treatment in the drinking water would also deplete the GI microbiota. The GI microbiome can have profound effects on systemic inflammatory processes and may influence lung disease (14,15), so examination of its effect in this model would be informative.

Yadava and colleagues present a tantalizing possibility that the lung bacterial microbiome plays a causal role in chronic lung inflammation and COPD (10). If these results hold up to the validation in other animal models of COPD and in humans, the microbiota could be a tangible goal for therapeutic interventions. Indeed, antibiotics have a beneficial effect on exacerbations of COPD (16) and might be able to be used in a more targeted approach based on the lung bacterial microbiome. Alternatively, manipulation of specific aspects of the immune response to the microbiome could improve outcomes in COPD. With this study, we truly are launching out into the deep, and whether the investigation of lung bacterial microbiome causality in COPD sinks or swims will depend on the ability to meet the substantial challenges posed by these investigations. ■

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How Can We Protect Susceptible Individuals from the Adverse Cardiovascular Effects of Air Pollution?

Air pollution is thought to be responsible for 7 million premature deaths worldwide each year, with the majority of deaths resulting from cardiovascular disease (1, 2). During the last 10 years, key mechanisms have emerged that link exposure to air pollution with the onset, progression, and clinical manifestations of cardiovascular disease (3). However, few studies have addressed whether these adverse effects of exposure to air pollution can be diminished or prevented. As such, our guidance to vulnerable individuals or those with established cardiovascular disease is based on expert consensus, rather than the results of rigorous clinical trials.

Chamber studies that permit controlled exposures to air pollutants under carefully regulated conditions have been invaluable in advancing our understanding of the health effects of air pollution in man. Even brief exposures to diesel exhaust at concentrations encountered in heavy traffic promote vasoconstriction (4), impair

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vasodilatation (5), and increase arterial stiffness (6). These effects are thought to occur as a consequence of millions of nanoparticles that penetrate deep into the lung and deliver reactive chemicals, instigating oxidative stress and inflammation (7). Indeed, removing nanoparticles from diesel exhaust through filtration prevents these cardiovascular effects (8). Although preventing exposure is clearly preferable, how can we identify and protect those at greatest risk of harm now? Can we harness our understanding of the pathophysiological effects of exposure to air pollution to design preventative strategies that limit their harmful effects?

In this issue of the *Journal*, Sack and colleagues (pp. 1000–1007) evaluate whether the use of antioxidant supplementation with ascorbate and *N*-acetylcysteine before exposure to diesel exhaust can prevent adverse vascular effects in a small, randomized, placebo-controlled clinical trial (9). They observe that exposure to diesel exhaust resulted in acute vasoconstriction in men and women without cardiovascular disease. Interestingly, these effects were more marked in individuals with variant alleles of the type 1 angiotensin II receptor (*AGTR1*), suggesting the adverse vascular effects of exposure to diesel exhaust may be mediated through the renin–angiotensin system. Perhaps surprisingly, antioxidant pretreatment not only did not prevent this effect but also appeared to augment the acute vasoconstrictor effects of exposure to diesel exhaust.

Unfortunately, seemingly paradoxical findings are not uncommon in studies of antioxidant supplementation, and there are a number of plausible explanations. First, in individuals without vitamin C deficiency, the absorption of high-dose oral ascorbate is limited, and supplementation may not significantly increase antioxidant levels in the vasculature. Limited bioavailability is unlikely to be the only explanation, as even direct intra-arterial infusions of vitamin C do not consistently reverse the endothelial dysfunction associated with cigarette smoking (10). There is some evidence that vitamin C supplementation can exert prooxidant effects (11) and impair vasodilatation to endothelial-derived hyperpolarizing factor (12). Together, these observations provide a plausible explanation for the enhanced vasoconstriction associated with antioxidant supplementation in the present study. Second, despite the evidence from cell and animal studies that air pollution induces oxidative stress, there remains little direct evidence to support this hypothesis in man. It is possible that the other mechanisms, such as activation of the autonomic nervous system or translocation of nanoparticles into the circulation, may account for the adverse cardiovascular effects of vehicle emissions.

Human exposure studies have made a major contribution to our understanding of the adverse health effects of air pollution. The contribution by Sack and colleagues is an important addition, and one of the few randomized controlled studies to evaluate the effectiveness of an intervention in modifying the effects of exposure (9). The study was well designed and included an exposure to filtered air and a matched placebo control. It seems unlikely, therefore, that the investigators have missed an important beneficial effect of ascorbate and *N*-acetylcysteine. Interestingly, studies in animals have shown that several therapies can attenuate the cardiovascular actions of exposures to particulate air pollutants, including statins (13), inhibitors of the renin-angiotensin system (14), endothelin receptor antagonists (15), β-blockers, and capsaicin receptor (*TRVP1*) antagonists (16). Whether use of these therapies will modulate the effects of air pollution on the cardiovascular system in man is not known.

A novel aspect of the study by Sack and colleagues was the use of stratification based on common variants of genes involved in oxidative stress, the renin-angiotensin system, and nociception (9). Although there was no difference in the vascular effects of exposure to diesel exhaust in individuals with variants in the glutathione-S-transferase (*GSTM1*) gene, those with the AC/CC allele in the AGTR1 or the CC/CT allele for the *TRPV1* gene had more marked vasoconstriction than those individuals without. Although the study was underpowered to formally identify effect modification by these genetic variants, this approach has the potential to provide novel mechanistic insight and identify susceptible individuals. Observational studies support the concept that elderly individuals or those with preexisting cardiovascular disease are more susceptible to air pollution, although it has been challenging to demonstrate this in controlled exposure studies, as these groups already have marked vascular dysfunction before exposure (17, 18). The current study by Sack and colleagues suggests an alternative approach to identifying susceptibility may be possible, but these observations need to be verified in larger studies with interventions targeting the renin angiotensin-system and alveolar nociceptive sensory receptors (9).

Although determining whether preventative strategies in susceptible individuals are likely to be effective is undoubtedly important, this research also serves to highlight that our environment is an important and modifiable risk factor for cardiovascular disease. Addressing the complex societal and political barriers to limiting our emissions is challenging, and in many countries, especially developing countries with large urban populations, air pollution is escalating to previously unseen levels. At present, the best the scientific community can do is support regulations that limit important sources of air pollution and pragmatic policies that aim to reduce risk through traffic restrictions, and provide advice to vulnerable individuals to minimize exposure during major air pollution episodes. ■

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Two Faces of Sarcoidosis
A Genetic Insight?

Sarcoidosis is characterized as a multisystem granulomatous disorder of unknown origin (1, 2). In many cases, it presents as a classical triad of erythema nodosum, bilateral hilar lymphadenopathy, and polyarthralgia, eponymously known as Löfgren's syndrome (LS) with a characteristically acute onset, relatively mild symptoms, and a benign self-limiting course (3). At the other end of the spectrum are those patients who have progressive, often unremitting disease with tissue destruction and fibrosis and significant long-term sequelae and significant extrathoracic disease. In terms of therapy for the former, it is often not needed, whereas for the latter group, a variety of immunomodulatory therapies are used, based on limited evidence and with variable effect (4). The underlying pathogenesis of sarcoidosis has been a controversial issue since it was first described, and the knowledge that granuloma are induced by such a wide variety of antigens from infectious agents to metal exposure in the workplace makes the comprehensive understanding of this condition subject to significant complexity, as with many other lung diseases (5). Genetics can be considered the ground floor of understanding for such conditions, but so far, this knowledge gap has remained unfilled.

In this issue of the *Journal*, Rivera and colleagues (pp. 1008–1022) use a fine-mapping genotyping platform to dissect the genetic architecture of sarcoidosis (6). They have presented the results of the largest genome-wide association study on LS and non-LS sarcoidosis phenotypes. In addition, the adopted bioinformatic, integrative approach they have employed, combining differential gene expression from publicly available sarcoidosis samples and expression and expression quantitative trait loci information obtained from various tissues and cell types related to immunity (from ENCODE [Encyclopedia of DNA Elements] and the National Institutes of Health Roadmap Epigenomics Mapping Consortium), facilitates translation of this knowledge to the clinic.

The initial study was undertaken in a sample of Swedish white patients and then replicated in four independent cohorts, three of white European descent (from Germany, the Netherlands, and the Czech Republic) and one of black African descent, for a total of more than 7,000 subjects. This replication and the additional gene centric analysis have led to a genuine tour de force of the genetic differences in immune-related genes for LS and non-LS phenotypes.

Rivera and colleagues report that the LS group is more genetically homologous, with almost an order of magnitude greater number of associated variants identified compared with the non-LS group and a small number of shared loci. Intriguingly, and as confirmed in many other genome-wide association studies, common genetic variants can only explain a small portion of the phenotype variability and heritability, emphasizing the likelihood of other genetic and regulatory elements to be involved (7). In non-LS, a significant number of non-HLA genes were identified, raising the possibility of additional "gene × factor" interaction across the chromosomes. In contrast, in LS there is a higher presence of HLA genes, suggesting the phenotypic variability to be