

Epigenetic Mechanisms in Human Reproduction and Disease: An Ethical Analysis

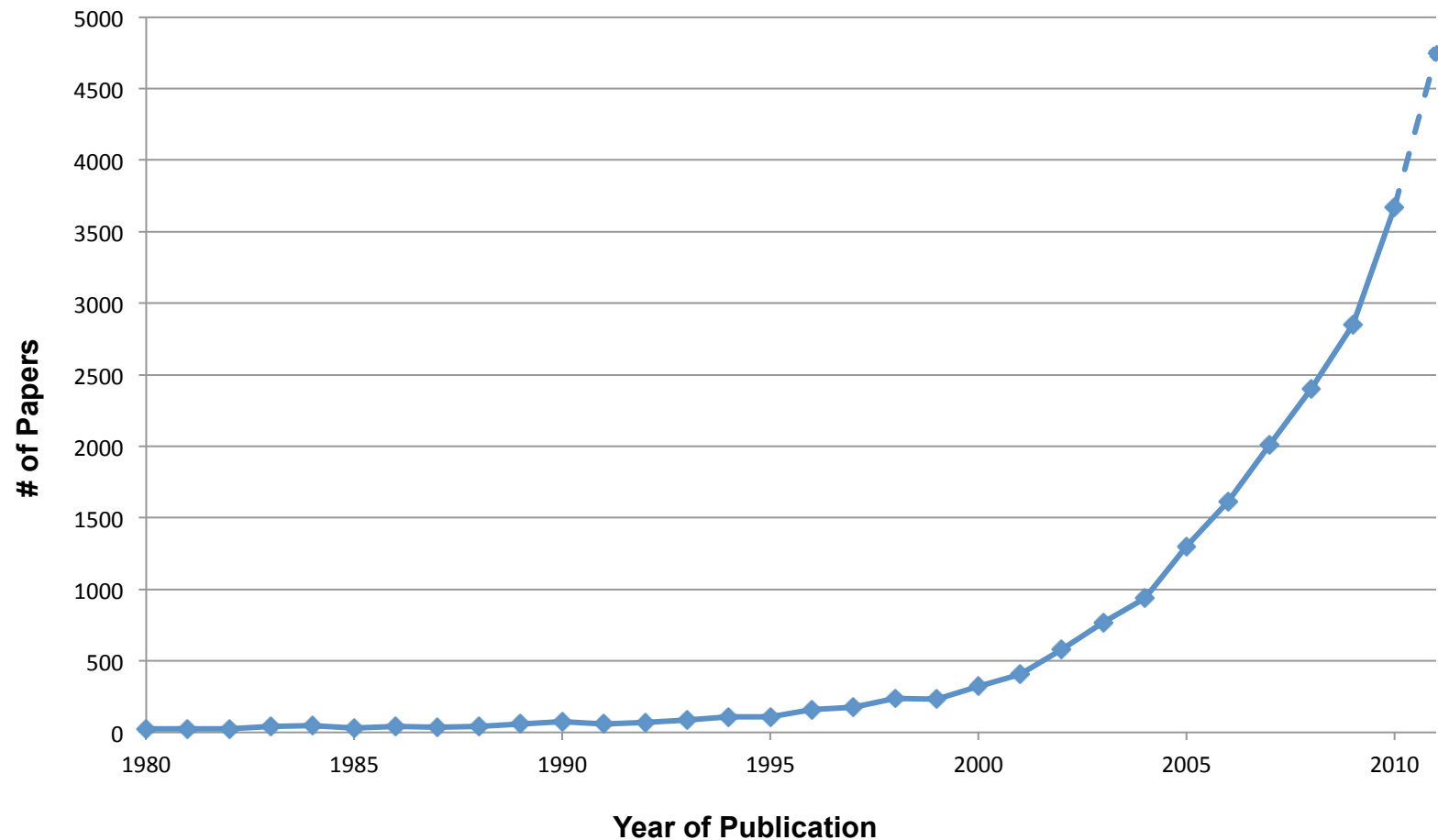
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Epigenetics-Related Papers in PubMed Database



JANUARY 19, 2010

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TIME

WHY YOUR DNA ISN'T YOUR DESTINY

The new science of epigenetics
reveals how the choices you
make can change your genes
—and those of your kids

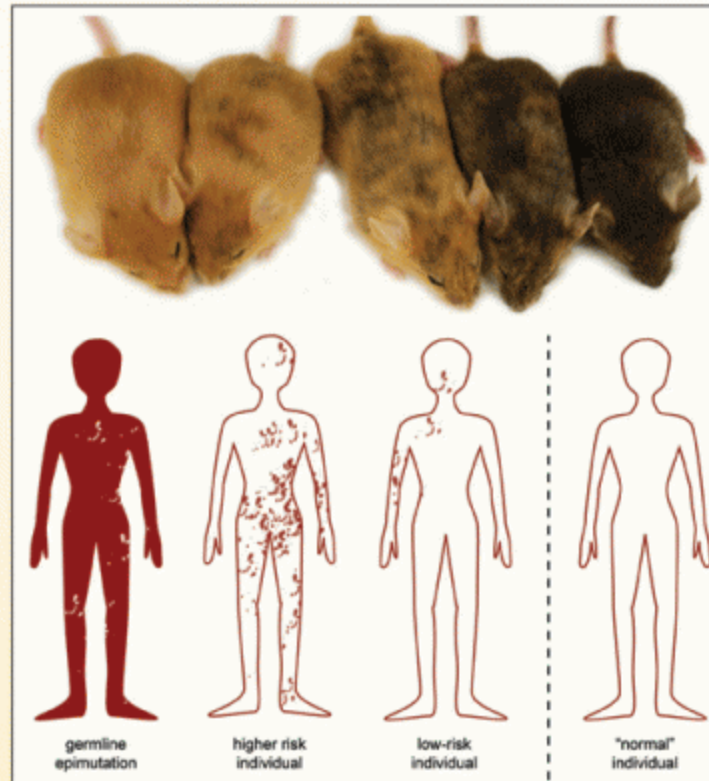
BY JOHN CLOUD

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epigenetics

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Special Issue on Environmental Epigenetics



Two Different Mechanisms of Inheritance

- **Genetic variation**
 - Hereditary change in DNA sequence
 - Spawned by mutation and recombination
- **Epigenetic variation**
 - Hereditary modification of gene expression
 - It does not result from a change in DNA sequence
 - Chemical modification of DNA or histone proteins that interact with DNA change the chromatin structure and affect the accessibility of DNA to regulatory proteins

Epigenetic Mechanisms Play Key Roles in Many Biological Processes

- Development
 - In utero
 - Childhood
 - Gamete formation
- Aging
- Pathogenesis of diseases
 - Imprinting disorders
 - Cancer
 - Autoimmune disease
 - Mental disorders
 - Diabetes
 - Hypertension
 - Obesity

Potential Triggers for Epigenetic Effects

- Environmental chemicals/toxins
- Drugs/pharmaceuticals
- Diet
- Exercise
- Stress
- Maternal care

Transmission of Epigenetic Information

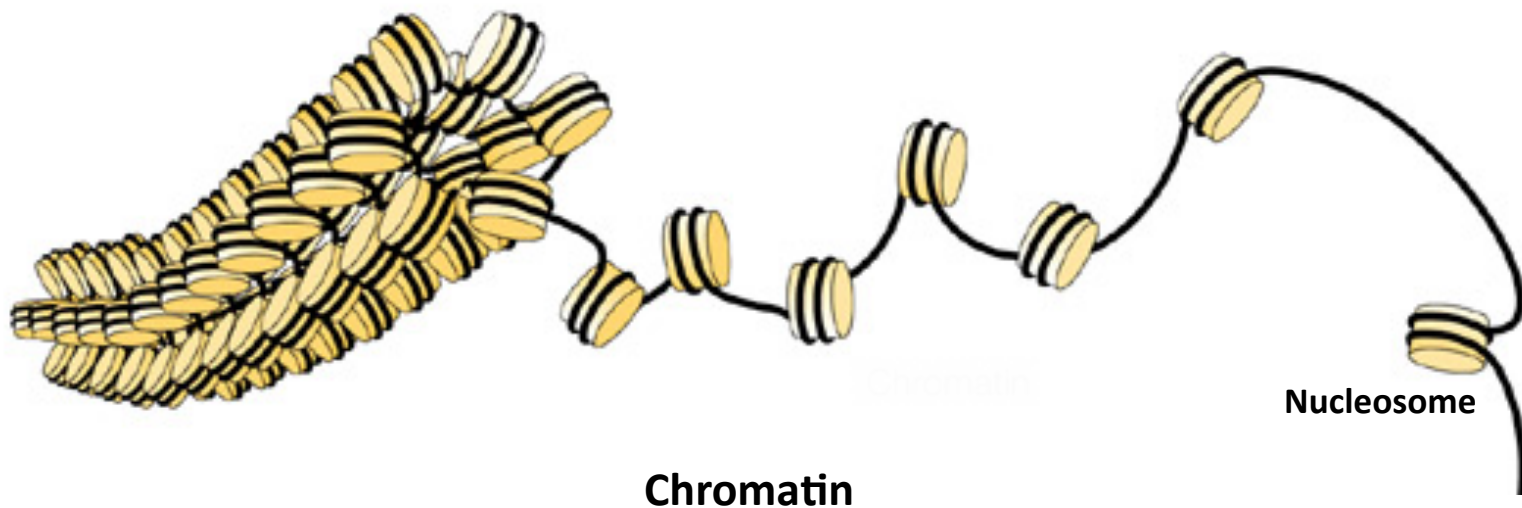
- **To progeny cells**
 - Occurs by mitosis and cytokinesis
- **To progeny organisms**
 - Occurs by meiosis/cytokinesis (gamete formation) and sexual reproduction
 - Example of *transgenerational inheritance*

Induction of Abnormal Epigenetic Changes Raises Potential Ethical Issues

- Assisted reproduction technology
- Handling of environmental toxins

Molecular Mechanisms that Mediate Epigenetic Phenomena

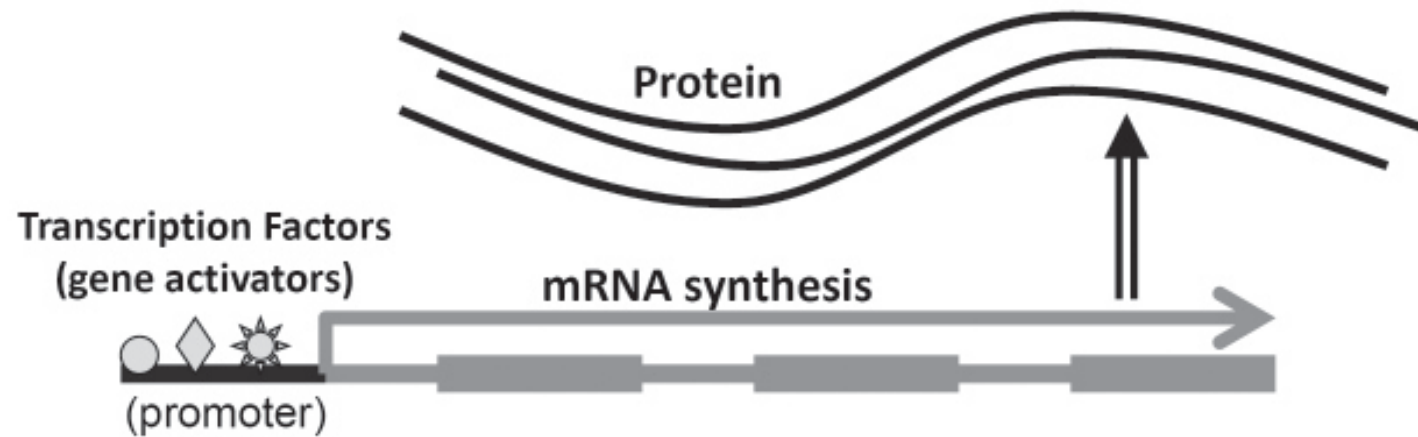
- DNA methylation (CpG dinucleotides)
 - Usually turns genes off
- Histone modifications (acetyl, etc.)
 - Acetyl tags usually associated with active genes



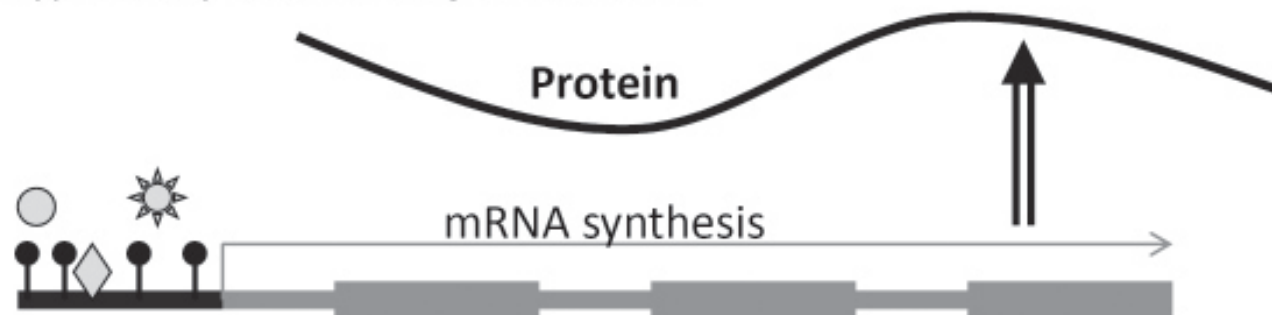
Chromatin Remodeling

- Methyl tags on DNA silence genes by:
 - Blocking transcription machinery from binding to DNA
 - Recruiting proteins that bind to methylated DNA, which then block transcription machinery from binding
- Acetyl tags on histone proteins allow expression
 - Loosen the interactions between histones and DNA, allowing easier access to the DNA

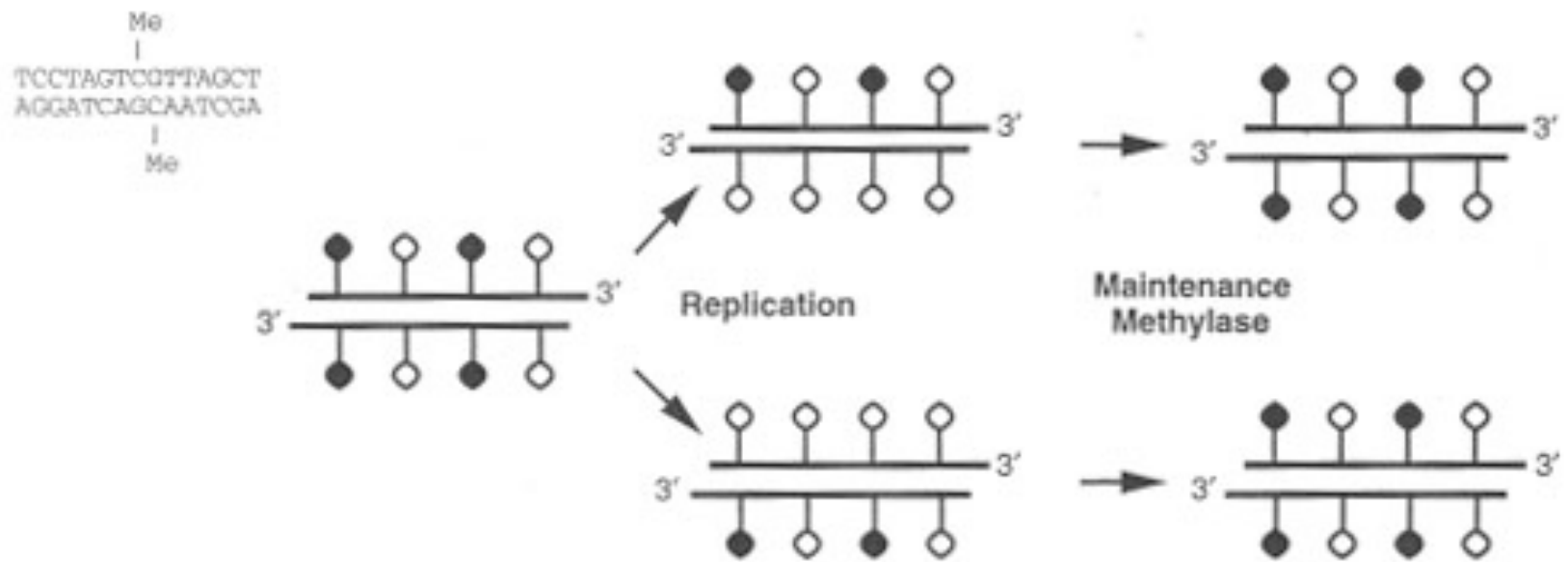
A) Gene hypo-methylation promotes gene activation



B) Gene hyper-methylation inhibits gene activation



Maintenance of Methylation



Some epigenetic tags can pass unchanged from parent to offspring even though there is a global erasure of most sites of methylation during gametogenesis and embryogenesis.

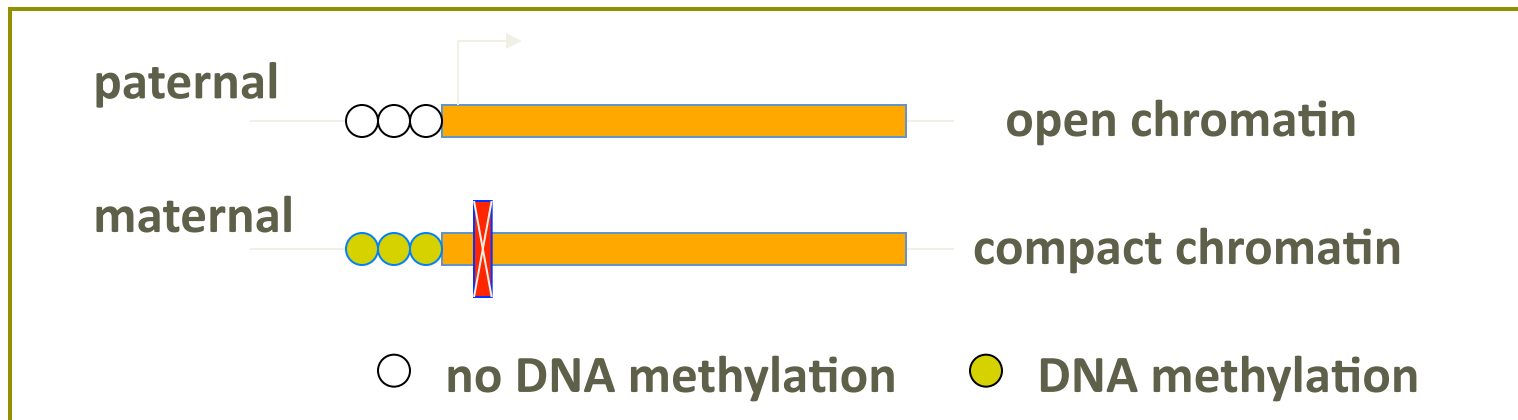
Epigenetics and Reproduction

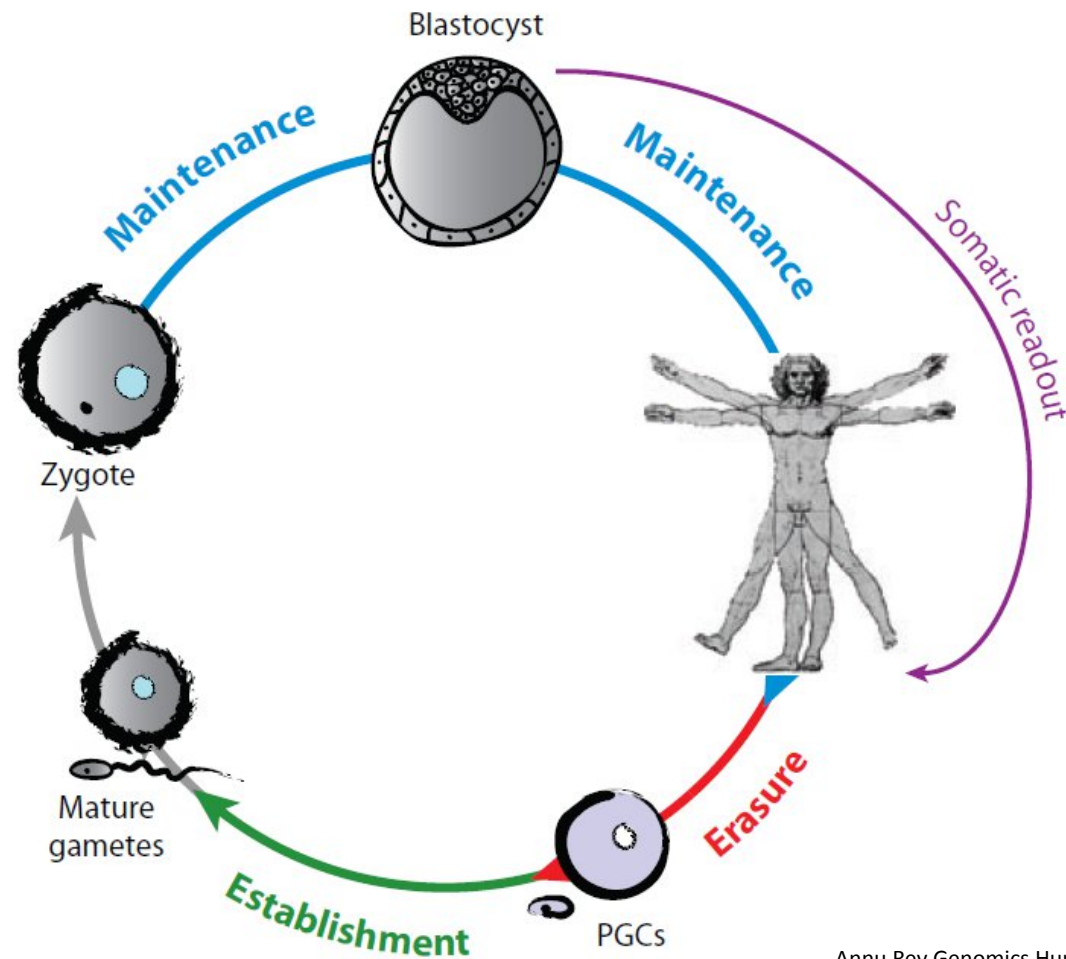
Genomic Imprinting

- Genomic imprinting is an epigenetic mechanism that produces functional differences between the paternal and maternal genomes.
 - One parent's copy of the gene is expressed while the other is silent.
- At least 80 imprinted genes in humans and mice.
 - Many of these are involved in embryonic and placental growth and development.

Genomic Imprinting

- Silencing of the genes is achieved by
 - DNA methylation
 - Histone modifications
 - Expression of non-coding RNAs



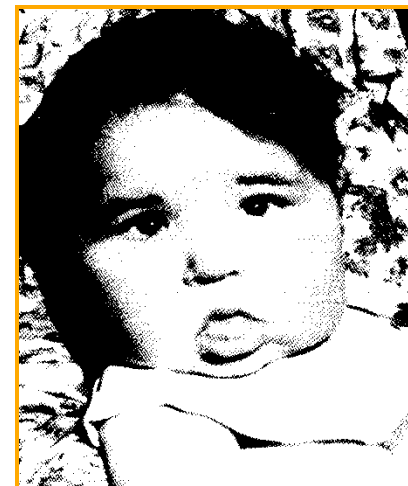


Annu Rev Genomics Hum Genet 9, 197-216 (2008)

These epigenetic marks are established during gamete formation and are maintained throughout all somatic cells of the individual.

Beckwith-Wiedemann Syndrome

- Incidence: 1/13,700 – Shuman *et al.*, 2005
- Overgrowth syndrome with predisposition for embryonal tumors
- Caused by genetic or epigenetic defects in an imprinted region on chr11p15.
- 15% familial cases (autosomal dominant)
- 85% sporadic cases
 - 10% genetic (UPD, mutations)
 - 60% epigenetic (aberrant methylation)
 - 20% unknown



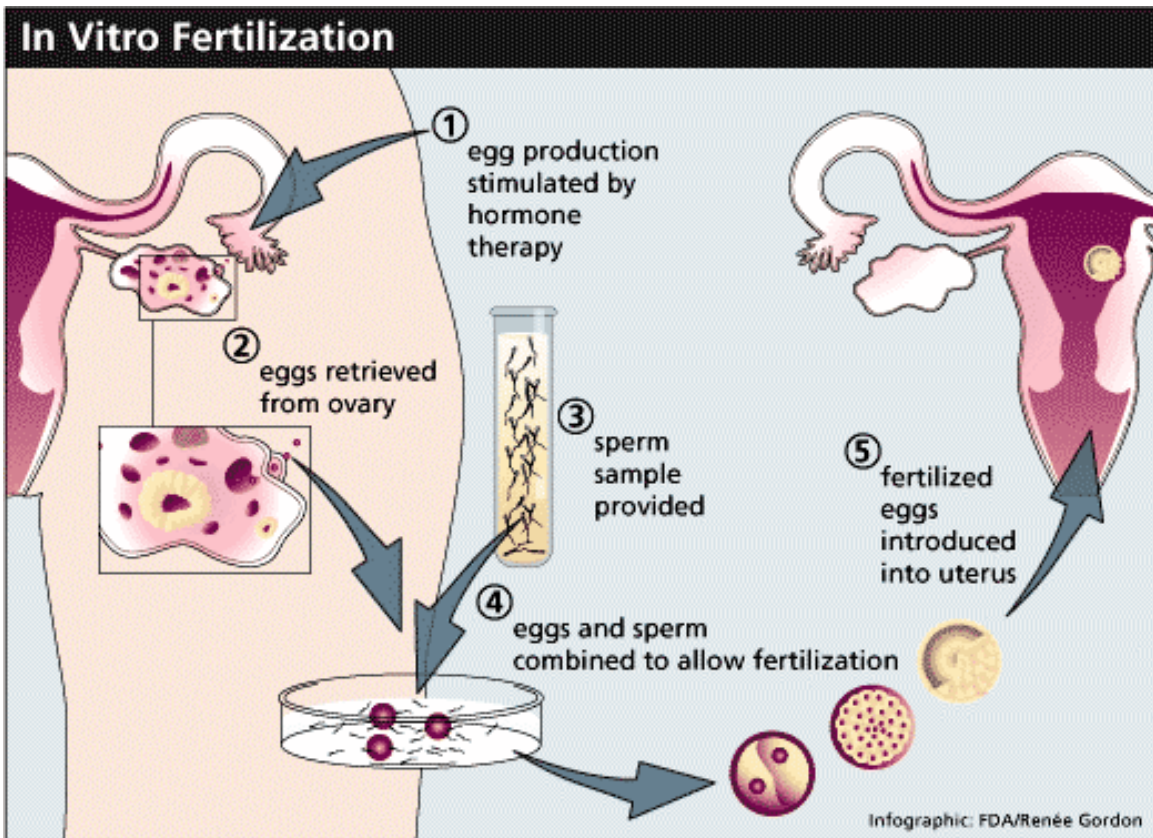
Angelman Syndrome

- Incidence: 1/15,000 – Cox *et al.*, 2002
- Neurogenetic disorder
 - severe mental retardation
 - ataxia
 - “happy puppet syndrome”
 - absence of speech
- Caused by genetic or epigenetic defects in an imprinted region on chr15q11-13 → loss of *UBE3A* expression
- Inheritance: most cases are sporadic
 - 85-90% genetic defects
 - 5% epigenetic defects



Imprinting Disorders and Assisted Reproduction Technologies (ARTs)

- Children conceived through in vitro fertilization have an increased risk of developing
 - **Beckwith-Wiedemann syndrome** – 6- to 9-fold increase (DeBaun et al., 2002; Halliday et al., 2004)
 - **Angelman syndrome** – Significant increase in frequency of disease caused by imprinting defects (Cox et al., 2002; Orstavik et al., 2003)
- Associated with loss of maternal methylation at specific loci, which may be due to
 - Hormonal induction of superovulation
 - Intracytoplasmic sperm injection
 - Culture conditions for embryo
 - Infertility or subfertility of the couple – predispose to epigenetic defects?



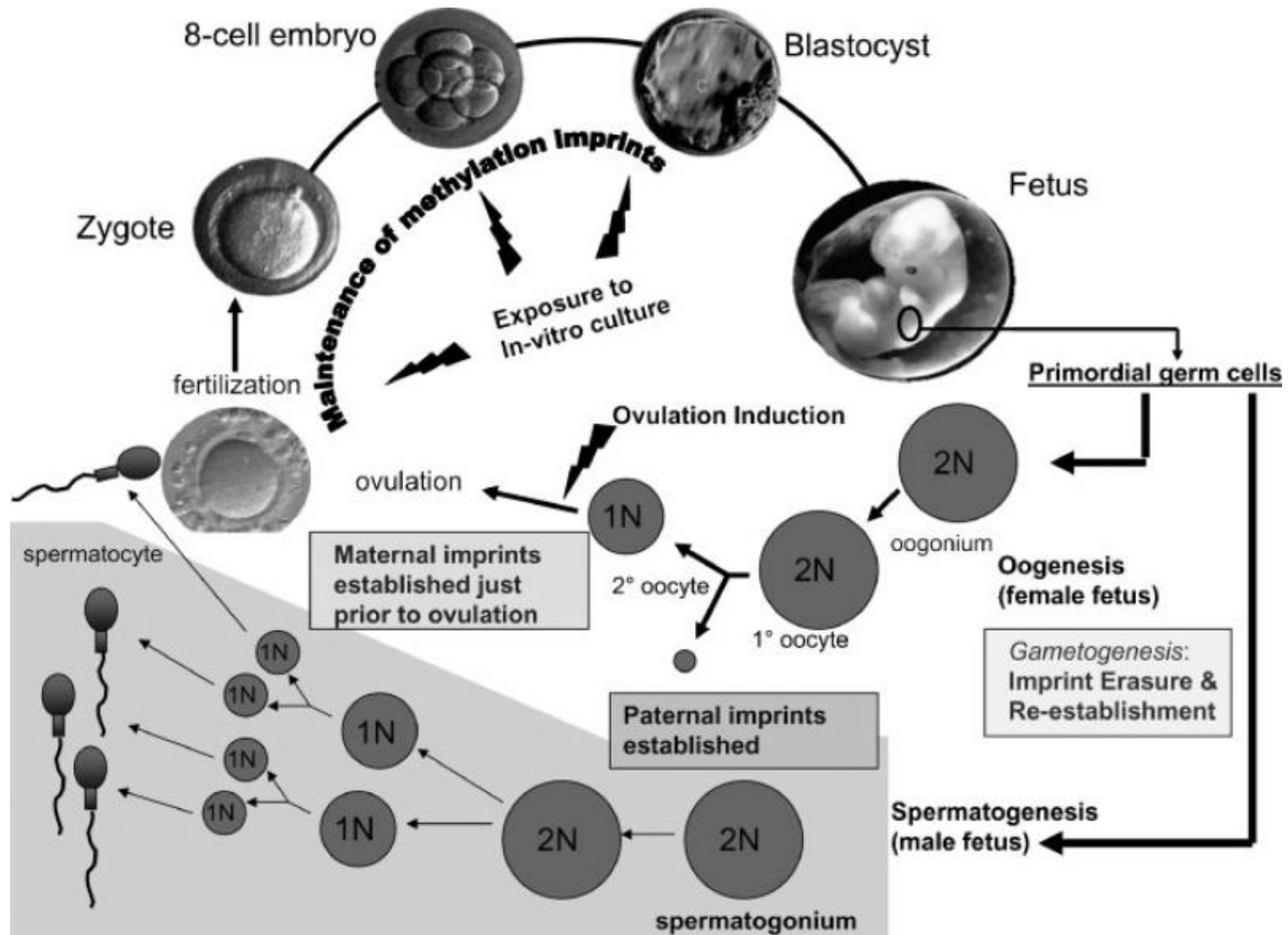
Advanced Fertility Center of Chicago

Cultured human blastocyst

Intracytoplasmic sperm injection



Phoenix Fertility Clinic



Ethical Concerns Related to ARTs

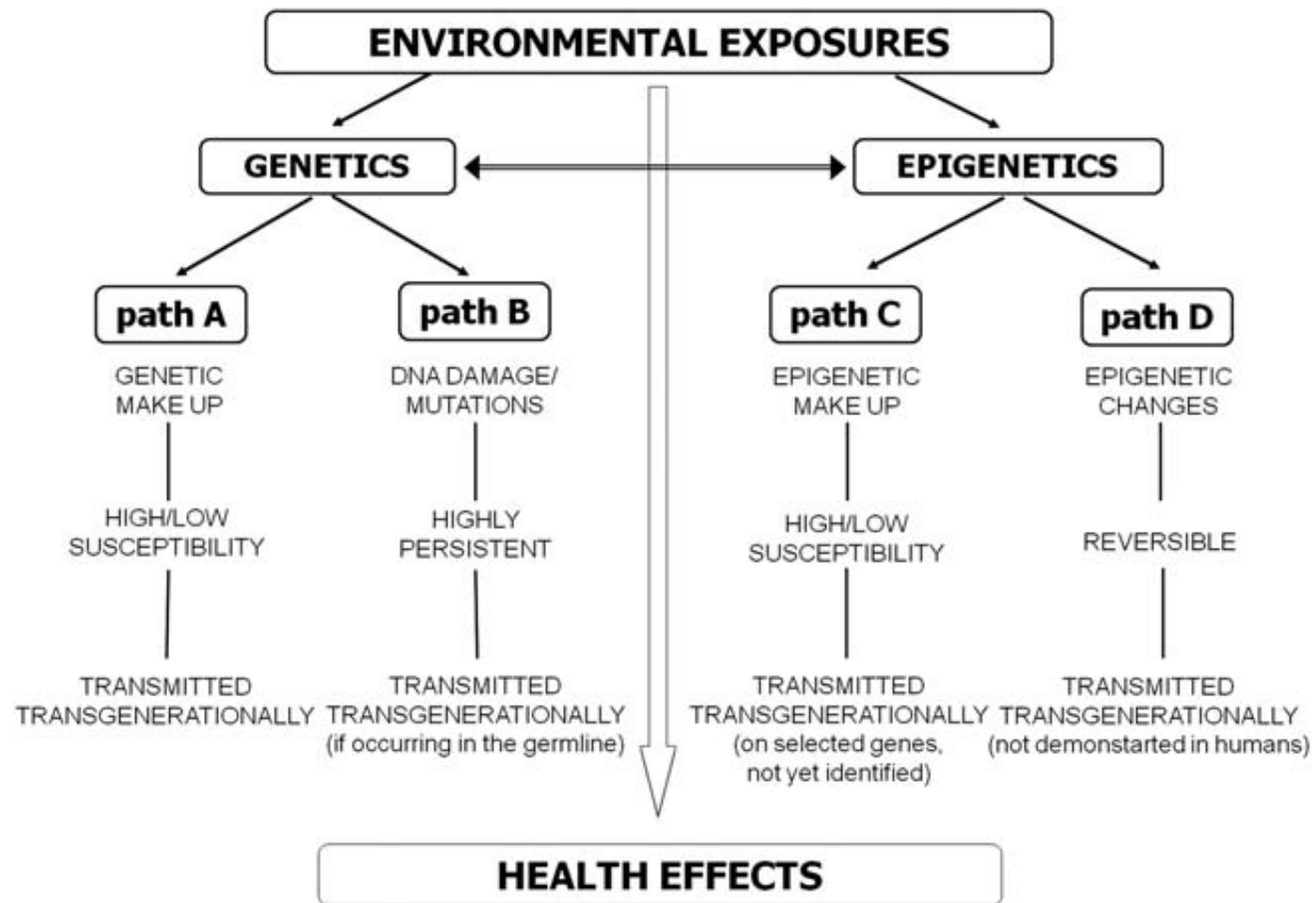
- Are congenital imprinting disorders just the “tip of the iceberg” in terms of safety concerns?

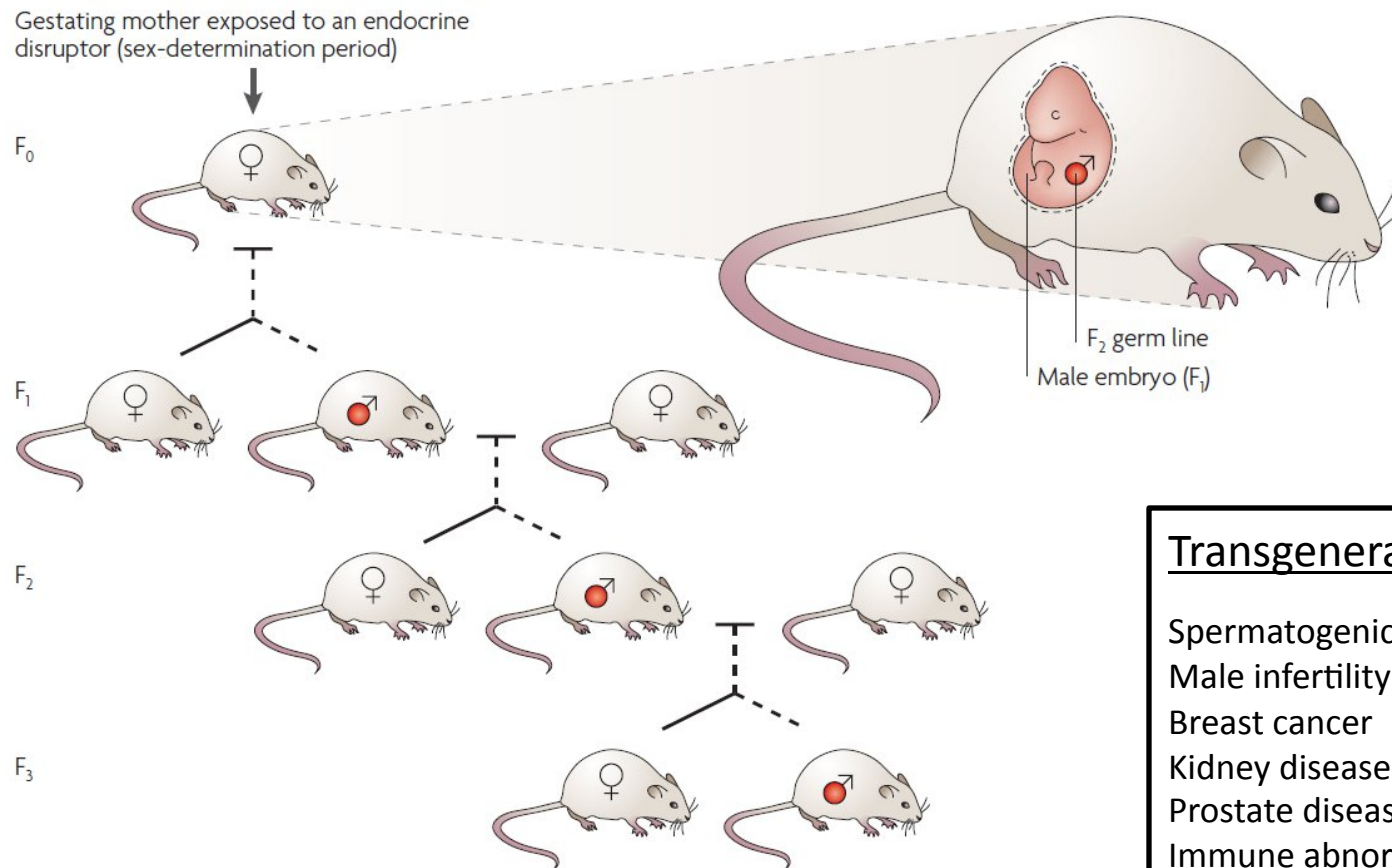
- Increased risk of cancer?
- Increased risk of adult onset diseases?
- Increased risk of mental disorders?

There is a need for careful monitoring and long-term follow-up of IVF/ICSI offspring, and additional research into the epigenetic effects of ARTs.

- Allow experimentation on human embryos to optimize culture conditions for IVF/ICSI?
- Informed consent
- Privacy and confidentiality
- Intergenerational equity

Epigenetics and Environmental Toxins





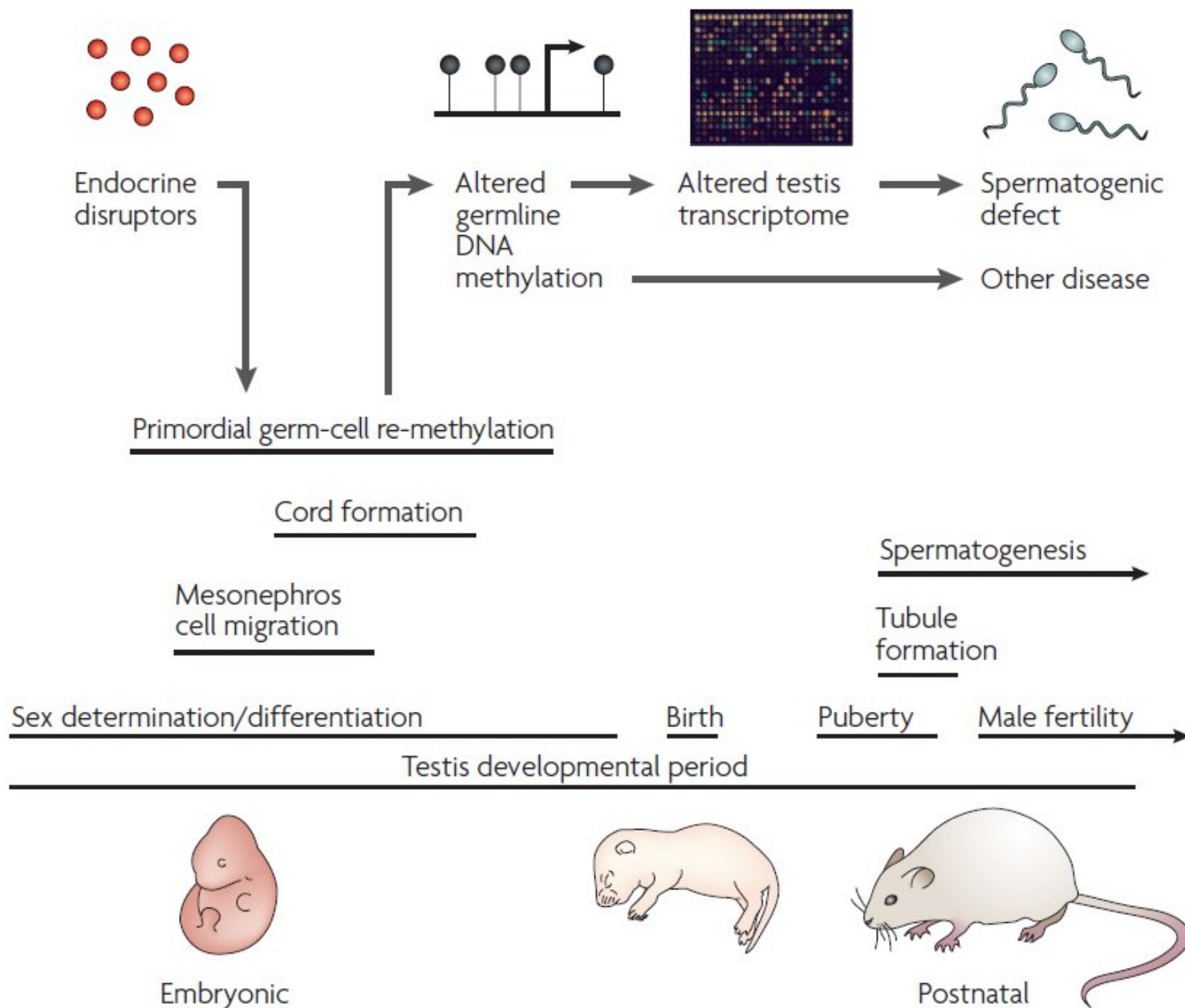
Jirtle and Skinner. *Nat Rev Genet* 8, 253-262 (2007)

Both male and female rat offspring develop disease following maternal exposure to vinclozolin, an anti-androgenic compound. Demonstrates that environmental exposures early in development have a role in susceptibility to disease in later life. Some of these environmental effects are passed on to 20-90% of the offspring in subsequent generations (up to 4th), but only through the male germline.

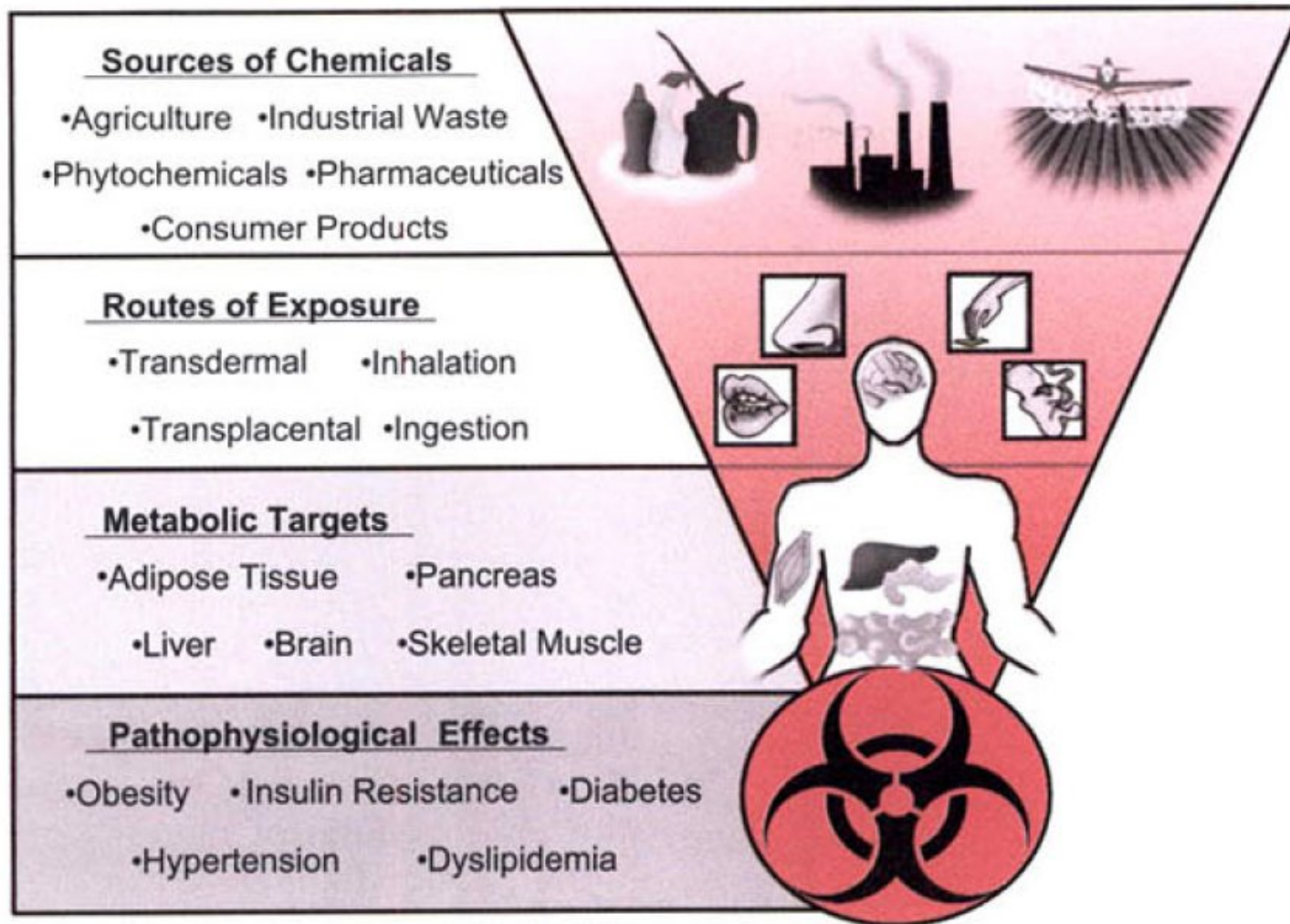
In a sense, you could say...

the “iniquity of the fathers” (or the mothers?) is
“visited upon the children and the children’s
children to the third and fourth generations”

Exodus 20:5-6; Exodus 34:6-7; Numbers 14:18; Deuteronomy 5:9-10



Sources and Targets of Metabolic Disruptors



Key Questions for Environmental Epigenetics

Jirtle and Skinner. *Nat Rev Genet* 8, 253-262 (2007)

- Which human genes result in enhanced disease susceptibility when they are epigenetically deregulated by environmental factors?
- What environmental factors deleteriously alter the epigenome, and at what doses?
- What role does the epigenome have in reproduction, development and disease etiology?
- Are there nutritional supplements that can reduce the harmful effects of chemical and physical factors on the epigenome?
- Can epigenetic biomarkers be identified that will allow for the detection of early-stage diseases?
- Can detection technologies be developed that will allow for a quick and accurate genome-wide assessment of the epigenome?
- Can epigenetics be integrated into systems biology as an important regulatory mechanism?

Ethical Concerns Related to Environmental Toxins and Epigenetics

- **Privacy and confidentiality**
 - Need addendum to Genetic Information Nondiscrimination Act (GINA) of 2008?
- **Environmental justice**
 - Non-random distribution of harmful environmental exposures in our society (Robert D. Bullard, 2005)
 - Populations exposed to environmental insults are more likely to have pre-existing health conditions, often with poor mgmt. (Richard G. Wilkinson, 1996)
 - Remediation of environment
- **Equitable access to health care**
 - Individual prevention, monitoring, treatment

Ethical Concerns Related to Environmental Toxins and Epigenetics

- **Intergenerational equity**
 - Remediation of environment
 - Intervention to restore epigenome for future generations?
- **Personal responsibility and stewardship**
 - Of our bodies
 - Of the environment



Pogo comic strip