DOHaD and EDCs: Past, Present and Future

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Program on Endocrine Disruption Strategies,

Commonweal

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

2008

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.

DOHAD and EDCs: Phase II

2018

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

Preconception Window of Sensitivity

Lancet. 2018 May 5;391(10132):1830-1841. doi: 10.1016/S0140-6736(18)30311-8. Epub 2018 Apr 16.

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

Stephenson J[1], Heslehurst N[2], Hall J[3], Schoenaker DAJM[4], Hutchinson J[5], Cade JE[5], Poston L[6], Barrett G[3], Crozier SR[7], Barker M[8], Kumaran K[9], Yajnik CS[10], Baird J[8], Mishra GD[4].

Environ Int. 2018 May 8;117:139-145. doi: 10.1016/j.envint.2018.05.003. [Epub ahead of print]

Associations of female exposure to bisphenol A with fecundability: Evidence from a preconception cohort study.

Wang B[1], Zhou W[1], Zhu W[1], Chen L[1], Wang W[1], Tian Y[1], Shen L[2], Zhang J[3]; Shanghai Birth Cohort Study.

Horm Behav. 2017 Oct 4. pii: S0018-506X(17)30246-5. doi: 10.1016/j.yhbeh.2017.09.017. [Epub ahead of print]

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

Harris EP[1], Allardice HA[1], Schenk AK[2], Rissman EF[3].

Environ Epigenet. 2018 Apr 26;4(2):dvy007. doi: 10.1093/eep/dvy007. eCollection 2018 Apr.

POHaD: why we should study future fathers.

Soubry A[1].

Mol Cell Endocrinol. 2016 Nov 5;435:2-6. doi: 10.1016/j.mce.2016.07.002. Epub 2016 Jul 5.

Maternal obesity and prenatal programming.

Elshenawy S[1], Simmons R[2].

Methods Mol Biol. 2018;1735:207-220. doi: 10.1007/978-1-4939-7614-0_11.

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

Fontelles CC[1,2], da Cruz RS[2], Hilakivi-Clarke L[2], de Assis S[2], Ong TP[3].

Curr Epidemiol Rep. 2017 Mar;4(1):46-55. doi: 10.1007/s40471-017-0098-8. Epub 2017 Jan 11.

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

Braun JM[1], Messerlian C[2], Hauser R[2,3].

Reprod Toxicol. 2017 Dec;74:174-180. doi: 10.101

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

Patel S[1], Hartman JA[2], Helferich WG[3], Flaws JA[4].

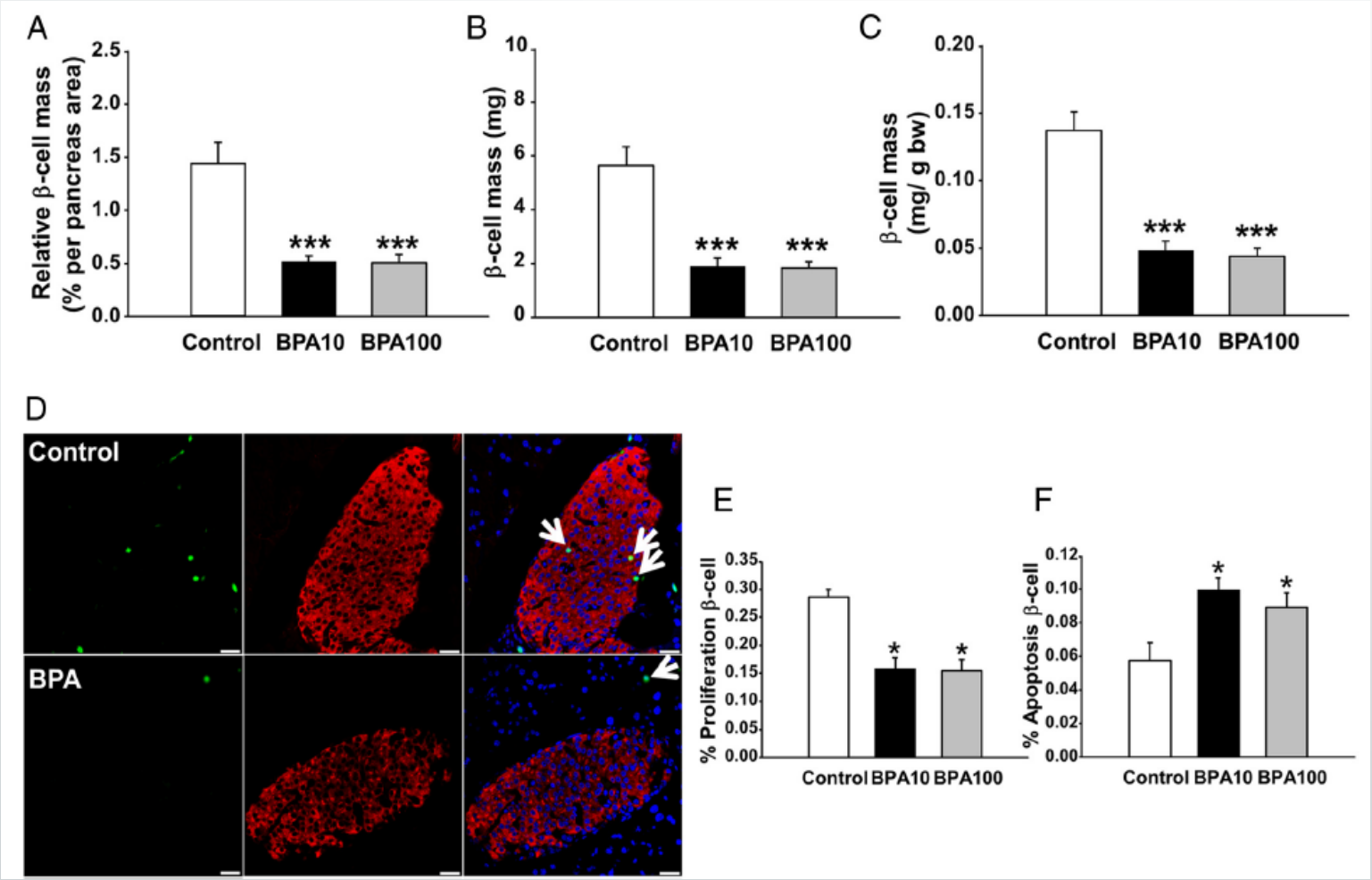
Aust J Prim Health. 2017 Apr;23(1):61-65. doi: 10.1071/PY16004.

Preconception weight management: an untapped area of women's health.

McPhie S[1], Skouteris H[1], Millar L[2], Olsson C[1], Campbell K[3], van der Pligt P[3], Dodd J[4], Hill B[1].

Pregnancy as a Sensitive Window for the Mother:

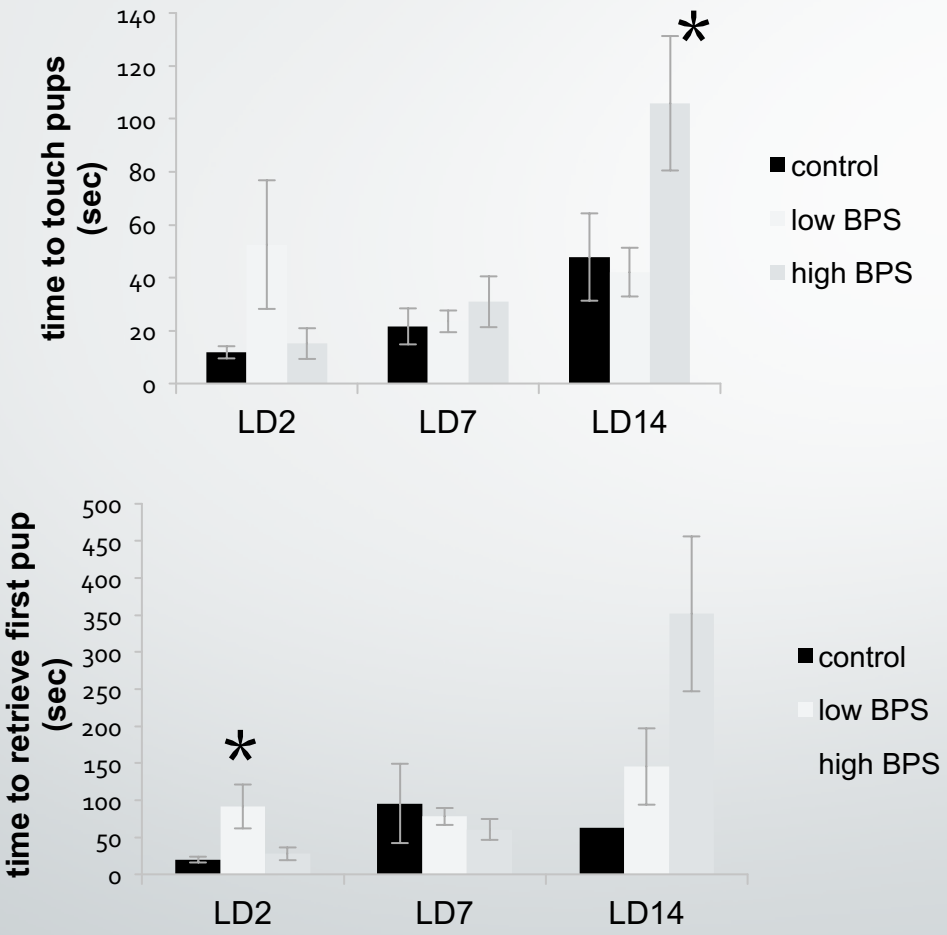
Pancreatic Beta Cell Mass is Decreased in BPA Treated Mothers 7 Months after Delivery



Angel Nadal, 2015, 2016

Pregnancy as a Sensitive Window for the Mother: Xenoestrogens Alter Some Aspects of Maternal Behavior After Pregnancy

Catanese & Vandenberg, Endocrinology 2016



Pups well retrieved to nest

Pups scattered in cage, not retrieved

Focus on Number of Windows of Susceptibility… and Their Interaction

In utero

Neonatal

Early Childhood

- Epigenetic control of development

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!

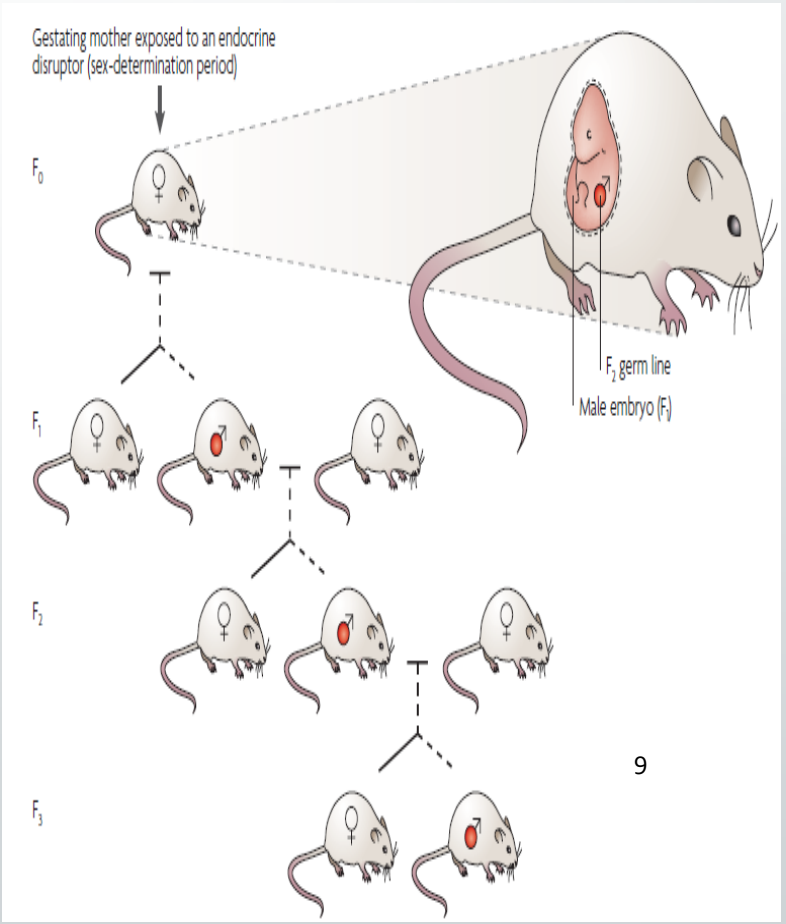
- Vinclozolin
- Methoxychlor
- BPA
- Phthalate (DEHP)
- BPA plus phthalates (DEHP plus DBP)
- Dioxin
- Jet fuel 8
- Permethrin plus DEET
- DDT
- TBT
- Cocaine
- Arsenite or DEHP (c.elegans)
- Atrazine
- Nutritional deprivation

In human terms….Expose pregnant mother to chemical

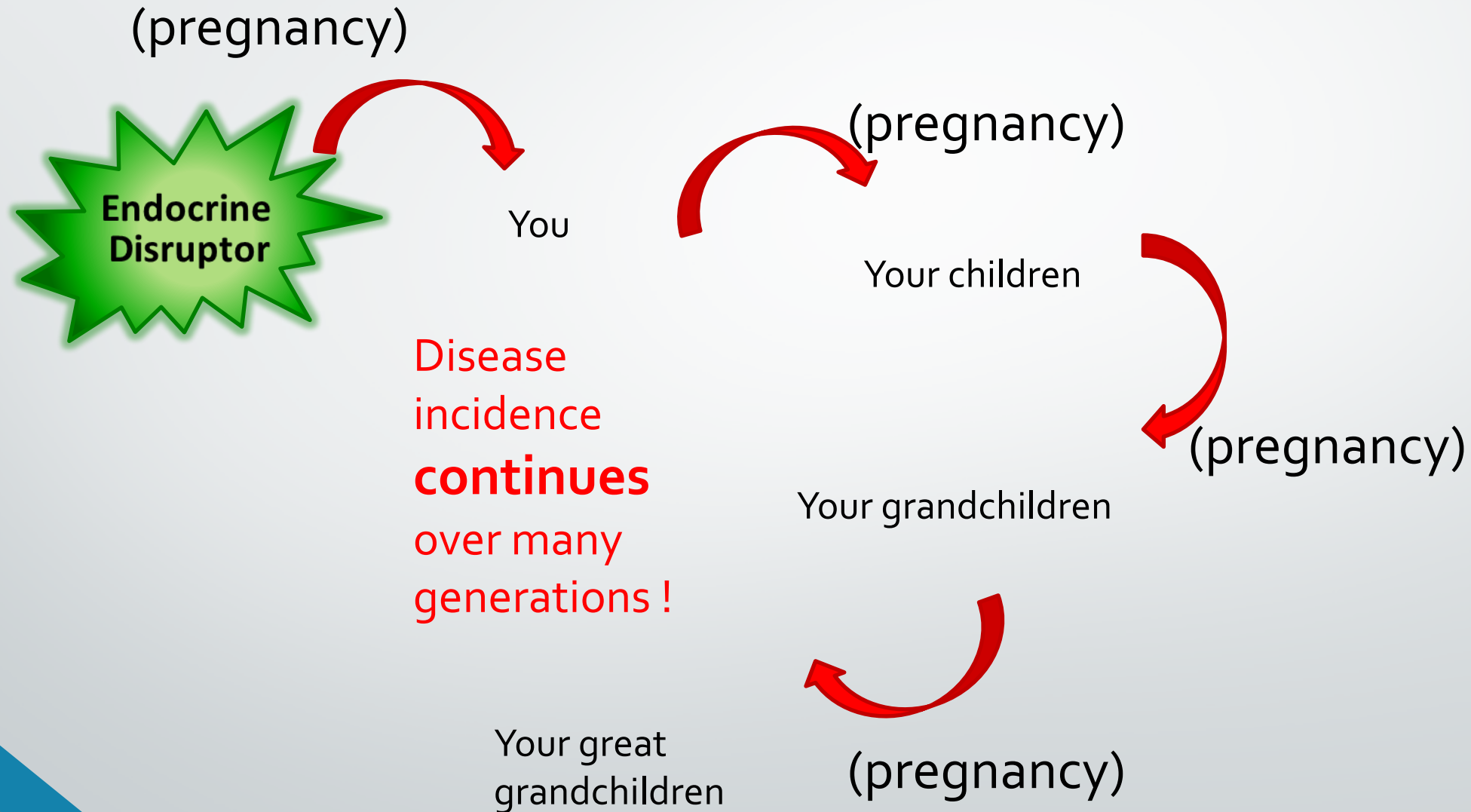
Effects of chemicals shows up in children,

and also in grandchildren and greatgrandchildren!

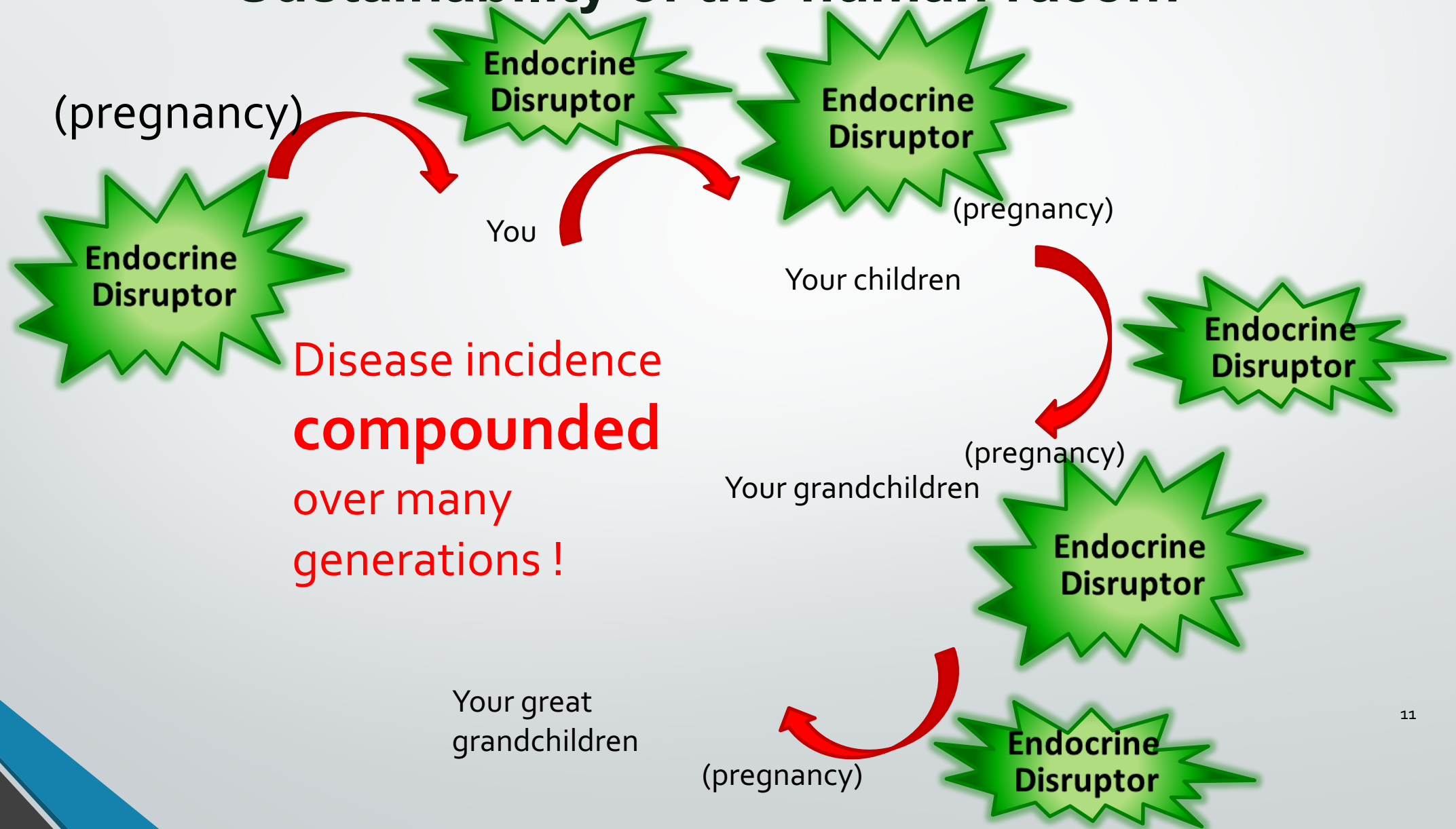
Obesity
Reproduction
Neurobehavior



Bad News: Transgenerational Inheritance



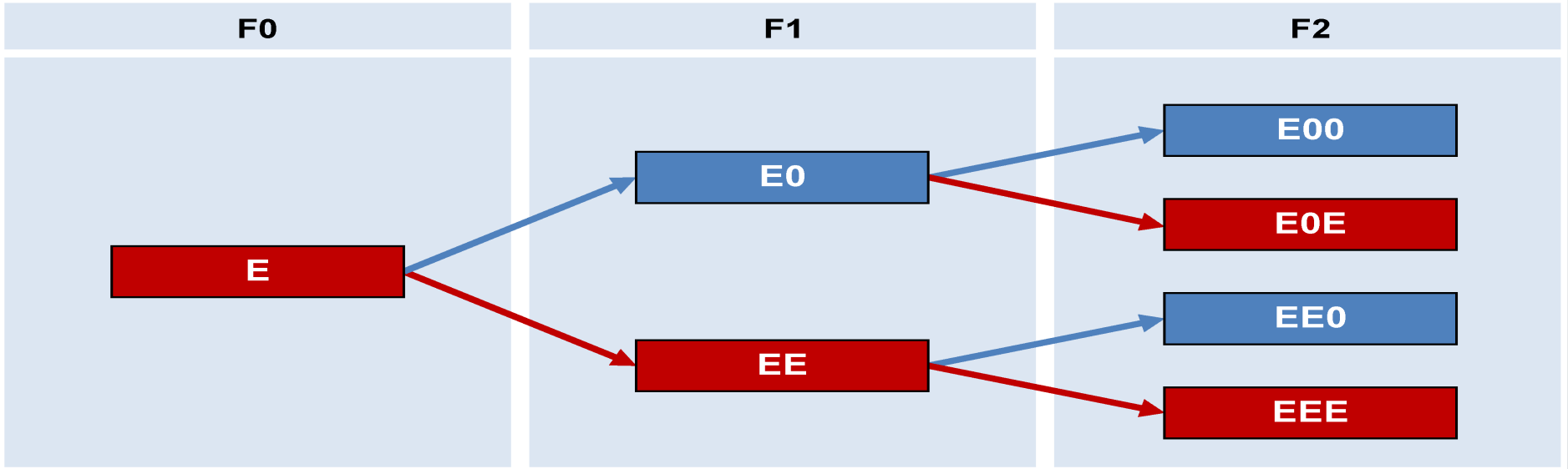
Transgenerational Inheritance and **Sustainability of the human race…**



Disease incidence **compounded** over many generations !

A New Multigenerational Exposure Paradigm

A

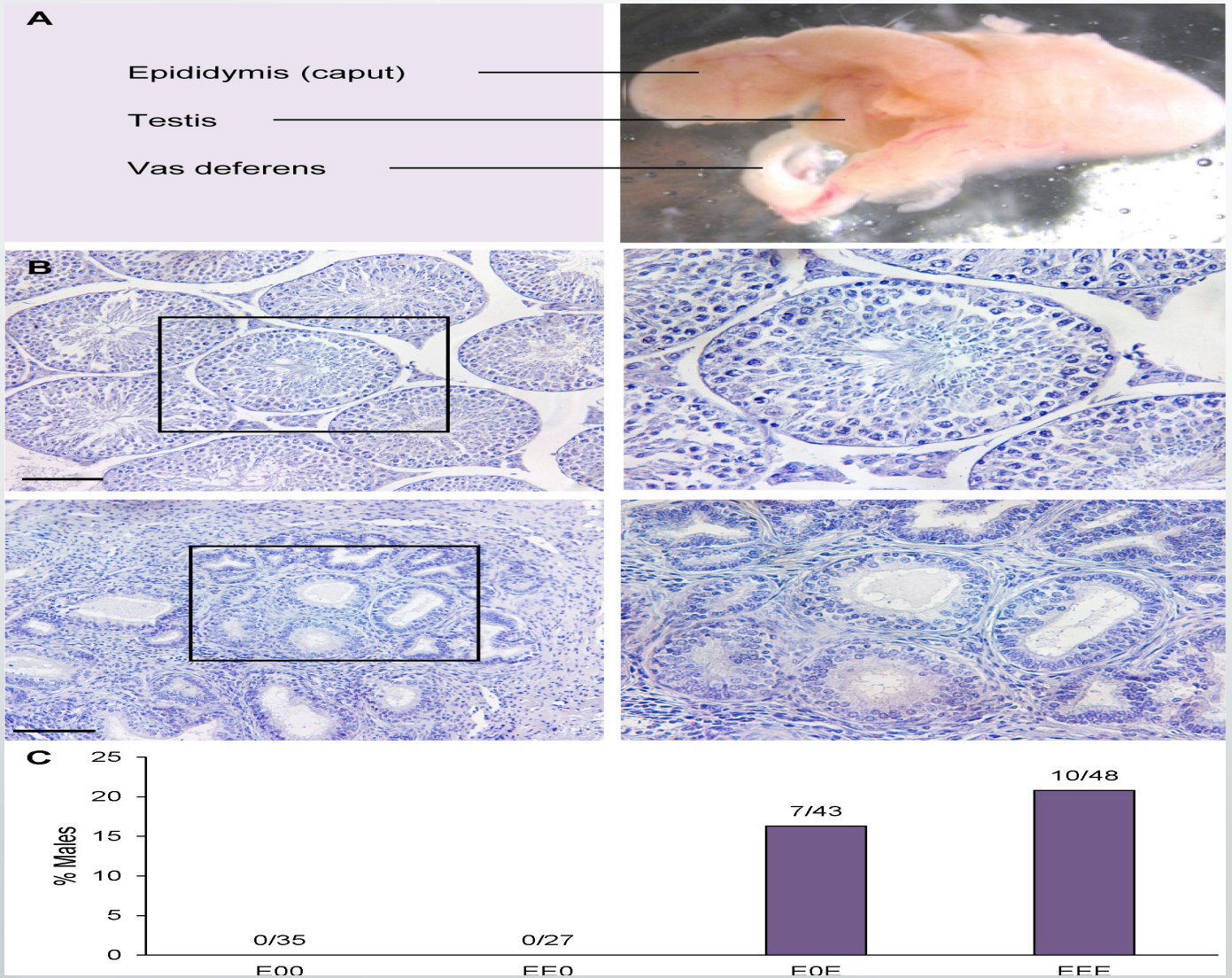


B

Abbreviation	Generation	Generations Exposed	Individual(s) Exposed
E	F0	1	Self
E0	F1	1	Father
EE	F1	2	Father and Self
E00	F2	1	Grandfather
E0E	F2	2	Grandfather and Self
EE0	F2	2	Grandfather and Father
EEE	F2	3	Grandfather, Father, and Self

T S Horan et al
Plos Genetics,
2018

Fibrotic, Infertile Testis After Multiple Generations of Estrogenic Exposure



Tegan S Horan et al
Plos Genetics
2018

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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