bicarbonate in acute illness and comparing different formulations of balanced crystalloids could delineate the respective contributions of each cation and anion to organ function and clinical outcomes. Someday the evidence may allow a verdict on whether the chloride anion is individually guilty of worsening patient outcomes, a contributing accomplice, or an innocent bystander.

Mechanism aside, for the 30 million patients treated with intravenous fluid each year, we believe the weight of the current evidence favors balanced crystalloids over saline. Saline's innocence can no longer be presumed. The burden of proof now lies with those who would defend saline's safety. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Promoting Neutrophil Apoptosis to Treat Acute Lung Injury

To the Editor:

We read with great interest the recently published work of Harris and colleagues in the *Journal* (1). Harris and colleagues explored the significance of neutrophil activity in acute lung injury (ALI) through thoughtful *in vitro* and *in vivo* experiments that aptly demonstrated the potential for therapeutically abrogating disproportionate neutrophilic inflammation by promoting apoptosis. We believe the implications of this study are significant and as such, we also appreciated the accompanying editorial by Summers (2), which deftly relayed why the strategy of abating overzealous neutrophil activity without placing excessive restraint on the host response holds great promise for advancing treatment of ALI. Our position is that of a lab that has devoted decades of research to neutrophil biology in inflammatory disorders, as well as one that has unfortunately often seen neutrophils overlooked, underappreciated, or not considered as viable targets of intervention.

Our pioneering studies agree with the notion that limiting neutrophil activity in the lung is beneficial in the context of ALI. Previous work in our lab used a two-hit mouse model of lung injury (LPS/immune complex) to, for the first time, diminish excessive activation of alveolar neutrophils by specific silencing of Btk (Bruton's tyrosine kinase). Targeted delivery of treatment to alveolar neutrophils *in vivo* elicited a dramatic protective effect by, among other things, ameliorating delayed neutrophil apoptosis and enhancing clearance of apoptotic neutrophils (3). Additionally, MMP-9 (matrix metalloproteinase-9) expression was reduced in neutrophils. This led us to neutrophil-specific silencing of MMP-9, which was observed to dampen proinflammatory neutrophil activity in our two-hit model. Likewise, the mice were protected from ALI. This work was predicated on earlier work that identified Btk as an important regulator of proinflammatory neutrophil activity, including cells from patients with ALI (4). Recently, we used a murine model of influenza-induced ALI to rescue animals from an otherwise lethal infection, and in parallel experiments we observed a significant drop in alveolar neutrophils as well as total white blood cells and multiple proinflammatory cytokines and chemokines present in the lung 7 days after infection (5). This was accomplished via intranasal delivery of the Btk inhibitor ibrutinib/PCI-32765, and because of the essential role of neutrophils in the early stages of infection, in these experiments treatment was administered 48 hours after infection. In addition, silencing of Btk in alveolar neutrophils enhanced neutrophil apoptosis (our unpublished results) and significantly decreased the formation of neutrophil extracellular traps (5). As Harris and colleagues noted in their Discussion, neutrophil inflammation is also an important component in chronic inflammation disorders such as chronic obstructive pulmonary disease. We have also used an atherosclerosis/chronic obstructive pulmonary disease comorbidity mouse model of apolipoprotein E–deficient mice that were regularly exposed to cigarette smoke and/or fed a proatherogenic diet, and whose treatments included ibrutinib or neutrophil-targeted siRNA to MMP-9, which we observed to have a dramatic protective effect (6, 7). Targeting either Btk or MMP-9 reduced arterial plaque growth and increased plaque stability, and furthermore ameliorated alveolar airspace enlargement as well as alveolar wall integrity and airway collagen deposition.

Evidence continues to mount supporting neutrophil apoptosis through targeted intervention as a means of treating inflammation-driven pathology. Harris and colleagues have again shown the instrumental aspects of promoting alveolar

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neutrophil apoptosis in the context of ALI. It is heartening to see fellow members of the innate immunology community further elevating this concept, as we believe it holds great promise for the development of new ALI treatments, which are in dire need of advancement. ■

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Erratum: Multiview Cluster Analysis Identifies Variable Corticosteroid Response Phenotypes in Severe Asthma

The article by Wu and colleagues (1), published in the June 1, 2019, issue of the *Journal*, omitted two grants: NIH P01 AI106684 (to Dr. Sally Wenzel) and a Center for Machine Learning and Health (CMLH) Fellowship in Digital Health (to Seojin Bang). This information should have been included in the footnote at the bottom of the first page.

The authors apologize for the oversight. ■

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