Idiopathic Pulmonary Fibrosis May Be a Disease of Recurrent, Tractional Injury to the Periphery of the Aging Lung

A Unifying Hypothesis Regarding Etiology and Pathogenesis

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• ***Context.*—Idiopathic pulmonary fibrosis is a progressive, fatal lung disease occurring in older individuals. Despite 50 years of accrued data about the disease, little progress has been made in slowing functional loss or in decreasing patient mortality.**

***Objective.*—To present a novel hypothesis on the etiology and pathogenesis of idiopathic pulmonary fibrosis.**

***Design.*—Published data are reviewed regarding the epidemiology, clinical presentation, natural history, radiologic findings, and pathologic findings in patients with idiopathic pulmonary fibrosis.**

***Results.*—Patients with idiopathic pulmonary fibrosis may be predisposed genetically to tractional injury to the peripheral lung. The result is recurrent damage to the epithelial-mesenchymal interface, preferentially at the outer edges of the basilar lung lobules where tractional stress is high during inspiration, compliance is relatively low, and there is a greater tendency for alveolar collapse at end-expiration. A distinctive ''reticular network of injury'' (the *fibroblast focus*) forms, attended by a prolonged phase of wound repair (*tear and slow repair*). Discrete areas of alveolar collapse are observed in scar at the periphery of the lung lobules. The cycle repeats over many years resulting in progressive fibrous remodeling and replacement of the alveoli in a lobule by bronchiolar cysts surrounded by scar (*honeycomb lung*). Abnormalities in surfactant function are proposed as a potential mechanism of initial lung damage. Age of onset may be a function of a required threshold of environmental exposures (eg, cigarette smoking) or other comorbid injury to the aging lung.**

***Conclusions.*—Evidence supporting this hypothesis is presented and potential mechanisms are discussed. A potential role for contributing cofactors is presented.**

(*Arch Pathol Lab Med.* 2012;136:1–10; doi: 10.5858/arpa.2011-0511-OA)

Idiopathic pulmonary fibrosis (IPF) is a specific form of progressive, fibrosing interstitial pneumonia of unknown etiology, occurring most frequently in older men, and confined to the lungs.[1,2] The prognosis historically for patients with IPF rivals that of many forms of cancer, with median survival estimates at less than 3.5 years from diagnosis. Clinical trials of potential treatments have failed to affect the progression of disease or the survival in patients with IPF, despite substantial advances in immunomodulatory and antifibrotic therapies.[3]

Most human diseases that are characterized by slowly progressive tissue fibrosis have underpinnings in pathologic inflammatory reactions. The best-known examples of these are the rheumatic autoimmune diseases, where tissue damage is mediated by immune dysfunction directed at self-antigens.[4] These diseases have served as excellent models for understanding immune system disorders and for designing effective anti-inflammatory treatment strategies. For patients with IPF, decades of empiric immunosuppressive therapy and more than 20 years of clinical trials with immunosuppressive and antifibrotic agents have led to the now widely held conclusion that IPF is not inherently an inflammatory disease, in contrast to previous assertions.[5] Moreover, the established fibrosis that occurs in IPF does not appear to be reversible using any therapies tested thus far.[2,6]

Current lines of research in IPF are focused on the molecular genetics of pathologic events likely occurring at the epithelial-mesenchymal interface of the alveolus.[7–12] Based on data derived from the study of samples from patients with IPF and in vitro laboratory investigations, researchers have concluded that IPF may be mediated by shortened survival of lung epithelial cells,[10] prolonged survival of myofibroblasts activated by unknown injury, or both.[11] None of the approaches have attempted to reconcile the complete body of evidence regarding the known clinical, radiologic, and histopathologic aspects of the disease. With an abundance of sophisticated laboratory methodology available, it is easy to lose sight of the data accrued on patients with IPF from decades of study. In the pages that follow, the key observational data related to IPF are presented, and

Accepted for publication October 11, 2011.

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The author has no relevant financial interest in the products or companies described in this article.

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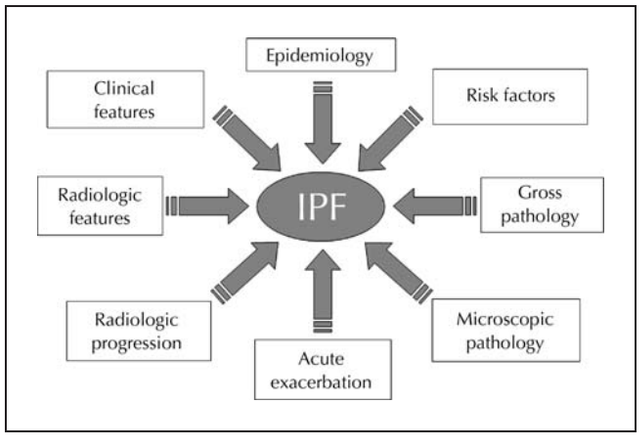

Figure 1. *Essential data to be incorporated in a hypothesis on etiology and pathogenesis of idiopathic pulmonary fibrosis (IPF).*

from these, a working hypothesis on the etiology and pathogenesis is proposed (Figure 1). A role for contributing cofactors is discussed.

EPIDEMIOLOGY OF IPF

At the beginning of the past century, pathologists encountered a diffuse lung disease in postmortem examinations, where the lungs were shrunken, cystic, and accompanied by fibrosis (so-called honeycomb fibrosis or simply honeycomb lung) (Figure 2, A and B). In time, this honeycomb remodeling was discovered to occur as a result of many different types of injury, but the mechanisms for that fibrosis remained elusive.[13,14]

We now recognize an idiopathic form of chronic, progressive, fibrosing interstitial pneumonia occurring primarily in adults and refer to it clinically as *IPF*. Idiopathic pulmonary fibrosis is a relentlessly progressive disease of older individuals, limited to the lungs, and associated with cigarette smoking, frequent history of dust and other environmental exposures, and ultimately, honeycomb transformation of the lungs. There is a male predominance and an estimated annual incidence of 30 000 in the United States, with a prevalence of 80 000.[2,15] The true incidence and prevalence in other countries remains unknown and few population-based studies are available.[16] The mortality data from previous studies suggest a median survival following diagnosis of 3.2 years, rivaling many forms of cancer. A familial form of unexplained lung fibrosis is described but occurs much less frequently and affects slightly younger patients.[17–23] Key questions that arise regarding the epidemiology of IPF are presented in Table 1.

Table 1. Key Questions Regarding the Epidemiology of Idiopathic Pulmonary Fibrosis (IPF)

Why is IPF a disease of older individuals?
Why are men more often affected than women?
Is there a significant preclinical phase? If so, how long does it last?
What is the true prevalence of the disease?
Are the familial and sporadic forms related?
Is IPF the same disease worldwide?

CLINICAL FEATURES AND NATURAL HISTORY OF IPF

Patients with IPF are typically older than 50 years at the time of their clinical presentation, although the age distribution, at presentation, is quite wide.[1] Slowly progressive breathlessness, especially with exertion, is the most common clinical complaint. Nonproductive cough is typically present and can be a difficult component of the disease to manage. Laboratory studies may show mild nonspecific elevation of antinuclear antibodies, but serology diagnostic of defined rheumatic disease is, by definition, absent. Pulmonary function testing most consistently reveals restrictive physiology, with decreased total lung capacity, forced vital capacity, and diffusing capacity for carbon monoxide. Oxygen desaturation with exercise is commonly present and the degree of desaturation during the 6-minute walk test has been shown to have prognostic value for the individual patient.[24] Patients with IPF suffer progressive decline in pulmonary function over the course of their illness. Functional decline may be episodic and unpredictable, with long periods of apparent stability expected. With each decline, patients may stabilize but never experience improvement in measured function.[1,2]

CLINICAL, ACUTE EXACERBATIONS OF IPF

Idiopathic pulmonary fibrosis seems to have 2 patterns of decline in lung function; one being slow and insidious and the other being episodic and more severe. When an episode of decline progresses with sufficient rapidness to demand clinical attention, the term *acute exacerbation of IPF* has been applied.[25] The causes of acute exacerbations remain unknown, despite ample hypotheses as to etiology, clinical predictors of outcome, and potential mechanisms of injury.[26–29] Infection seems not to be a common initiating factor.[30] A recent study suggested subclinical aspiration as a plausible cause, based on right-left asymmetry of the exacerbation on imaging correlated to the patient's preferred side for sleeping.[31] Key questions related to risk factors and clinical manifestations of IPF are presented in Table 2.

IMAGING STUDIES OF IPF

With the advent of high-resolution computed axial tomography (HRCT), a consistent picture of IPF has emerged.[2] This is a disease of the basal and peripheral lungs that progresses centrally and toward the lung apices over time. The characteristic appearance is that of patchy, coarse, subpleural reticulation; distortion of lung architecture; and the presence of pleural-based cysts, a required feature for a confident diagnosis of what thoracic radiologists refer to as *usual interstitial pneumonia*'' (UIP).[32] The term *UIP* is not a radiologic term but a histopathologic one, first coined by Averill Liebow[33] in his original description of the pathology of the ''usual'' and most common form of lung fibrosis occurring in adults (discussed

Table 2. Key Questions Regarding the Clinical Presentation and Characteristics of Idiopathic Pulmonary Fibrosis (IPF)

Why is cigarette smoking reported by most patients?
Why are dust and other inhalational exposures so common?
Does gastroesophageal reflux (or microaspiration) play a role in the etiology of IPF?
Does gastroesophageal reflux (or microaspiration) play a role in the progression of IPF?
Why do patients with IPF have a nonproductive cough?
What are ''acute exacerbations'' of IPF, and are they a consequence of the underlying disease?
Do all patients with IPF develop acute exacerbations?

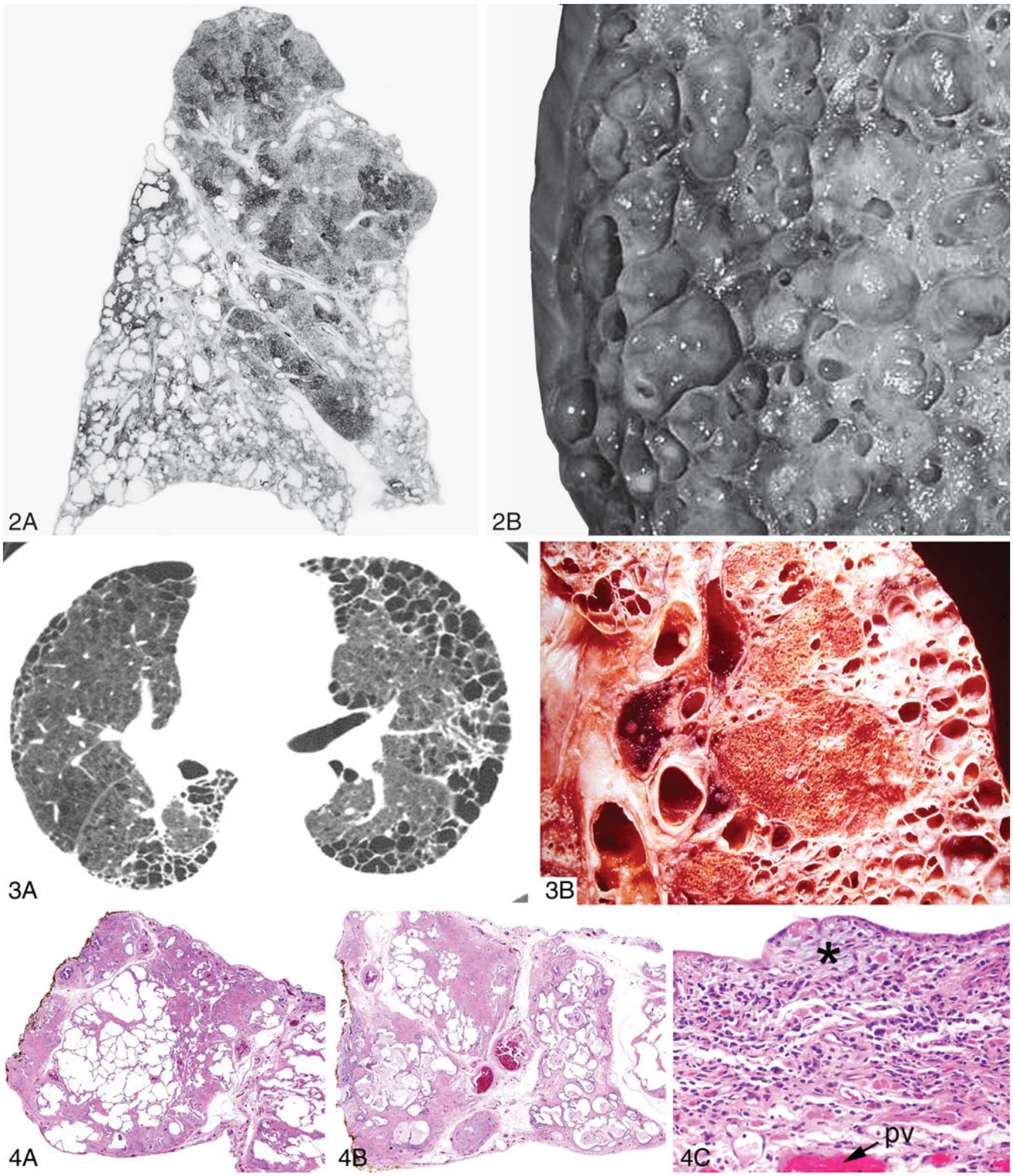

Figure 2. *Gross honeycomb lung. A, Paper-thin Gough-Wentworth section of whole lung from a patient with idiopathic pulmonary fibrosis (IPF). Note the near-total replacement of the lower lobe by honeycomb cysts and relative sparing in the upper lobe (Courtesy of the Charles B. Carrington, MD, Memorial Lung Pathology Collection—received originally from Jethro Gough, MD). B, Gross autopsy lung from a patient with IPF showing rigid, distended subpleural cysts surrounded by fibrotic lung. Reprinted with permission from Practical Pulmonary Pathology: A Diagnostic Approach. Leslie KO, Wick MR, eds; 2nd ed., page 219; by Elsevier, copyright 2011.*

Figure 3. *Comparison of high-resolution computed axial tomography (HRCT) and gross lung honeycomb patterns. A, This HRCT demonstrates the characteristic features of usual interstitial pneumonia (UIP). Note the asymmetry of peripheral honeycomb cysts (image courtesy of Richard Webb, MD). B, Gross pathology of advanced honeycomb fibrosis in UIP. The confluent honeycomb cysts form a band under the pleura and extend into the lung along interlobular septa.*

Table 3. Key Questions Regarding the Radiologic Features of Idiopathic Pulmonary Fibrosis (IPF)

Why is this disease asymmetrical, despite consistent involvement of both lungs?
Why does reticulation begin at the pleura and first involve the lung bases?
Why are the reticulations in usual interstitial pneumonia ''heterogeneous'' in both distribution and density along the pleura?
Why does the disease affect the posterior lung more than it does the anterior portions?
What are honeycomb cysts, and are they related to nearby traction bronchiectasis?

below). On HRCT, subpleural disease is variable in distribution along the pleura, with skip areas occurring frequently (''broken sawtooth pattern'' according to M. Maffessanti, MD, and G. Dalpiaz, MD, oral communication, 2009) and some asymmetry from side to side expected. When subpleural honeycombing is identified at the bases, increased reticular lines are nearly always present in the upper lung zones.[2] A gradient toward the apex occurs, with abnormalities accruing from base toward the apex as the disease progresses.

Today, a characteristic HRCT in the appropriate clinical and physiologic setting obviates the need for a surgical lung biopsy in most practice settings (Figure 3, A and B). When IPF is a clinical concern, a less-than-diagnostic HRCT scan may be overridden by a diagnostic surgical lung biopsy (ie, UIP histopathology precedes UIP radiology).[34] Key questions that must be addressed regarding the radiologic characteristics of IPF are presented in Table 3.

HISTOPATHOLOGY OF IPF

Before the common availability of the surgical lung biopsy and lobar resections for lung diseases, the histopathologic attributes of IPF in its earlier stages were unknown. Liebow[33] was the first to describe a pattern of lung fibrosis in biopsies and autopsy lungs that he recognized as the *usual* (ie, most common) form of lung fibrosis. For Liebow, this UIP was heterogeneous in causation, with roughly half of cases being idiopathic. We now recognize UIP as the histopathologic manifestation of IPF.[2,35] Unfortunately, decades of confusion have accumulated regarding the histopathology of UIP, both for pulmonologists and for pathologists alike.

In patients with clinical and radiologic IPF, UIP is a distinctive and highly recognizable pattern of lung fibrosis. However, when trying to establish a histopathologic diagnosis of UIP, many different forms of advanced lung fibrosis tend to be lumped together and called *UIP*. Usual interstitial pneumonia in IPF has a distinctive histopathologic appearance, with a ''patchwork'' pattern of scar formation alternating with zones of normal lung in the biopsy, referred to as *temporal heterogeneity*.[35,36] In this formation, fibroblast foci (FF) exist at the interface between fibrosis and uninvolved lung, and microscopic honeycombing is nearly always present, in the classic example, even when the burden of fibrosis in the biopsy seems small (Figure 4, A through C).

Currently we recognize that a *UIP pattern* of disease can occur in other conditions, such as in some patients with rheumatoid arthritis[37] and chronic hypersensitivity pneumonitis,[38] but when this occurs, the fidelity of the UIP pattern often is not as robust as that seen in IPF (eg, more inflammation, less peripheral lobular distribution, more airway-centered inflammation and scarring). A patchwork of scar seems to result in these diseases as a late manifestation of airway-centered scarring where fibrosis extends from the center of lobules to their periphery.

In patients with IPF, UIP histopathology in lung specimens recapitulates the patchy, peripheral lobar distribution seen on HRCT distribution. Under the microscope, coarse, peripheral, *lobular* fibrosis is characteristic. Partially or completely scarred lobules, devoid of alveolar spaces, are present. In this scar tissue, small cysts lined by respiratory epithelium are seen, surrounded by airway smooth muscle. These *microcysts* are connected to the more-proximal airways and, with continued respiration, form into larger cysts. These are the presumptive precursors to the macroscopic cysts visible on imaging (Figure 5).

Another hallmark of UIP is the *fibroblast focus*, a microscopic patch of fibroblastic repair found in variable numbers at the edge of established scar. A recent 3-dimensional reconstruction study has shown that the fibroblast focus in UIP is not a discrete focus but an interconnected ''reticulum of repair'' (Figure 6, A and B).[39]

The occurrence of similar structures in other forms of lung pathology suggests that these are lines of tractional injury to the epithelial-mesenchymal interface of the peripheral alveoli (Figure 7, A and B).

In all lung biopsies of UIP, the FF have a very similar appearance in 2-dimensional sections, which is remarkable unless they all form at the same time (days before biopsy), or they exist for prolonged periods as immature fibroblastic ''plugs'' without complete resolution. If this were not the case, one would expect to see progressively less cellular and collagenized FF in any given lung biopsy specimen as a natural part of the well-documented 10 to 14 day natural cycle of wound repair. Key questions that arise from the pathology of UIP in IPF are presented in Table 4.

NEED FOR A UNIFYING HYPOTHESIS

The clinical, radiologic, and histopathologic observations in IPF present a distinctive and possibly unique picture. These demand our attention and must be accounted for as we move forward in our exploration and eventual understanding of this disease. Based on this

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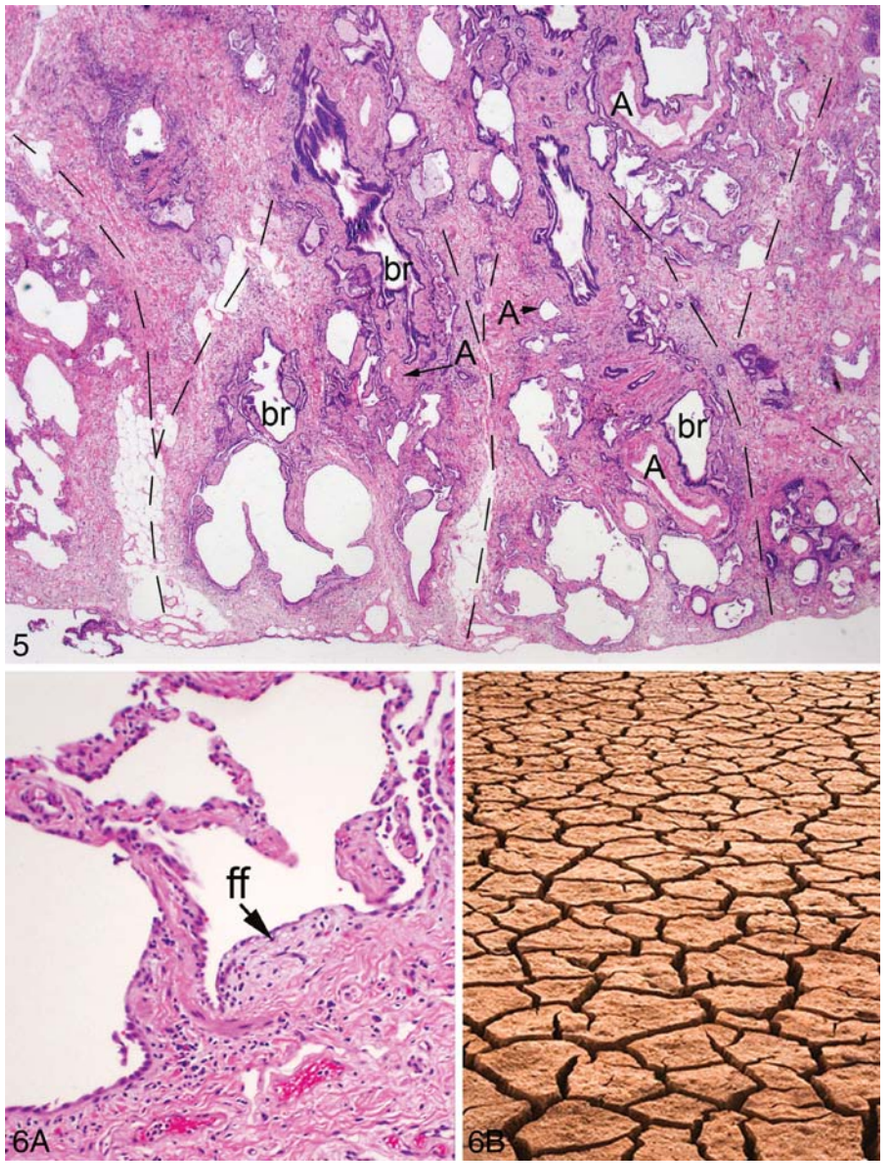
Figure 4. *Usual interstitial pneumonia. A, At very low magnification, a ringlike pattern of peripheral lobular scarring with central preserved lung distorted by traction emphysema. B, Another patient with idiopathic pulmonary fibrosis, showing the variable involvement of lobules by fibrosis and microscopic honeycombing. C, The fibroblast focus (asterisk), which usually appears as shown in this tissue section: a ''bulge'' of immature fibroblasts in pale, myxoid stroma, covered by a layer of reactive type 2 cells, variable chronic inflammation, with dense fibrosis beneath. The dilated veins at the bottom of the figure are in pleura in this photograph (pv) (hematoxylin-eosin, original magnifications ×12.5 [A and B] and ×200 [C]).*

Figure 5. *Histopathology of advanced lung remodeling in idiopathic pulmonary fibrosis (IPF). The lung lobules are outlined (dashed lines) to emphasize the residual lobular architecture in the advanced remodeling of IPF. This final stage of alveolar destruction causes a diminution of the lobular size and an overall decrease in lung volume. Note the residual pulmonary arteries (A) and bronchioles (br). A few dilated alveolar ducts remain but the alveoli are conspicuously absent (hematoxylin-eosin, original magnification ×12.5).*

Figure 6. *Two-dimensional (2D) versus 3-dimensional (3D) representations of fibroblast foci (ff). A, The ff in 2D tissue sections has been shown in 3D reconstruction to be a reticulum of interconnected repair, similar to the cracks that form in a dry river bed (B) (hematoxylin-eosin, original magnification ×200 [A]). B, Photograph of dry river bed, courtesy of photographer Peter Pallagi, Gilbert, Arizona (no copyright).*



body of evidence, a unifying hypothesis for the etiology and pathogenesis of IPF is proposed.

HYPOTHESIS

Idiopathic pulmonary fibrosis is a disease of recurrent stretch injury to the peripheral and basal lung occurring over many years in predisposed individuals. The tractional forces related to respiration are highest in the areas where disease appears first on chest imaging and in pathologic examination, corresponding to regions prone to physiologic alveolar collapse at rest. Inherited or acquired abnormalities in surfactant function likely play a role, given this lipoprotein's unique role in reducing tractional injury related to alveolar collapse and rapid reopening during respiration.

Some Key Observations Addressed by This Hypothesis

IPF Is a Disease of Older Adults.—The actual age of onset and speed of progression could be influenced by the type and amount of exposure accrued during a patient's lifetime. Most patients with IPF are prior cigarette smokers or report other inhalational exposures. Factors other than inhalational injury may also be at play, such as autoimmune inflammatory disease. The patient predisposed to develop IPF may have their disease modified by such events (eg, UIP in asbestos is IPF with asbestos exposure, UIP in rheumatoid arthritis is IPF modified by rheumatoid lung disease, etc). This idea is appealing because UIP pattern fibrosis is not the *common* manifestation of any of these diseases in the lung. Logically, if surfactant abnormalities are genetically programmed in patients with IPF, any defect would need to be sublethal and possibly activated or exacerbated later in life to explain the observed onset of clinical disease.

IPF Produces Peripheral and Bibasilar Abnormalities on HRCT.—The posterior lung bases are a region naturally predisposed to alveolar collapse at rest. When the alveoli are pulled open by the actions of the chest wall and diaphragm, mechanical forces are high at the pleural surface, and these must be transmitted to the deeper

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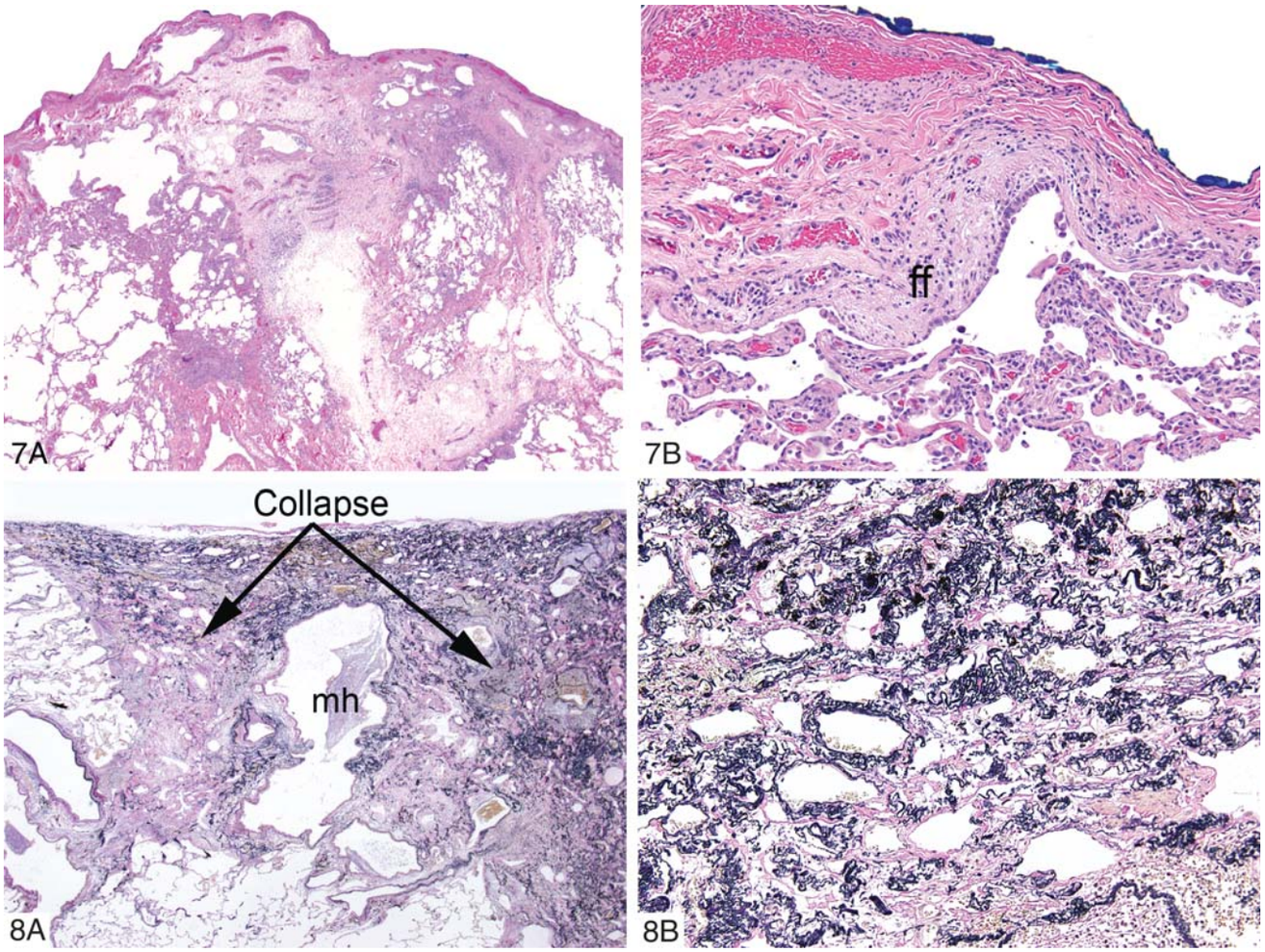

Figure 7. *Fibroblast foci in recurrent pneumothorax. Slides from a 22-year-old woman with recurrent pneumothorax that required surgical intervention to repair. A, At very low magnification, thick areas of subpleural fibrosis extend into the underlying lung. B, At higher magnification, fibroblast foci (ff) are seen at the edge of scar (hematoxylin-eosin, original magnifications ×12.5 [A] and ×200 [B]).*

Figure 8. *Alveolar collapse in idiopathic pulmonary fibrosis (IPF) demonstrated by elastic tissue stains. A, The established fibrosis surrounding microscopic honeycomb (mh) cysts is laced with coiled and convoluted elastic tissue fibers suggesting alveolar collapse in collagen (staining eosinophilic). B, At higher magnification, abundant black elastic tissue fibers speak to condensation of normal alveolar elastic tissue embedded in pink collagen fibers (Movat pentachrome, original magnifications ×12.5 [A] and ×200 [B]).*

lobules rapidly and efficiently.[40,41] In the patient with IPF, a combination of mechanical stress in the periphery and an increased tendency for alveolar collapse in the same regions occurs. These factors act together to cause lines of shear stress and fracture of the epithelial-mesenchymal interface because collapsed alveoli are suddenly pulled open during inspiration. The notion of alveolar collapse in IPF is not new. Myers and Katzenstein[42] demonstrated ultrastructurally that foci of epithelial necrosis occur in UIP attended by complex alveolar infolding consistent with collapsed alveolar walls (see further discussion below in ''Microscopic Honeycombing Is a Marker for Complete Alveolar Destruction of a Lobule''). Later, Galvin and Franks[43] reviewed the distribution conundrum of IPF in an excellent radiologic-histopathologic analysis of IPF and supported the notion of alveolar collapse in IPF. In their 2010 article they wrote[43(p697)]: ''Structures with a smaller radius of curvature and subsequent increased surface tension are unstable and thus more likely to collapse. Once initiated, the process, powered by the increasing disparity between the enlarging alveolar ducts and the collapsing small alveoli that surround them, is more likely to continue.''

This alveolar-collapse model would also help explain the tendency for disease to accrue microscopically at the periphery of lung lobules in UIP, given similar mechanical requirements during inhalation for transmission of outward force along a gradient from the periphery toward the lobule center.[40]

Without an animal model of the disease, we can only speculate on the exact sequence of events involved. How the formation of a reticulum of stretch injury in the peripheral lung (and peripheral edges of the lobules within) leads to persistent alveolar collapse is not clear from any available data and remains the missing piece to the puzzle. We can appreciate the steps before and after collapse in static lung tissue sections, but not the act of collapse. The presence of a complex elastic tissue matrix in fibrotic areas of UIP suggests the elastic fibers of collapsed alveolar walls and provides visual support for that being

Table 4. Key Questions Regarding the Gross and Microscopic Features of Idiopathic Pulmonary Fibrosis (IPF)

Why does microscopic fibrosis affect the periphery of the lung lobule?
Why are portions of the lobules commonly spared in surgical lung biopsies?
Do other diseases manifest a ''UIP-pattern'' of histopathology? If so, what are their similarities and differences?
Why are gross honeycomb cysts subpleural?
What is microscopic honeycombing, and how is it related to the cysts seen on chest imaging?
Why is microscopic honeycombing present in UIP biopsies, even when little overall fibrosis is evident?
What is the fibroblast focus?
How can we account for an injury mechanism if the fibroblast focus is actually a network of linear injury?
Does a fibroblast focus occur in other lung diseases? Are there characteristics common to all diseases where a fibroblast focus occurs?
Why does a fibroblast focus always seem to be at the same ''stage'' of repair?
Why is diffuse alveolar damage the most common finding when patients with IPF develop so-called acute exacerbations?

Abbreviations: UIP, usual interstitial pneumonia.

the mechanism of alveolar attrition in the disease (as opposed to destruction by dissolution) (Figure 8, A and B).

Another consequence of lobular alveolar collapse and scar formation at the edges of the lung lobules may be reflected in the greater-than-expected incidence of pulmonary hypertension in IPF[44,45] and the peculiar observation that pleural effusions rarely (if ever) occur in patients who have been diagnosed with IPF (R. Webb, MD, oral communication, 2007). The progressive collapse of peripheral lobular alveoli in scar may ultimately slow or impede the passage of venous blood and interstitial fluid into collecting channels of the interlobular septa and across the visceral pleura. This ''blockage'' in IPF appears to be effective even under the increased hydrostatic pressure produced by heart failure.

Surfactant Abnormalities Have Been Identified in IPF Patients.—Ample data exist regarding lavage and serum surfactant abnormalities in IPF, but those studies have, until now, lacked a mechanism to explain how such abnormalities might initiate or contribute to disease pathogenesis.[46–56] Surfactant is implicated in the pathogenesis of IPF for several reasons. First, it is unique to the lung (like IPF). Surfactant plays a critical role in preventing alveolar collapse at end-expiration and reduces alveolar surface tension during inspiration, thereby, increasing the mechanical efficiency of respiration.[57] Less than complete failure in these 2 functions might be survivable into adult life. Second, premature infants deficient in surfactant develop diffuse alveolar damage early after beginning respiration.[58] This likely occurs from global alveolar trauma related to high alveolar surface tension during inspiration, but a role for an alternate consequence of surfactant deficiency in this setting is difficult to discount. Third, the natural properties of this lipoprotein are highly complex and affect alveolar health on several levels, including defense.[59] Fourth, heritable forms of surfactant dysfunction have been reported to produce interstitial lung disease and possibly UIP in a subset of patients with familial idiopathic interstitial pneumonia.[17,60] The specifics of this surfactant dysfunction are unknown in IPF but may be similar in mechanism to the recognized forms of inherited lung disease related to aberrations of surfactant.[23,59,60]

A Reticulum of FF Occurs at the Periphery of the Lung Lobules in IPF.—In IPF, FF occur most consistently in direct apposition to the scarred matrix because they exist as a marker for stress fracture to the epithelial-mesenchymal interface at the alveolar surface (Figure 9, A and B). Fibroblast foci can be observed in other lung diseases, most often where shear stress is known to occur. The best example of this was demonstrated earlier (Figure 7, B) in the otherwise healthy young individual, who developed recurrent spontaneous pneumothorax. The 3-dimensional configuration of FF in non-IPF settings remains to be discovered. An unexplained peculiarity of FF in UIP, and in other conditions where they can be observed, is their remarkably consistent appearance under the microscope. This peculiarity might not be immediately intuitive. The lack of transitional lesions reflecting later events in wound repair is remarkable and likely speaks to some degree of disordered wound repair at these sites.[61] Alternatively, the constant motion created by respiration may create in the lung a unique setting for wound repair. Organizing pneumonia provides a more common (but morphologically different) pathway for repair in the lung with the formation of fibroblastic polyps *within* alveolar spaces and terminal airways. Although FF are distinctive in UIP, the possibility that they might be an epiphenomenon simply related to fibrosis and tractional stress cannot be completely discounted.

Microscopic Honeycombing Is a Marker for Complete Alveolar Destruction of a Lobule.—The idea that honeycomb remodeling results from dilation of the small intralobular airways is not new.[13,14] Rudimentary 3-dimensional reconstruction of honeycomb lungs, more than 40 years ago, suggested this mechanism. Also, the lining of microscopic honeycomb cysts in IPF is, in fact, airway respiratory mucosa, and the walls of these cysts resemble the smooth muscle of the terminal airway. In the advanced fibrosis in IPF, the only components missing are the alveolar spaces. Entire regions of the peripheral lung are composed entirely of closely apposed respiratory bronchioles and pulmonary arteries, embedded in a fibrous matrix replete with elastic tissue, resembling collapsed and fused alveolar walls. Once the alveoli in a lobule have fully collapsed and become incorporated into the scar, continued respiratory motion presumably causes progressive dilatation of the residual respiratory bronchioles until grossly (and radiologically) visible cysts form (Figure 10, A and B). Microscopic honeycombing appears to precede radiologic honeycombing by a yet to be defined period (likely, many years, based on anecdotal observations and limited retrospective studies).

Gastroesophageal Reflux Disease and Occult Microaspiration in IPF.—Gastroesophageal reflux disease is common in patients with IPF, although it is often discounted as a secondary consequence of lung fibrosis with resultant increased pressure gradients across the diaphragm. As early as 1998, Tobin and colleagues[62] described a high incidence of gastroesophageal reflux disease in patients with IPF and proposed a role for it in the pathogenesis of the disease. Although it seems reasonable to assign an important potential role for

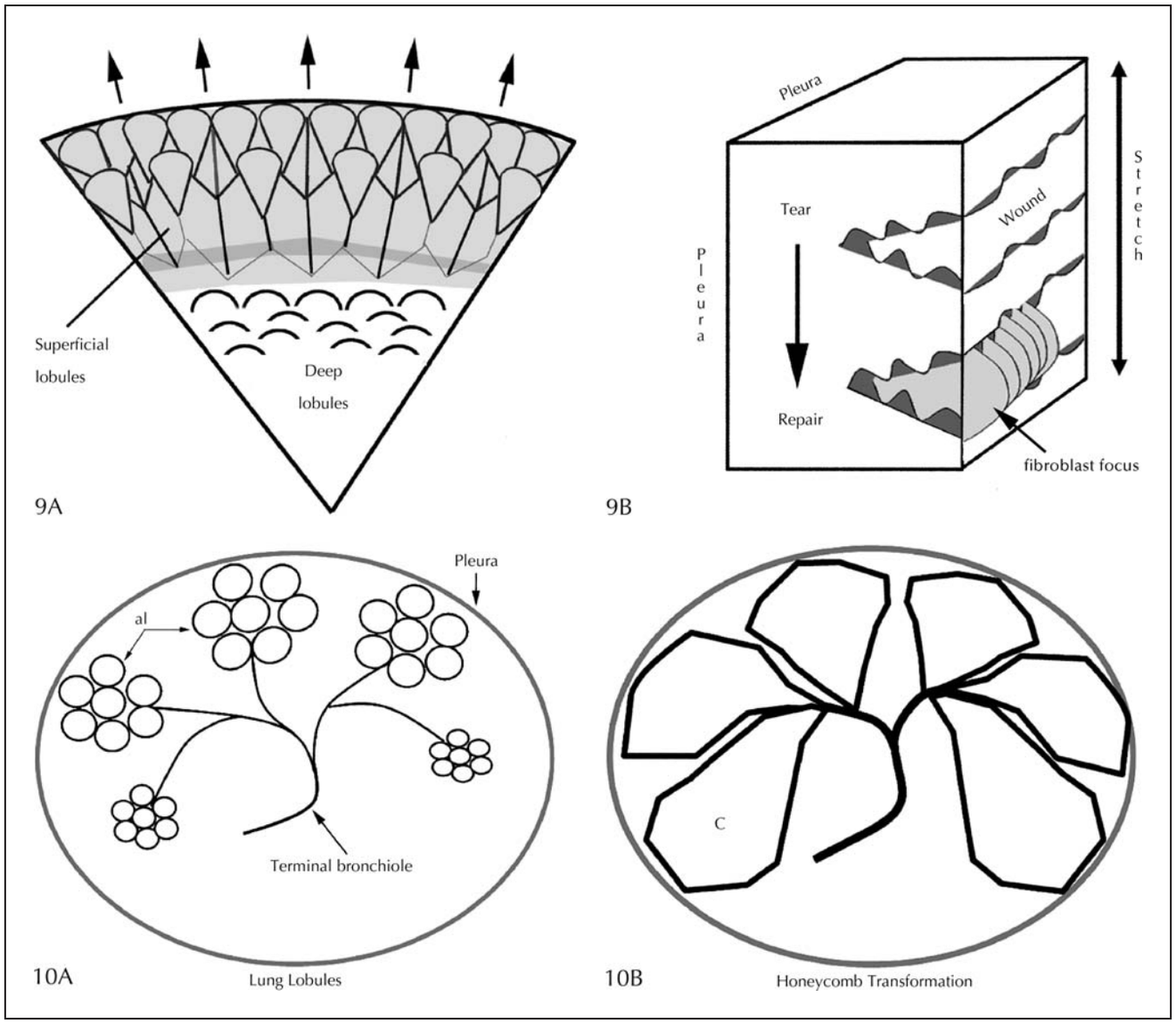

Figure 9. *Lung architecture at the periphery and proposed mechanism of stretch injury. A, Schematic drawing of the superficial and deep lobules of the lung. The structural relationships between the superficial and deep lung lobules are important in the mechanics of lung ventilation (Modified from Nagaishi C.* Functional Anatomy and Histology of the Lung: *Fig. 45. Baltimore, MD, and London, England: University Park Press; 1972:28). B, The hypothesis proposed implicates shear forces in the peripheral lung that lead to tears in the epithelium, followed by prolonged fibroblastic repair.*

Figure 10. *Conceptualized process by which lung lobules become foci of microscopic honeycombing. This histopathologic manifestation of advanced lung remodeling with microcyst formation seems to precede the radiologic finding of honeycomb cysts by an undefined period. The alveoli (al) in the involved lobules (A) become obliterated in scar, and the terminal ends of the respiratory bronchioles and alveolar ducts expand to form (B) aggregations of mucous-filled cysts (C).*

microaspiration in the pathogenesis of acute exacerbation (see below), a primary etiologic role for reflux in all patients with IPF remains to be proven. Treatment of reflux has been shown to improve survival in patients with IPF.[63]

Acute Exacerbation of IPF.—Acute exacerbation of IPF may occur as a direct consequence of relatively rapid increases in mechanical stress acting on areas already modified by fibrous remodeling. Alternatively, acute exacerbation could be an independent injury not directly related to the underlying primary mechanism of disease. Acute exacerbation is rarely the initial presentation in IPF,[64] and when this occurs, the background histopathology of UIP may be difficult to discern through the overlay of acute lung injury. Interestingly, it is not uncommon for patients newly diagnosed with IPF to recall a prior severe bout of ''pneumonia'' as the event that began their respiratory decline. Such events may represent early acute exacerbations. If acute exacerbations do occur at higher rates in preclinical disease, the injury must be less than global in the lung. Otherwise, the nearly normal lung parenchyma required for the diagnosis of UIP (''temporal heterogeneity'') would be absent in subsequent biopsies.

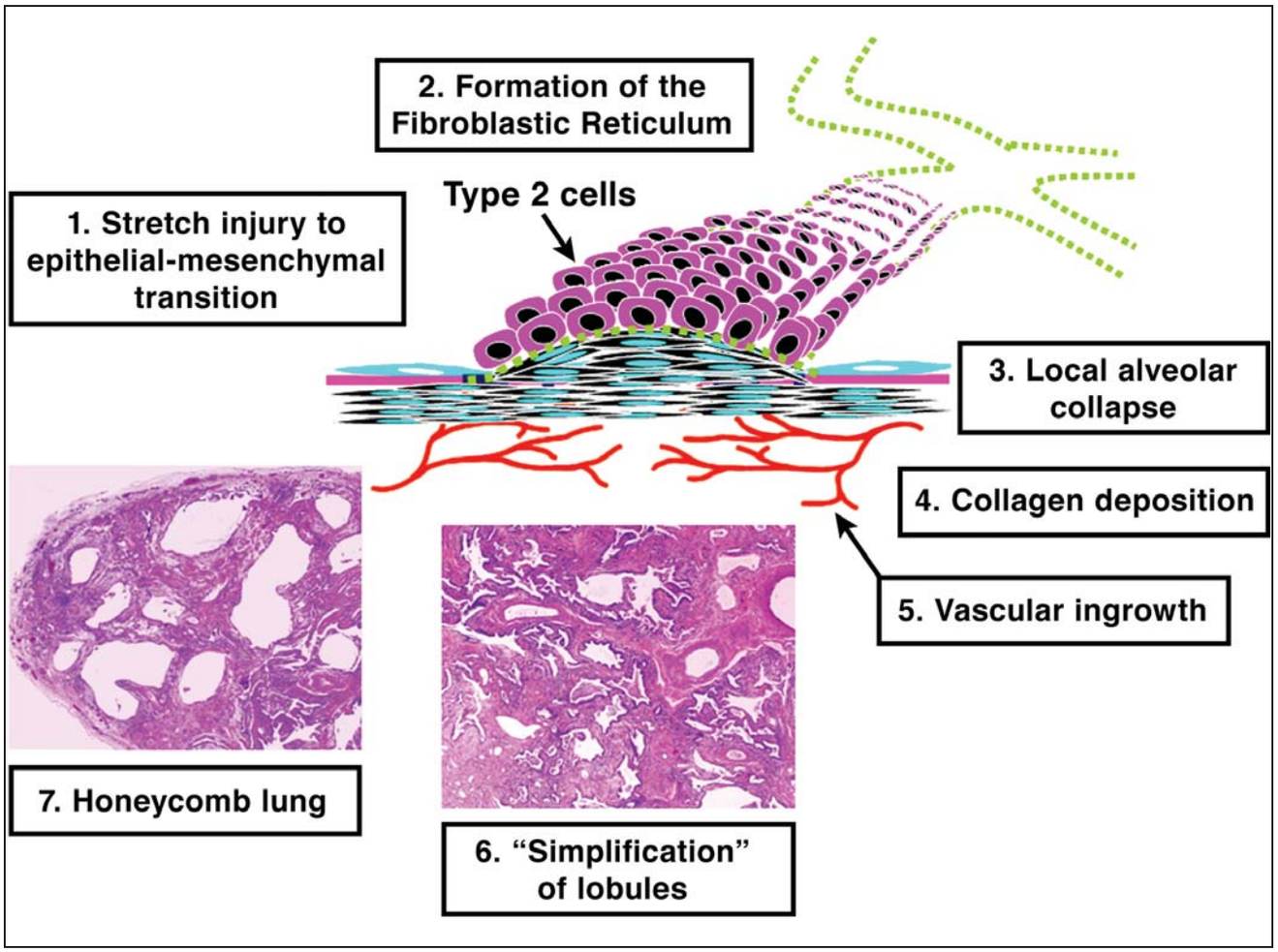

Figure 11. *Proposed pathogenetic sequence of events in idiopathic pulmonary fibrosis. The cycle may consist of (1) initial stretch injury to the epithelial-mesenchymal interface, with (2) formation of the fibroblastic reticulum. Type 2 cells proliferate over the tear in the lung and reconstitute the alveolar interface with air. (3) Localized persistent collapse of alveoli occurs from unknown mechanisms and is (4) attended by collagen deposition and (5) eventual vascular ingrowth. (6) The simplified lobules (or portions of lobules), devoid of alveoli, consist only of terminal airways. These dilate over time because of respiration and become (7) honeycomb lung. Reprinted with permission from Practical Pulmonary Pathology: A Diagnostic Approach. Leslie KO, Wick MR, eds; 2nd ed., page 219; by Elsevier, copyright 2011.*

Conclusions

All scientific study begins with observation. In the absence of an animal model of IPF, a viable hypothesis regarding etiology and pathogenesis must reconcile a sizeable body of fundamental observations about the disease, accrued over decades of study. Without a unifying hypothesis, isolated molecular genetic and proteomic abnormalities gleaned from the patient with IPF must be viewed as data in search of context. Biomechanical forces involved in respiration may cause recurrent and progressive tractional injury to alveoli at the peripheral bases of the aging lung. This injury may occur as a function of an inherited genetic abnormality of surfactant. This molecule's unique role in reducing alveolar surface tension protects the alveolar parenchyma from tractional injury when areas of physiologic collapse are subjected to sudden opening. The stretch injury produces a reticular network of FF, which over time results in permanent alveolar collapse and piecemeal fibrous remodeling of affected lung lobules (Figure 11).

The earliest events in the process remain unclear, the pathobiology of the fibroblast focus in IPF and other diseases is still undefined, and the specific events that result in persistent alveolar collapse require further study. A hypothetic construct for integrating the results of laboratory investigations may finally help provide insight into this enigmatic and deadly disease.

The critical review of the manuscript was provided by Athol Wells, MD, Steven Nathan, MD, and Thomas Colby, MD. Their generous input and suggestions are not intended as an endorsement by them for the concepts outlined.

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