paraseptal emphysema. And although neutrophil elastase activity was not measured in this study, it might be speculated that neutrophil elastase might be an important driver of paraseptal emphysema development. A high amount of neutrophil elastase activity has been linked to emphysema in humans and animals (11). Moreover, increased elastase concentrations in sputum are associated with increased risk of exacerbations (12), suggesting that further understanding of the cellular and molecular orchestration leading to emphysema might give insight that ultimately will translate to modifying therapies for many people suffering from COPD.

A question that arises from this work is how paraseptal emphysema develops. The current notion for the pathologic sequence of events from cigarette smoke to centrilobular emphysema development starts with the inflammation of small airway walls occurring in the center of the lobule. This process leads to bronchiolar–alveolar attachments and surrounding alveolar wall destruction. Because paraseptal emphysema occurs adjacent to the pleura and septa and emphysema animal models have marked changes in capillary segments (i.e., a higher number of nonconnecting segments) on the pleural surface (13), disruptions of pulmonary and/or pleural capillaries might also contribute to paraseptal emphysema. It can be speculated that pulmonary perfusion deficiency may lead to misbalanced inflammatory response and tissue damage repair, resulting in paraseptal emphysema.

In conclusion, the authors should be commended for this elegant contribution to pathologic differences in the small airways and cellular composition between paraseptal and centrilobular emphysema. After a long time, this work brings paraseptal emphysema to the center of the stage. ■

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Alejandro A. Diaz, M.D., M.P.H.
Harvard Medical School
Brigham and Women's Hospital
Boston, Massachusetts

ORCID ID: 0000-0001-5037-2919 (A.A.D.).

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Rewiring the Immune Response in COVID-19

At the time of writing, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues globally, with nearly 15 million documented cases and more than 600,000 deaths worldwide (1). Many countries have recently seen falls in the number of confirmed cases and are beginning to cautiously reopen following lockdown measures, whereas others are experiencing a continued increase, "second waves" of infection, or localized outbreaks following an initial reduction in cases (2, 3).

This pandemic represents the greatest public health, clinical, and scientific challenge of our generation. Containing viral spread has necessitated unprecedented social and economic change as lockdowns only "temporarily" limit morbidity and mortality. Identifying effective therapies and/or a vaccine remain our only long-term solutions. Simply put, research is the only exit strategy (2–5).

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Great progress has been made in understanding the pathophysiology of coronavirus disease (COVID-19), the disease caused by infection with SARS-CoV-2. Current concepts regard COVID-19 as a biphasic illness: an initial viral phase with suggested mean duration of 7 days followed by a "hyperinflammatory phase" characterized by host-mediated organ damage and what is widely referred to as a "cytokine storm" (6). A subset of patients with COVID-19 display features consistent with hemophagocytic lymphohistiocytosis (HLH), a fulminant hypercytokinemic syndrome associated with multiorgan failure, cytopenias, and abnormal liver function tests (7). There are, however, important differences in the inflammatory profile of HLH and severe COVID-19, suggesting a distinct pathophysiology. The respiratory manifestation of this systemic inflammatory response is acute respiratory distress syndrome (ARDS), and approximately 30% of patients with COVID-19 from the initial series in Wuhan met criteria for ARDS (8). This model of a hyperinflammatory syndrome occurring a week or more after initial infection, leading to ARDS and a need for mechanical ventilation, is further supported by the benefits of dexamethasone in the recently published RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial (9). In this large, open-label, United Kingdom–based trial, dexamethasone significantly reduced COVID-19 mortality, with the largest effect in those requiring mechanical ventilation (9). Most notably, in the supplementary material, patients starting dexamethasone >7 days after symptom onset demonstrated the most significant benefit, whereas those treated in the first 7 days from symptom onset did not, validating the proposed model of a late hyperinflammatory response that can be therapeutically targeted.

In parallel to evidence of excess inflammation, reports of profound viral-induced immunosuppression have emerged. Specifically, deficient production of IFN-α and -β in blood is reported in patients with severe disease, whereas a separate study describes deficient IFN-γ and TNF-α production (10, 11). Taken together, severe COVID-19 appears to involve a delicate and dynamic balance between excess inflammation and deficient antiinflammatory and antiviral defenses.

The clinical presentation and immunological profile of COVID-19 is therefore unique, and intensive research aimed at characterizing this is ongoing. Most mortality is likely to be driven by host responses rather than the virus, and there is clear evidence of end-organ damage without evidence of viral invasion.

It is a remarkable triumph for clinical and translational research that we know so much about the inflammatory response to SARS-CoV-2 only 6 months after the publication of its gene sequence. Nevertheless, key questions remain about its pathophysiology: which components of the inflammatory response are key "makers" rather than "markers," and what should be therapeutically targeted (12)? What inflammatory characteristics distinguish between the different stages of disease, and is this useful for risk stratification? Finally, some aspects of the immune response remain less well characterized, and in particular, the contribution of neutrophils to COVID-19 remains unclear (13).

In this issue of the *Journal*, McElvaney and colleagues (pp. 812–821), in a single-center study from Dublin, Ireland, aim to provide fresh insight into the inflammatory response to COVID-19 (14). The study compared 20 patients requiring intensive care admission for severe COVID-19 infection, 20 patients who were hospitalized with stable COVID-19 infection (who did not require ICU admission), and 15 healthy controls. The study confirmed prior observations with elevated IL-6, IL-1β, soluble TNF receptor-1, and IL-8 in the plasma of severe cases requiring ICU admission, with elevated ratios of IL-6 and IL-1β to the antiinflammatory cytokine IL-10. Metabolic reprogramming of immune cells refers to complex alterations in cell metabolism, typically occurring upon activation by external stimuli such as cytokines, leading to profound change to their function. Neutrophil metabolic reprogramming, or what the authors refer to as "rewiring," is reported in cystic fibrosis and other conditions in response to inflammatory cytokines and low-level endotoxemia (15). These observations are extended here with increased levels of HIF1-α, PKM2, and cytosolic lactate in neutrophils from patients with COVID-19. Importantly, however, precise mechanisms for these effects remain undefined and are likely to be multifactorial given the combined effects of proinflammatory mediators and hypoxemia in severe COVID-19. Finally, the authors assessed plasma alpha-1 antitrypsin (AAT), which is increased in COVID-19 compared with healthy controls. As IL-6 levels were higher in the more severely ill patients with COVID-19, interestingly, AAT was similarly increased, and the authors demonstrate that positive outcomes were associated with a lower IL-6 relative to AAT. The authors interpret this as meriting a trial of AAT supplementation as AAT modulates inflammatory cytokine production. Nevertheless, because the differences in IL-6:AAT ratios are primarily driven by high IL-6, directly targeting IL-6 represents an equally logical strategy.

This work extends the characterization of COVID-19 by proposing two novel potential targets: neutrophil metabolic reprogramming and a relative AAT deficiency. There are >500 therapeutic trials in COVID-19 worldwide, and as recently reviewed in the *Journal* (12), many duplicate existing trials or have limited mechanistic work underpinning their choice of target or design. Therefore, studies such as that presented here are important to validate potential targets before embarking on therapeutic trials. Demonstrating a mortality benefit with dexamethasone is a significant breakthrough in antiinflammatory therapy for COVID-19; however, the mortality rates of 17.8% (patients not requiring oxygen), 23.3% (patients requiring oxygen) and 29.3% (patients requiring invasive mechanical ventilation) remain high, and novel therapies will be required (9). How should we prioritize? Anti–IL-6 (such as tocilizumab), anti–IL-1β (such as anakinra), anti-TNF (e.g., infliximab), IFN, or exogenous AAT? If the immune system has been rewired, how do we know which wires to cut?

Although many more trials will report in 2020, the efficiency of therapeutic development for COVID-19 will require a means of prioritizing targets or many trials will never complete. In this respect, translational studies such as this, in addition to proof-of-concept phase 2 programs such as ACCORD (Accelerating COVID-19 Research and Development) in the United Kingdom, are the key to rapidly prioritize or discard potential therapies (16). ■

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James D. Chalmers, M.B. Ch.B., Ph.D.
Division of Molecular and Clinical Medicine
University of Dundee
Dundee, United Kingdom

Sanjay H. Chotirmall, M.D., Ph.D.*
Lee Kong Chian School of Medicine
Nanyang Technological University
Singapore, Singapore

ORCID IDs: 0000-0001-5514-7868 (J.D.C.); 0000-0003-0417-7607 (S.H.C.).

*S.H.C. is Associate Editor of *AJRCCM*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

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Subclinical Acute Kidney Injury Is Acute Kidney Injury and Should Not Be Ignored

Serum creatinine (SCr) has long been known to be an imperfect biomarker of kidney function (1). Although consensus definitions of acute kidney injury (AKI) using SCr exist, they remain limited (2). More specifically, owing to the nature of renal reserve, it often takes a significant amount of (tubular) injury to translate into a rise in SCr concentrations from baseline (3). Over the last decade, countless investigations have sought to discover and validate biomarkers of AKI that can identify patients who have early kidney injury (4). This concept of elevation in kidney injury biomarkers in the absence of changes in traditional markers (SCr and urine output [UO]) has been dubbed "subclinical AKI" (5). However, given the mounting evidence and multiple methods of detecting this injury, perhaps it needs a different name because it will not be subclinical for much longer. It is with this backdrop that, in this issue of the *Journal*, Dépret and colleagues (pp. 822–829) investigated plasma proenkephalin A (penKid), a 5-kD stable breakdown product of enkephalins that accumulates in the setting of reduced glomerular filtration (GFR) as a biomarker of subclinical AKI in critically ill patients (6).

However, this new work is not the first to look at subclinical AKI; in 2011, Haase and colleagues published a pooled multicenter analysis of prospective studies focused on NGAL (neutrophil gelatinase–associated lipocalin), an iron-binding protein that is upregulated in the setting of ischemic kidney injury (7). In a compilation of 2,322 critically ill patients, they demonstrated that patients who had elevated NGAL concentrations in the absence of changes in SCr (NGAL[+]/SCr[−]) had similar outcomes compared with those with elevations in SCr in the absence of changes in NGAL (NGAL[−]/SCr[+]). However, both these groups experienced more adverse outcomes (need for renal replacement therapy, longer length of ICU stay, and higher inpatient mortality) compared with those with no elevations in SCr or NGAL.

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