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Life-Long Implications of Developmental Exposure to Environmental Stressors: New Perspectives

Philippe Grandjean, Robert Barouki, David C. Bellinger, Ludwine Casteleyn, Lisa H. Chadwick, Sylvaine Cordier, Ruth A. Etzel, Kimberly A. Gray, Eun-Hee Ha, Claudine Junien, Margaret Karagas, Toshihiro Kawamoto, B. Paige Lawrence, Frederica P. Perera, Gail S. Prins, Alvaro Puga, Cheryl S. Rosenfeld, David H. Sherr, Peter D. Sly, William Suk, Qi Sun, Jorma Toppari, Peter van den Hazel, Cheryl L. Walker, and Jerrold J. Heindel*

The Developmental Origins of Health and Disease (DOHaD) paradigm is one of the most rapidly expanding areas of biomedical research. Environmental stressors that can impact on DOHaD encompass a variety of environmental and occupational hazards as well as deficiency and oversupply of nutrients and energy. They can disrupt early developmental processes and lead to increased susceptibility to disease/dysfunctions later in life. Presentations at the fourth Conference on Prenatal Programming and Toxicity in Boston, in October 2014, provided important insights and led to new recommendations for research and public health action. The conference highlighted vulnerable exposure windows that can occur as early as the preconception period and epigenetics as a major mechanism that can lead to disadvantageous “reprogramming” of the genome, thereby potentially resulting in transgenerational effects. Stem cells can also be targets of environmental stressors, thus paving another way for effects that may last a lifetime. Current testing paradigms do not allow proper characterization of risk factors and their interactions. Thus, relevant exposure levels and combinations for testing must be identified from human exposure situations and outcome assessments. Testing of potential underpinning mechanisms and biomarker development require laboratory animal models and in vitro approaches. Only few large-scale birth cohorts exist, and collaboration between birth cohorts on a global scale should be facilitated. DOHaD-based research has a crucial role in establishing factors leading to detrimental outcomes and developing early preventative/remediation strategies to combat these risks. (*Endocrinology* 156: 3408–3415, 2015)

The Developmental Origins of Health and Disease (DOHaD) paradigm is one of the most rapidly expanding areas of biomedical research today. This field originated with early observations that malnutrition and low-level exposures to drugs and toxic substances (eg, alcohol and methylmercury) might be well tolerated by a pregnant woman, but her gestating fetus would be afflicted by adverse effects, some of which might become apparent only later in life (1, 2). The field has now broadened to encompass consideration of a variety of environmental and occupational hazards, whether chemical, physical, or biological, and both deficiency and oversupply of nutrients and energy. When these environmental stressors disrupt

early developmental processes they may cause changes in cellular gene expression, cell numbers or location of cells that persist and then lead to increased susceptibility to disease/dysfunctions later in life.

The fourth Conference on Prenatal Programming and Toxicity (PPTOX IV) in Boston, October, 2014, brought together researchers interested in understanding the role of environmental stressors in developmental programming. As before (3, 4), the goal of the conference was to stimulate and exchange research results and to discuss their implications and how to further develop and strengthen research in this field. This article presents a brief summary of important insights and recommenda-

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Abbreviations: BPA, bisphenol A; EDC, endocrine disrupting chemical; DOHaD, Developmental Origins of Health and Disease; PPTOX IV, fourth Conference on Prenatal Programming and Toxicity.

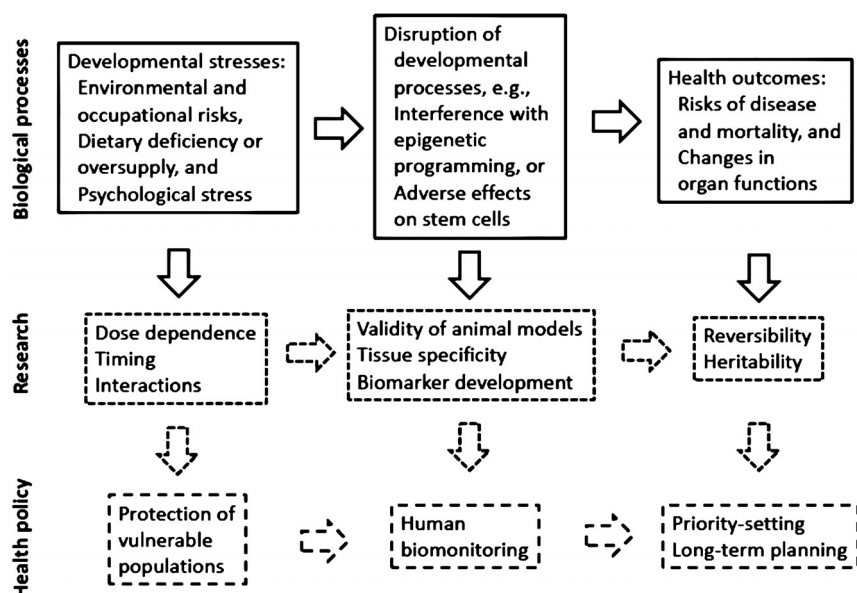


Figure 1. Links between processes involved in Developmental Origins of Health and Diseases, the major research issues, and the health policy implications.

tions that emerged from the conference presentations and discussion sessions. Figure 1 outlines the major issues discussed. Abstracts and presentations are available at the conference web site (<http://www.endocrine.org/meetings/pptox-iv>).

Stress as a Risk Factor

PPTOX IV highlighted the fact that psychological stress itself is an environmental stressor that can affect DOHaD with a variety of long-term or delayed consequences. Stress can be a significant risk factor, as demonstrated by analyses of epigenetic markers (5). As with other stressors, such as environmental chemicals or nutritional imbalance, the effects depend on the type of stress, as well as the strength and timing and duration of the exposure. For example, some stressors may alter sperm miRNAs, which

could then result in transgenerational effects (6). Also, maternal stress during pregnancy may exert androgenic action and alter sexually dimorphic development endpoints in the child (7). Further, accelerated shortening of telomeres has been identified as a potential biomarker of stress environments, including social stress, and social disadvantage has been linked to accelerated telomere shortening in children (8).

Experimental studies suggest that later-life stress can modify the effects of early environmental chemical exposure (as a hypothesized 2-hit mechanism), and new data show that lead exposure and stress interact to produce lower Bayley scores in the child than those associated with lead exposure alone. Stress during devel-

opment may act via novel pathways that may lead to the discovery of new biomarkers of developmental perturbation. Thus, stress should be considered as a covariate or “exposure” in human and animal studies of DOHaD, in line with the exposome concept that aims at integrating assessment of the totality of hazards.

Vulnerable Windows of Exposure

Historically, DOHaD research on environmental stressors has focused primarily on exposures during pregnancy and early childhood and their effects on the health of the offspring across the lifespan. However, presentations at PPTOX emphasized that the preconception period in both females and males is also a sensitive developmental window (9). Even before conception, both types of gametes

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are vulnerable to external stressors, and may transmit the effects of these exposures to the subsequent generations through a variety of possible mechanisms. Although past research has mainly focused on mutations and nondisjunction, new research shows that tRNA fragments are loaded into sperm as they travel through the epididymis, thereby allowing transfer of genetic material from somatic cells via exosomes to the germ cells. This sets the stage for potential paternal inheritance through induced disruption of the male reproductive tract. Developmental effects mediated through the father also may involve other mechanisms, such as changes in DNA methylation, retained histone modifications and noncoding RNAs in somatic and germ cells. Thus, the known vulnerable windows of exposure have expanded to include the preconception period.

Mechanisms of Environmental DOHaD Effects

Although several mechanisms are thought to be involved in the altered programming induced by environmental stressors during development, the main attention is on epimutations (10). Although epigenetic effects do not affect the DNA base sequence as such, they constitute a complex system of regulatory machinery that determines whether or not the DNA is accessible to transcriptional factors and whether the resulting mRNA reaches the translation stage (11). Environmental stressors have the potential to alter gene expression and modify disease susceptibility through alterations to methylation of cytosin-phosphate-guanine dinucleotide sequences, eg, in promoter regions that regulate common genes, in transposable elements adjacent to genes with metastable epialleles, and in regulatory elements of imprintable genes. Toxicants can also affect gene expression by directly impacting the proteins that read, write, or erase epigenetic marks. One particularly compelling example is the histone methyltransferase enhancer of zeste homolog 2, whose reduced function in response to environmental estrogens leads to persistent changes in epigenetic programming that underlie uterine leiomyoma in a rat model (12).

PPTOX participants expect that data arising from human studies will be aided by the rapid advances in technology for assessing the “methylome” and “epigenome.” However, several conceptual and analytical challenges must be overcome in environmental epidemiology studies that aim at identifying exposure-linked epigenetic changes. Epigenetic profiles vary across normal cell and tissue types, in order to coordinate cell type-specific functions, and exposure-induced changes may or may not be

conserved across all cells and tissues within an individual. Human studies therefore need to carefully select the appropriate tissue to assay for a given hypothesis. Even within cell types present in cord blood, differences in methylation patterns exist, and statistical methods to adjust for cell mixture are emerging to adjust for DNA methylation changes in different tissues. Furthermore, reference epigenomic maps, such as the National Institutes of Health’s Roadmap Epigenomics Program, can help researchers distinguish cell type-specific epigenetic differences from those associated with exposure. Because blood is often more readily available from human cohorts than the cell types directly involved in disease, linking exposure-related epigenetic changes to a health outcome may be complicated. New studies document that prenatal alcohol exposure is associated with epigenetic changes in the offspring, especially when taking into account maternal mutations in the alcohol dehydrogenase gene (*ADH1B*). In addition, exposure to bisphenol A (BPA), an environmental estrogen, can disrupt the normal imprinting by epigenetic changes in the embryo (13).

In addition to epigenetic mechanisms, other potential pathways include shortening of telomere length (indicative of premature aging), especially apparent among children in lower socioeconomic groups, who may be more vulnerable due to concomitant stress exposures (8). Further, increased copy number variants can be of importance, but their origin and the causal factors are unclear at this point (14).

Transgenerational Inheritance

PPTOX IV highlighted transgenerational inheritance as an important and fast moving new research focus (15). Although transgenerational (or multigenerational) inheritance has been demonstrated in experimental models, the mechanisms are still unclear by which the effects of exposure are transmitted through the germline to the next generations. A wide range of factors, including chemical exposures, dietary changes, and other stressors are known to induce transgenerational effects, and the health outcomes impacted by this phenomenon also are quite varied and growing (16). For example, developmental exposure to BPA affects the social interactions of the F1, F2, F3, and F4 offspring, as well as induces multigenerational effects on metabolic phenotypes. Also, maternal exposure to dioxin perturbs antiviral immune responses in the F1 generation, with some of these effects being observed in the F3 generation. Thus, the list of factors that can cause transgenerational effects continues to expand.

Although epigenetic mechanisms are thought to be involved in these transgenerational effects, as indicated by epigenetic changes shown to occur across generations, the actual mechanism of transgenerational transfer still remains to be elucidated. Historically, Lamarckism attracted much attention, and one perceived implication was that this mechanism of evolution would protect against extinction, because a species would be able to rapidly adapt to new environmental challenges. However, we now know that the ability to respond to the environment may also introduce detrimental effects. Thus, transgenerational inheritance of adverse effects from environmental stressors may predispose to, rather than protect against species extinction.

Key Role of the Placenta

PPTOX IV focused on the important role that the placenta plays in influencing changes in fetal development and programming. Although the placenta regulates the intrauterine environment via transport of nutrients, water, gases, and waste products, the maternal-fetal barrier may allow transfer of environmental chemicals. The placenta also acts as an immune-endocrine organ producing hormones and growth factors important in fetal growth. The placenta displays strikingly sexually dimorphic differences in morphology, gene expression and in DNA methylation patterns and in recently discovered miRNA changes (17). Thus, the placenta can provide useful biomarkers of exposure and of the progeny's risk of later susceptibility to diseases, as influenced by sexual dimorphism at the basic level after conception and in response to in utero environmental factors (18). Poorly explored but important aspects are the communication within the feto-maternal unit, the cell-type specificity of responses supporting the use of layer/cell type instead of whole placenta samples, how disruptions in placental function may affect the maternal reproductive system, including corpus luteum maintenance and physiology, and the dynamic temporal changes (ontogeny) in epigenetic modifications to identify the primary causes and pathways. More attention needs to be focused on processes in the placenta and their role in guiding fetal development. Some effects of maternal nutrition or exposure to environmental chemicals on the fetus may well be indirect via effects on the placenta, thus opening a new area of scientific focus related to the DOHaD paradigm (see <http://www.nichd.nih.gov/research/HPP>).

Experimental and Epidemiological Approaches

An important feature of the PPTOX conference was the focus on integrating animal and epidemiology studies and the need for multidisciplinary collaboration. Nonhuman systems provide the ability to control the timing, dose, and routes of exposure and to advance the speed at which we can examine effects of early life exposures. The focus of animal research should not just be on individual environmental chemicals but on the variety of factors, such as nutrition, psychological stress, as well as other environmental chemicals, and their interactions during the periconceptional, gestational, and early postnatal periods that lead to DOHaD outcomes across the lifespan. Exploration of cellular and molecular mechanisms that incorporate both human and nonhuman in vitro models is a key to establishing causality. Study designs and data analysis need to accommodate the potential existence of nonlinear effects. These research possibilities clearly call for multidisciplinary collaboration.

Prospective follow-up of birth cohorts is particularly important to examine the effects of early-life environmental stressors on growth, development, and long-term health. Although some countries have generated very large general-population cohorts, many smaller birth cohorts are particularly promising, because they include detailed exposure assessment within populations in which wide differences in exposures occur, thereby providing increased statistical power to detect DOHaD effects. Given the large expenses in maintaining and following national cohorts, extant birth cohorts should be built upon and extended by adding more refined measures of adverse exposures while exploring interaction with other stressors and genotype. Similarly, because some cohorts are enriched for specific phenotypes, the availability of blood samples and other biological samples provides a gold mine for research into developmental exposures and their late effects. Motivating cohort members and parents is of utmost importance, and they are most motivated by contributing to research on an important issue and often link their participation to sending a message about global pollution by acting locally to support community-based evidence building. Academic-community research partnerships are important to insuring that the research is vigorous but also to be sure questions asked are relevant to informing potential solutions that would be socially/culturally feasible. Ideally, such research should be combined with targeted approaches to prevention to enable formal studies of intervention effects during different periods of development.

Exposure Assessment

When assessing exposure, special attention must be paid to imprecision, including the timing in regard to developmental windows of vulnerability. This issue is crucial, because exposures measured with a greater degree of random imprecision will, on average, be affected by a greater bias toward the null hypothesis. Thus, for chemicals with variable exposures and rapid metabolism and elimination from the body, a single urine assessment during gestation is not likely to be representative of the actual exposure during critical windows. This consideration is important, because developmental effects may be caused by a wide variety of causal factors, and available methods for exposure assessment are susceptible to varying sources of error that will affect the observable associations with suspected outcomes. A further complication is the fast pace of change of the regulatory mechanisms that control development itself, particularly in organisms with short ontogeny times in which differences of a few minutes might be responsible for wide differences in exposure outcomes.

An additional focus that was highlighted at the conference is to unravel complex exposures in regard to disease outcomes. Progress is being reported in developing the so-called exposome and in applying new approaches to environment-wide association studies (19, 20). In addition, developments in analytical chemistry and metabolomics methodologies allow nontargeted assessment of multiple exposures and simultaneous measurement of profiles of substances that can be meaningfully built into multivariate analyses. Likewise, modeling of proxy variables that represent exposure settings and risk factors provides a promising avenue that will at least inspire more targeted analyses to generate support for plausible causal connections. Mixtures represent a serious challenge, especially when exposures are interrelated. Epidemiological studies may not be able to identify single culprits within complex exposure mixtures, and the choice of study population and setting is therefore crucial. Likewise, because the realistic dimensions of experimental models must employ a reductionist strategy, they may not allow detailed characterization of the joint effects of multiple stressors operating at wide ranges of exposure levels. Thus, proper guidance must be extracted from epidemiology studies to select the most relevant mixture exposures to model in the laboratory.

Early and Late Outcomes

Neurodevelopment is probably the outcome that has received the greatest interest due to the availability of tests

and the significance of brain development for adult functioning as well as the risk of medical diagnoses of increasing frequency, such as attention-deficit/hyperactivity disorder and autism spectrum disorders. PPTOX IV highlighted novel computer-based methods with eye-motion tracking ability that are being developed for assessing sexually dimorphic cognitive functions, such as spatial and physical reasoning, and learning and memory strategies that can be used with newborns. Such tests will be useful for evaluating the effects of endocrine disrupting chemicals (EDCs) under circumstances in which confounding would be minimal. Likewise, automated assessment methods are increasingly being used to enhance validity and reliability of outcome data. Such methods have been used to document the adverse effects from ambient air pollution on the prospective development of cognitive function in elementary school children (21). In some studies, support has been obtained from functional magnetic resonance imaging data that have shown dysregulation of cortical activation in exposed children. Because these techniques remain expensive and complex, their use in population-based studies is still in its infancy. Because aging begins in utero, sowing the seeds of late-age neurodegeneration may involve developmental exposures to neurotoxins as a basis for environmental influences on Alzheimer's disease risk, although so far demonstrated only in animal models.

Obesity, diabetes and other metabolic diseases are fast growing research fields that featured prominently at PPTOX IV. Although considerable animal model data support a role for environmental chemicals including air pollution and a variety of EDCs in causing either obesity or diabetes, the field is expanding to include more general metabolic disruption. Birth cohort data indicate that developmental exposures to environmental chemicals, such as phthalates, persistent organic pollutants, and BPA, can act as obesogens in children (22). Sexually dimorphic effects have been documented as a result of developmental exposures, eg, to the fungicide tolylfluanid on β -cell function and adiposity, because effects are observed in male mice only. Similar sex-dependent differences have been shown in regard to prenatal air pollution exaggerating weight gain and impairing insulin sensitivity, again only in male mice. These results clearly illustrate the importance of examining both sexes and not lumping the results. Future studies should further consider the combined effects of environmental chemical exposures and nutritional changes, such as high-fat and high-carbohydrate diets as well as later-life stressors. These lines of multidisciplinary research will underscore the role of developmental exposures to environmental factors in the etiology of major metabolic diseases that occur later in life.

To be successful, epidemiology and experimental animal model research must join forces to elucidate the causal associations in regard to developmental exposures to stressors.

The immune system, with its complex and overlapping positive and negative feedback loops is exquisitely sensitive to environmental cues. Developmental exposures dampen antibody responses to routine immunizations and increase susceptibility to infectious agents, which can have far-reaching public health implications (23). Developmental exposures may affect the highly regulated differentiation of hematopoietic stem cells, and even small changes in the function of these cells may serve as harbingers of health effects that may not be observed until later in life and may be magnified across the life span (24). There is also growing evidence that some developmental exposures increase the chances of developing autoimmune diseases later in life, perhaps by epigenetic reprogramming of immune cells (25, 26). Finally, a new area of research is the impact of environmental exposures on the microbiome, and in turn the associated risks of childhood and adult onset disease and dysfunction.

Several EDCs are suspected to be involved in carcinogenesis, particularly in prostate and breast cancers (27, 28). Until recently, the effects of certain EDCs on prostate cancers were somewhat puzzling, because this cancer is androgen sensitive, and most EDC research attention has been on androgen antagonists and/or estrogen agonists. However, cancer stem cells play a critical role, and prostate stem cells have been found to be exquisitely sensitive to EDCs through membrane-associated receptors that cross talk with the nuclear transcription factors (29). Breast cancer also is now better understood and, in addition to the traditional estrogen effects, the role of progesterone has received strong support. Here again, BPA interacts with the progesterone pathway thereby contributing to its carcinogenic effects (30).

Communication and Policy Implications

The DOHaD issues represent an area of public health research in which the uncertainties need to be spelled out alongside the long-term health implications. There is a need for honest and balanced information for a variety of audiences, including patient groups, study participants, students in search of a career or thesis project, colleagues from related fields, decision makers, and regulatory agencies. This research field will only thrive and develop meaningfully if shortcomings are acknowledged and interpreted in the light of the potential effects on life-course health and disease. Simplistic interpreta-

tion of experimental models or epidemiological associations should be avoided, and a public health perspective included to allow for consideration of appropriate interventions to promote health, also in the absence of detailed documentation.

As groups of scientists have helped formulate policies in areas such as nuclear proliferation, similar action would be appropriate in regard to using DOHaD research to inspire targeted prevention that can have advantageous effects in the long term. During recent years, nongovernmental organizations have organized panels of scientists to inform delegates attending meetings about the Stockholm Convention, thereby bridging the gap between academic research and decision-making. Such interactions with regulatory agencies also are needed on a national and regional level. Researchers in the field need to complement their current focus on individual chemical substances or dietary ingredients with systematic evidence that integrates multiple stress factors. The DOHaD perspective requires a new focus on developmental exposures and how they act in combination, with the additional impact of developmental stages and genetic factors.

This type of information-sharing should be interpreted as part of the role as researcher, because the translation of research and the possible implications of the results requires expertise that only exists with the researchers themselves. Although discussions on policy decisions may present challenges and even become contentious, the participation of scientists, including social scientists, should be viewed as essential in correcting misunderstandings and in providing a public health and scientific perspective.

Harmful DOHaD effects constitute a global problem that likely differs regionally, for example, in regard to the obesity epidemic vs malnourishment, or the short-term benefits in tropical countries from using persistent pesticides vs their adverse effects induced far away and possibly transferred to future generations. Therefore, lines of scientific communication need to be implemented to and within developing countries to identify and apply safer chemicals as well as improved control of environmental stressors in general.

Conclusions

The DOHaD concept has clearly documented that “a good start lasts a lifetime,” and the implications of this paradigm on public health are compelling (31). Vulnerable exposure windows occur as early as the preconception period. Epigenomics has emerged as an important mechanism for environment effects on health, and environmental stressors may result in disadvantageous epigenetic

“reprogramming.” Such effects may result in multigenerational and transgenerational effects, thereby burdening future generations. In addition, stem cells can be targets of environmental stressors, and again this mechanism paves the way for effects that can last a lifetime. Although the placenta is a transient organ, how it adapts and responds to maternal and paternal environmental stressors can lead to longstanding health effects. Stressors that can produce changes in DOHaD include complex environmental exposures such as dietary deficiencies or oversupply, drugs, environmental chemicals, and psychological stress. Characterization of all of these risk factors, along with their interactions, will be impossible using current laboratory test approaches. Relevant exposure levels and combinations for testing therefore need to be identified from human exposure situations. Further, associations between exposures and outcomes observed in human studies need to be supported by mechanistic studies in the laboratory setting. Thus, these different research approaches need to be better linked in order to gain deeper and more systematic insight into DOHaD as a key mechanism in environmentally induced disease and dysfunction. Extended dialogue and collaboration between epidemiologists and basic science researchers should be stimulated. Further, although only few large-scale birth cohorts exist, collaboration between smaller birth cohorts in many countries should be facilitated, and methodologies should be shared.

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