild interstitial fibrosis and focal background emphysema, in keeping with the association between DIP and cigarette smoking. Fig. 18.11.1.4 HRCT appearances in a patient with histologically proven DIP. There is extensive ground-glass attenuation with no traction bronchiectasis or admixed reticular abnormalities. Although typical of DIP, these appearances are nonspecific, denoting a high likelihood of reversible inflammatory disease. Fig. 18.11.1.5 Biopsy from a patient with respiratory

bronchiolitis– associated interstitial lung disease showing macrophages with similar histological appearances to those of DIP, but the aggregation is centred on bronchioles where there is also a mild chronic inflammatory cell infiltrate within the airway walls.

18.11.1 Diffuse parenchymal lung disease 4171 Cryptogenic organizing pneumonia See Chapter 18.11.3. Rare idiopathic interstitial pneumonias Lymphocytic interstitial pneumonia The histopathological pattern of lymphocytic interstitial pneu- monia is most commonly found in patients with rheumatological disease and in immunodeficiency syndromes but can rarely occur as an idiopathic disorder. The histological findings consist of dif- fuse interstitial lymphocytic infiltration (Fig. 18.11.1.7), variably associated with follicular bronchiolitis. The HRCT features consist of patchy and sometimes extensive ground-glass attenuation with a variable nodular component. Corticosteroid and immunosuppres- sive therapy is effective in over 50% of cases. Pleuroparenchymal fibroelastosis Idiopathic pleuroparenchymal fibroelastosis is a rare condition characterized by histologic evidence of dense intra-alveolar fibrosis and corresponding prominent alveolar wall elastosis with fibrous thickening of the involved visceral pleura. Clinical presentation is often in the fourth or fifth decade of life, with no gender predilec- tion. Radiographic hallmarks are pleural and adjacent parenchymal fibrosis in a predominant upper lobe distribution. Symptoms in- clude cough and shortness of breath evolving over 6 months to years, with a significant number of patients having experienced recurrent infections and recurrent pneumothoraces. Disease pro- gression occurs in 60% of patients with death from disease in 40% in initial reports, although these series are dominated by severe dis- ease and are unlikely to be representative of the whole spectrum of pleuroparenchymal fibroelastosis. There is presently no effective treatment available. Diagnostic approach Diagnosis is complicated by the large number of disorders grouped within the diffuse parenchymal lung diseases. A systematic diag- nostic algorithm, based upon careful clinical evaluation and a logical sequence of tests, is essential. This approach can be broken down into in two phases: Phase 1 1 clinical history 2 clinical examination 3 chest radiography 4 pulmonary function tests 5 selective blood tests Phase 2 1 high-resolution computed tomography 2 bronchoalveolar lavage 3 lung biopsy Phase 1 Clinical history In most patients, the presentation is insidious dyspnoea, vari- ably accompanied by cough which is usually nonproductive. The duration of dyspnoea is diagnostically important: an acute pres- entation narrows the differential diagnosis considerably (see Table 18.11.1.2). Wheeze is a useful discriminatory symptom as the pres- ence of an airway-centred component informs the differential diagnosis. Disorders with variable but sometimes prominent wheeze include hypersensitivity pneumonitis, sarcoidosis, Fig. 18.11.1.6 A case of acute interstitial pneumonia (AIP) showing the exudative phase of diffuse alveolar damage with hyaline membranes lining alveolar walls, indicating AIP when present in an idiopathic setting. Fig. 18.11.1.7 A case of lymphoid interstitial pneumonia showing dense interstitial chronic inflammation diffusely involving the alveolar parenchyma, in this case associated with minimal interstitial fibrosis.

 lymphangioleiomyomatosis, and Langerhans cell histiocytosis. Other less frequent respiratory symptoms are also diagnostic- ally useful. Pleuritic chest discomfort often occurs in the rheum- atological diseases and occasionally in drug-induced disease, but never in idiopathic pulmonary fibrosis or hypersensitivity pneumonitis. Haemoptysis may be indicative of diffuse al- veolar haemorrhage due to capillaritis, occurring in certain dis- orders: haemoptysis may be trivial, even when haemorrhage is severe. A history of pneumothorax should prompt suspicion of cystic lung disease, especially Langerhans cell histiocytosis and

lymphangioleiomyomatosis. The previous medical history may provide crucial information, including diagnoses of rheumatological disease or other relevant systemic diseases (including vasculitis). Even when no previous sys- temic diagnosis has been made, the nature of preceding systemic symptoms may point strongly to a hitherto undiagnosed rheumato- logical disorder. Knowledge of underlying cardiac and malignant disease is also essential as disseminated malignancy and cardiac failure may both simulate diffuse parenchymal lung disease, clinic- ally and radiologically. A detailed list of medications serves to alert the clinician to the possibility of drug-induced lung disease. The agents most frequently responsible include nitrofurantoin, metho-trexate, and bleomycin but a long list of other drugs occasionally cause lung disease. The comprehensive website, pneumotox.com, provides a rapid and fruitful means of checking possible pulmonary toxicities. The occupational history should include all occupations from school-leaving: diseases caused by some exposures (including as- bestos exposure) manifest decades later. Environmental conditions in which pneumoconiosis most commonly arise include sawing, grinding, and drilling. Hypersensitivity pneumonitis arises from the inhalation of organic dusts including fungal contaminates of hay (as in farmers lung) and avian proteins found on the bloom and in the excreta of domestic birds. Many other organic antigens can give rise to hypersensitivity pneumonitis, with over 200 causes now recognized. Other relevant historical information includes foreign travel, which may raise the possibility of parasitic infection as an explan- ation of pulmonary eosinophilia. A history of cigarette smoking identifies a predisposition to Langerhans cell histiocytosis, DIP, and RB-ILD and is also a risk factor for exacerbations of pulmonary vas-culitis. Paradoxically, smoking appears to protect against the devel- opment of sarcoidosis and hypersensitivity pneumonitis. Clinical examination Digital clubbing is common in IPF and NSIP, and is not infre- quent in hypersensitivity pneumonitis, but is unusual in the other diffuse parenchymal lung diseases. Predominantly basal fine end inspiratory crackles are a cardinal feature of the CFA clinical syn- drome and are expected in IPF and variably present in the other idiopathic interstitial pneumonias. Sporadic crackles are heard in many diffuse parenchymal lung diseases, but are seldom present in sarcoidosis. Expiratory wheeze is indicative of airway disease. Inspiratory squawks are strongly predictive of hypersensitivity pneumonitis or obliterative bronchiolitis. In advanced disease, clinical evidence of secondary pulmonary hypertension should be sought, as oxygen supplementation may have a pivotal role in management. Relevant systemic findings include ocular disease (in sarcoid- osis or vasculitis), skin disease (in sarcoidosis or rheumatological disease), musculoskeletal signs (in rheumatological disease) and neurological abnormalities (mononeuritis multiplex in sarcoidosis, rheumatological disease, and vasculitis; a wide variety of central and peripheral signs in sarcoidosis). Chest radiography Chest radiography was formerly a central part of the evaluation of diagnosis of diffuse parenchymal lung disease. Although HRCT has now supplanted chest radiography in routine diagnosis, the chest radiograph continues to provide useful information. Radiographic findings suggestive of pulmonary fibrosis are a required feature of the CFA clinical syndrome. Patients with fibrosing lung diseases tend have reduced lung volumes. If other clinical features are indicative of IPF, normal-sized or large lungs on chest radiography are suggestive of the coexistence of emphy- sema and pulmonary fibrosis, a frequent association in cigarette smokers with IPF. Large or normal sized lungs on chest radiog- raphy, in association with nodular or reticular shadowing, also occur in Langerhans cell histiocytosis, lymphangioleiomyomatosis (a disorder involving smooth muscle proliferation arising in pre-menopausal women), and the closely related disorder, tuberous sclerosis. Idiopathic bronchiectasis or cystic fibrosis, with increased radiographic volumes due to hyperinflation, can also be mistaken radiologically for diffuse parenchymal lung disease, although the clinical profile of chronic purulent

sputum production is usually discriminatory. The distribution of disease is often helpful. Primary fibrosing disorders, including IPF, fibrotic NSIP, pulmonary fibrosis in rheumatologic disease and asbestosis, produce predominantly basal reticular or reticulonodular abnormalities, which may also be overtly peripheral when disease is not advanced. By contrast, granulomatous disorders, including sarcoidosis and hypersensitivity pneumonitis (as well as tuberculosis and allergic bronchopulmonary asbestosis) most often have a predominantly upper and mid zone distribution. In the correct clinical setting, chest radiographic findings typical of sarcoidosis (predominantly upper zone fibrotic change, variably associated with lymphadenopathy and hilar retraction towards the apices) often suffice for a confident diagnosis. The size and shape of abnormalities is sometimes diagnostically useful, although this aspect of radiological evaluation has largely been supplanted by HRCT. Chest radiographic nodules of more than 5 mm in diameter are often present in Wegener's granulomatosis, lymphoma, and other malignancies. Cavitating nodules are a frequent feature in Wegener's granulomatosis, but necrotizing carcinomas and multiple staphylococcal abscesses should also be considered. The presence of nodules of differing size and shape is strongly suggestive of metastatic malignancy. An alveolar filling pat- tern, consisting of widespread confluent shadowing, usually denotes the presence of life-threatening disease. The differential diagnosis includes pulmonary oedema (due to left ventricular failure or mi- tral stenosis), diffuse alveolar haemorrhage, uraemia, drug-induced lung disease (and other forms of diffuse alveolar damage), infection (especially opportunistic infection in immunosuppressed patients) and alveolar proteinosis. When widespread confluent shadowing is chronic, alveolar cell carcinoma, lymphoma, and pulmonary eo- sinophilia should also be considered.

18.11.1 Diffuse parenchymal lung disease 4173 Previous chest radiographs are often highly revealing, especially in the patient presenting with multifocal consolidation. Waxing and waning of consolidation effectively excludes malignant disease and is strongly suggestive of immunologically mediated disorders, including cryptogenic organizing pneumonia, vasculitis, and pul- monary eosinophilia. Fixed consolidation may also occur in all of these disorders but should also prompt suspicion of lymphoma, al- veolar cell carcinoma, and chronic infection. Pleural thickening, with or without effusion, occurs commonly in rheumatological disease, rheumatoid arthritis, and systemic lupus erythematosus. Pleural abnormalities also occur commonly in asbestosis and in Churg–Strauss granulomatosis and Wegener's granulomatosis. The presence of pleural disease should always prompt consideration of a second disease process, including ma- lignancy, heart failure, tuberculosis, pulmonary embolism, and drug-induced lung disease. Pleural involvement is not a feature of uncomplicated hypersensitivity pneumonitis or IPF and is seldom present in the other idiopathic interstitial pneumonias, although oc- casionally encountered in sarcoidosis and cryptogenic organizing pneumonia. Symmetrical hilar lymphadenopathy is usually indicative of sar- coidosis, but tuberculosis, lymphoma, and other malignancies should always be considered, especially if the changes are unilateral. Lymphadenopathy is seldom present on chest radiography in other diffuse lung diseases, with the exception of silicosis. Hilar calcifica- tion occurs in sarcoidosis, silicosis, and tuberculosis. Pulmonary function testing In most patients with diffuse parenchymal lung disease, there is a restrictive ventilatory defect with reduced gas transfer (DLCO). Arterial oxygen tensions (Pao2) are normal or mildly reduced until disease is advanced, although the alveolar–arterial oxygen gra- dient is often widened in associated with Paco2 levels that are at the lower end of the normal range. In early disease, maximal exercise testing may unmask abnormalities or, when normal, may reassure the clinician that the disease is not clinically significant. In IPF, maximal exercise testing typically a fall in the Pao2 and widening of the

alveolar–arterial oxygen gradient (A–a gradient), reflecting ventilation–perfusion mismatch and, at maximal exercise, impair- ment of diffusion. The anatomical dead space to tidal volume ratio (VD/VT) normally falls on exercise in the healthy individual but is unchanged or increases in restrictive lung disease. Striking rises in the VD/VT ratio are strongly suggestive of disproportionate pul- monary vascular limitation. A mixed (restrictive-obstructive) ventilatory defect is seen in dis- orders in which airway involvement is associated with diffuse par- enchymal lung disease. This ventilatory pattern most commonly occurs in hypersensitivity pneumonitis, sarcoidosis, and rheumato- logical disorders. The coexistence of pulmonary fibrosis and emphy- sema, usually found in cigarette smokers with IPF or fibrotic NSIP, may also give rise to a mixed ventilatory defect, but more commonly, there is spurious preservation of lung volumes and a dispropor- tionate reduction in DLCO. Blood tests Routine haematology and biochemical tests have little discrim- inatory value in the diffuse lung diseases. A peripheral blood eo- sinophilia (above 1.5 × 109/litre) is a prerequisite for diagnosis of Churg–Strauss vasculitis and may also be indicative of pulmonary eosinophilia (although not always present in that disorder). Increased levels of angiotensin converting enzymes are a helpful an- cillary diagnostic finding in some patients with sarcoidosis and may also confirm ongoing disease activity. Routine immunoglobulin es- timation may disclose hypogammaglobulinaemia in undiagnosed granulomatous disorders but has no diagnostic value in other dif- fuse lung disorders. Autoantibody testing is an essential part of routine evaluation. The presence of a positive antinuclear antibody, with specific extractable nuclear antigen profiles, or rheumatoid factor, may disclose an oc- cult systemic rheumatological condition. The autoantibody profile is sometimes indicative of the likely pattern of pulmonary involve- ment. In systemic sclerosis: the anti-DNA topoisomerase auto- antibody is often associated with clinically significant pulmonary fibrosis whereas the anticentromere antibody is linked to pulmonary vascular disease. The anti-t-RNA synthetase autoantibodies occur when polymyositis is associated with diffuse parenchymal lung disease. Other common associations include anti-Sm in systemic lupus erythematosus, SS-A, and SS-B in Sjögren’s syndrome and the anti-RNP autoantibody in mixed connective tissue disease. Mild increases in antinuclear antibody and rheumatoid factor titres are commonly found in IPF and idiopathic fibrotic NSIP but appear to have no clinical significance. Increased antineutrophil cytoplasmic antibodies with a cytoplasmic pattern are strongly suggestive of Wegener’s granulomatosis or microscopic polyangiitis. The peri- nuclear (pANCA) pattern is less discriminatory. The presence of specific precipitins to organic antigens is often diagnostically useful in hypersensitivity pneumonitis. However, positive precipitins are not, in isolation, diagnostic, confirming only the presence of immunological recognition. Avian precipitins, for example, are often present in healthy pigeon breeders. Moreover, the absence of precipitins does not exclude a diagnosis of hypersensi- tivity pneumonitis: avian proteins causing disease in an individual may be species specific or, even, specific to a single bird. Phase 2 High-resolution computed tomography High-resolution computed tomography provides a three- dimensional anatomical reconstruction of both lungs, resulting in improved diagnostic accuracy, compared to chest radiography. Several HRCT patterns can now be viewed as pathognomonic and HRCT is often diagnostic in other patients when the findings are integrated with clinical information. The diagnostic use of HRCT essentially consists of an evaluation of the distribution and pattern of disease. A detailed review of the rapidly enlarging HRCT litera- ture lies beyond the scope of this chapter and the reader is referred to sources listed in the ‘Further reading’ section. HRCT is much more sensitive than chest radiography, leading to the earlier diagnosis of limited disease. While this is sometimes highly advantageous, the sensitivity of HRCT sometimes causes its own problems. The detection of limited abnormalities in cigarette smokers, or when HRCT is used as a screening tool in rheumato-

logical disorders, sometimes leads to difficulty in assigning clinical significance to the findings. In this context, pulmonary function tests have a pivotal role but are sometimes difficult to interpret when functional impairment is minor, due to the wide normal range: a

section 18 Respiratory disorders 4174 forced vital capacity (FVC) of 75% of predicted can equally represent a minor fall or a major reduction from premorbid values of 80% and 120% of predicted, respectively. Absence of oxygen desaturation on maximal exercise testing is especially helpful in this scenario. A simple HRCT diagnostic algorithm can be usefully be ap- plied to apparently idiopathic diffuse lung disease. Confirmation of fibrosing disease is readily demonstrated by the presence of reticular abnormalities, anatomical distortion or, when ground-glass attenu- ation predominates, traction bronchiectasis. The essential prelim- inary question is whether HRCT appearances are typical of IPF (i.e. predominantly basal reticular abnormalities, with or without honeycombing, with little ground-glass attenuation). If not, it is ap- propriate to look for the HRCT features of fibrotic NSIP, sarcoidosis, hypersensitivity pneumonitis, and organizing pneumonia with fi- brosis, disorders which, with IPF, account for up to 95% of diagnoses in apparently idiopathic disease. When HRCT appearances are not typical of one of these disorders and disease is progressive, IPF with atypical HRCT features is the most frequent diagnosis made at sur- gical biopsy. HRCT has some other advantages. Even when the HRCT diag- nosis is uncertain, the signs of fibrosis listed earlier often make it clear that disease is irreversible. The identification of reversible dis- ease is less straightforward. Prominent ground-glass attenuation often denotes inflammation, but only when there is no admixed re- ticular pattern or traction bronchiectasis. HRCT is also invaluable in allowing the thoracic surgeon to select optimal sites for biopsy, by which means the full range of morphological abnormalities and disease severity can be sampled. Serial HRCT is sometimes useful in monitoring changes in disease severity, especially when pulmonary function trends are inconclusive, although HRCT should be used for this purpose in order to cast light on clinically important questions in individual patients and not performed rigidly by protocol. Finally, HRCT is often revealing when disease processes are ad- mixed. In rheumatological disorders and in smoking-related dis- ease, patterns of functional impairment are often complex and an assessment of the extent of interstitial disease allows a better understanding of the presence and likely functional impact of em- physema and airway disease. The complications of diffuse lung dis- ease are often disclosed by HRCT. Lung malignancy is increased in prevalence in fibrosing lung disease but can sometimes be difficult to detect on chest radiography when interstitial fibrosis is exten- sive. Infection is also sometimes masked in extensive disease, and this applies especially to aspergillomas, which tend to develop in fibrobullous sarcoidosis. Bronchoalveolar lavage When first employed, it was hoped that BAL might replace diag- nostic surgical biopsy or provide accurate prognostic information, and that serial BAL might disclose important changes in disease ac- tivity. Further evidence did not support these expectations, and the role of BAL has now been down-graded. However, BAL has an an- cillary diagnostic role in diffuse lung diseases and is also sometimes helpful in excluding infection. Granulomatous and drug-induced lung diseases are characterized by an excess of lymphocytes with or without granulocytes. The presence of a BAL lymphocytosis is oc- casionally pivotal in alerting the clinician to the possibility that a fibrosing process may be due to hypersensitivity pneumonitis or sar- coidosis. Bronchoalveolar lavage can also be diagnostic in some rare lung disorders, including alveolar proteinosis (milky effluent; PAS- positive material), Langerhans cell histiocytosis (increased numbers of Langerhans cells identified by CD1a staining), alveolar haemor- rhage (iron-laden macrophages) and hard metal lung disease (bi- zarre multinuclear giant cells). By contrast, a BAL

neutrophilia is an expected finding when pulmonary fibrosis is moderately exten- sive and has little diagnostic value, particularly where clinical and HRCT evaluation are characteristic of IPF. It appears increasing likely, based on recent data, that the observed linkage between dis- ease progression and a BAL neutrophilia in rheumatological disease reflects the presence of more severe disease, which is, itself, more likely to progress. BAL is an essential part of the diagnostic algorithm in patients pre- senting acutely with widespread interstitial abnormalities. Diffuse alveolar haemorrhage does not always manifest with haemoptysis but is readily disclosed by BAL. In patients receiving immunosup- pressive drugs, increased treatment may be urgently required in the hope of reversing disease progression. However, acute decompen- sation due to opportunistic infection may be excluded more confi- dently only with BAL. Lung biopsy Assessment of a surgical lung biopsy offers the important advantage that further investigation is unlikely to clarify the situation and a final diagnosis must now be made, integrating all clinical, radio- logical, and histological information. A confident diagnosis leads to more confident management, with a more accurate evaluation of the balance of risk and benefit with suggested treatments. Clinicians are better able to inform the patient of the likely natural history and treated course of disease. In many patients, a firm diagnosis can be made from clinical and HRCT data, and a surgical biopsy is redun- dant. In other cases, a biopsy is contraindicated by advanced age, the severity of disease, major comorbidity, or the wishes of the pa- tient. The acquisition of biopsies from more than one lobar site in- creases the likelihood of obtaining representative tissue. The limited thoracotomy approach used historically has now been supplanted by video-assisted thoracoscopic surgical procedures, which are less invasive, provide equivalently sized samples and are associated with less morbidity. The morbidity and mortality associated with diagnostic sur- gical biopsy are low provided that pulmonary reserve is adequate. However, postoperative mortality increases significantly when dis- ease is extensive and exceeded 15% in one IPF series in which the average level of functional impairment were severe. Thus, if the DLCO level is less than 35% of predicted, a surgical biopsy should be performed only if considered indispensable. The histological diag- nosis is, in any case, less prognostically useful in advanced disease. Mortality is very similar in IPF and fibrotic NSIP when DLCO levels are less than 35%, despite striking differences in survival when dis- ease is less severe. Transbronchial lung biopsies Transbronchial lung biopsies (TBLB) are most useful in diagnosing airway-centred disorders. In sarcoidosis and lymphangitis carcin- omatosis, the histological appearances are sufficiently characteristic to allow a confident diagnosis to be made from very small biopsy specimens. However, for most diffuse lung diseases, including the idiopathic interstitial pneumonias, their morphological complexity

 renders the overall pattern of disease difficult to meaningfully evaluate without a larger surgical biopsy. Over the recent years, transbronchial lung cryobiopsy (TBLC) has emerged as a promising new technique in the diagnostic evalu- ation of diffuse parenchymal lung disease. Originally developed to treat endobronchial tumours, TBLC confers the advantage of being able to harvest larger and architecturally better-preserved pieces of lung parenchymal tissue compared to TBLB. Several studies have reported improved diagnostic yield with TBLC compared to con- ventional TBLB; this enabled a definitive histological pattern to be identified with a high level of confidence in significantly more sam- ples harvested by TBLC than TBLB. Whether this translated to a change of initial consensus at diagnosis or enabled the multidiscip- linary team to reach a definitive diagnosis is less clear. Safety issues are also a concern, namely, a higher risk of significant bleeding, and to a lesser extent, pneumothorax, with TBLC. It was also noted that most studies excluded patients with a DLCO of less than 35%, where

surgical lung biopsy might have been contraindicated, thus not of- fering an advantage in this respect to patients with marginal lung function. At present, surgical lung biopsy remains the gold standard procedure for obtaining a histological diagnosis in diffuse paren- chymal lung disease but the reader is alerted to the possibility that TBLC may supplant surgical biopsy in the near future as more data are rapidly accumulated. Transbronchial needle aspiration In patients with suspected stage I and II sarcoidosis, transbronchial needle aspiration (TBNA) of intrathoracic lymph nodes by conven- tional TBNA or endosonography (endobronchial or oesophageal ultrasound -guided) may be a useful tool in detecting the pres- ence of noncaseating granulomas. In the largest yet multicentre randomized control trial comparing the diagnostic yield of bron- choscopy (with transbronchial or endobronchial mucosal bi- opsy) vs. endosonography for stage I and II sarcoidosis, the use of endosonographic nodal aspiration compared with bronchoscopic biopsy resulted in a greater yield (80% vs. 53%) with an equivalent safety profile. Key clinical issues Integrated diagnosis Although a histological diagnosis made at surgical biopsy was once viewed as definitive in diffuse parenchymal lung disease, it is now widely accepted that all clinical, radiological, and histopathological data must be integrated into the final diagnosis. The limitations of a histological diagnosis are now better understood. ‘Sampling error’ consists of the acquisition of nonrepresentative tissue: in some pa- tients with IPF, there are lung regions with the histological appear- ances of fibrotic NSIP, but this finding has no prognostic significance. Sampling error can be minimized by ensuring that large samples are taken, by sampling more than one site, and by selecting the sites of biopsy to sample the full range of disease morphology and severity, based on HRCT appearances. However, diagnostic variation be- tween pathologists remains problematic, with less agreement than documented with many clinically useful tests. Moreover, in some cases, there is ‘appropriate’ interobserver variation, reflecting the fact that histological appearances occasionally lie intermediate between classical entities. To complicate matters further, the diagnostic sig- nificance of a histological pattern is critically dependent upon the clinical context. For example, usual interstitial pneumonia is the re- quired histological pattern in IPF but sometimes has a better out- come when occurring in patients with rheumatological disorders, drug-induced lung disease, or hypersensitivity pneumonitis. Thus, the gold standard for diagnosis in diffuse parenchymal lung disease is now a multidisciplinary diagnosis, with participation by clinicians, radiologists and, when applicable, histopathologists. As a useful rule of thumb, in nonbiopsied cases the clinical and HRCT evaluation is, on average, equally influential, and careful clinical as- sessment should not be curtailed because of the ready availability of HRCT. In patients undergoing surgical biopsy, clinical and HRCT findings are usually inconclusive and the histological features tends to carry the most diagnostic weight. However, it is accepted that the final diagnosis should differ from the histological diagnosis in a significant minority of patients, when all available information is integrated. The principles of management The chronic diffuse parenchymal lung diseases can be broadly subclassified into five patterns of longitudinal disease behaviour, based upon cause, severity, the relative degree of inflammation and fibrosis, and observed change in the short term. Each clinical pattern is associated with a separate approach to management.

1. Reversible and self-limited disease is usually caused by an ex- trinsic agent (as in drug-induced disease, hypersensitivity pneu- monitis and RB-ILD) but may also be idiopathic as in a subset of patients with sarcoidosis. Disease usually responds to with- drawal of an offending agent, therapy is often unnecessary, and monitoring consists of confirming that disease has regressed.

2. Reversible major disease with risk of progression, with or without supervening fibrosis is often a feature of drug-induced lung dis- ease and this category also applies to some patients with crypto- genic organizing pneumonia, DIP, cellular and some fibrotic NSIP, hypersensitivity pneumonitis, and sarcoidosis. High-dose therapy is usual, often with corticosteroids, and the short-term response is quantified, often at four to six weeks. Once inflam- mation is controlled and the residual level of functional impair- ment has been quantified, treatment is gradually reduced with monitoring centred around serial pulmonary function tests, usually at three to four monthly intervals. In this way, the min- imum dose required to maintain control of disease is established.
3. Residual but stable fibrotic disease is most commonly encoun- tered in sarcoidosis, following drug-induced lung disease, and in patients with formerly active rheumatological disorders. Treatment is not required but long-term monitoring is needed to ensure that disease is truly stable, usually with serial pulmonary function tests until a long-term ‘track record’ of disease stability has been established.
4. Progressive fibrotic disease, in which stabilization is a realistic goal, is frequently seen in sarcoidosis, hypersensitivity pneu- monitis, rheumatological conditions, and in many patients with fibrotic NSIP. In this scenario, long-term therapy is often re- quired and long-term monitoring with serial pulmonary func- tion tests, often at increasing time intervals, is needed to ensure

section 18 Respiratory disorders 4176 that stabilization has been achieved and maintained. Aggressive initial treatment is usually warranted to ensure optimal control of disease activity. 5. Inexorably progressive fibrotic disease is the hallmark of IPF, but an IPF-like course is sometimes observed in idiopathic fi- brotic NSIP, rheumatological disease, and in a small subset of patients with chronic hypersensitivity pneumonitis. Long-term treatment may slow disease progression and reduce mortality, as evidenced by recent data on anti-IPF specific therapies (such as pirfenidone and nintedanib—discussed further in Chapter 18.11.2). The early realization that fibrotic disease may be relentlessly progressive, either because IPF is diagnosed or because disease continues to progress despite treatment, is especially important when lung transplantation or, in cases where this may not be possible, effective palliation, is realistic. Monitoring is performed to quantify disease progression, usu- ally at three to four monthly intervals. This schema is proposed in order to capture key thought processes of clinicians and to serve as a rationale for treatment and moni- toring decisions. In many cases, the pattern of disease behaviour is evident at presentation, but careful short-term observation is highly informative in other instances. When should a surgical biopsy be performed? A broad classification of disease behaviour also serves as a rational- ization of when to recommend a diagnostic surgical biopsy. When the underlying diagnosis is uncertain and the clinician is unable to assign likely disease behaviour, and therefore management is diffi- dent, a surgical biopsy is usually warranted (age, disease severity, and comorbidity permitting). However, if the diagnosis is uncertain but the pattern of disease behaviour is already clear, a diagnostic bi- opsy is much less likely to inform management. For example, when it is already known from previous investigations that fibrotic abnor- malities are long-standing and wholly stable, a histological diagnosis is unlikely to change management. When considering whether or not to recommend biopsy, it is useful to construct scenarios in which long-term management may differ significantly depending upon histological findings. It is important to reach an early decision. The empirical approach of initiating treatment, with recourse to biopsy if the response is unsat- isfactory, has serious flaws. Modification of the histological appear- ances by treatment may make diagnosis more difficult and, more importantly, deterioration during the interim period may make

the biopsy more hazardous, as well as increasing the likelihood of side effects to treatment, including postoperative infection and impaired wound healing. Thus, the best time to perform a biopsy is shortly after presentation, before treatment is instituted. FURTHER READING BAL Co-operative Group Steering Committee (1990). Bronchoalveolar lavage constituents in healthy individuals, idiopathic pulmonary fi- brosis, and selected comparison groups. Am Rev Respir Dis, 141, S169–S202. Bjoraker JA, et al. (1998). Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med, 157, 199–203. Bradley B, et al. (2008). Interstitial lung disease guidelines: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax, 63, Suppl. 5, v1–v58. Desai SR, Wells AU (2007). Imaging. In: Costabel U, du Bois RM, and Egan JJ (eds). Diffuse parenchymal lung disease, pp. 29–43. Karger, Basel. Flaherty KR, et al. (2001). Histologic variability in usual and nonspecific interstitial pneumonias. Am J Respir Crit Care Med, 164, 1722–7. Flaherty KR, et al. (2004). Idiopathic interstitial pneumonia. What is the effect of a multi-disciplinary approach to diagnosis? Am J Respir Crit Care Med, 170, 904–10. Joint American Thoracic Society and European Respiratory Society Group (2000). Idiopathic pulmonary fibrosis: diagnosis and treat-ment. International consensus statement. Am J Respir Crit Care Med, 161, 646–64. Joint American Thoracic Society and European Respiratory Society Group (2002). International multidisciplinary consensus classifica- tion of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med, 165, 277–304. Joint American Thoracic Society and European Respiratory Society Group (2013). Update of the international multidisciplinary con- sensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med, 188, 733–48. Katzenstein AL, Myers JL (1998). Idiopathic pulmonary fibrosis: clin- ical relevance of pathologic classification. Am J Respir Crit Care Med, 157, 1301–15. Liebow AA (1975). Definition and classification of interstitial pneu- monias in human pathology. In: Basset F, Georges R (eds). Progress in respiration research, pp. 1–33. Karger, New York. Muller NL, Colby TV (1997). Idiopathic interstitial pneumonias: high-resolution CT and histologic findings. Radiographics, 17, 1016–22. Nicholson AG, et al. (2004). Inter-observer variation between patholo- gists in diffuse parenchymal lung disease. Thorax, 59, 500–5. Nicholson AG, et al. (2000). The prognostic significance of the histo- logic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med, 162, 2213–17. Pajares V, et al. (2014). Diagnostic yield of transbronchial cryobiopsy in interstitial lung disease: a randomized trial. Respirology, 19, 900–6. Reddy TL, et al. (2012). Pleuroparenchymal fibroelastosis: a spec- trum of histopathological and imaging phenotypes. Eur Respir J, 40, 377–85. von Bartheld MB, et al. (2013). Endosonography vs conventional bronchoscopy for the diagnosis of sarcoidosis: the GRANULOMA randomized clinical trial. JAMA, 309, 2457–64. Wells AU (2003). High resolution computed tomography in the diag-nosis of diffuse lung disease: a clinical perspective. Semin Respir Crit Care Med, 24, 347–56. Wells AU (2004). Histopathologic diagnosis in diffuse lung disease: an ailing gold standard. Am J Respir Crit Care Med, 170, 828–9. Wells AU, Hansell DM, Nicholson AG (2007). What is this thing called CFA? Thorax, 62, 3–4.

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