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The Nature of Nurture: Refining the Definition of the Exposome

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We Need an Output of Environmental Exposures as Tangible as the Mutated Gene

NATURE VERSUS NURTURE

Historical debates concerning human biology and behavior have frequently focused on contributions of nature, ie, the inherited characteristics with which we are born, and nurture, ie, life's influences after birth. Indeed, the concept of nature vs nurture has guided our understanding of human biology for decades, if not centuries. A series of discoveries has greatly advanced the knowledge of our nature. Watson and Crick's unraveling of the double helix revolutionized the understanding of our genetic makeup (Watson and Crick, 1953). The polymerase chain reaction allowed amplification and manipulation of genes (Saiki *et al.*, 1988). Identified links between specific genes and disease (Saiki *et al.*, 1985) led to new diagnostic tools and treatments. These advances spurred the Human Genome Project with success in sequencing the entire human genome (Lander *et al.*, 2001; Venter *et al.*, 2001). This epic undertaking of biomedical science and technology was completed with amazing speed and celebrated with great fanfare. But the limitation of genetics to predict disease rapidly became obvious; as noted by Dr Venter shortly after the completion of human genome sequence, "We simply do not have enough genes for this idea of biological determinism to be right (McKie 2001)."

Genome-wide association studies (GWAS) have revealed genetic associations and networks that improve understanding of disease, but these still account for only a fraction of disease risk. With the majority of disease causation being nongenetic, the need for improved tools to quantify environmental contributions seems obvious. The simple distinction between genes and environment is blurred by knowledge that environmental exposures cause permanent genetic changes via mutagenesis and also have long-term impact on gene expression through epigenetic mechanisms. Importantly, epigenetic mechanisms are central to differentiation and development, impacting genome function before birth and throughout life.

The epigenome is highly reliant on nurture, ie, the nature and timing of environmental exposures and external forces. Randy Jirtle, a pioneer in epigenomics stated "The nature vs. nurture argument is rapidly proving to be irrelevant, because we're finding that the 2 forces interact in highly specific ways that alter gene behavior (Duke Health, 2006)." Although Dr Jirtle suggests the argument is becoming irrelevant, the reality is that biomedical research is overwhelmingly focused on the gene side of this debate. The tools and knowledge of our nature are far ahead of those for the environment. If we want to focus on the interaction between nature and nurture, we need better ways of cataloguing and integrating the complex exposures and forces that represent nurture. Such a framework is provided by the exposome.

THE EXPOSOME: A WILD IDEA

In 2005, Dr Christopher Wild coined the term "exposome" and provided the basis for the concept (Wild, 2005). In brief, Dr Wild suggested that the exposome "encompasses life-course environmental exposures (including lifestyle factors), from the prenatal period onwards." Science and medicine have responded slowly to the concept (Rappaport and Smith, 2010), perhaps because the original definition appeared confined to exposure assessment. A more appropriate position for the exposome is on par with the genome as a foundation for contemporary medicine and public health. This is not to diminish the importance of chemical exposures but rather to place those exposures within the broader context of diet, behavior, and other exogenous and endogenous agents (Jones *et al.*, 2012). With systematic information on exposures, environment-wide association studies (Patel *et al.*, 2010) could become much more powerful and complement GWAS and deep sequencing studies.

In our view, the exposome is even more expansive than what Dr Wild described 9 years ago. The exposome captures the essence of nurture; it is the summation and integration of external forces acting upon our genome throughout our lifespan (Miller, 2014). What we eat, where we live, the air we breathe, our social interactions, our lifestyle choices such as smoking and exercise, and the inherent metabolic and cellular activity manipulate the biology encoded by our genome. This measurable quantity of the exposome represents a biological index of our nurture and is the context in which specific exposures have impact on health.

To date we have not seen much about the exposome in the pages of toxicology and biomedical science journals because the exposome was framed as a challenge to the field of exposure assessment. Although there is no doubt that exposure science will play an integral role, the exposome demands more. The exposome must explicitly include how our bodies respond to environment pressures, including epigenetic changes and mutations, as well as the complex chemistry resulting from the biochemical reactions that sustain our lives. This prompts a refined definition:

***Exposome:* The cumulative measure of environmental influences and associated biological responses throughout the lifespan, including exposures from the environment, diet, behavior, and endogenous processes**

There are 3 distinct differences between our definition and that of Dr Wild. The first is the concept of the cumulative biological responses. This captures the ongoing adaptations and maladapations to external forces and chemicals and represents the body's response to these challenges. The second is the inclusion of behavior. This is used in a very broad context to include personal and volitional actions and those that result from family, community, or social units. It goes beyond lifestyle to include the dynamic interaction with our surroundings, including relationships, interactions, and physical and emotional stressors. A third change is the addition of "endogenous processes." Our bodies are complex biochemical reaction vessels with countless reactions occurring at any time. Glycolysis, oxidative respiration, microsomal p450s, and many other systems are generating new species and breaking down others. Even the microbes that constitute our microbiome play an important role and fall under the "endogenous processes." The complex exposures are still at the heart of the definition, but the lingering damage; the DNA mutations or adducts, epigenetic alterations, and protein modifications are just as important as the chemicals themselves. In fact, they provide the evidence of an actual effect and may be more readily interrogated, eg, decades after exposure.

As toxicologists, we are especially interested in studying the impact of chemicals on biological systems. Research on the exposome is the epitome of such an endeavor. Although exposome research will likely be led by environmental health sciences (exposure science, environmental epidemiology, and toxicology), it will require the involvement from a wide range of disciplines. *This is not a challenge restricted to those interested in the environment, it is a critical question open to all interested in biology*. The revised definition makes this demonstrably clear.

A central challenge to exposome research is the *need for an output from environmental exposure research that is as tangible as the mutated gene*—something that epidemiologists and physicians can insert into existing frameworks of public health and medical models for disease prevention and management. With a broader definition, exposome research can begin to provide the tangible and quantifiable entities that medicine and public health desperately need. The success of the Human Genome Project exposed an imbalance in the nature-nurture interaction. Elucidating the exposome, ie, developing an integrated science of nurture, will help fulfill the promises of the Human Genome Project. Upon the publication of the first draft of the human genome, Francis Collins stated "What more powerful form of study of mankind could there be than to read our own instruction book? (Collins 2000)" The answer, of course, is to read the subsequent chapters that explain the interactions between our genes and our environment that determine health and disease.

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