repeated measurements in the clinical setting. A noninvasive test of neutrophil exocytosis would be required before this biomarker could be translated to the clinical setting.

Neutrophil exocytosis–specific inhibitors with antiinflammatory activity have been developed and tested in animal models (10). Could these small-molecule drugs have therapeutic potential in CF lung disease? Although this is an enticing prospect, our understanding of the process of neutrophil degranulation is still in its infancy; therefore, it is difficult to predict whether the neutrophil activation process would be an appropriate therapeutic target. If the major driver for enzyme release is cell death rather than exocytosis from live neutrophils, then pursuing the antiprotease shield mechanism would likely be a more successful approach. Ultimately, longitudinal studies directly assessing neutrophil degranulation will be required to determine exactly how NE and other neutrophil-derived products damage the airways, to better define the best targets for antiinflammatory treatment in patients with CF. ■

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Associations between Ozone and Fine Particulate Matter and Respiratory Illness Found to Vary between Children and Adults

Implications for U.S. Air Quality Policy

Exposure to particulate matter and ozone has severe repercussions on public health in the United States and globally. Fine particulate matter (or $PM_{2.5}$, particulate matter with aerodynamic diameter of 2.5 μm or less) has been associated with exacerbations of asthma and chronic obstructive pulmonary disease, cardiovascular disease mortality, and lung cancer (1–4). Ozone exposure has been linked to increased risks for asthma exacerbations and other respiratory illnesses, as well as to cardiovascular disease mortality (5, 6). Fossil fuel combustion–related emissions of particulate matter and precursors of ozone have been estimated to cause approximately 210,000 premature deaths annually in the United States (7). Further, combustion-related emissions that affect air quality also are the major drivers of climate change. There is new evidence that the effect of climate change on wildfires could double the

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numbers of premature deaths resulting from fine particulate matter exposure by 2100 (8).

The National Ambient Air Quality Standards (NAAQS), established by the U.S. Environmental Protection Agency (EPA) under the Clean Air Act, are the federal standards for air quality levels that are designed to protect the health of even the most vulnerable populations with a margin of safety. As part of the process for establishing the NAAQS, the U.S. EPA reviews and evaluates the "most policy-relevant science, including key science judgments that are important to inform the development of the risk and exposure assessments," in a process called an Integrated Science Assessment (9).

U.S. EPA review of the science has relied on investigations such as the Six Cities Study, which initially found that exposure to fine particulate matter was associated with premature mortality and later found that reductions in fine particulate matter concentrations with EPA enforcement were associated with a decrease in mortality (10). The U.S. EPA estimated in 2011 that control of particulate matter will result in 230,000 adult lives saved by 2020 (11).

Multicity studies have provided evidence for the associations of fine particulate matter and ozone exposures with cardiopulmonary mortality, but not for morbidity. National data on hospitalizations are only available from Medicare, the U.S. system that provides health insurance for adults 65 years and older, and therefore may not be representative of other populations. As noted in this issue of the *Journal* by Strosnider and colleagues (pp. 882–890), evidence for morbidity effects of these pollutants on populations not covered by Medicare has only been found in single-city studies (12). Reliance on these single-city studies for this purpose has been problematic, however, as the characteristics of air pollution and population characteristics vary by city, along with each study's methodology, which makes it difficult to pool these studies to form an evidence base that can be generalized to reflect the U.S. population, let alone populations in other countries.

Strosnider and colleagues have accessed a unique database, maintained by the National Environmental Public Health Tracking Network (13), which contains emergency room visit data for conditions related to environmental exposures, such as respiratory illness. Using daily data at the county level from 17 states, representing 45% of the U.S. population, they were able to analyze associations among ozone, fine particulate matter, and respiratory emergency room visits for all ages in this sample. Ambient air pollution levels were modeled and downscaled to census tract centroids and population-weighted to the county level. Using a two-stage process, the authors fit time-series models and then distributed lag models to account for air pollution effects up to 1 week after exposure, adjusting for pollutants, temperature, dew point, and other variables.

In general, the results of Strosnider and colleagues support the U.S. EPA's determination of a likely causal link between exposures to either fine particulate matter or ozone and respiratory illness (12). However, for the first time, they found that fine particulate matter exposure was more strongly associated with respiratory emergency department visits among children, rather than adults. In contrast, effects were stronger among adults than children for ozone exposure–respiratory emergency department visit relationships. Other pollutant/illness associations they examined also yielded differences by age group. These findings provide evidence that reliance on Medicare data for estimating effects of ozone and fine particulate matter may not accurately estimate effects on populations younger than 65 years. As noted by the authors, age differences in the pollution effects of respiratory illness are supported by varying rates of emergency department visits for respiratory outcomes by age, disease pathology, age-specific patterns of exposure, and even pollutant characteristics.

There are limitations in any study. Although the authors used a robust approach in their analyses, model misspecification, that is, that their statistical model inadvertently missed important variables or proposed a wrong statistical functional form, could always be a possibility. However, the authors conducted sensitivity analyses that indicated that this is unlikely. Misclassification of the respiratory outcomes, if present, also does not appear to be a likely candidate to bias the study results in a particular direction. Exposure error in the pollution model (but likely random with respect to the outcome) and the national representativeness of the final sample are also concerns that may limit the usefulness of the study. However, the estimates provided here are the best evidence to date of age differences in the effects of ozone and fine particulate matter on respiratory illness, which will be very valuable in assessing whether the NAAQS need to be reevaluated.

Ideally, the results of this study would be used in U.S. EPA rulemaking, but it is important to note that these data are based on confidential emergency room visit records, which are maintained by state agencies and were aggregated to protect patient privacy. The currently proposed transparency (so-called "Secret Science") rule by the U.S. EPA would prohibit regulators from considering studies for review in rulemaking that do not provide the underlying data (14). If this rule is approved, then it is possible that these study findings might not be taken into consideration for any changes in the NAAQS on fine particulate matter or ozone, as they are based on personal patient data. In fact, the seminal Six Cities Study results on fine particulate matter and mortality would probably also not be able to be used under the proposed rule. This would be unfortunate, as the best available science would not be included in U.S. EPA's rulemaking, and thus would not provide the best NAAQS to protect the nation's public health. Other recent actions by the U.S. EPA, including disbanding expert science panels that made recommendations on new standards for ozone and particulate matter, as well as moves to eliminate consideration of health cobenefits in calculating costs of pollution rule-making, also bring into question the agency's commitment to defend the public from exposure to harmful levels of these contaminants. ■

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BMP9 Morphs into a Potential Player in Portopulmonary Hypertension

The last 30 years of pulmonary hypertension research is a qualified translational success story. Patients with portopulmonary hypertension (PoPH) have benefitted from inclusion in the licensed indications for novel therapies, despite small numbers of patients enrolled in studies (1). There has, however, been very little movement in our parallel understanding of the pathophysiology. Perhaps as a consequence of this gap between evolving treatments aimed primarily at other disease causes, as well as our lack of mechanistic insight in PoPH, outcomes for patients remain poor. Modern registry data demonstrate 5-year survival stuck around 40% for patients with PoPH, in contrast to the improving survival in other disease forms (2). With a paucity of funded research, limited preclinical modeling, and no real external drivers for industry to engage in this question rather than focus resources on subsets of patients in phase 3 trials, there has been little in the way of new hypotheses to consider. An added complication is that patients have two disease processes, pulmonary hypertension and liver disease, and the relationship between the degree and nature of liver disease and splanchnic and pulmonary pressures has not been clearly resolved (3).

In this edition of the *Journal* (pp. 891–902), Nikolic and colleagues report a potentially fundamental advance in our understanding of disease (4). BMP9 (bone morphogenetic protein 9), a ligand of the TGF-β (transforming growth factor-β) superfamily that has a selective binding affinity to the BMPR2 (bone morphogenetic protein receptor type 2)/ALK1 (activin receptor-like kinase 1) complex, is significantly reduced in PoPH but not in other forms of pulmonary arterial hypertension (PAH). BMP9 is emerging as an important and novel regulator of vascular homeostasis (5). The concept that BMP signaling may be important in the liver vasculature has clear precedent. Hereditary hemorrhagic telangiectasia (HHT) is characterized by arteriovenous malformations that affect organs heterogeneously. They are found commonly in the liver, and HHT is associated in around 80% of individuals with mutations in ALK1 and the circulating coreceptor endoglin (6). In addition to the established link between HHT, BMP signaling, and PAH, the genetics of PAH have been pointing for some time to the critical importance of this specific ligand and its receptor complex. Completing the tertiary receptor/ligand complex, mutations in BMPR2 and BMP9 cause PAH (7). Fitting beautifully with the human genetics, the BMPR2/ALK1/endoglin tertiary complex is highly expressed in the pulmonary endothelium, and BMP9 circulates at physiological levels (8). To complete the background story, BMP9 is produced predominantly by the liver (9).

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