example, HCRIS does not include a Neuroscience ICU category. The *Dartmouth Atlas* regions also do not account for political and legislative geographic boundaries, nor were they developed to address critical illness or "regionalization" (15) of ICU care. Other confounding factors such as direct hospital competition, health system integration, and use of ICU telemedicine, which may affect ICU bed supply and movement of patients within defined areas, could also not be measured in their data.

Notwithstanding these limitations, the present study by Wallace and colleagues (12) highlights the complexity of the critical care bed supply in the United States and offers valuable insights into the changes in critical care beds that occur at the regional level and their relationship to the regional populations. However, future studies investigating hospital, ICU, and insurer characteristics at the national and regional levels are still needed to advance our understanding of the U.S. critical care enterprise. ■

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A First Glimpse at the Early Origins of Idiopathic Pulmonary Fibrosis

Familial pulmonary fibrosis (FPF) is most often diagnosed by the presence of clinically evident idiopathic pulmonary fibrosis (IPF), or any idiopathic interstitial pneumonia, in at least two members of the same family (1). For almost 30 years, we have known that asymptomatic family members recruited on the basis of FPF have detectable abnormalities shared by their symptomatic relatives (2). Further studies have demonstrated that significant percentages of asymptomatic, or self-identified unaffected, family members in these FPF kindreds have physiologic, radiologic, and histopathologic abnormalities (3, 4). This suggests that a lack of respiratory symptoms, or loss of function, should not be a benchmark on which to exclude disease affection status. Although this may not be the most comforting message, in this issue of the *Journal*, Kropski and colleagues (pp. 417–426) provide further evidence that this statement is almost certainly true (5). We must consider what obligation we might have to inform our patients with FPF that some of their asymptomatic family members may be at risk for, or in some cases may already have, the same disease.

Kropski and colleagues present the collected data and cross-sectional analysis of 75 asymptomatic, or minimally symptomatic, first-degree relatives recruited on the basis of FPF who completed a battery of testing, including respiratory questionnaires, blood sample collection, high-resolution chest CT, and in most cases, bronchoscopy with transbronchial biopsy (5). Although there is much to be learned from a review of this data, and from subsequent analysis of this population, this study provides evidence that radiologic, histopathologic, genetic, and other potentially pathogenic abnormalities noted in patients with pulmonary fibrosis can be detected in asymptomatic relatives recruited on the basis of a family history of PF. A number of peripheral blood biomarkers previously found elevated in patients with FPF and IPF (e.g., matrix metalloproteinase-7) (6) were also noted to be elevated in these asymptomatic relatives and were, in some cases, associated with the imaging findings. There was no evidence that cellular inflammation played a strong role in early

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stages of FPF. Some of these potentially pathogenic processes deserve further comment.

Comparable to previous findings by the Vanderbilt group in patients with IPF (7), this manuscript demonstrates that 30% of the asymptomatic relatives of FPF kindreds have detectable herpesvirus DNA in their lungs. Those with detectable viruses were more likely to have increased measures of endoplasmic reticulum stress. Similarly, herpesviruses have been demonstrated to lead to endoplasmic reticulum stress and pulmonary fibrosis in aged mice (8). However, it should be also noted that endoplasmic reticulum stress was also commonly found in those without detectable herpesviruses in this study (5), and a similarly elevated prevalence of herpesviruses in the lungs of patients with IPF has not always been found in other studies (9, 10).

In addition, this study confirms that reduced telomere length likely occurs early in the course of pulmonary fibrosis, as suggested by the fact that genetic variants in, or adjacent to, numerous genes controlling telomere length have now been associated with both FPF and IPF (*DKC1, NHP2, NOP10, OBFC1, TERT, TERC,* and *TINH2*) (11–17). Although the precise mechanisms by which reduced telomere length leads to pulmonary fibrosis remain uncertain, cellular senescence and/or apoptosis and genomic instability are thought to play some role (18).

Finally, this manuscript provides further evidence that the *MUC5B* promoter polymorphism (rs35705940) is associated with both FPF and an increased expression of MUC5B protein in the lung (19). Although it is intriguing that both the *MUC5B* promoter polymorphism and the resultant increase in MUC5B protein expression appear to be present in early (5, 20) as well as late (5, 19) stages of pulmonary fibrosis, it remains unclear how increases in MUC5B expression contribute to pulmonary fibrosis. Further complicating this story, *MUC5B* deficiency has recently been identified to result in critical impairments in macrophage host defense and bacterial burden in the lungs of an animal model (21), and the *MUC5B* promoter polymorphism appears to have an inverse relationship with the bacterial burden in the lower airways of patients with IPF (22).

Although the authors should be congratulated for this study, there are also limitations worth noting. Accumulating evidence suggests that early stages of sporadic IPF that are comparable to these findings in FPF (5) may be also detectable (23). However, we should be cautious in extrapolating the findings of early disease detection in FPF to sporadic IPF. FPF tends to present earlier than sporadic IPF (24) and can have imaging (25) and histopathologic (5) findings discordant from those expected to be present in sporadic IPF. Although the authors should be applauded for their collection and phenotypic characterization of this valuable cohort, the controls for the bronchoalveolar lavage analyses were on average 13 years younger than the asymptomatic family members. Given the prominent role that age alone may have in this disorder (26), these age differences potentially limit the strength of some of the conclusions that can be drawn. In addition, we do not know whether the development of pulmonary fibrosis can result from each of these potentially pathogenic processes independently or whether the cumulative and/or cooperative effects of multiple processes will be required for the transition to a progressive, clinically evident disease. Finally, as the authors duly note, the greatest value of this cohort will come from the longitudinal follow-up evaluations that hopefully will allow us to determine what factors predict progression from detectable abnormalities to pulmonary fibrosis. If we can ultimately agree that a lack of respiratory symptoms should not alone exclude the detection of FPF, perhaps we should consider what abnormalities are sufficient to define disease in FPF. ■

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Preventing the NET Negative in Primary Graft Dysfunction

Primary graft dysfunction (PGD) is a form of acute lung injury triggered by ischemia/reperfusion injury after lung transplantation. It affects 10–35% of lung allograft recipients and is the major cause of early morbidity and mortality after lung transplant (1). In addition, PGD has been associated with an increased risk of chronic lung allograft dysfunction, which is the major cause of late mortality after lung transplantation (2). Prior studies have proposed several risk factors for the development of PGD based on the donor, recipient, and surgical variables (3). The pathogenesis of PGD is not well understood. An inflammatory cascade initiated by ischemia/reperfusion injury after lung transplant, which ultimately leads to an influx of neutrophils into the lungs, has been suggested as the underlying etiology of the development of PGD (4). Given the unclear pathogenesis and lack of any established therapy for PGD, it is crucial to characterize the cellular and molecular pathways leading to PGD to develop targeted therapies. In this issue of the *Journal*, Sayah and colleagues (pp. 455–463) present evidence that neutrophil extracellular traps (NETs) develop after ischemia/reperfusion injury, and recruitment is dependent on platelets (5). Further, they find increased NETs in the bronchoalveolar lavage of human lung transplant recipients with PGD compared with subjects without PGD. Interestingly, the prevention of NET formation using an antiplatelet agent or intraalveolar disruption of NETs using DNase I protects against PGD in a mouse model of orthotopic lung transplant.

Previous studies in animal models have suggested a role for neutrophils in the inflammatory response after graft reperfusion and found that disrupting neutrophil infiltration can reduce lung injury after transplant (4, 6). One of the consequences of neutrophil infiltration and activation can be the formation of NETs, extrusions of neutrophil DNA–protein complexes generated by cell death in a process called NETosis (7). Prior work by Looney and colleagues found that NETs were involved in lung injury in a mouse model of transfusion-related acute lung injury (8). Disruption of platelet function with aspirin decreased NET formation and the severity of lung injury (9). The group has extended their work by investigating the contribution of NETs to lung injury, using two mouse models of ischemia/reperfusion pathology, a hilar clamp model, and an orthotopic left lung transplant model with prolonged cold ischemia time. The models provide complementary results on the involvement of NETs in ischemia/reperfusion injury, as both models resulted in NET formation. However, the hilar clamp model had a significant increase in NETs in the plasma and not the bronchoalveolar lavage (BAL), whereas the transplant model had an increase in NETs in the BAL and not the plasma. These data suggest the two models are not equivalent in the compartmentalization of NET formation initiated after lung ischemia and may provide different insights into the effect of ischemia/reperfusion on the lung.

The findings in the orthotopic left lung transplant model are particularly interesting, as they reflected the clinical scenario with elevated levels of NETs detected in patients with PGD grades 2 or 3 in the BAL, and not the plasma. Disruption of NETs with administration of DNase I markedly reduced lung injury after transplant, supporting a pathogenic role for NETs. In addition to reducing the indices of lung injury, DNase I treatment was also associated with a reduction in neutrophils in the BAL. These data are interesting and support a role for NETs not only in promoting lung injury but also in augmenting the recruitment or expansion of neutrophils. To address the mechanism of NET formation after transplant, the authors drew on their experience