AJRCCM: Strength in Breadth

Welcome to the special issue of the *Journal* which coincides with the 2023 American Thoracic Society (ATS) International Meeting in Washington, DC. We are all proud of the *American Journal of Respiratory and Critical Care Medicine* (*AJRCCM*) as the flagship journal of the ATS, and we have tried to showcase as many aspects of respiratory medicine as we can, from the cradle to the grave, from the very chronic to the hyperacute illnesses and from the bedside to basic biology; we want to give space to all. Given space constraints, we do not have room for many aspects of our hugely diverse specialty, but watch this space: these missing manuscripts are in the pipeline and will soon arrive.

There is a strong early-life and developmental stream. Alveolar and pulmonary vascular hypoplasia is well described in congenital diaphragmatic hernia. Wagner and colleagues (pp. 1214–1226) turn the spotlight in a different direction, on the airway stem cells, demonstrating a proinflammatory phenotype and defective airway epithelial differentiation that are reversed by nuclear factor-κB inhibition in rat tracheas and human cells. The need to abandon developmental silos is demonstrated by Burchert and colleagues (pp. 1227–1236). Preterm survivors have excess cardiovascular and respiratory morbidity, and, in a randomized controlled trial, aerobic training improved maximal oxygen uptake (VO_2max) in term and preterm patients with hypertension. Maybe the ever-increasing numbers of preterm survivors who all too frequently have reduced exercise capacity are the next group for pulmonary rehabilitation.

Adult airway disease is also strongly featured. The complex interactions between type 2 inflammation and antiviral immunity are highlighted by another randomized controlled trial (Woehlk and colleagues, pp. 1161–1170). Sublingual immunotherapy increased epithelial-cell resistance to viral infection, one probable mechanism whereby this treatment reduces asthma attacks. Chronic obstructive pulmonary disease (COPD) is represented by two Concise Clinical Reviews and an Original Contribution. "It ain't necessarily so" (Ira Gershwin, *Porgy and Bess*), and "COPD exacerbations" may be worsened or mimicked by a number of other respiratory diseases (Celli and colleagues, pp. 1134–1144). There are two thoracic organs of interest—the right lung and the left lung—and a third related structure, the esophagus. It's good to talk, and Wang and colleagues (pp. 1145–1160) highlight the multiple bidirectional interactions between these two embryologically linked systems, with the possibility of therapeutic manipulation. Rustam and colleagues (pp. 1171–1182) report on the array and disarray of the distal airways in COPD, with a unique atlas based on single-cell transcriptomics of more than 111,000 cells that, in the future, may unlock the mechanisms of distal airway remodeling in COPD.

Beyond airway disease, the genetics of idiopathic pulmonary fibrosis are featured, based on an analysis of more than 2,000 patients (Peltjo and colleagues, pp. 1194–1202). Rare variants in *TERT* and *RTEL1* were highlighted, and pediatric pulmonologists might well want to start looking for these in childhood interstitial lung disease, another example of the importance of exiting silos. The nihilism around early diagnosis of lung cancer has long since gone. A new approach is the use of plasma DNA fragmentomics, which, in a study of nearly 800 patients with cancer and control subjects, showed promise for the early diagnosis of this fell disease (Wang and colleagues, pp. 1203–1213).

At the sharpest of sharp ends, critical care is represented by a Perspective and an Original Contribution. Based on lessons learned from the EOLIA (ECMO to Rescue Lung Injury in Severe ARDS) trial, an impressive experimental study compares extracorporeal carbon dioxide removal as an alternative to conventional extracorporeal membrane oxygenation (Brusatori and colleagues, pp. 1183–1193) and shows that it may have concerning effects on hemodynamics and pulmonary hypertension. The coronavirus disease (COVID-19) pandemic forces us to confront the fact that, even in the highest-income settings, resources are not unlimited, and, under any healthcare system, rationing is inevitable, however politically unpalatable though that fact may be. Dessap and colleagues (pp. 1126–1133) take a sober look at the implications of this in a Critical Care Perspective and highlight a frugal innovation approach that may ultimately lead to a more realistic way forward that is hopefully more resilient, more inclusive, and more equitable. This does mean that we all need to abandon the "ostrich approach" of sticking our heads in the sand and assuming what we do not like and do not see does not exist.

All the original manuscripts have thoughtful accompanying editorials by experts in the field, assessing the contributions and giving context. We also have some hors d'oeuvres, which unusually follow after the main courses above, namely clinical Images and Letters. The Research Letters in particular allow opportunities to report new information and pilot data that will stimulate ideas and research while not yet being substantial enough for the entrée menu. They are also well worth reading carefully because the five Letters in this issue are far more than a mere *amuse bouche*, covering topics from the ionocyte to ICU detailed respiratory monitoring (Wang and colleagues, pp. 1249–1253, and Telias and colleagues, pp. 1239–1243, respectively) via ozone products (He and colleagues, pp. 1243–1246), T cells in hypersensitivity pneumonitis (Sendama and colleagues, pp. 1246–1248), and whether type 2 biologics are safe in high-parasite-burden regions (Lifar and colleagues, pp. 1253–1255). Likewise, the Images are always more than mere stamp-collecting: bronchoscopy allowing the rapid diagnosis of postoperative pulmonary vein stenosis (Tonai and colleagues, pp. 1237–1238) and

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endobronchial ultrasound to access an intracardiac sarcoma (Irfan and colleagues, pp. e73–e74).

Look out also for the page highlighting our emerging young investigators who have done so much to make this and all our prior issues so stellar, and who are the future of the specialty. Above all, the patient education and information section reminds us that we all exist to serve patients.

Finally, huge thanks are due to the *AJRCCM* family, Associate Editors and the Editorial Board, the authors and editorialists who have sent us such fantastic manuscripts, and the unseen army of reviewers, without whose hard grunt work we could not function. If you are in Washington, come along to the ceremony honoring our top reviewers and vow to be one of them in 2024. And, of course, a huge shout out to the editorial team, without whose largely unseen work in the engine room the *Journal* would not exist. And to the ATS members and beyond: keep sending us your best work, as we seek to drive the *Journal* to ever greater heights going forward. Vivat, vivat ATS and *AJRCCM*! ■

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Can Allergen Immunotherapy Improve Antiviral Immunity in Patients with Allergic Asthma?

Allergen exposure and respiratory virus infections are the key triggers for acute asthma exacerbations (1). The susceptibility to virus infections and asthma exacerbations is often attributed to deficient IFN synthesis in the airway mucosa because virus-infected bronchial epithelial cells (BECs) from people with asthma seem to produce less innate antiviral IFNs *in vitro* relative to BECs from healthy people (2). Understanding whether altered IFN production is an intrinsic property of BECs in asthma or arises secondary to immune-mediated inflammation has important implications for developing therapies for viral infections and asthma exacerbations. It is known experimentally that allergic inflammation can impair IFN production via alarmins such as IL-33 (3), T2 cytokines such as IL-4 and IL-13 (4), and allergen–IgE interactions (5), prompting researchers to determine if inhibiting allergic pathways in patients with asthma enhances antiviral IFN production and protects against viral infections.

Evidence that allergen immunotherapy (AIT) is beneficial in allergic diseases has accumulated in recent decades (6). AIT induces immunological tolerance, reduces asthma exacerbations, and probably has a disease-modifying effect, with some improvements persisting long after treatment concludes (6). The beneficial effects of AIT involve direct effects on mast cells and basophils and induction of regulatory cells, cytokines, and IgE-blocking antibodies. AIT is associated with fewer lower respiratory tract infections in people with allergic asthma (7), though the mechanisms involved and whether there is protection against viral or bacterial infections are not clear.

In this issue of the *Journal*, Woehlk and colleagues (pp. 1161–1170) report the findings of their randomized, double-blind, placebo-controlled trial of house dust mite sublingual allergen immunotherapy (HDM-SLIT) to determine if this intervention enhances BEC antiviral responses in allergic asthma (8). The study recruited 39 people with HDM sensitization and suboptimal asthma control despite maintenance inhaled corticosteroids, to which HDM-SLIT or placebo was added for 24 weeks. BECs (collected by bronchoscopy at baseline and at Week 24) were activated *in vitro* with the viral nucleic acid mimic polyinosinic:polycytidylic acid (poly I:C). The primary outcome measure was IFN-β and IFN-λ gene expression in BECs and the extent to which this changed between baseline and Week 24. Recruited patients had asthma of varying severity, and the placebo and HDM-SLIT groups were generally well matched.

The key findings were as follows. At baseline, there were no between-group differences in poly I:C–induced IFN-β and IFN-λ expression. At Week 24, poly I:C–induced IFN-β mRNA and protein

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