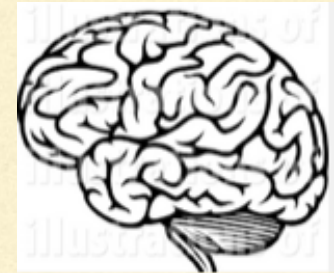
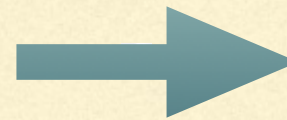
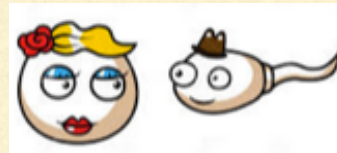
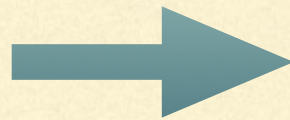


Time Bomb

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

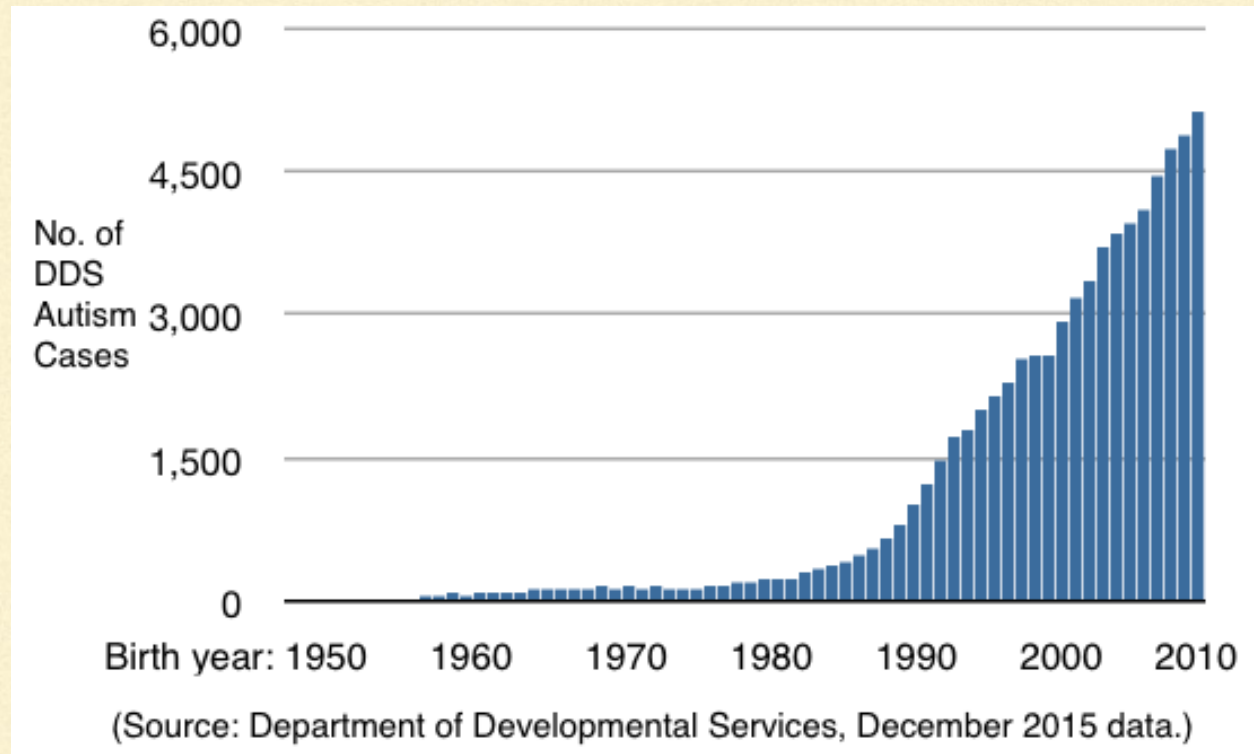


Jill Escher, MA, JD
@JillEscher

Escher Fund  Humans start as molecules
for Autism
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

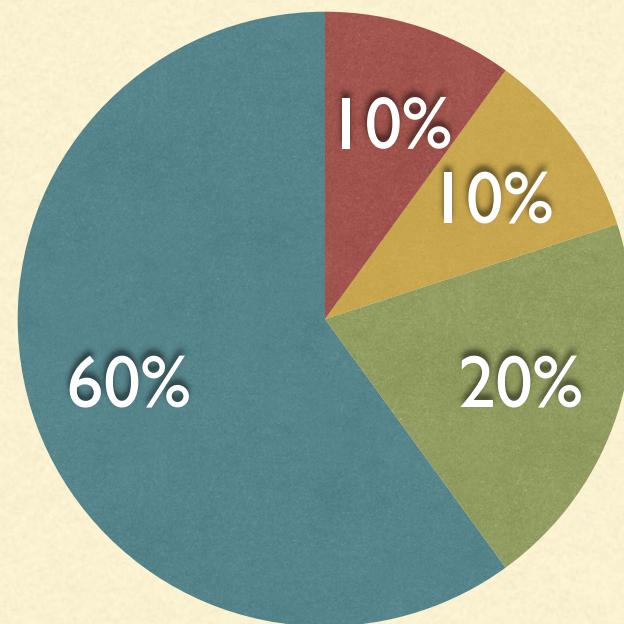
100s of genes contribute—about 10% of cases can be attributed to known genomic errors, 10% more forecast

PROXIMAL FETAL STRESSORS

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

UNKNOWN

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



ARE WE ASKING THE RIGHT QUESTIONS?



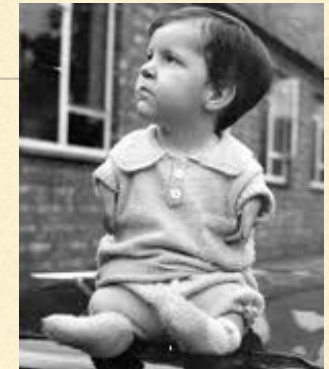
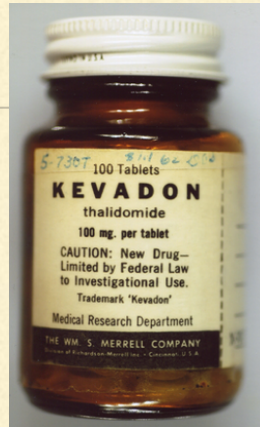
Old paradigm: genes or environment?



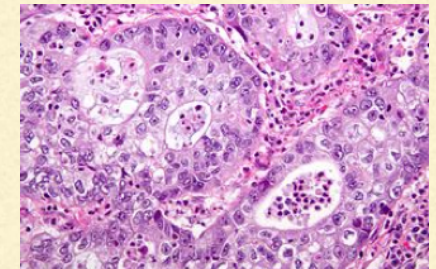
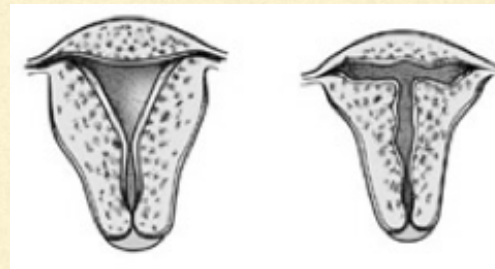
New paradigm: genes and environment

TOXICANT + SOMATIC = "TERATOGEN"

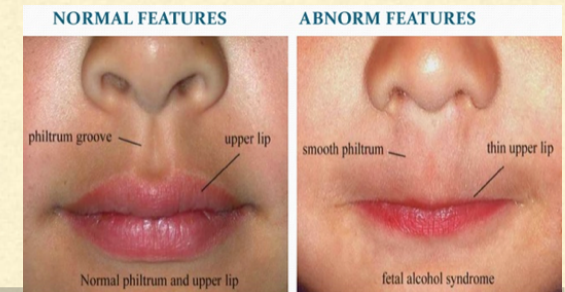
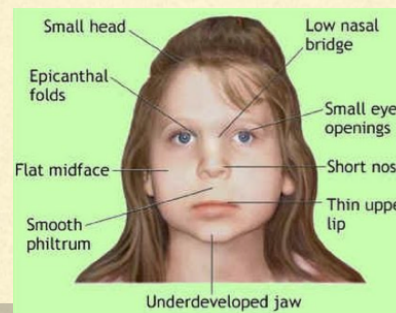
Thalidomide



DES (Diethylstilbestrol)



Fetal Alcohol Syndrome



BIOLOGY LESSON: WHERE DID YOU COME FROM?

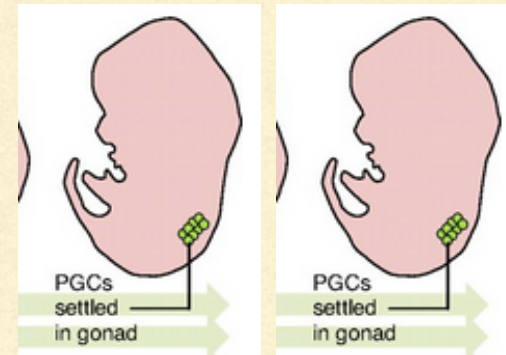
Did your development start at conception—
your father's sperm + your mother's egg?



eg, 2000

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

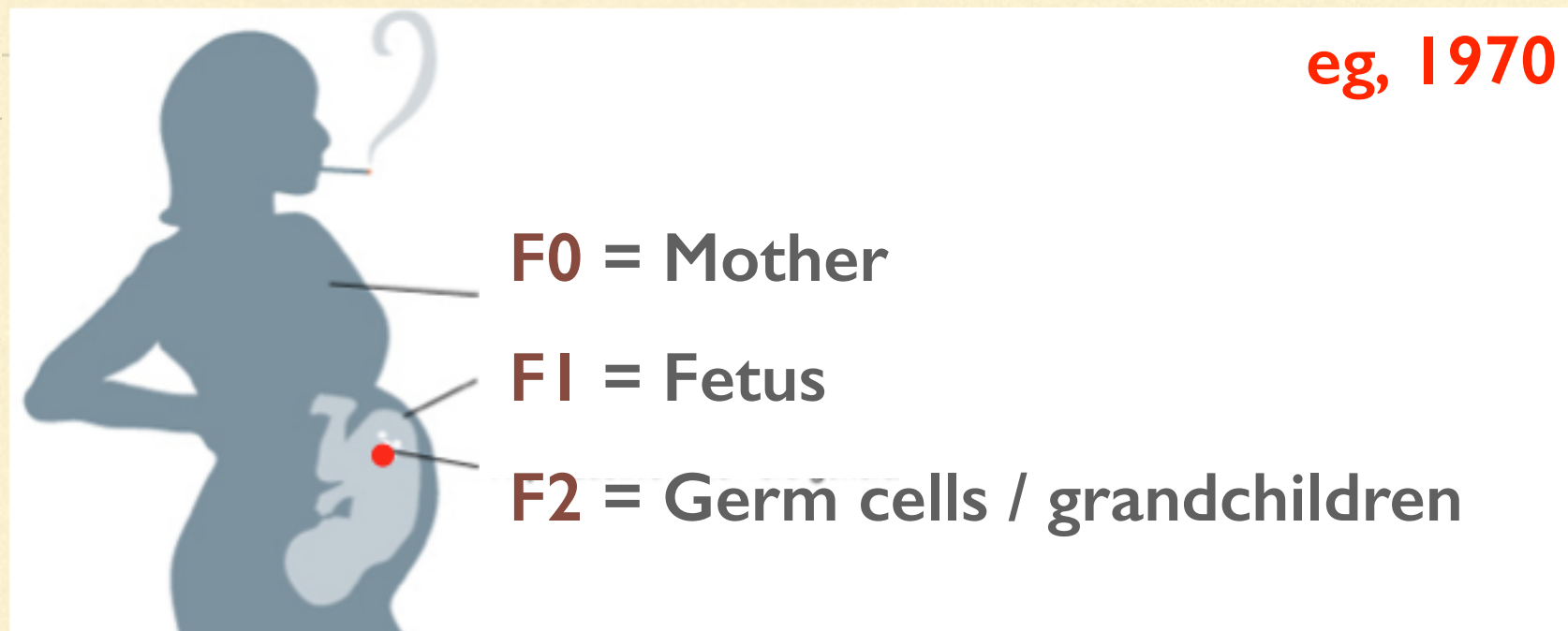
Mom **Dad**



eg, 1970

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

TOXICANT + GAMETE = “TIME BOMB”



A pregnant woman carries two generations.



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

eg, 2000

WELCOME TO THE WORLD OF GENETIC TOXICOLOGY

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

Immediate effects, for example:

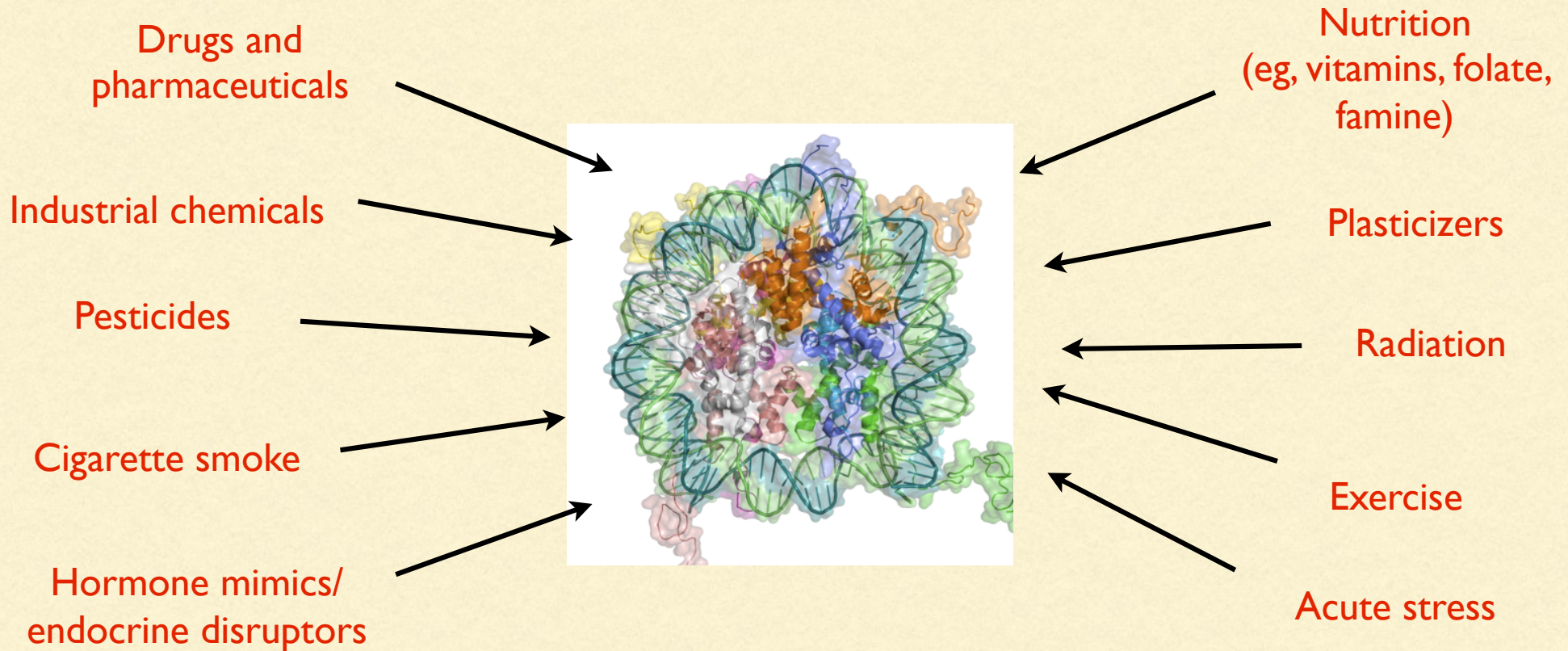
- Hypo or hypermethylation of DNA, which “escape” post-conception reprogramming (some escapee genes are associated with neurodevelopment)
- Errors of genomic imprinting
- ncRNAs and cytoplasmic events
- Other “epigenetic” artifacts

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.”

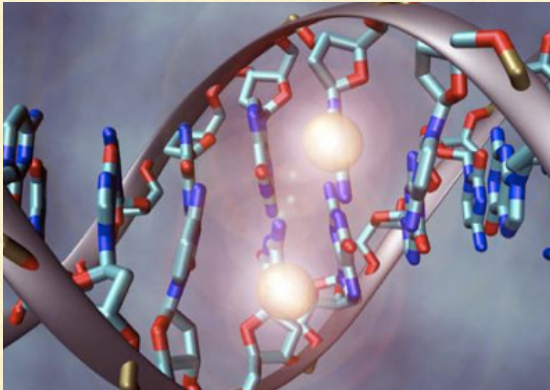


EPIGENETIC FACTORS CAN UP-REGULATE OR DOWN-REGULATE GENE EXPRESSION

For example:

Methylation

Chemical tags on DNA.

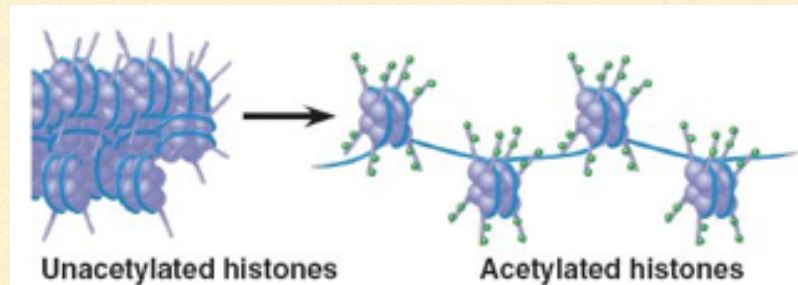


Lab of Moshe Szyf

“Don’t bother transcribing this gene.”

Histone modification

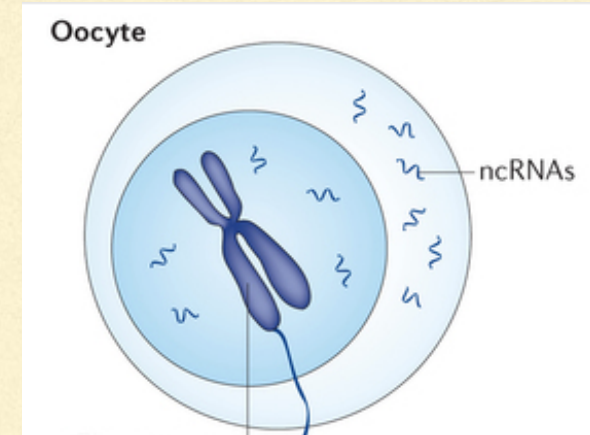
Chemical tags on DNA structural proteins.



“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?



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.

PRE-NATAL SOURCE

DATE	TIME	WEEK	STATUS	REMARKS
3-1-65	12:30	12	—	The first check
3-2-65	10:00	13	OK	Placenta on abdomen (at 24 cm) vertical in position. It is a bit high at 28 (at 30) - less necessary. 8 weeks - now 9 1/2 days - they above 820 - then 840. At 30, 320 on frequency of 200 - 250.
3-8-65	10:00	14	OK	Placenta 200 at 9:14:55. NB. Cast. R. Adipose fetal. B. 2000 & a supplement. R. diethylstilbestrol 2x 100 (10) - 5 mg. 8/10 days / 1000 mg of 200 - 250 mg.
3-14-65	10:00	15	OK	Subtotal 200
3-21-65	10:00	16	OK	At 200 - 250 mg. L. diethylstilbestrol 2x 100 (10) - 5 mg. 8/10 days / 1000 mg of 200 - 250 mg.
3-28-65	10:00	17	OK	(at 200 - 250 mg. L. diethylstilbestrol 2x 100 (10) - 5 mg. 8/10 days / 1000 mg of 200 - 250 mg.)
4-4-65	10:00	18	OK	Fetal weight 4.1. At 300 - 350 mg. L. diethylstilbestrol 2x 100 (10) - 5 mg. 8/10 days / 1000 mg of 200 - 250 mg.
4-11-65	10:00	19	OK	At 400 - 450 mg. L. diethylstilbestrol 2x 100 (10) - 5 mg. 8/10 days / 1000 mg of 200 - 250 mg.
4-18-65	10:00	20	OK	At 500 - 550 mg. L. diethylstilbestrol 2x 100 (10) - 5 mg. 8/10 days / 1000 mg of 200 - 250 mg.
4-25-65	10:00	21	OK	At 600 - 650 mg. L. diethylstilbestrol 2x 100 (10) - 5 mg. 8/10 days / 1000 mg of 200 - 250 mg.
5-2-65	10:00	22	OK	At 700 - 750 mg. L. diethylstilbestrol 2x 100 (10) - 5 mg. 8/10 days / 1000 mg of 200 - 250 mg.
5-9-65	10:00	23	OK	At 800 - 850 mg. L. diethylstilbestrol 2x 100 (10) - 5 mg. 8/10 days / 1000 mg of 200 - 250 mg.
5-16-65	10:00	24	OK	At 900 - 950 mg. L. diethylstilbestrol 2x 100 (10) - 5 mg. 8/10 days / 1000 mg of 200 - 250 mg.
5-23-65	10:00	25	OK	At 1000 - 1050 mg. L. diethylstilbestrol 2x 100 (10) - 5 mg. 8/10 days / 1000 mg of 200 - 250 mg.

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.

3.

Card 4--Drugs Taken During Pregnancy (Steroids & Thyroid)

Name: June Gilbert

Family number	19
Order of sib	2
Birthdate	09/03/65
Kind of Drug (1st)	44
Average dosage per week (mg, cc, or gr)	100.0
Total dosage (mg, cc, or gr)	00700.0
Duration taken (weeks)	07
Certainty of duration	1=yes 2=no
Certainty of dosage	1=positive 2=uncertain 3=uncertain-think it's more 4=uncertain-think it's less
Method of treatment	1=by mouth 2=by injection 3=by suppository 4=unknown
Date of first medication	01/06/65
Certain?	1=yes 2=no
Date of last medication	02/26/65
Certain?	1=yes 2=no
Kind of Drug (2nd)	10
Average dosage per week (mg, cc, or gr)	250.0
Total dosage (mg, cc, or gr)	2250.0
Duration taken (weeks)	19
Certainty of duration	1=yes 2=no
Certainty of dosage	1=positive 2=uncertain 3=uncertain-think it's more 4=uncertain-think it's less
Method of treatment	1=by mouth 2=by injection 3=by suppository 4=unknown
Date of first medication	03/08/65
Certain?	1=yes 2=no
Date of last medication	07/21/65
Certain?	1=yes 2=no

No Card 5

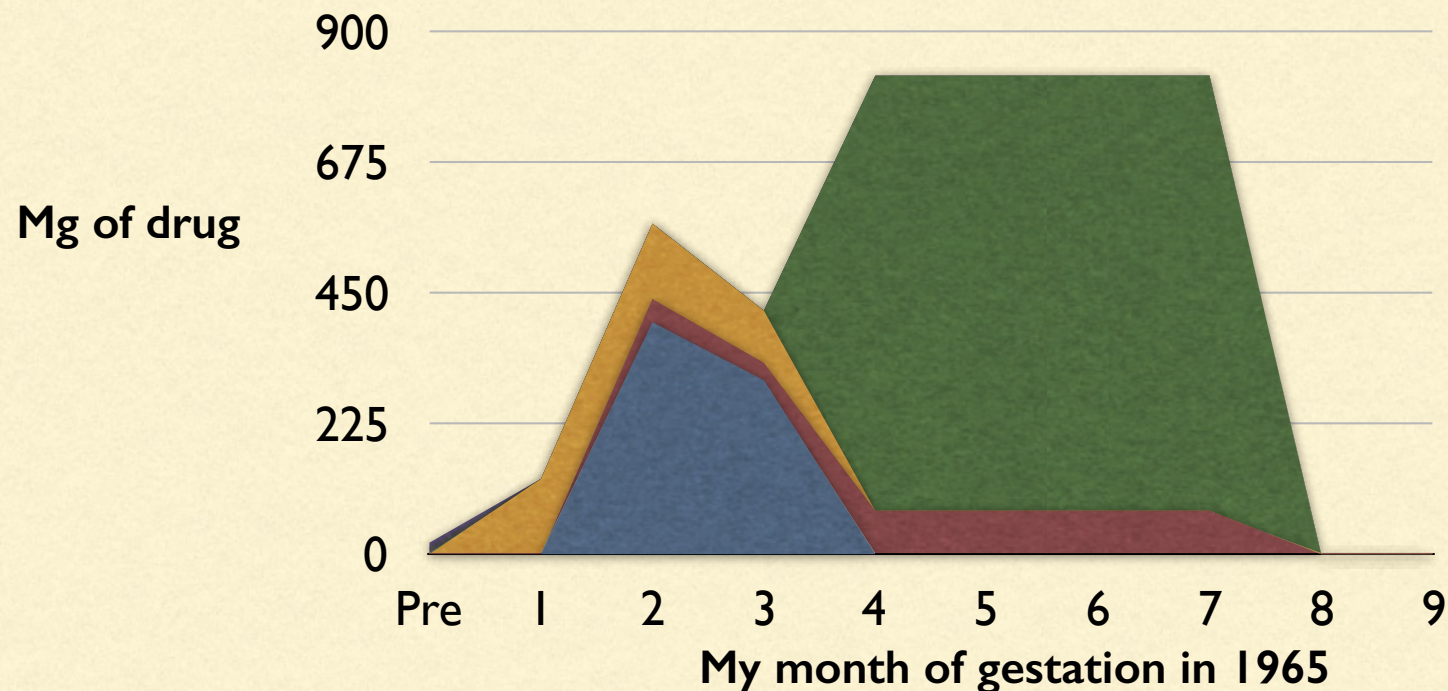
In 2010, I obtained my mother's 1965 obstetric records. What did they mean?

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

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

WHAT WERE MY FETAL EXPOSURES?

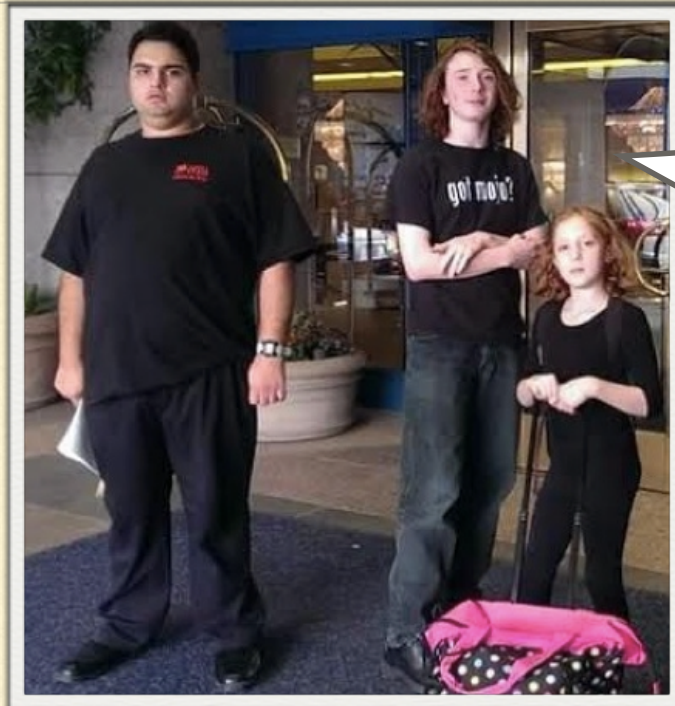
Progestins, estrogens, corticosteroids. Why? "To prevent miscarriage."
"Mad Men" era of maternal medicine. Such drugging was common.



- 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



"Really?"

Yes... **desPLEX**[®]
to prevent ABORTION, MISCARRIAGE and
PREMATURE LABOR

*recommended for routine prophylaxis
in ALL pregnancies . . .*

96 per cent live delivery with **desPLEX**
in one series of 1200 patients*—
— bigger and stronger babies, too.†

No gastric or other side effects with **desPLEX**
— in either high or low dosage*†,‡

[Each **desPLEX** tablet starts with 25 mg. of diethylstilbestrol, U.S.P.,
which is then ultramicronized to smooth and accelerate absorption and
activity. A portion of this ultramicronized diethylstilbestrol is even in-
cluded in the tablet coating to assure prompt help in emergencies.
desPLEX tablets also contain vitamin C and certain members of the
vitamin B complex to aid detoxification in pregnancy and the effec-
tion of estrogen.]

For further data and a generous
trial supply of **desPLEX**, write to:
Medical Director

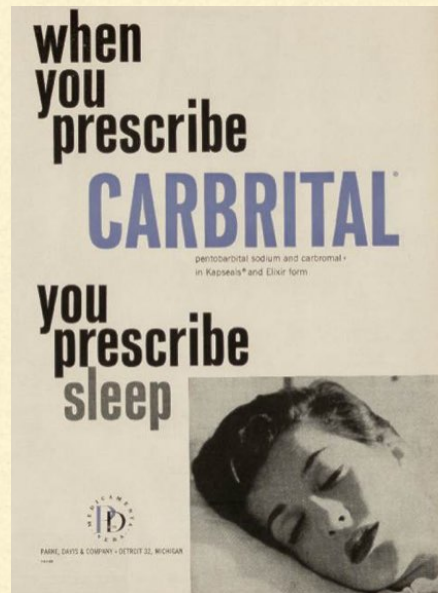
REFERENCES: 1. Corwin, E. M., et al., *Am. J. Obst. & Gynec.* 63:379, 1953.
2. Gilman, L., and Kugelmeier, A., *ibid.* 73: 30-31, 1956.
3. Karmali, M. J., *ibid.* 68: 47-48, 1952.
4. Kule, J. W., *ibid.* 67: 1071-1074, *ibid.* 68: 47-48, 1954.
5. Kule, J. W., *ibid.* 68: 47-48, 1954.

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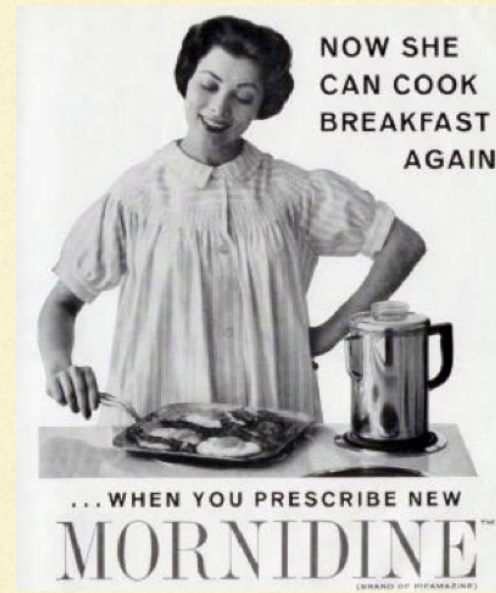
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specifically for weight reduction

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RESEARCH & DEVELOPMENT

PRELUDIN (amphetamine) is a potent stimulant. It is contraindicated in patients with hypertension, heart disease, and other conditions in which stimulation of the central nervous system is contraindicated. It should be used with caution in patients with glaucoma, epilepsy, and other conditions in which stimulation of the central nervous system is contraindicated. It should be used with caution in patients with diabetes mellitus, hyperthyroidism, and other conditions in which stimulation of the central nervous system is contraindicated. It should be used with caution in patients with a history of drug abuse. It should be used with caution in patients with a history of mental illness. It should be used with caution in patients with a history of alcoholism. It should be used with caution in patients with a history of drug abuse. It should be used with caution in patients with a history of mental illness. It should be used with caution in patients with a history of alcoholism.

LET'S NOT FORGET OTHER EXPOSURES



Pesticides (eg, DDT)



Agent Orange (dioxin)



Plasticizers
(eg, BPA, phthalates)



Flame retardants
(eg, PBDEs)



PCBs



Air pollution



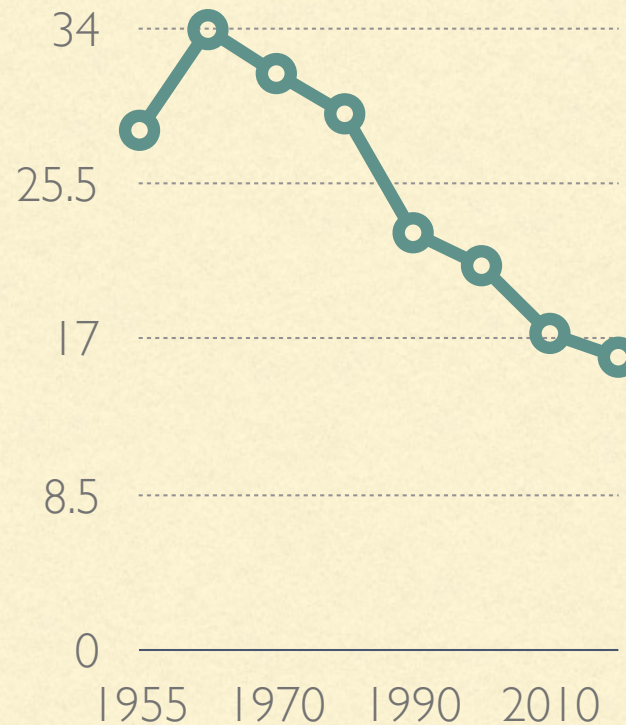
Radiation

PREGNANCY SMOKING WAS COMMON

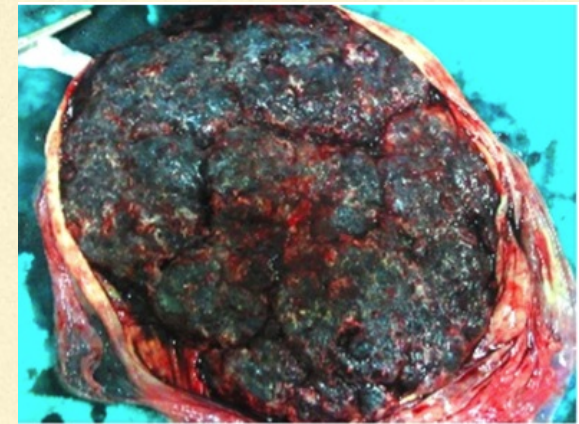
Doctors sometimes recommended it as an appetite suppressant



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



Environmental Epigenetics Symposium
NEW FRONTIERS IN AUTISM RESEARCH

Inaugural Online Symposium: Early Germline Events in the Heritable Etiology of ASDs.

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 heterogeneous de novo genomic alterations in ASD subjects"

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

A free 2-hour webinar taped October 1, 2015, bridging the worlds of human germline biology and de novo events seen in autism genomics. Watch it at asfpodcast.org/?p=85

Environmental Epigenetics Symposium
NEW FRONTIERS IN AUTISM RESEARCH

Webinar: March 3, 2016, 1-3pm EST

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

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 Hoyt, PhD, and Lisa Chadwick, PhD

Heritable epigenetic effects of germline exposure to toxicants
• Watch "A Tale of Two Mice"
• Hear a talk on germline effects of endocrine-disrupting chemicals

Analysis of chemical exposures and life stage factors that contribute to genetic disease
• Hear "Approaches to Identifying Germ Cell Mutations"

With commentary by:
Cathrine Hoyt, Lisa Chadwick, PhD, UMC
PhD, NIEHS

A free 2-hour webinar, open to researchers and the public.
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