populations that should be targeted for early detection of IPF. This is a critically important mission. Although there has been considerable progress in the development of novel therapeutic options for IPF, it is highly unlikely that any of the drugs currently in the pipeline will be able to reverse the extensive lung remodeling that is often observed when patients initially present. On the other hand, it is possible that therapeutic targeting of minimal fibrotic lesions—before extensive remodeling and bronchiolization have occurred—will allow complete eradication of the disease. Thus, to truly eradicate IPF, we need a paradigm shift from focusing on developing cohorts of patients already diagnosed with IPF toward cohorts of individuals highly likely to develop the disease. We could use these cohorts to develop and test algorithms for early detection. Then we could implement a multistep strategy to eradicate IPF: identification of a population with high risk for ILA and performing chest CT screenings when appropriate; in subjects with ILA, identification of patients who will develop IPF; and last, systematic study of interventions aimed at preventing progression to IPF. In an editorial in 2012 (9) discussing an early report on ILAs (10), Dr. David Lederer compared our traditional symptom-linked diagnosis of IPF to diagnosing coronary artery disease only after the patient presented with a myocardial infarction and called for new ways for risk prediction and early detection of IPF. Seven years later, the article by Hobbs and colleagues (8) suggests that we can move forward—that we can diagnose IPF while the horse is still in the barn. ■

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The Respiratory Mucosa: Front and Center in Respiratory Syncytial Virus Disease

Infantile bronchiolitis is a major scourge of early childhood, and winter outbreaks fill the pediatric wards with wearisome regularity. Most cases are caused by respiratory syncytial virus (RSV), which was first isolated in 1956. Despite a vast amount of research in both human and animal models, a deep understanding of the inefficiency of protective immunity and, indeed, of the pathogenesis of RSV disease has been frustratingly slow to come by.

Most infants will be infected by RSV before their second birthday, with the risk of severe disease peaking at just 2 months of age. Despite the relative antigenic stability of the virus, reinfections with RSV occur throughout life. Studying disease in infants with primary disease presents considerable technical and logistical challenges; therefore, animal models (especially cotton rats, mice, and cows) have been widely used to enhance our understanding of primary infection and vaccine-enhanced disease. These models have been central in our efforts to understand the host immune response to RSV and the role of these responses in causing inflammatory bronchiolitis, but they do not recapitulate human disease in every detail.

Although animal models have advanced our understanding of the pathogenesis of bronchiolitis, a role for the type 2 immune

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responses (typical of atopic asthma and antihelminth immunity rather than antiviral responses) has been proposed (1). Type 2–biased responses have been suggested as a link between bronchiolitis and postbronchiolitic recurrent wheeze (2, 3), but it is not perfectly clear that prevention of RSV disease would modify the risk. Blanken and colleagues showed that prevention might substantially improve subsequent lung health in later childhood (4), but such an effect was not subsequently seen in large prevention studies in other settings (5).

With the prospect of even more effective and useful RSV immunoprophylaxis, novel therapeutics, and vaccines, it is increasingly apparent that observations from experimental models must be validated in human studies. In particular, the focus needs to be on the site of infection: the ciliated mucosal respiratory epithelium. To this end, in a study presented in this issue of the *Journal*, Vu and colleagues (pp. 1414–1423) (6) sought parallels to the previous finding that the airways of neonatal mice had increased numbers of type 2 innate lymphoid cells (ILC2s) after RSV infection (7), as was also observed in neonatal mice with rhinovirus infection (8). They compared children admitted to pediatric intensive care wards (who mostly required mechanical ventilation) with those admitted to general wards.

When they examined nasopharyngeal cells (9) collected from the subjects, they found that the frequency of ILC2s was indeed increased in infants with more severe disease. In addition, they found that levels of the ILC2-activating alarmin IL-33 and the ILC2-secreted type 2 cytokines IL-4 and IL-13 were also elevated in infants with severe disease. In agreement with other recent studies (10), levels of IFN-γ were paradoxically lower in patients with severe disease, supporting an association between enhanced severity and diminished antiviral immunity.

Vu and colleagues also provide further support for the association between premature birth and RSV severity. This association is well known, but the mechanisms underpinning it seem to be complex. Lower maternal antibody titers at birth predispose to infection, and smaller airway size may increase the likelihood of airway plugging, a feature of severe disease (11). However, another likely contributor is the rapid development of the respiratory immune system in early life, when ILC2s are particularly abundant (12). Indeed, the present analysis by Vu and colleagues demonstrates that among infants hospitalized with RSV, ILC2s were most abundant in those less than 3 months of age. This may help explain the high rate of severe disease at 2 months of age, when ILC2s may be particularly prevalent in the airway. Vu and colleagues also found that IL-4 levels were higher in infants less than 3 months of age, in agreement with previous studies (13).

Given the possibility that ILC2s and T-helper cell type 2 (Th2) mediators might play a pathogenic role, further studies of the dynamics of ILC2 abundance in the airway are needed. Many issues remain to be addressed, such as the effects of ILC2s in the airway before infection. These cells are elevated in normal neonatal mice (7, 12), but is this the case in human infants? If so, this might provide an added thread to our understanding of the association between age and severity of disease. To explore this possibility, Vu and colleagues incorporated gestational age into a multivariable logistic regression model and demonstrated that both younger gestational age and higher airway IL-4 levels were associated with severity. However, it is possible that these factors reflect an existing immune profile of the airway rather than an acute response to infection.

Although ILC2-mediated enhanced type 2 immunity to RSV infection may reciprocally diminish antiviral type 1 immunity (including IFN-γ levels, and potentially $CD8^+$ tissue resident memory cell activity in reinfection [14]), a consequential increase in viral load is not seen in severe disease (10, 15). Indeed, IFN-γ and IL-33 have reciprocal effects on respectively inhibiting and enhancing ILC2 activity (16). In severe RSV disease, where IFN-γ levels are relatively low and IL-33 levels are relatively high, activation of lung-resident ILC2s (and/or migration of ILC2s to the lung) apparently results. It remains unknown whether type 2 inflammation contributes to the control of RSV load in infants (regardless of severity) or whether it is simply pathologic. By improving our understanding of ILC abundance and activity in the developing healthy neonatal respiratory tract, we may be able to gain additional insights into the contribution of these cells to the host response to RSV infection.

Future studies of the mucosal immune response throughout infection and into convalescence are warranted to answer these questions. Our incomplete understanding of the relative contributions of viral replication and host inflammatory responses continues to hamper the development of novel therapies, possible immune modifiers, and vaccines. An obvious question remains unanswered: if Th2 responses are important, why is RSV bronchiolitis characterized by airway neutrophilia (17) rather than eosinophilia?

Vu and colleagues are to be applauded for tackling these difficult questions head on. By focusing on the hard-to-measure responses in the airway mucosa, they were able to gain novel insights that enable a nuanced interpretation of mechanistic animal studies, and demonstrate the potential importance of ILC2s and type 2 cytokines in RSV disease and its sequelae. These new findings support the concept that type 2–driven immunopathology plays a part in severe RSV disease, but much remains to be discovered about the dynamic, ILC-rich airway in early life and during mucosal infections. ■

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Vaping-induced Acute Lung Injury: An Epidemic That Could Have Been Prevented

The epidemic of vaping-related acute lung injury is a public health disaster. As of October 3, 2019, the CDC had received reports of 1,080 lung injury cases from 48 states and one U.S. territory, with 18 deaths confirmed in 15 states (1). Almost 80% of the cases are younger than 34 years of age, with 38% younger than 21 years. Many, but not all, of the cases involved vaping of products containing tetrahydrocannabinol (THC). The research letter by Triantafyllou and colleagues (pp. 1430–1431) in this issue of the *Journal* describes the features of six cases seen this past summer at the University of Pittsburgh Medical Center (2).

The cases are emblematic of those reported to the CDC. They were young men who presented with respiratory and gastrointestinal complaints who reported regular use of vaporized cannabis and nicotine products. The patients showed evidence of a systemic inflammatory response with leukocytosis, and chest imaging showed bilateral, multifocal ground-glass opacifications. The patients were treated with antibiotics until cultures came back as negative, and most patients received corticosteroids. Two of the patients required mechanical ventilation. Fortunately, no one died. The case descriptions from the University of Pittsburgh team are similar to those of a larger case series published earlier this year (3).

One common finding in the two published case series is the prevalence of use of a cannabis product known as "Dank Vape." What are Dank Vapes? According to the CDC, Dank Vapes are the most prominent in a class of largely counterfeit brands, with common packaging that is easily available online and used by distributors to market THC-containing cartridges (4). Public health officials in Wisconsin and Illinois, two of the states hit hardest by the vaping-related acute lung injury epidemic, interviewed 86 patients, and 66% said they had used THC products labeled as Dank Vapes (4). Most (89%) of the THC-containing products used by the patients were obtained from friends, family, school, dealers, or off the street. Interestingly, most of the patients used universal "vape pens" for which prefilled THC cartridges can be used, as opposed to the closed pod devices sold for proprietary nicotine-containing products (e.g., JUUL). Use of devices with a tank designed to be filled with nicotine-containing liquid or THC oil was reported by 18 (21%) patients, and 14 (16%) reported aerosolizing THC concentrates by "dabbing," a process involving vaporizing extracts of a concentrate (often butane hash oil) that has been placed on a hot surface.

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