

Germline Disruption in Historical and Personal Context

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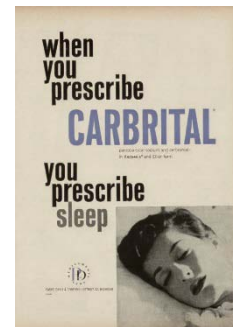
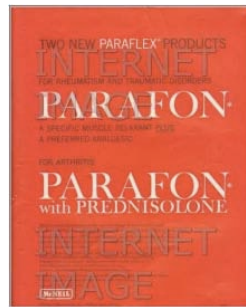
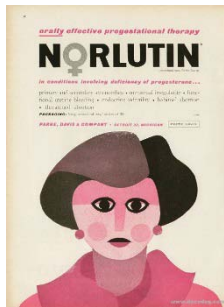
Thesis

Pharmaceutical and other novel exposures of the recent past may have impaired germline development in a subset of people, contributing to the rising incidence of neurodevelopmental abnormality, including ASDs.

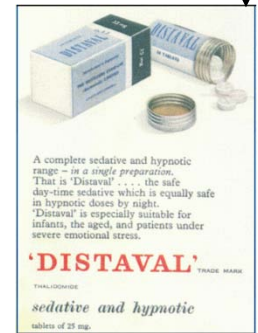
Use of prenatal pharmaceuticals surged in the mid-century

New synthetic drugs for pregnancy proliferated, and the placenta was mistakenly considered a barrier to harm. *Some examples:*

DES

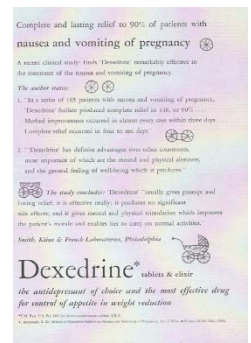
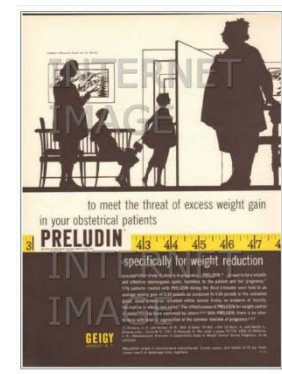
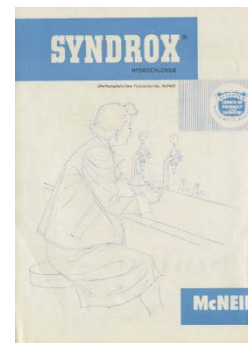
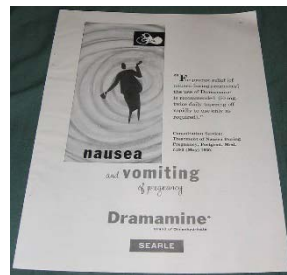
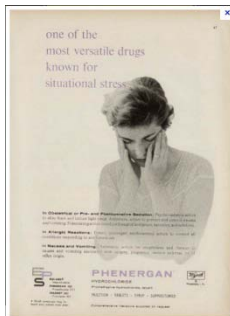


Thalidomide



Synthetic Hormones

Sedatives/Hypnotics



Anti-Nausea Drugs

Weight Loss Drugs, etc....

Drug use, early pregnancy only, 50,282 mother-child pairs, 1958-65

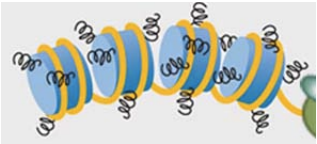
Anti-nausea, antihistamines	6,194	12%
Amphetamines, autonomic NS drugs	4,657	9%
Sedatives, tranquilizers, antidepressants	3,122	6%
Hormone drugs (synthetic and natural)	2,327	5%
Analgesics, antipyretics (aspirin)	15,909	32%
Immunizing agents (polio vaccine)	9,222	18%
Antimicrobials, antiparasitics (antibiotics, sulfa)	8,088	16%
Caffeine, xanthine derivatives	5,773	11%
Anesthetics, relaxants	2,657	5%
Bromides, fluorides, iodides, certain vitamins	2,542	5%
Cough medicines	948	2%
Gastrointestinal drugs	440	0.9%

Epigenetic germline effects?



“It is widely accepted that endocrine-disrupting chemicals can induce molecular epigenetic changes, such as DNA methylation and histone modification.”

—David Crews, PhD, and Andrea Gore, PhD, Univ. of Texas, Austin (Env. Health Perspectives 2011, 119: 1-3).



“The epigenome ... is most vulnerable during early development when the DNA synthetic rate is high and when the germline is undergoing extensive epigenetic remodeling.”

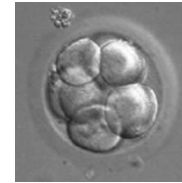
—Dana Dolinoy, PhD, University of Michigan, (Letter to FDA 2013)

“[E]ndocrine disruptors ... have been shown to exhibit transgenerational effects in animal models relevant to ASD.”

—Janine LaSalle, PhD, UC Davis (Journal of Human Genetics 2013, 1–6)

Some windows of germline vulnerability

- Pre-conception, fertilization, and early embryo

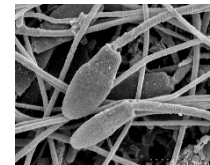


- Fetal germ cell development, (most susceptible period)



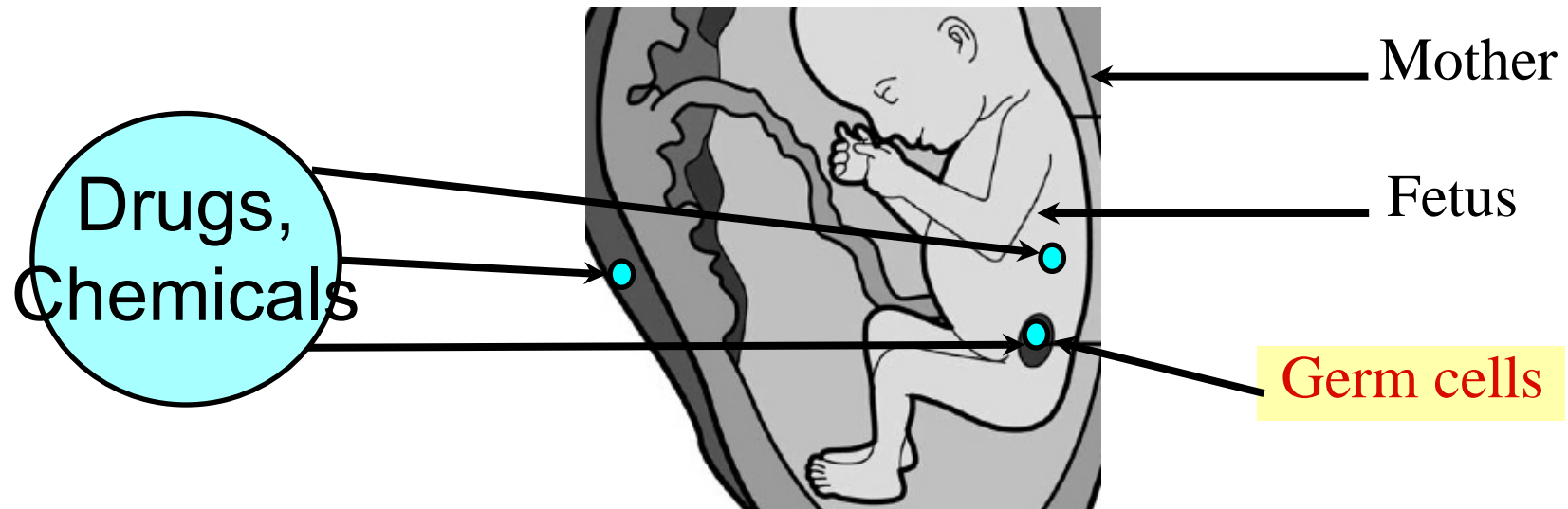
fetal
germ
cells

- Spermatogenesis through male's lifetime



Note that some chemicals, such as dioxin, can persist in tissue for years or decades, affecting sperm or egg long after initial exposure. *Exposure need not necessarily coincide with window of susceptibility.*

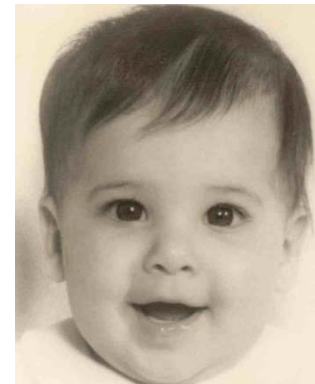
Pregnancy exposures can affect three generations at once



- **Paradigm shift:** Drugs taken by pregnant women can affect grandchildren.
- **Somatic v germ cells:** Different effects in different generations.
- **Latency period:** Pregnancy drugs of the 1960s, for example, may cause abnormalities in grandchildren born 1980s-today.

Potential Case Study: Me

- Born 1965 in Los Angeles
- Normal development
- No autism or developmental or psych conditions in ancestry or extended family
- Had three kids: normal conceptions, pregnancies, deliveries, no unusual exposures, no genetic anomalies, normal microarrays.
- Yet two have incapacitating abnormal neurodevelopment. Labeled “idiopathic autism.”



Me



Son, 14



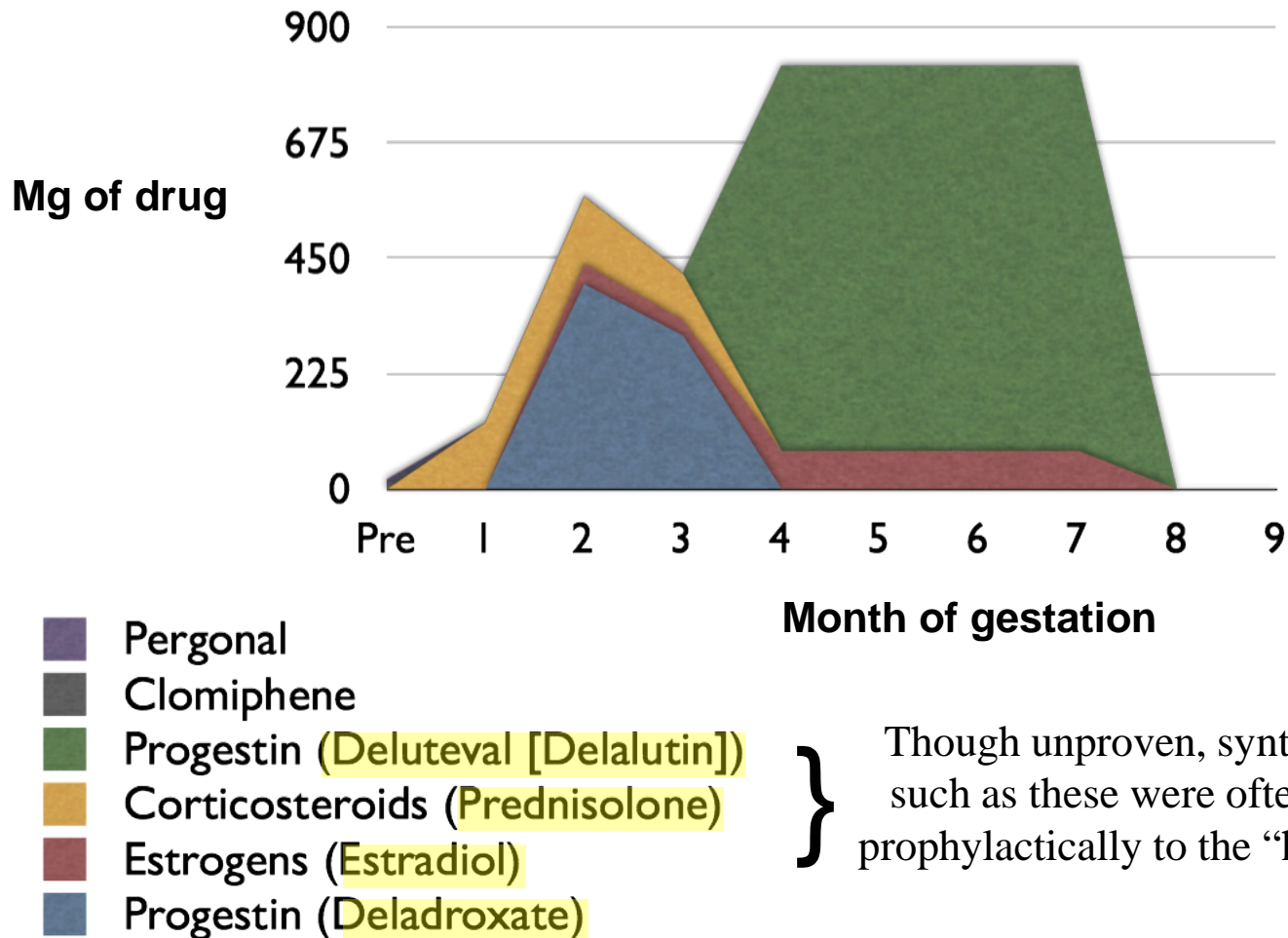
Daughter, 7

Access to one's own prenatal records is exceedingly rare.
I had no idea I had been exposed to anything, much less...

[illegible]

A Mix of Synthetic Steroid Hormones

I was prenatally exposed to heavy doses of powerful fake hormone drugs then used in pregnancies considered “at risk”: progestins, estrogens, corticosteroids.



We need to know more.

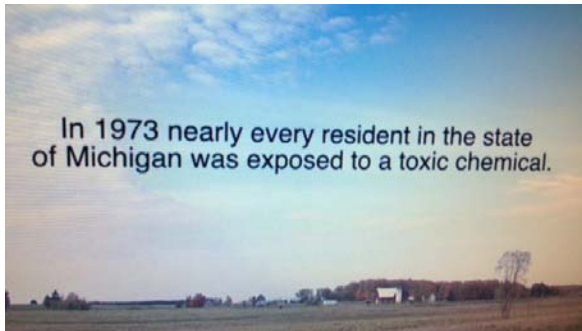
Broader exposures worth studying



Pesticides (DDT)



Agent Orange (dioxin)



Flame retardants



PCBs

Many other candidates from our toxic soup



Smoking



Recreational drugs



Air pollution



Nuclear testing



Superfund sites

Projects We've Kickstarted

- **Epidemiology:** Denmark study to evaluate germline effects of prenatal pharmaceuticals and smoking.
- **Prevention:** Eg, FDA petition to consider impacts of prenatal pharmaceuticals on “weakest link” (germline).
- **Environmental Epigenetics Symposium:** Co-sponsorship with UC Davis MIND Institute and Autism Speaks.
- **History:** Research on history of prenatal pharmaceutical use, 1950s-70s.
- **Medical records:** Efforts to allow all Americans access to their prenatal exposure records.
- **Laboratory studies:** To evaluate effects of synthetic hormone exposure.



Recommendations for Next Phase

IACC to pursue and monitor epigenetics in ASD, including:

- **Epidemiology:**

- Expanding scope of existing and new projects
- Continue longitudinal cohorts
- Genome sequencing and determination of “exposome”

- **Animal models:**

- Test germline impacts of relevant exposures through multiple generations
- Behavioral and molecular assays relevant to autism

- **Assays:**

- Develop high throughput assays for epigenetic markers
- Support ascertainment of ancestral exposures, including feasibility

- **Bioinformatics:** Linking data and resources, incorporate relevant outcomes into NDAR

- **Risk communication:** Ethical, evidence-based communication of risks of exposure