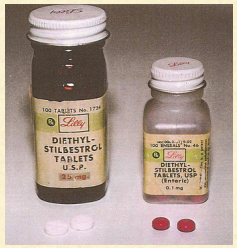
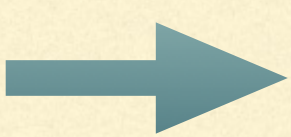
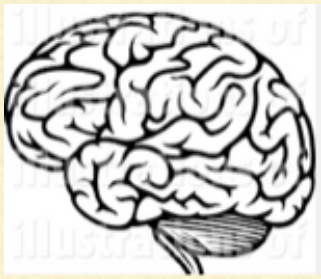
Time Bomb

A journey into old exposures, gametic glitches, and the autism explosion





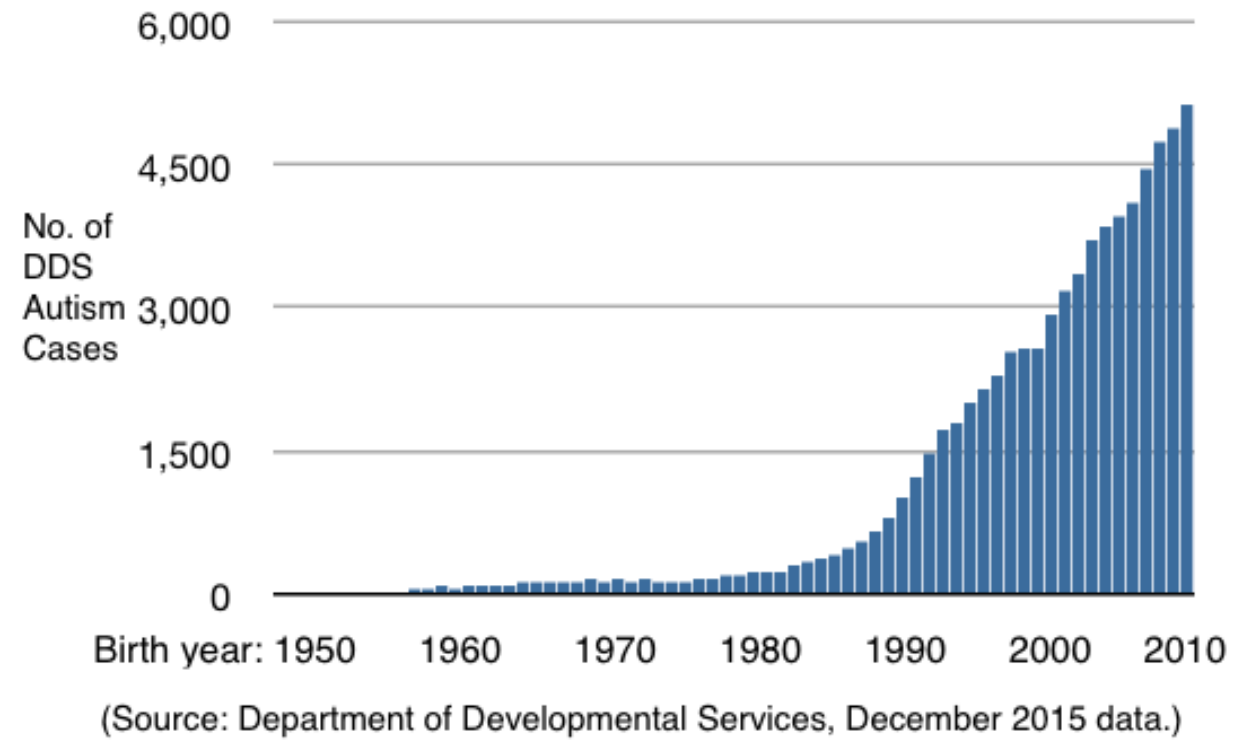


Jill Escher, MA, JD
@JillEscher

Escher Fund for Autism
Humans start as molecules
GermlineExposures.org

DRAMATIC SURGE IN SERIOUSLY DISABLING AUTISM CASES

Calif. Department of Developmental Services
Autism Cases by Birth Year 1943-2010

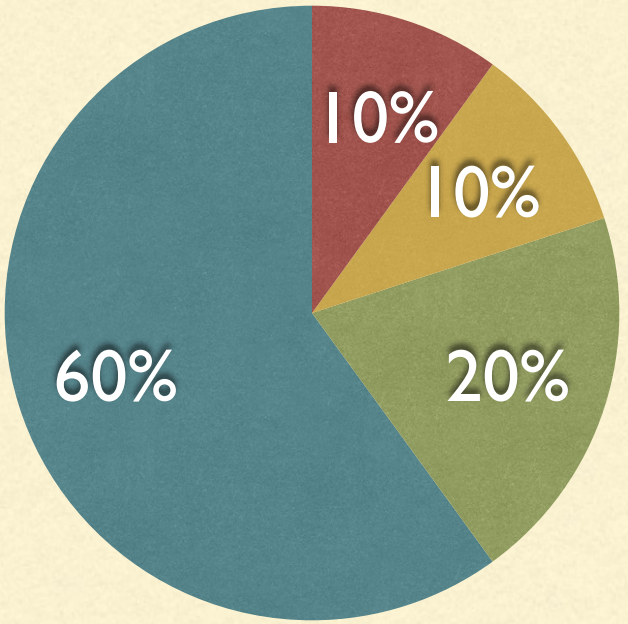


Should be seen as an epidemic of dysregulated neurodevelopment.

WHAT'S CAUSING AUTISM?

GENES

100s of genes contribute—about 10% of cases can be attributed to known genomic errors, 10% more forecast



PROXIMAL FETAL STRESSORS

le, prematurity, multigravidas, hypoxia, certain drugs, infection, maybe 20%

UNKNOWN

Probably at at least 60% of cases, but strong evidence of heritability

ARE WE ASKING THE RIGHT QUESTIONS?

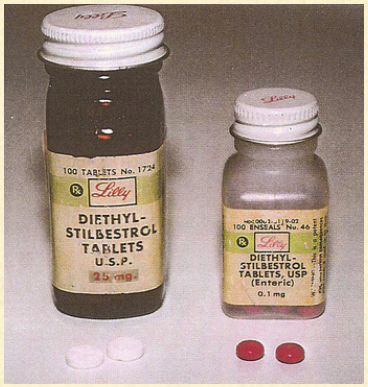
Old paradigm: genes or environment?

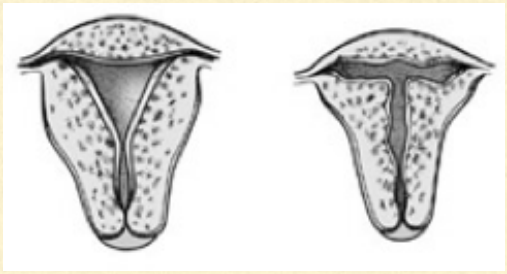
New paradigm: genes and environment

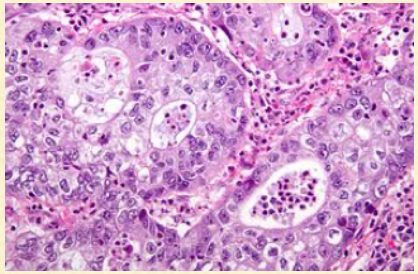
TOXICANT + SOMATIC = "TERATOGEN"

Thalidomide

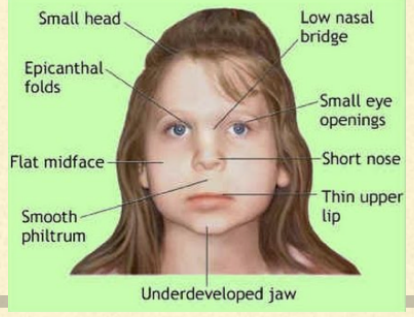
DES
(Diethylstilbestrol)

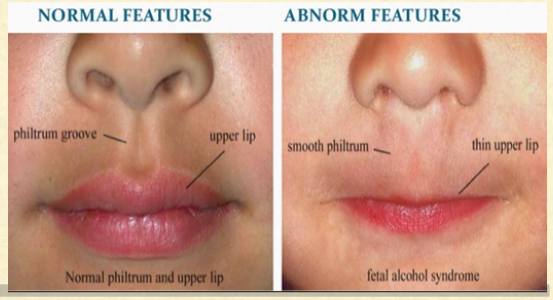






Fetal Alcohol Syndrome



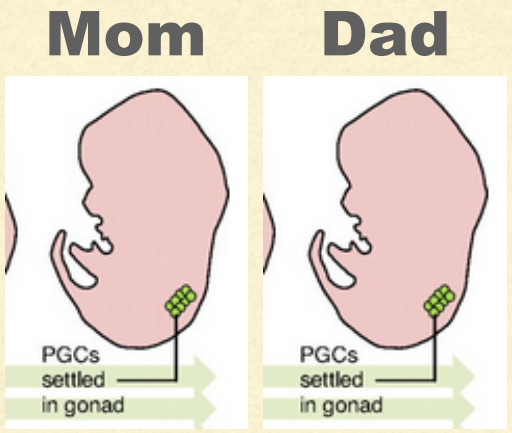


BIOLOGY LESSON: WHERE DID YOU COME FROM?

Did your development start at <u>conception</u>—
your father's sperm + your mother's egg?

eg, 2000

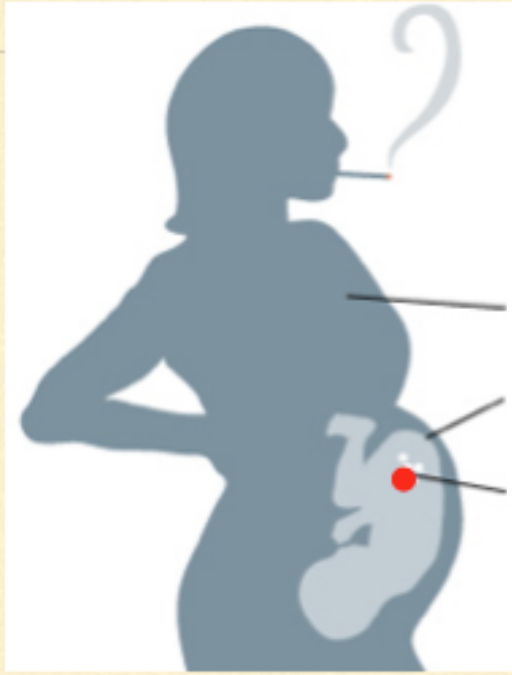
No, it started in your parents' **early embryonic egg and sperm, or "primordial germ cells"** (eg, 30 years <u>before</u> conception, in your grandmothers' wombs).



eg, 1970

Alas, gametic development is a somewhat lost realm of biology.

TOXICANT + GAMETE = "TIME BOMB"



eg, 1970

F0 = Mother

F1 = Fetus

F2 = Germ cells / grandchildren

A pregnant woman carries <u>two</u> generations.

Germ cells are sensitive to **steroid hormone signals, mutagens, epimutagens**. Those vulnerable F2s will emerge as human organisms <u>a generation later</u>.

eg, 2000

WELCOME TO THE WORLD OF GENETIC TOXICOLOGY

In other words, zap a gamete… what could possibly go wrong…?

Immediate effects, for example:

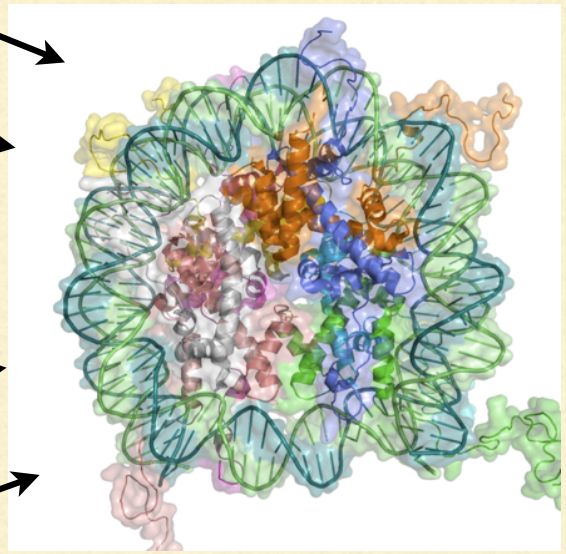
- Hypo or hypermethylation of DNA, which "escape" post-conception reprogramming (some escapee genes are associated with neurodevelopment)
- Errors of genomic imprinting
- ncRNAs and cytoplasmic events
- Other "epigenetic" artifacts

Downstream effects, for example:

- Destabilizing of transposons, increasing risk for mutations
- Point mutations / CNV's of exome
- Point mutations / CNV's of regulatory genes ("switches")
- Somatic mosaicism

EPIMUTAGENESIS: EXPOSURES CAN ALTER HOW GENES WORK

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



Drugs and pharmaceuticals

Industrial chemicals

Pesticides

Cigarette smoke

Hormone mimics/ endocrine disruptors

Nutrition (eg, vitamins, folate, famine)

Plasticizers

Radiation

Exercise

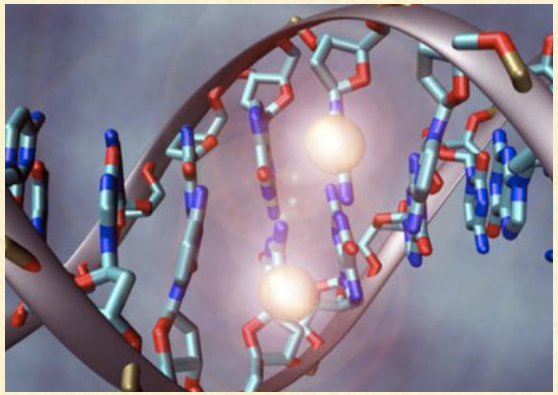
Acute stress

EPIGENETIC FACTORS CAN UP-REGULATE OR DOWN-REGULATE GENE EXPRESSION

For example:

Methylation

Chemical tags on DNA.

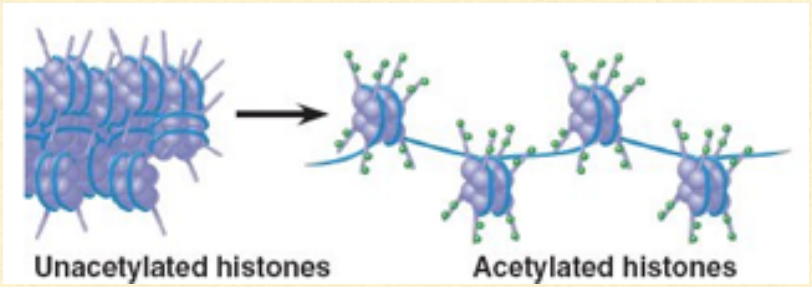


Lab of Moshe Szyf

"Don't bother transcribing this gene."

Histone modification

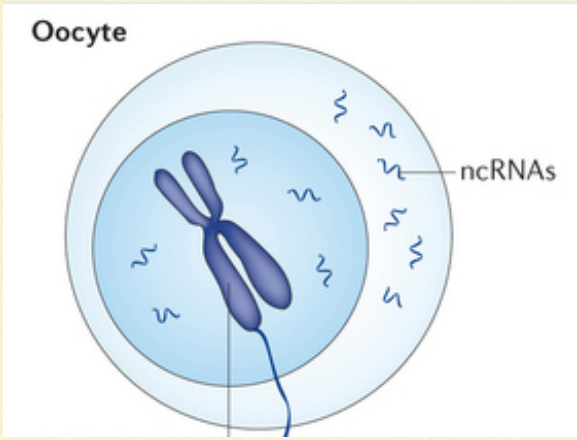
Chemical tags on DNA structural proteins.



"This gene is open for business!"

ncRNAs

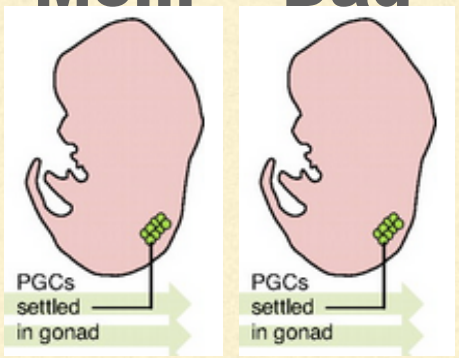
Can regulate gene output

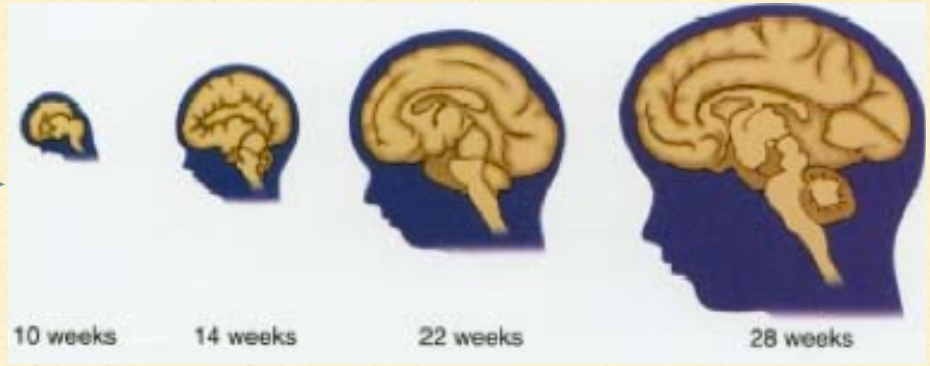


May carry environmental info via gametes

WHAT DOES ALL THIS HAVE TO DO WITH NEURODEVELOPMENT?

Mom **Dad**





Primordial germ cells **Mature gametes** **CNS development**

Genetic and epigenetic coding, including imprinting, contribute to intricate and complex process of brain development. **Healthy brains depend on subtle control of gene expression, dosage and timing, not just Mendellian "genetics."**

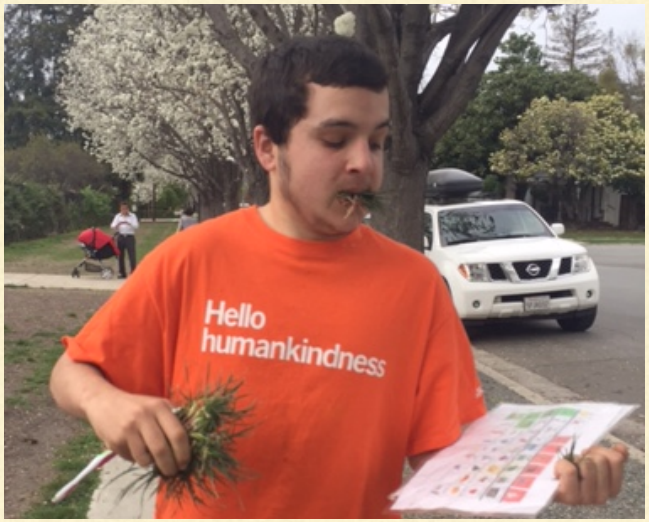
Programming for the brain starts in those two little germ cells.

A GERMLINE EXPOSURES STORY

I was born in 1965 in Los Angeles.

I have three beautiful, genetically normal children from three low-risk, normal pregnancies.

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

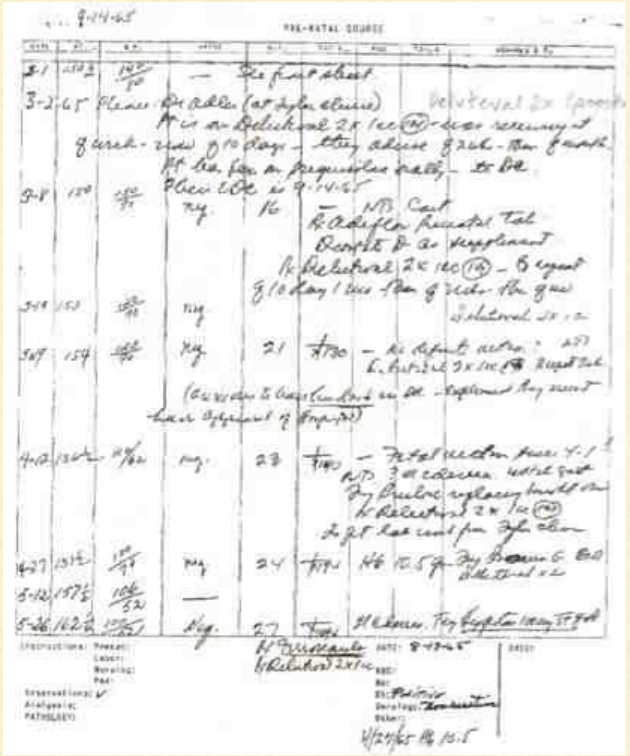


Son, 17

Daughter, 10

A TRIO OF UNEXPECTED DISCOVERIES

1.



In 2010, I obtained my mother's 1965 obstetric records. What did they mean?

2.

Prenatal Exposure to Synthetic Progestins and Estrogens: Effects on Human Development

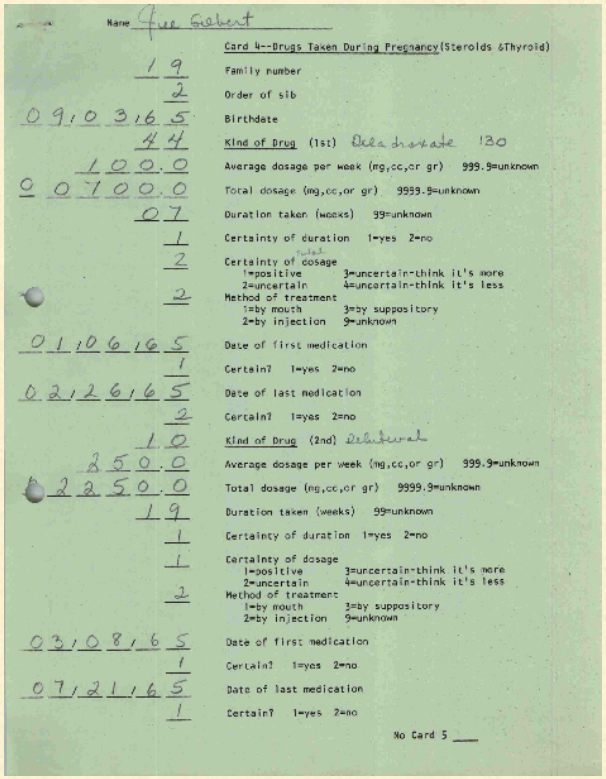
June Machover Reinisch, Ph.D.,[1] and William G. Karow, M.D.[2]

Seventy-one offspring of mothers administered combinations of synthetic progestins and estrogen for the maintenance of at-risk pregnancy were evaluated for their performance on IQ and personality tests. Siblings born of untreated pregnancies acted as controls. Hormone-exposed subjects were partitioned into three treatment subgroups dependent on the ratio of progestin to estrogen administered to their mothers during pregnancy. No difference in IQ was obtained among the three treatment subgroups even when scores were adjusted for sibling score and prenatal and perinatal complications. Responses to the personality questionnaire provided significant differences among the three groups. The group exposed to the progestin regime (progestin alone or in combination with very low doses of estrogen) and the estrogen regime (higher doses of estrogen than progestin) were most dissimilar. Progestin regime exposed subjects were characterized as more independent, sensitive, self-assured, individualistic, and self-sufficient. In contrast, the subjects exposed to the estrogen regime were more group oriented and group dependent. Analysis of difference scores generated by subtracting the score of an unexposed sibling from that of the exposed cosibling provided similar results. A general discussion is presented on the efficacy of hormone treatment for pregnancy maintenance, augmented fetal wastage of males, birth order and treatment, maternal knowledge of treatment and its possible postnatal effects on the offspring, and drug effects on the fetus.

KEY WORDS: synthetic progestin; estrogen; diethylstilbestrol; humans; personality; IQ; pregnancy maintenance; prenatal.

In 2011, I discovered I had been a subject in a study (Reinisch 1977) examining fetal effects of synthetic steroid hormone drugs.

3.



Name Sue Gebert

Card 1--Drugs Taken During Pregnancy (Steroids & Thyroid)

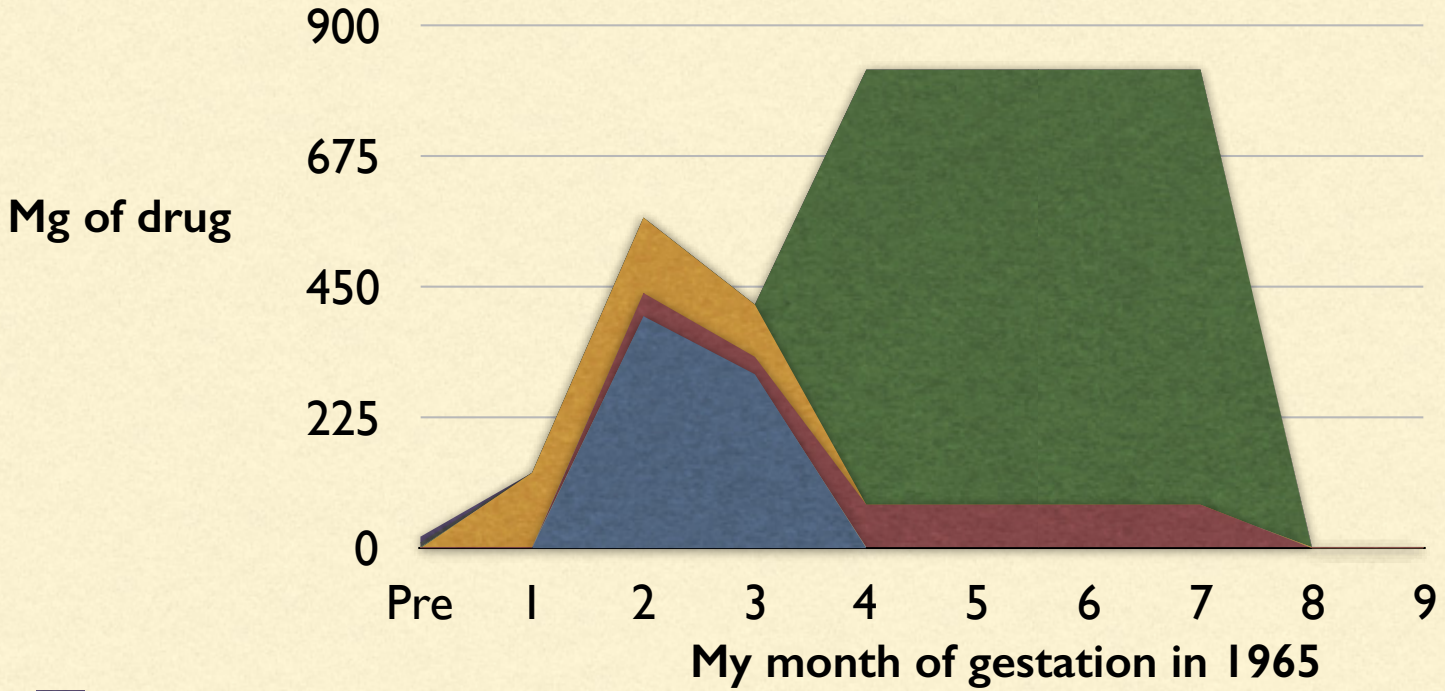
19 Family number
2 Order of sib
09 03 16 5 Birthdate
44 Kind of Drug (1st) Delalutin 130
100.0 Average dosage per week (mg,cc,or gr) 999.9=unknown
00700.0 Total dosage (mg,cc,or gr) 9999.9=unknown
07 Duration taken (weeks) 99=unknown
1 Certainty of duration 1=yes 2=no
2 Certainty of dosage (Total) 1=positive 3=uncertain-think it's more 2=uncertain 4=uncertain-think it's less
2 Method of treatment 1=by mouth 3=by suppository 2=by injection 9=unknown
01 06 16 5 Date of first medication
1 Certain? 1=yes 2=no
02 26 16 5 Date of last medication
2 Certain? 1=yes 2=no
10 Kind of Drug (2nd) Delalutin
250.0 Average dosage per week (mg,cc,or gr) 999.9=unknown
2250.0 Total dosage (mg,cc,or gr) 9999.9=unknown
19 Duration taken (weeks) 99=unknown
1 Certainty of duration 1=yes 2=no
1 Certainty of dosage 1=positive 3=uncertain-think it's more 2=uncertain 4=uncertain-think it's less
2 Method of treatment 1=by mouth 3=by suppository 2=by injection 9=unknown
03 08 16 5 Date of first medication
1 Certain? 1=yes 2=no
07 21 16 5 Date of last medication
1 Certain? 1=yes 2=no

No Card 5 ___

In 2013, I obtained records from the Kinsey Institute detailing my prenatal drug exposures.

WHAT WERE MY FETAL EXPOSURES?

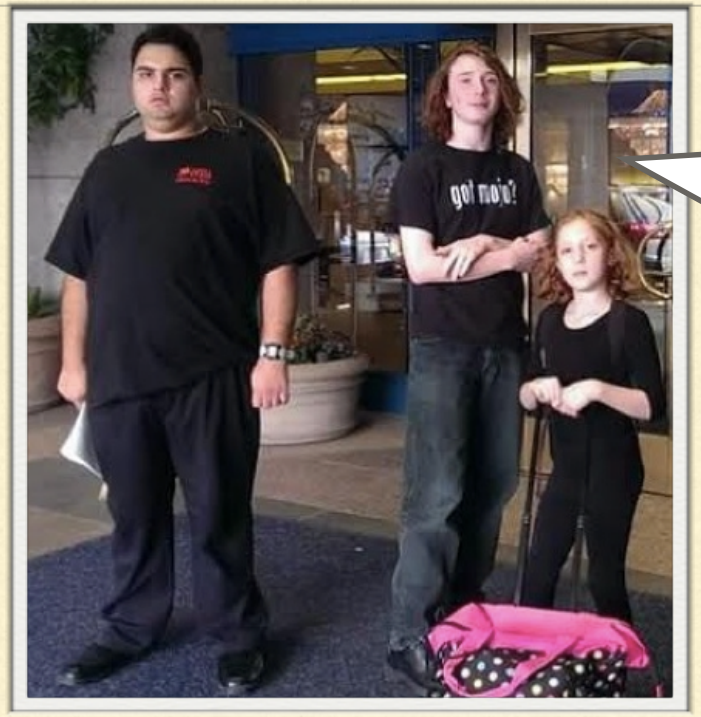
Progestins, estrogens, corticosteroids. Why? “To prevent miscarriage.”
“Mad Men” era of maternal medicine. Such drugging was common.



- Pergonal
- Clomiphene
- Progestin (Deluteval [Delalutin])
- Corticosteroids (Prednisolone)
- Estrogens (Estradiol)
- Progestin (Deladroxate)

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

MANY OTHERS SHARE MY STORY

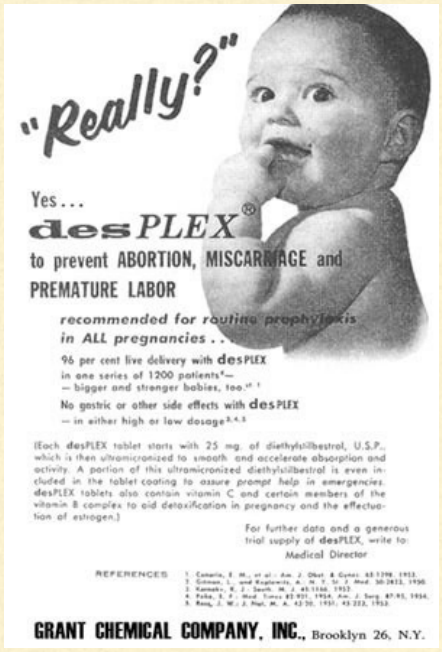


We started as eggs when our mom was a fetus.

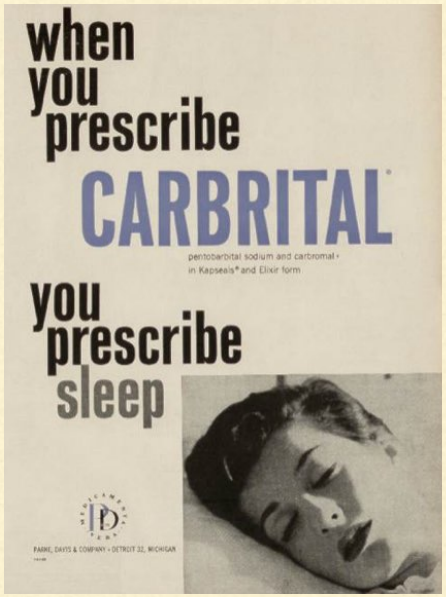
Example: Joan Hutchens was also exposed prenatally to an "anti-miscarriage" hormone regimen in 1965. Three of her five children have idiopathic autism.

PREGNANT WOMEN WERE HEAVILY MEDICATED IN THE POST-WAR DECADES

Synthetic hormones

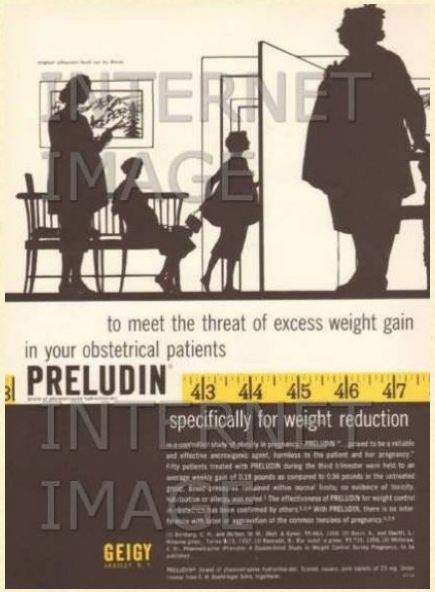


Sedatives, barbiturates



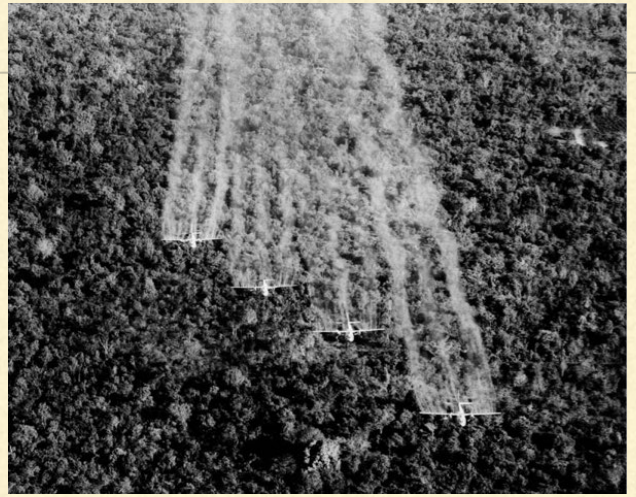
Anti-nausea drugs

Amphetamines



LET'S NOT FORGET OTHER EXPOSURES

Pesticides (eg, DDT)



Agent Orange (dioxin)

Plasticizers
(eg, BPA, phthalates)

Flame retardants
(eg, PBDEs)

PCBs

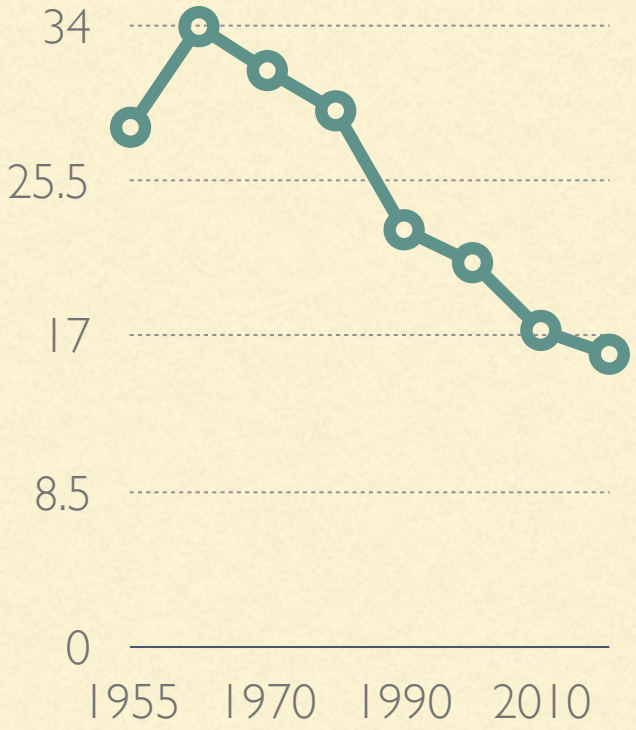
Air pollution

Radiation

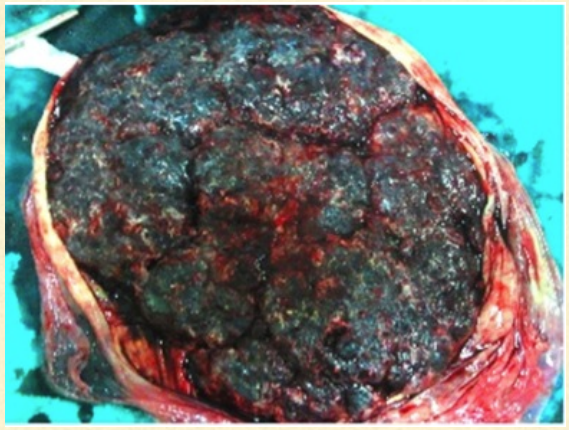
PREGNANCY SMOKING WAS COMMON

Doctors sometimes recommended it as an appetite suppressant

Smoking prevalence among US females



Cigarette smoke = mutagenic and epimutagenic components



Placenta from a tobacco-exposed pregnancy

TOXIC COMPONENTS OF CIGARETTES

(Short list)

Ammonia
Arsenic
Benzene
Benzo(a)pyrene
Carbon monoxide
DDT/pesticides
Formaldehyde
Hydrogen cyanide
Nicotine
Radiation
Tar

IN ASD, GRANDMATERNAL PREGNANCY SMOKING IS COMMONLY REPORTED

Families had no history of autism. Sampling of the F1 interviewees' F2's:

These potential "time bombers" may raise important questions about germline mutagenesis or epimutagenesis in ASD.

GERM CELLS: OUR MOST VITAL ASSET

What the public must recognize is that mankind's most vital asset is not its material wealth but its germ plasm—the very stuff of life.

Since the germinal cells are what determine the health, intellectual capacity, and all the other prime attributes of future generations, everything possible must be done to protect those—humanity's most precious possessions.

—Geneticist James Neel, 1969

GENETIC TOXICOLOGY SHOULD BE THE NEXT FRONTIER IN AUTISM RESEARCH

LEARN MORE AT GERMLINEEXPOSURES.ORG

Germline Exposures

A project of: Escher Fund for Autism — Humans start as molecules

Webinar 1: "Early Germline Events in the Heritable Etiology of ASDs"

Featuring **Amander Clark**, PhD, Department of Molecular and Cell Biology, UCLA: "Molecular dynamics and epigenomic vulnerabilities of the early germline in humans"

Ryan Yuen, PhD, Center for Applied Genomics, Hospital for SickKids: "Overview of heterogenous de novo genomic alterations in ASD subjects"

Commentary by Patrick Allard, PhD, Janine LaSalle, PhD, Lisa Chadwick, PhD, and Stephan Sanders, PhD

Webinar 2: "Environmental Exposures and the Germline: Investigating Causes of Epigenomic and Genomic Errors"

Featuring **Dana Dolinoy**, PhD, University of Michigan: "Heritable epigenetic effects of germline exposure to toxicants"

Carole Yauk, PhD, Health Canada: "Analysis of chemical exposures and life stage factors that contribute to genetic disease"

Commentary by Cathrine Hoyo, PhD, and Lisa Chadwick, PhD

Escher Fund for Autism — Humans start as molecules
GermlineExposures.org

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AUTISM SCIENCE FOUNDATION