
 Humans start as molecules
Escher Fund for Autism
 GermlineExposures.org

Autism: An Epigenetic Epidemic?

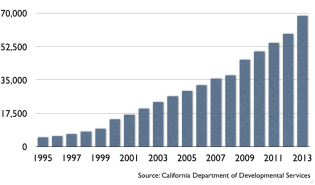
Jill Escher, MA, JD
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Morgan Autism Center Conference, September 20, 2014

A Provocative Hypothesis

Despite lacking known genetic or environmental risk factors, it was almost inevitable that my children, and countless others, would suffer some degree of neurodevelopmental abnormality.

California Autism Population
(Substantial disability only)




Year	Population (Substantial disability only)
1995	~5,000
1997	~6,000
1999	~7,500
2001	~9,000
2003	~11,000
2005	~13,500
2007	~16,000
2009	~19,000
2011	~23,000
2013	~27,000

Source: California Department of Developmental Services

Why?

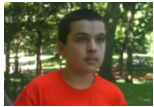
Case Study




I was born in 1965 in Los Angeles and developed normally. No history of developmental, intellectual, or mental disability in my or my husband's family histories.

My children are genetically normal, physically beautiful, and come from three low-risk, full-term pregnancies, with normal conceptions, and deliveries.

Yet two of my children are severely neurodevelopmentally disabled, nonverbal "autistic," will need lifelong 24/7 1:1 care.



Son, 15

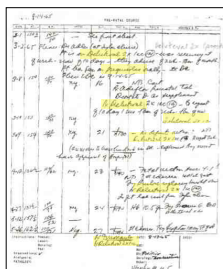


Daughter, 8

No one had a clue what could have caused this.

A Rare Discovery and "Aha" Moment

In 2010, I had discovered I had been an early fertility treatment child.
 In 2011, I heard a podcast... "a girl of course is born with all her eggs." (Duh!)
 Perhaps I—and my eggs—had been exposed to something?

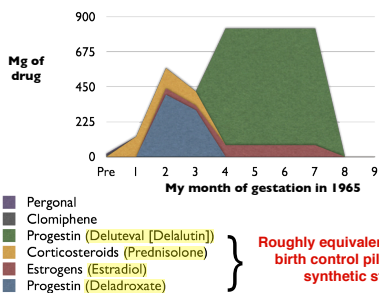


Oh, yes indeed!

From my mother's 1965 obstetric records.

I Had Been Prenatally Exposed to Heavy, Continual Doses of Synthetic Steroid Hormones

Progestins, estrogens, corticosteroids. Why? "To prevent miscarriage."
 "Mad Men" era of maternal medicine. Such drugging was common.



Roughly equivalent to 20-30,000 birth control pills' worth of synthetic steroids.

Why Does This Matter?

Because toxic pregnancy exposures put three generations at risk



We Have Forgotten the Prenatal Drug Craze

Synthetic hormones



Sedatives, barbiturates



Anti-nausea drugs



Amphetamines



And don't forget:

Plus

- Diuretics
- Antihypertensives
- Anaesthesia
- X-rays
- Analgesics
- Recreational drugs
- Hormonal contraceptives


Smoking




Synthetic sweeteners




We Have Forgotten Pervasive 20th Century Toxicity




Pesticides (eg, DDT)



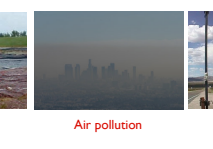
Agent Orange (dioxin)



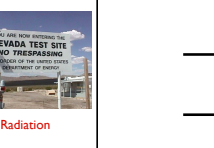
Plasticizers (eg, BPA, phthalates)



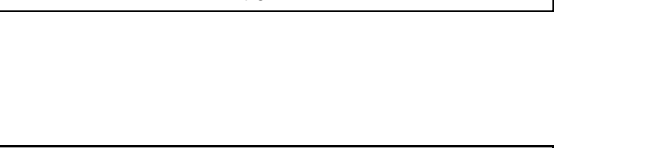
Flame retardants (eg, PBDEs)



PCBs



Air pollution



Radiation

Adverse epigenetic effects found.

But We Now Know Environmental Epigenetics

Epigenetics: "Heritable changes in gene expression caused by mechanisms other than alterations to underlying DNA sequence."

An interface between the environment and the genome.

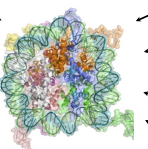
Drugs and pharmaceuticals

Industrial chemicals

Pesticides

Cigarette smoke

Hormone mimics/
endocrine disruptors



Nutrition

Plasticizers

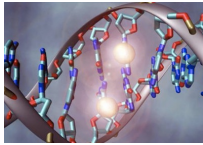
Radiation

Exercise

Acute stress

How Epigenetics Works: Two Examples

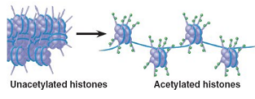
DNA Methylation
Chemical tags on DNA.



Lab of Misha Spyt

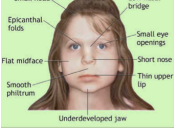
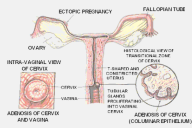

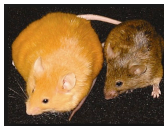
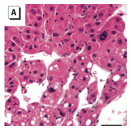

“Don’t bother transcribing this gene.”

Histone Modification
Chemical tags on DNA structural proteins.




“This gene is open for business!”

Adverse Somatic Epigenetic Effects: Fetal Exposures


<p>Alcohol</p>  <p>Small head Low nasal bridge Epicanthal folds Small eye openings Flat midface Short nose Thin upper lip Smooth-philtrum Underdeveloped jaw</p> <p>Fetal alcohol syndrome</p>	<p>DES</p>  <p>ABNORMALITIES DUE TO DES EXPOSURE</p> <p>ECTOPIC PREGNANCY FALLOPIAN TUBE OVARY VAGINA UTERINE FUNDUS VAGINA CERVIX VAGINA</p> <p>Cancer, infertility, autoimmune</p>	<p>Fetal starvation (Dutch Hunger Winter)</p>  <p>Heart disease, diabetes, schizophrenia</p>
<p>Lack of methyl donors (eg, folate, B12)</p>  <p>Agouti mouse color and obesity.</p>	<p>Fetal BPA exposure</p>  <p>Mouse liver tumors.</p>	<p>Thalidomide</p>  <p>Stunted limb growth.</p>

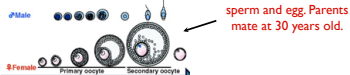
But What About Our Germline, that 3d Generation?

The germ cells that will make Baby are created in the **fetuses** that will be his parents (ie, in the wombs of Baby’s grandmothers, 1970).



Germ cells specified, **epigenetic reprogramming, parent-of-origin marks (imprinting)**, 1970.







Germline is the long, vulnerable molecular phase of the human lifecycle

Germ cells mature further and become sperm and egg. Parents mate at 30 years old.

Baby! (2000)

After fertilization, another wave of reprogramming (2000).





Some Critical Windows for Our Germline Epigenome and Some Exposures of Concern

- **Fetal germ cells:** grandmaternal pharmaceuticals, drugs and smoking
- **Early childhood:** childhood pharmaceuticals, x-rays
- **Males—pre-puberty, spermatogenesis:** pharmaceuticals, poor nutrition
- **Females—peri-conception to about week 4:** IVF, ICSI, maternal synthetic hormones, antidepressants and other pharmaceuticals, drugs and smoking

But who says epigenetic dysregulation has anything to do with autism?

Autism Research Implicating Epigenetics:

Differences in gene regulation in ASD

- Methylation differences in twins discordant for autism. (Mill 2013)
- Methylation differences in post-mortem autism brains. (Ladd-Acosta 2013)
- ASD brains had more genes that were up- or down-regulated in an individual-specific manner. (Ben-David 2014)
- Methylation differences in ectodermal cells of ASD children born to older mothers. (Berko 2014)
- Abnormal epigenetic modification in autism brains. (Nardone 2014)

ASD risk increase with epigenetically adverse exposures

- Increased autism risk with valproic acid, antidepressants, thalidomide. (many)
- PDE5s associated with autism risk and Dup15q syndrome. (Woods 2012)
- ICSI assisted fertility treatment raises risk of autism. (Sandin 2013)
- Association between maternal agricultural pesticide exposure and autism. (Shelton 2014)
- Multigenerational behavioral effects of BPA, vinclozolin, nicotine in animal models. (Crews 2012, Wolstenholme 2012, Skinner 2008, Zhu 2014)

ASD risk increase with parental endocrine abnormalities

- Maternal obesity/diabetes associated with increased risk of autism. (Trakowski 2012)
- Mothers with PCOS more likely to have daughters with pervasive developmental disorders (Palomba 2012)
- Paternal obesity associated with increased risk of autism in offspring. (Suren 2014)

ASD connected to epigenetically vulnerable imprinted genes

- Epigenetic mechanisms in disorders with autism symptoms: Rett, Fragile X, Angelman, Prader-Willi, Beckwith-Wiedemann, Dup 15q syndromes. (many)
- Several autism risk genes are imprinted genes. (many)
- Gender bias in ASD (5:1 male, female) may be due to germline epigenetic phenomena. (many)

Grandparental associations in ASD; and population/exposure associations

- Older grandmothers associated with risk of autism. (Golding 2010)
- Father born to older fathers (grandfather of ASD child) associated with risk of autism. (Frans 2013)
- Male urogenital abnormality in population associated with sharply higher autism rates. (Rzhetsky 2014)

Many Others Share My Story

Some examples:

Name, year of birth	In Utero exposure	Childrens' diagnoses
Janice, b. 1965	Antimiscarriage drugs	Autism (3)
Jennifer, b. 1970s	Antimiscarriage drugs	Autism (3)
Liza, b. 1965	Antimiscarriage drugs	Autism (1)
Chrissy, b. 1968	Antimiscarriage drugs	Learning disabilities (1) conduct disorder (2)
Gabriel, b. 1968	Antimiscarriage drugs	Autism / mental illness (1)
Cherie, b. 1964	Antinausea drugs	Autism (1)
Veronica, b. 1954	DES (synthetic estrogen)	Autism (1)
Jamie, b. 1965	General anaesthesia	Autism (2)
Glenn, Stuart, Bill, Anna, many others, b. 1960s-70s	Cigarette smoke	Autism, various

I noticed that their unexposed siblings tended to have typically developing children, while exposed siblings often also had children with neurodevelopmental abnormalities.

* Most names have been changed to protect privacy

Genes v. Environment: A Dead Paradigm

During critical windows, certain exposures can alter our genetic material, the molecular programming of our egg and sperm.

Therefore, **heritability is more than genetics**. It includes “epigenetics.”

And therefore, while you can't have a “genetic” epidemic, you can have an epigenetic epidemic.

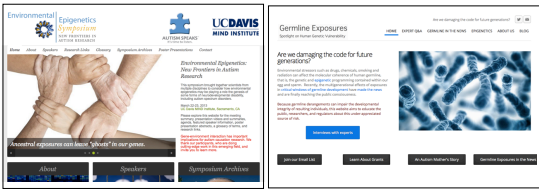
We must undertake studies to examine this question head-on. Three pilot efforts are underway:

- Denmark
- California
- Boston/Providence


But we need more.

Thank you!

For more information, please see:



AutismEpigenetics.org GermlineExposures.org

Escher Fund  for Autism
GermlineExposures.org
