It is then reasonable to speculate that both aspirin and 5-LO inhibitors benefit AERD through the same final common pathway; namely, the blockade of PgD2 production. The LTE4 receptor is highly expressed on epithelial cells and mast cells. Engagement of these receptors on epithelial cells (15), in part through their secretion of IL-25, IL-33, and TSLP (thymic stromal lymphopoietin), can indirectly drive mast cell activation and PgD2 production. But CysLTs, including especially LTE4, also act directly on mast cells to cause PgD2 production (16). Thus, an intriguing solution to the paradox of both 5-LO inhibitors producing decreased CysLT expression and aspirin administration's increased CysLT expression being beneficial in AERD would be that both agents ultimately act to decrease PgD2.

In summary, this study points to the central role of the mast cell in the pathogenesis of AERD, with mast cell–derived PgD2 potentially being a central pathogenic mediator. And any mechanism that blocks PgD2 pathways, including CysLT synthesis inhibitors, cyclooxygenase inhibitors, or perhaps in the future, CRTH2 antagonists, can form the basis for clinical improvement. ■

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Indoor Endotoxin Exposure and Ambient Air Pollutants Interact on Asthma Outcomes

It is now quite well established that ambient (outdoor) air pollution is a health risk and contributes substantially to the global burden of disease. The mortality and morbidity burden resulting from ambient air pollution has increased during the last 2 decades (1). Human populations breathe complex mixtures of air pollutants, allergens, and irritants. It has been known for some years from small controlled clinical trials that ambient air pollutants such as ozone (O_3) (2), nitrogen dioxide (NO_2) (3), and combinations of these gaseous pollutants (4) interact with allergens on physiological outcomes in people with allergic asthma. Much more has been learned in recent years about the effects of fine particles (particulate matter <2.5 μm in aerodynamic diameter [$PM_{2.5}$]) on asthma and other chronic diseases (5). A major constituent of $PM_{2.5}$ in urban environments is diesel exhaust particles, which have been shown to bind the major grass pollen allergen (6).

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However, in Western societies, most people spend the vast majority of their time indoors, where the mix of air pollutants, allergens, and irritants is different. The predominant indoor allergens include those derived from house dust mites, pets, cockroaches, and molds. Endotoxin is a constituent of gram-negative bacteria, often found in house dust and some occupational settings, which increases the risks for asthma and chronic bronchitis, but perhaps paradoxically also appears to confer some protection against the development of asthma in children (7, 8).

In this issue of the *Journal*, Mendy and colleagues (pp. 712–720) report a large cross-sectional analysis of data from the National Health and Nutrition Examination Survey (9). This paper presents some novel findings of synergistic interactions between house dust endotoxin and ambient air pollutants on asthma in both children and adults. The participants in dust sampling were reasonably representative of the US population, although the Midwest region was slightly oversampled. A well-standardized, highly sensitive endotoxin assay was used.

A two-stage model strategy was used to estimate ambient air pollutants ($PM_{2.5}$, NO_2, and O_3). At the first stage, meteorological data and chemical reaction kinetics were used to estimate the annual average concentrations of air pollutants at grid level (36×36 km) by the Community Multiscale Air Quality model. At the second stage, a Downscaler model and monitored air pollution data were used to downscale the estimated air pollution concentrations into a finer grid level (12×12 km). This method has been validated and is useful for health risk assessment. However, the introduction of remote sensing data, land use information, and road information as predictors, as well as application of a machine learning method, could further improve exposure assessment for future studies (10). The measurement error would be smaller, leading to unbiased effect estimates (11).

Well-validated asthma outcomes from the National Health and Nutrition Examination Survey were analyzed by Mendy and colleagues (9). A wide range of serum allergen-specific IgE was measured *in vitro*, so the classification of atopy was as good as possible. The statistical analysis allowed for the relevant potential confounders including age, sex, ethnicity, socioeconomic status, household smoking, body mass index, and urbanization, which were fitted to multivariate logistic models.

Importantly, the geometric mean concentrations of $PM_{2.5}$, O_3, and NO_2 were not particularly high; all were well below the U.S. Environmental Protection Agency National Ambient Air Quality standards for annual averages. More interactions between endotoxin and air pollutants were found on emergency room (ER) visits for asthma in the last 12 months than would have been expected by chance. Specifically, higher endotoxin and $PM_{2.5}$ concentrations were associated with ER visits in all participants, and higher endotoxin and NO_2 concentrations were associated with ER visits in children. Interactions were mostly confined to those participants sensitized to aeroallergens.

These important findings are both biologically and epidemiologically plausible. We agree with the authors that further prospective cohort studies are needed to confirm whether similar interactions can be demonstrated in patients with other conditions such as chronic obstructive pulmonary disease, and we would add bronchiectasis, cystic fibrosis, and idiopathic pulmonary fibrosis. New strategies are needed to reduce ambient $PM_{2.5}$ and NO_2 concentrations, such as reductions in primary emissions and ammonia (12), through incentives for greater use of electric vehicles and increasing pollution taxes (13). Indoor endotoxin concentrations could be reduced by measures such as household hygiene and cleaning, avoidance of biomass fuels (14), choice of home flooring, and keeping pets such as dogs outdoors (15). There may also be some role for home air purification units, including high efficiency particulate air filters to reduce airborne concentrations (16).

At a time when some politicians appear determined to ignore the evidence and water down long-standing protections to public health, demonstration of new interactions between indoor and outdoor air pollutants serve as an important reminder of how much still remains to be understood. The confirmation of health effects at concentrations below current standards emphasizes the importance of adequately protecting our patients with chronic lung diseases. If anything, after considering other recent studies, ambient air quality standards need to be further strengthened. ■

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Genetics, Chronic Obstructive Pulmonary Disease, and the Arrow of Time

On November 23, 1963, the day after John Kennedy died in Dallas, the city that hosted the annual meeting of the American Thoracic Society this year, a new children's television program was aired in the United Kingdom. It was called *Doctor Who* and is still running on BBC America 56 years later. Its key premise was that the Doctor could travel in space and time, thereby contravening our accepted idea that time and events flow in a linear fashion from past to future. This concept, often called time's arrow, was elegantly reviewed by the late Stephen Jay Gould in his book *Time's Arrow, Time's Cycle* (1), which contrasted the linear modern view of time with older views that could be summarized as "what goes around, comes around." From the Enlightenment onward, scientists have accepted a fairly straightforward view of cause and effect in medicine, but this approach has been challenged with the advent of "big data" and the possibility that new, nonlinear relationships will emerge that will increase our understanding of disease.

Genetics is one of the areas that have benefited most from these new computational approaches, which are essential for understanding the inherited contribution to complex multifaceted chronic conditions like chronic obstructive pulmonary disease (COPD). The recognition of the existence of specific abnormalities, such as alpha-1 antitrypsin deficiency and cutis laxa, which lead to premature emphysema, and the genetic associations of SNPs with lower lung function have stimulated the search for more genes associated with both states. Associations with some SNPs, such as the α-1 nicotinic acid receptor and hedgehog interacting protein, were relatively easy to identify (2). However, much larger studies that used genome-wide association study methodologies, including COPD-focused studies like ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoint) (3, 4) and COPDGene (5), were needed before consistent results began to emerge from groups of SNPs that predicted lower lung function or the presence of clinically diagnosed COPD. Data from the UK Biobank study added 43 new genes to the list of associations for impaired lung function in adults (6), and the search for an even better definition of these relationships continues. What is less clear is what knowledge of these genetic risk factors tells us about the functional abnormality we can measure or the structural damage that we believe should precede functional problems.

In this issue of the *Journal*, Oelsner and colleagues (pp. 721–731) provide us with new information that addresses this problem (7). They used a weighted genetic risk score (GRS) for impaired lung function based on 95 SNPs, including those already identified in multiple data sets as relating to lung function and the new candidates from the UK study (6). They determined the ability of these genes to predict either impaired lung function or a diagnosis of COPD in participants in two different populations: the MESA (Multi-Ethnic Study of Atherosclerosis) Lung cohort, a general sample of U.S. adults (8), and the SPIROMICS (Subpopulations and Intermediate Outcomes in COPD Study) cohort of smokers with or at risk of developing COPD (9). Participants in these studies had high-quality inspiratory and expiratory computed tomography (CT) scans that permitted the quantification of lung density, airway morphology, especially small airway abnormalities using parametric response mapping (10) which was available in the SPIROMICS population and the total small airway count in both population which has been reported as being in other population-based studies studying early COPD (11). Using appropriate statistical modeling and relevant sensitivity analyses, they found that the GRS predicted both the risk of impaired lung function and the chances of having moderate/severe COPD, although the explanatory power was at best modest. The GRS was associated with a range of structural abnormalities on the CT scans, especially thinner airway walls and fewer small airways. However, when they combined the CT variables with conventional clinical predictors of COPD incidence, not only did the C-statistic, a measure of the accuracy of the prediction, rise above 0.9 but the GRS contributed no additional information, irrespective of the ethnicity of the participants.

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