An exposome perspective: Early-life events and immune development in a changing world

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Advances in metagenomics, proteomics, metabolomics, and systems biology are providing a new emphasis in research; interdisciplinary work suggests that personalized medicine is on the horizon. These advances are illuminating sophisticated interactions between human-associated microbes and the immune system. The result is a transformed view of future prevention and treatment of chronic noncommunicable diseases, including allergy. Paradigm-shifting gains in scientific knowledge are occurring at a time of rapid global environmental change, urbanization, and biodiversity losses. Multifactorial and multigenerational implications of total environmental exposures, the exposome, require coordinated interdisciplinary efforts. It is clear that the genome alone cannot provide answers to urgent questions. Here we review the historical origins of exposome research and define a new concept, the metaexposome, which considers the bidirectional effect of the environment on human subjects and the human influence on all living systems and their genomes. The latter is essential for human health. We place the metaexposome in the context of early-life immune functioning and describe how various aspects of a changing environment, especially through microbiota exposures, can influence health and disease over the life course. (J Allergy Clin Immunol 2017;140:24-40.)

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> "Human biology should be primarily concerned with the responses that the body and the mind make to the surroundings and ways of life…little effort has been made to develop methods for investigating scientifically the interrelatedness of things. Epidemiological evidence leaves no doubt that many chronic and degenerative disorders which constitute the most difficult and costly medical problems of our societies have their origin in the surroundings and in the ways of life rather than in the genetic constitution of the patient. But little is known of these environmental determinants of disease."
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> — Rene J. Dubos, Keynote Lecture at the 25th Annual Meeting of the American Academy of Allergy, Asthma & Immunology, 1969[1]

Almost 50 years have passed since renowned microbiologist Rene Dubos (1901-1982) addressed his colleagues in allergy and immunology with the Robert A. Cooke keynote lecture entitled "Spaceship Earth."[1] For the previous decade, Dubos had been performing studies with germ-free (GF) and specific pathogen-free mice to determine the effects of nutrition, stress, maternal care, housing conditions, social interactions, and sanitation on immune function and health over the life course. His research extended into the transgenerational health effects of these variables. Much of this groundbreaking work is captured in his classic reviews[2,3] and the book *Man Adapting*.[4]

The message was simple and applies equally today: rapid changes in the modern environment are intertwined with immune health through synergistic biological, psychological, social, and ecological factors. Multifactorial investigations with new conceptual and experimental methods characterizing health promotion and health risks throughout life would be required to solve complex problems. Thus modernity demands a new systems approach from scientists involved in allergy and immunology. Dubos referred to this novel approach as "environmental biology" in the context of human ecology, a new paradigm in which single-variable examinations will not suffice. Rather, this must encompass a simultaneous merger of bench, epidemiologic, and clinical investigations with an aim toward studying a subject

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Abbreviations used
DC: Dendritic cell
GF: Germ-free
GIT: Gastrointestinal tract
GWAS: Genome-wide association study
NCD: Noncommunicable disease
PCB: Polychlorinated biphenyl
SCFA: Short-chain fatty acid
TLR: Toll-like receptor

from the perspective of synergy: examining interactions between exposures (some positive and some negative) across time. In his words, the way forward was to understand "the response of the total organism to the total environment."[5]

At the 1969 American Academy of Allergy, Asthma & Immunology meeting, Dubos made 3 additional forward-thinking arguments to his audience. First, he opined that the manifestations of allergy in the broadest sense of the term (ie, altered reactivity to the changing westernized environment) would not be fully realized for decades. In other words, he was positing that an impending epidemic of noncommunicable diseases (NCDs), including mental disorders, was not unrelated to allergy in both its narrow clinical definitions (ie, comorbidity with allergic diseases and asthma) and its etymological root (ie, "altered reactivity" based on an evolutionary mismatch with the total modern environment means virtually all NCDs are indeed in the realm of allergy). Second, he underscored that changes to the health of the external environment (eg, biodiversity losses and environmental degradation) were matters of importance to allergy and immunology. Third, although he conceded that much of the technology to objectively measure multiple factors, especially clinically relevant molecular biology, at community and population scales were not available (then) or cumbersome to implement (an argument that still exists), the future burden of NCDs should be enough to galvanize a different approach to population health.

Four months before the lunar landing, Dubos called for a "massive effort similar to the one initiated by NASA" to help allergists and immunologists understand health from the perspective of the total environment. The idea was to study genes–total environment interactions over time with exposures that also include social policies and practices. He sought not simply to understand the single or even synergistic ways in which several objectionable pollutants damage health, act as allergens, and cause altered reactivity but also to learn the elements of an environment that actually promote human health over the life course.[5,6] He pleaded for knowledge of the total environment that equates to health wherein it is defined not simply as being free of atopic dermatitis but a state conducive to reaching human potential.

BEYOND THE GENOME

Half a century later, the total environment perspective is of massive importance not only to personal and public health but also to planetary health. The very limited causative role played by pure genetic factors in patients with chronic disease,[7] as witnessed by the tremendous global increases in NCDs, especially allergic diseases,[8] underscores the urgency of the total environment perspective. Thus despite elegant mechanistic insights provided by genome-wide association studies (GWASs), we are learning the hard way that environmental exposures, both detrimental and nourishing, manifest in personal and population health outcomes. Moreover, GWASs demonstrate that genes alone cannot explain major health disparities, nor can they explain why NCDs do not occur randomly in westernized populations. Instead, NCDs operate in a slanted direction, where the burden points to the socioeconomically disadvantaged.

The multifactorial study of health as mediated by total environmental exposures over the life course, as originally proposed, has taken various names, including the developmental origins of health and disease concept,[9] the envirome,[10] environomics,[11] and, more recently, the exposome.[12] In each case the nomenclature is unified by understanding that although genetic factors matter, total health is not a genetic trait. It is also understood that the environment is not a static variable. and certain windows of vulnerability (for disease risk) and opportunity (for health promotion) can present themselves in interactions between genes, environment, and time (Fig 1).

Remarkable advances in objectively measured end points allow for assessments of biological tissue, immune programming, and related physiology, such as oxidative stress, hormonal activity, and neuropeptides. Moreover, the increase in high-throughput molecular -omics techniques can produce large data sets from analysis of functional proteins (proteomics), metabolites (metabolomics), gene expression (epigenomics and transcriptomics), and genetic influences on drug/isolated nutrient metabolism (pharmacogenomics).[13] The potential application of -omics in conjunction with bioinformatics and biostatistics represents an important step toward narrowing the gap between GWASs and the obvious need for environment-wide association studies of individual subjects and communities in their total dynamic environment.

Despite their many differences, NCDs are most often united by the common threads of immune dysfunction and chronic low-grade inflammation. More recently, we are learning that alterations of the human microbiome, microorganisms, and their collective genome residing in an anatomic niche are deeply connected to most NCDs, including mental disorders.[14] In part, this might explain the high levels of overlap between NCDs, such as allergic diseases and mental disorders.[14,15] The emerging science of the microbiome and its influence on early-life immune priming to be discussed below has forced a total environment perspective.

Although the term dysbiosis is often confined to its definition as perturbations of gut microbiota, it formally translates as "difficult living" or "life in distress." Climate change, biodiversity losses, pollution, environmental degradation, rapid urbanization, and a general disconnection from nature are causing distress at the global scale. Planetary distress in the Anthropocene is pressing on the discipline of allergy and immunology and the patients encountered.[16]

Today, we are past time for a NASA-like effort. Carefully designed, -omics–inspired megacohort studies with expert input from transdisciplinary teams will help provide a blueprint for the total environment that promotes health. Specifically, the exposome is not merely pollutants; diet, tobacco, and other lifestyle factors meet the internal/skin microbiome, and stress and immune function meet social capital, socioeconomic status, and/or the presence or absence of green space and other potentially beneficial aspects of natural environments. The term total environment can often become constricted.

We define the exposome as the aforementioned, plus the policies and practices that drive global NCDs.[17] For example, the sum of combined marketing–dietary choice evidence meets