DOHaD and EDCs: Past, Present and Future

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The Disease Paradigm: Developmental Origins of Health and Disease (DOHaD)

A bad start...lasts a lifetime!

• The environment during development.. stress, nutrition, environmental exposures, infections and drugs:
  • Alters epigenetic programming of cell and tissue differentiation (via alteration in growth factor and hormone concentrations).
  • Alter gene expression and/or protein regulation, numbers of cells and/or cell location. ( “functional changes”).
  • “Functional" changes lead to a tissue that “looks” normal but is metabolically abnormal, permanently altering how it functions.
  • Changes persist throughout life.
  • Programming changes lead to increased susceptibility to disease across the lifespan.
DOHaD and EDCs: Phase I

Focus on:
- Animal models.
- Development as the developmental window.
- Molecular mechanisms/epigenetics...methylation focus.
- Separate focus on EDCs and nutrition and stress.
- Focus on neurodevelopmental and reproductive diseases.

2008
DOHAD and EDCs: Phase II

- New Sensitive Windows of Exposure
- New Diseases
- New Tissues
- New Chemicals
- Expanded Epigenetic Mechanisms

2018

DOHaD has gone viral!
Preconception Window of Sensitivity

Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health.

Effects of maternal or paternal bisphenol A exposure on offspring behavior.

Investigation of Paternal Programming of Breast Cancer Risk in Female Offspring in Rodent Models.

Fathers Matter: Why It’s Time to Consider the Impact of Paternal Environmental Exposures on Children’s Health.

Preconception exposure to dietary levels of genistein affects female reproductive outcomes.

Preconception weight management: an untapped area of women’s health.
Pregnancy as a Sensitive Window for the Mother: Pancreatic Beta Cell Mass is Decreased in BPA Treated Mothers 7 Months after Delivery

Angel Nadal, 2015, 2016
Pregnancy as a Sensitive Window for the Mother: Xenoestrogens Alter Some Aspects of Maternal Behavior After Pregnancy

Pups well retrieved to nest

Pups scattered in cage, not retrieved

Catanese & Vandenberg, Endocrinology 2016
Focus on Number of Windows of Susceptibility... and Their Interaction

- Epigenetic control of development

In utero
Neonatal
Early Childhood

Preconception
Pre-Puberty
Puberty
Adult
Pregnancy
Pregnancy (mother)
Aged

How many windows, what are they?
What is the mechanism of sensitive windows outside of development?
How do windows interact over the lifespan?
Transgenerational Inheritance:
It is a real... and potentially VERY important Window!

- Vinclozolin
- Methoxychlor
- BPA
- Phthlate (DEHP)
- **BPA plus phthalates (DEHP plus DBP)**
- Dioxin
- **Jet fuel 8**
- Permethrin plus DEET
- DDT
- TBT
- Cocaine
- Arsenite or DEHP (c.elegans)
- Atrazine
- **Nutritional deprivation**

In human terms....Expose pregnant mother to chemical

Effects of chemicals shows up in children,

and also in grandchildren and great grandchildren!
Bad News: Transgenerational Inheritance

Endocrine Disruptor

You

Disease incidence continues over many generations!

Your children

Your grandchildren

Your great grandchildren

(pregnancy)
Transgenerational Inheritance and Sustainability of the human race…

Disease incidence compounded over many generations!
A New Multigenerational Exposure Paradigm

![Diagram showing multigenerational exposure paradigm]

**Table B**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Generation</th>
<th>Generations Exposed</th>
<th>Individual(s) Exposed</th>
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<tr>
<td>E</td>
<td>F0</td>
<td>1</td>
<td>Self</td>
</tr>
<tr>
<td>E0</td>
<td>F1</td>
<td>1</td>
<td>Father</td>
</tr>
<tr>
<td>EE</td>
<td>F1</td>
<td>2</td>
<td>Father and Self</td>
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<tr>
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<td>F2</td>
<td>1</td>
<td>Grandfather</td>
</tr>
<tr>
<td>E0E</td>
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<tr>
<td>EEE</td>
<td>F2</td>
<td>3</td>
<td>Grandfather, Father, and Self</td>
</tr>
</tbody>
</table>
Fibrotic, Infertile Testis After Multiple Generations of Estrogenic Exposure

Phenotypes increased in severity with successive generations of neonatal estrogen exposure.
Time to Focus on Multiple Interacting Windows of Sensitivity and Stressors and Interacting Stressors

• In utero exposure...assess as adults.
• In utero exposure...assess both offspring as adults and mothers after pregnancy.
• In utero plus neonatal exposure.
• In utero and neonatal plus adult exposure (same or different chemical, or diet).
• Preconception exposure.
• Preconception plus in utero exposure (same or different chemical or diet or stress).
• Preconception plus in utero/neonatal and adult exposure (same or different chemical or diet or stress).
• In utero exposure...mate over generations with additional exposure for each generation in utero (plus or minus additional adult exposures).
New Disease Focus: Obesity, Diabetes, Fatty Liver, Metabolic Syndrome

• The obesity and EDC field is ~10 years old.
• Significant research progress on the role of environmental chemicals in obesity, type 2 diabetes, and aspects of metabolic syndrome.
• Researchers have identified:
  • Chemicals of concern (>40)
  • Sexually dimorphic differences
  • Epigenetic mechanisms
  • Metabolism disruptors
Developmental Origins of Health and Disease and EDCs

Need more focus on:

• Other tissues ...bone, muscle, GI tract, adrenal, placenta, pineal.

• More diseases: psychiatric, neurodegenerative, immune, crohn’s disease, gluten sensitivity...

• Examination of more chemicals as EDCs...same old-same old.

• Interaction of windows across the lifespan and generations.

• Interaction between chemicals, nutrition and stress...break down the silos.

• Intervention and prevention strategies.

• Better integration of animal and human data....chemicals, diseases, endpoints.

• Improved communication of the importance of both the developmental origins of both health and disease...impact policy, physicians and community.
Nothing in Disease Etiology Makes Sense Except in the Light of Altered Tissue Programming!

Thank You

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