[Translating Basic Research Into Clinical Practice]

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Synergistic Environmental Exposures and the Airways Capturing Complexity in Humans—An Underappreciated World of Complex Exposures

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Paradoxically, the vast majority of research models intended to understand the relationship between exogenous exposures and lung disease are reduced to a single inhalant. This approach is understandable given the practical challenges of investigation, but it is problematic in terms of translation to the real-world human condition. Furthermore, use of data from such models can lead to underestimation of effect, which may adversely influence regulatory imperatives to protect public health based on the most robust information. Efforts to incrementally introduce layers of complexity to observational and experimental systems have revealed pathophysiology previously "hidden" within simplified models. Capturing the effects of co-exposure to traffic-related air pollution and allergens is a paradigmatic example and illustrates the influence of co-exposures across a plethora of clinical and subclinical end points within the respiratory tract. From DNA methylation in the epithelium, to inflammatory mediators and allergen-specific antibodies in the airway, to airflow limitation and symptoms, the addition of a common second exposure induces profound changes. In addition, genetic variation significantly alters the product of these relationships, and capturing multidimensional interactions may reveal susceptible populations who are particularly affected by these exposures and may merit focused measures for protection. Collectively, better modeling, and ultimately deeper knowledge, of these complex relationships has important implications for personalized health and prevention, development and refinement of pharmacologic agents, and public health responses to climate change and the staggering burden of pollution-driven disease worldwide.

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Despite the reality of our world, in which we inhale mixtures of immunologically active components, our research models are dominated by reductionist approaches to understanding exposure-response relationships. Although observational (eg, epidemiologic) approaches are inherently better able to reflect the product of real-world complexity, they are poorly able to dissect causal pathways. Experimental models can fill this gap, aiming to understand the precise exposure conditions

ABBREVIATIONS: Th_2 = T helper 2; TRAP = traffic-related air pollution

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that lead to adverse health effects, and thus helping to critically focus and direct efforts to remediate, prevent, and treat the adverse conditions resulting from these exposures. Even within the experimental arena, however, our increasingly sophisticated ability to capture the myriad end points of dynamic pathophysiological processes has not been matched in terms of our understanding of the inputs into these sensitive systems. Exposomics[1] is a nascent attempt to capture the depth of these myriad stimuli, but it remains lagging relative to the proliferation and precision of technologies that measure the product of exposure; bold efforts are underway to narrow that gap, and yet the resolution-limiting step still seems careful attention to exogenous environmental contributions to the system (without which interpretation of, and action upon, the modifiable system elements will remain problematic).

Given these issues, the goal of the present article was to delineate the risks of simplified exposure models, illuminate the value of understanding the effects of co-exposures, and discuss the translational implications of looking beyond simple exposure models in terms of clinical concerns and for public health. It is acknowledged that the perspective is focused on airways disease and relies heavily on this clinician-scientist's experience with a particular model and, furthermore, and that a full treatment of synergistic exposure-response relationships is beyond the scope of this article. However, the context is broadened, where possible, to make more points of more general interest to the reader.

The concept of interaction between multiple exposures is not new, and it has long been appreciated that co-exposures may have agonistic (additive or multiplicative) or antagonistic effects.[2] Furthermore, it is recognized that observation on the population level obscures individual differences, the resolution of which has important implications for not only understanding exposure-effect relationships but also for more precisely targeting preventive and therapeutic initiatives.[3] Moreover, the burgeoning of investigation into gene-environment interactions has provided additional insight into how genetic variation can further alter these relationships (eg, through gene-exposure-exposure, gene-gene-exposure, subsequent layered modifying effects). Knowledge of these interactions potentially informs our approach to forestall, remediate, and manage adverse outcomes.[4]

Historical examples of where a careful examination of co-exposures provided insight are woven throughout the literature in epidemiology, toxicology, and controlled experimental models. Although the present review is centered on airways disease, we recall the seminal work of Selikoff and others to delineate the staggering potency of cigarette smoking combined with inhalation of asbestos in terms of risk for lung cancer.[5] Other potent combinations (Fig 1) include diesel exhaust particles plus viruses (eg, influenza), particulate matter plus endotoxin, nitrogen dioxide plus allergen, endotoxin plus allergen, and diesel exhaust plus allergen (Fig 2). The changes induced by co-exposures can be dramatic. For example, exposure to diesel particulate matter prior to infection with influenza (in mice) led to large increases in eosinophils, both within the airway lumen and infiltrated into the surrounding tissue, compared with that observed with influenza alone.[6] In another illustrative example, elevated exposure to both allergens and common respiratory viruses substantially increased the risk of admission for asthma (above the risk associated with either exposure alone).[7] Another study showed how diesel exhaust particles decrease the production of IL-12 normally associated with exposure to endotoxin, leading to unopposed production of T helper 2 (Th_2) cytokines.[8] Endotoxin, along with course particulate matter in particular, markedly increased neutrophilic inflammation and upregulated macrophage surface receptors in the lower airway.[9] Other studies have illustrated the potency of allergen combined with endotoxin, in terms of both neutrophilic and eosinophilic inflammation,[10] and others have reported a potential mechanism (increased CD14 expression)[11] for this phenomenon.

In some cases, one must explore a multilayered combination of exposures (beyond combinations of two factors alone) to spotlight airways disease,[12] demonstrating that even the laudatory efforts to examine pairs of inhalants may prove simplistic in the future. As noted previously, exposomics boldly and innovatively attempts to tackle this complexity but to date has remained more conceptual than concrete[13-16] and framed from a systemic rather than lung-focused perspective. However, some very helpful proof-of-concept studies are emerging, and the field is likely to accelerate further in importance and impact.[17,18] Importantly, such cohesive approaches, from an agnostic lens (without preconceived notions of the range of effects that can result from exposure combinations), may reveal unknown pathways that can be leveraged to reduce disease burden. Although targeted studies tend to pursue combinations that are suspected or assumed to

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