New Technologies and New Understandings of Human Being

GENETIC RISK

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Abstract

- Most new technologies developed today are evaluated using risk-assessment frameworks aimed at detecting adverse effects for human bodies.

- This presentation argues that risk models used to evaluate the safety of novel technologies across the 20th and early 21st centuries invoke 19th century constructions of the human mind/body that are ontologically divergent from the systems construction of human openness being carved out by emerging fields, most especially environmental genomics.

- The formulation of life and its vulnerabilities offered by environmental genomics deconstructs nineteenth century boundaries delineating the somatic body, mind and environment by focusing instead on the complex and synergistic interactions among DNA, RNA, proteins, cells, etc. and nuanced environmental inputs whose convergence optimizes or destabilizes atomic and molecular bodily processes.

What kind of *being* are we?

- Western Being articulated in Cartesian mind-body dichotomy, wherein body(nature) is instrument of mind (spirit)

- The concept of machine beings – with roots in the idea of the automaton – can be traced to ancient Greek and Chinese societies

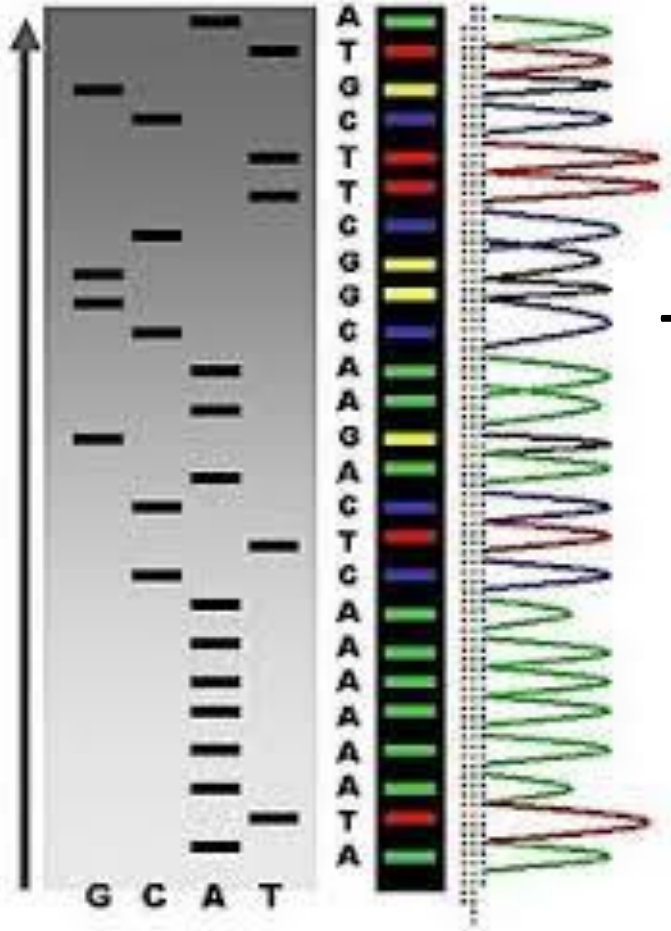
- 19th century modeled being after technology. We are enamored with our technological inventions because they separate us from nature

- We have modeled our bodies (our *being*) after machines because of the control they afford over the environment

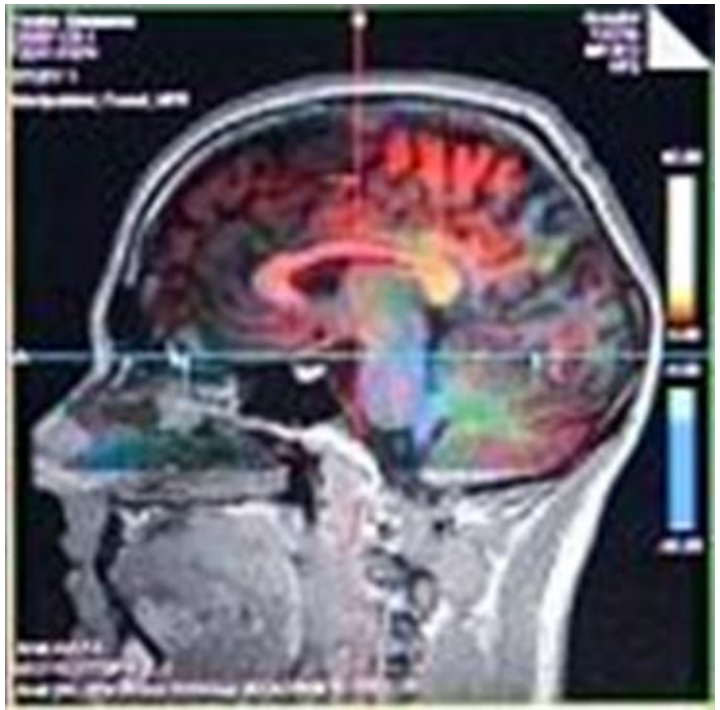
E.V. Odle's *The Clockwork Man* 1923

Today's machines promise to reveal hidden interiorities of our *being*.

Our visualization technologies often produce *Atomistic Mechanism*, e.g., disembodied genetic code and the quest for universal neural phenotypes

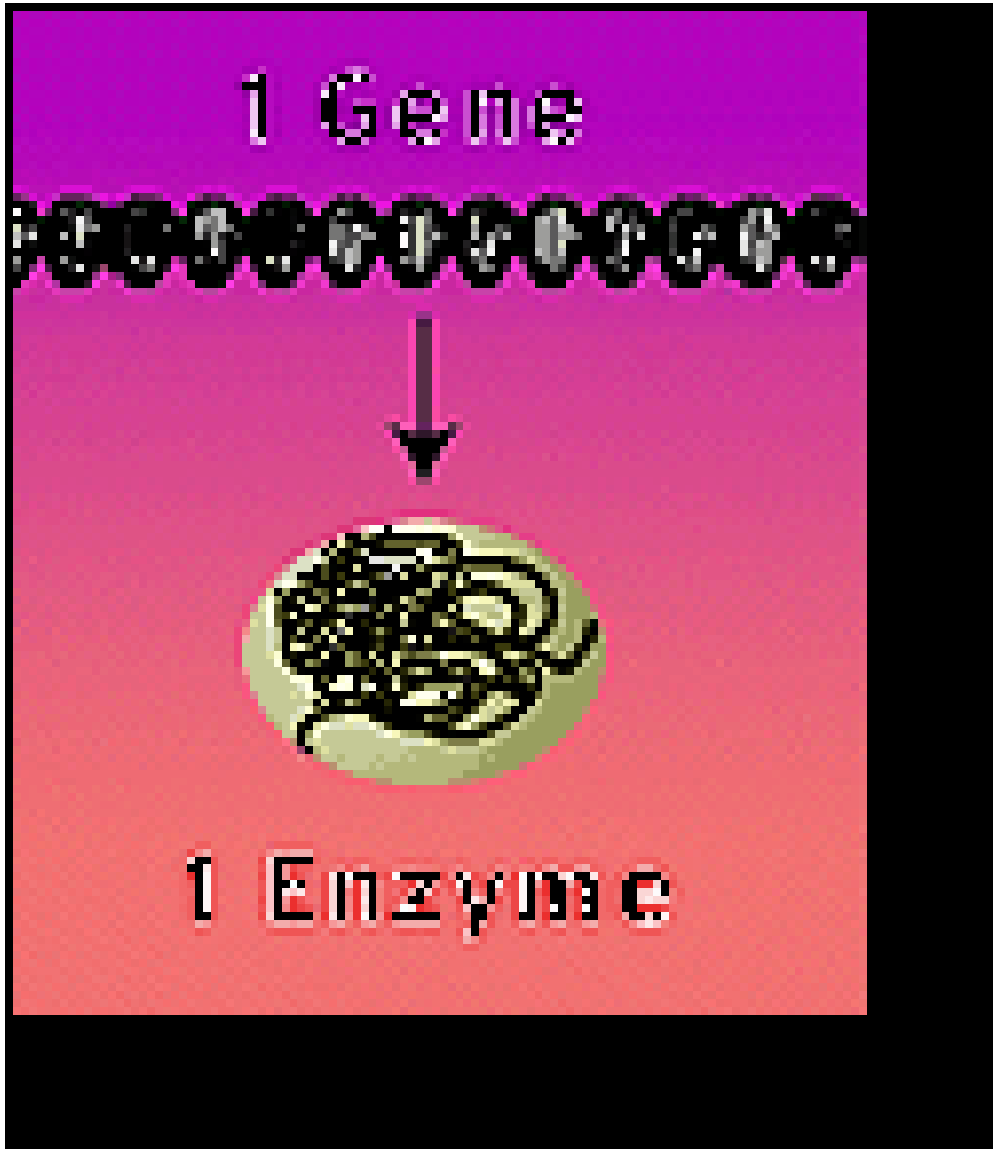


Trait – Brain – Gene -
Trait – Brain –Gene…

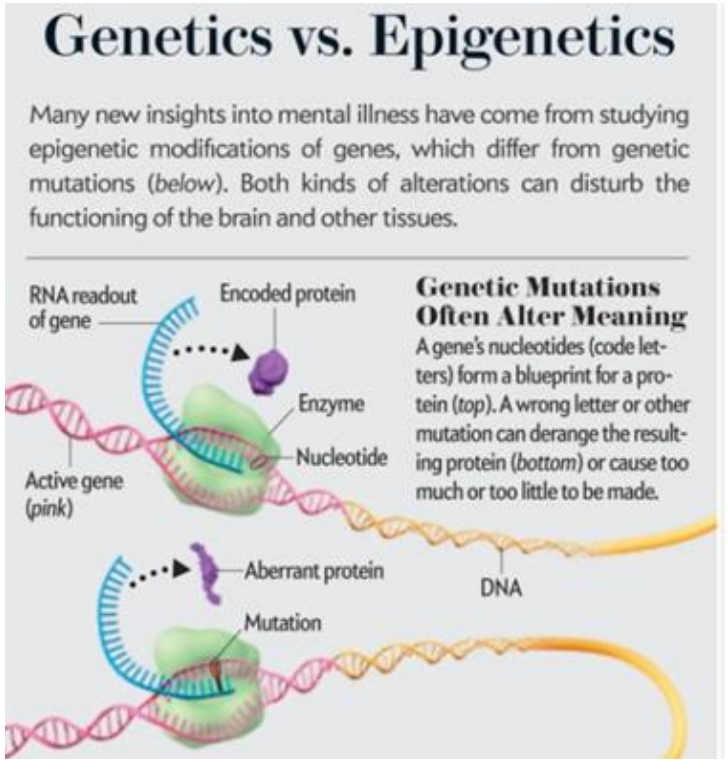


Reductionism and Determinism: One-Gene One Enzyme, One-Gene, One Disease

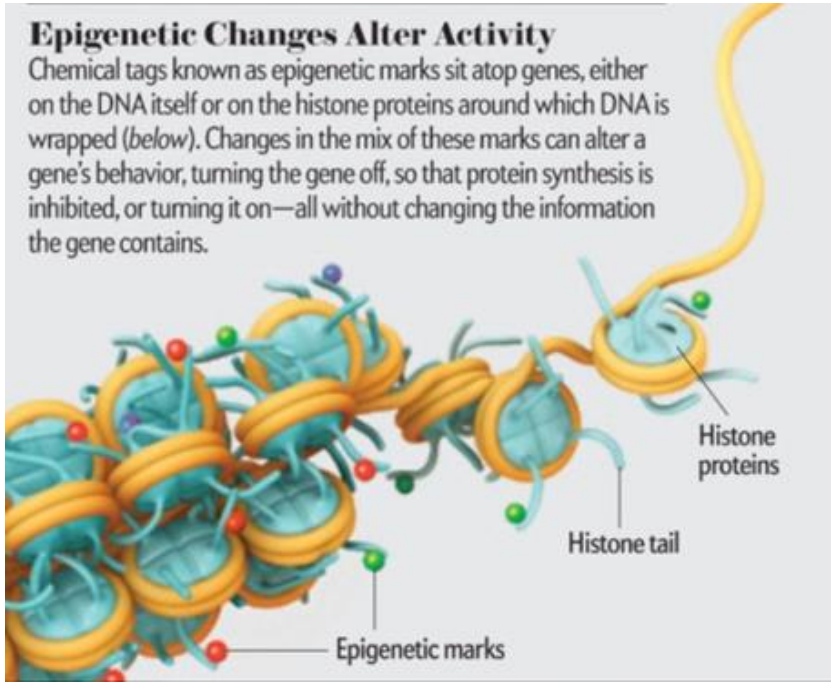
- One-Gene One Enzyme theory proven wrong.
- A disease such as Alzheimer's can result from (a) different mutations of the same gene, or (b) from mutations of different genes (Insel & Collins, 2003). Moreover, often the same mutation in the same gene can result in variable phenotypic manifestations. Finally, the "extent of pathology, the location of pathology, or the age of onset can be influenced by modifier genes, by environmental factors, or by poorly understood effects that contribute to differences in severity" (p. 617).
- Image http://en.wikipedia.org/wiki/File:One_gene,_one_enzyme.gif



Atomistic Mechanism Proven Wrong



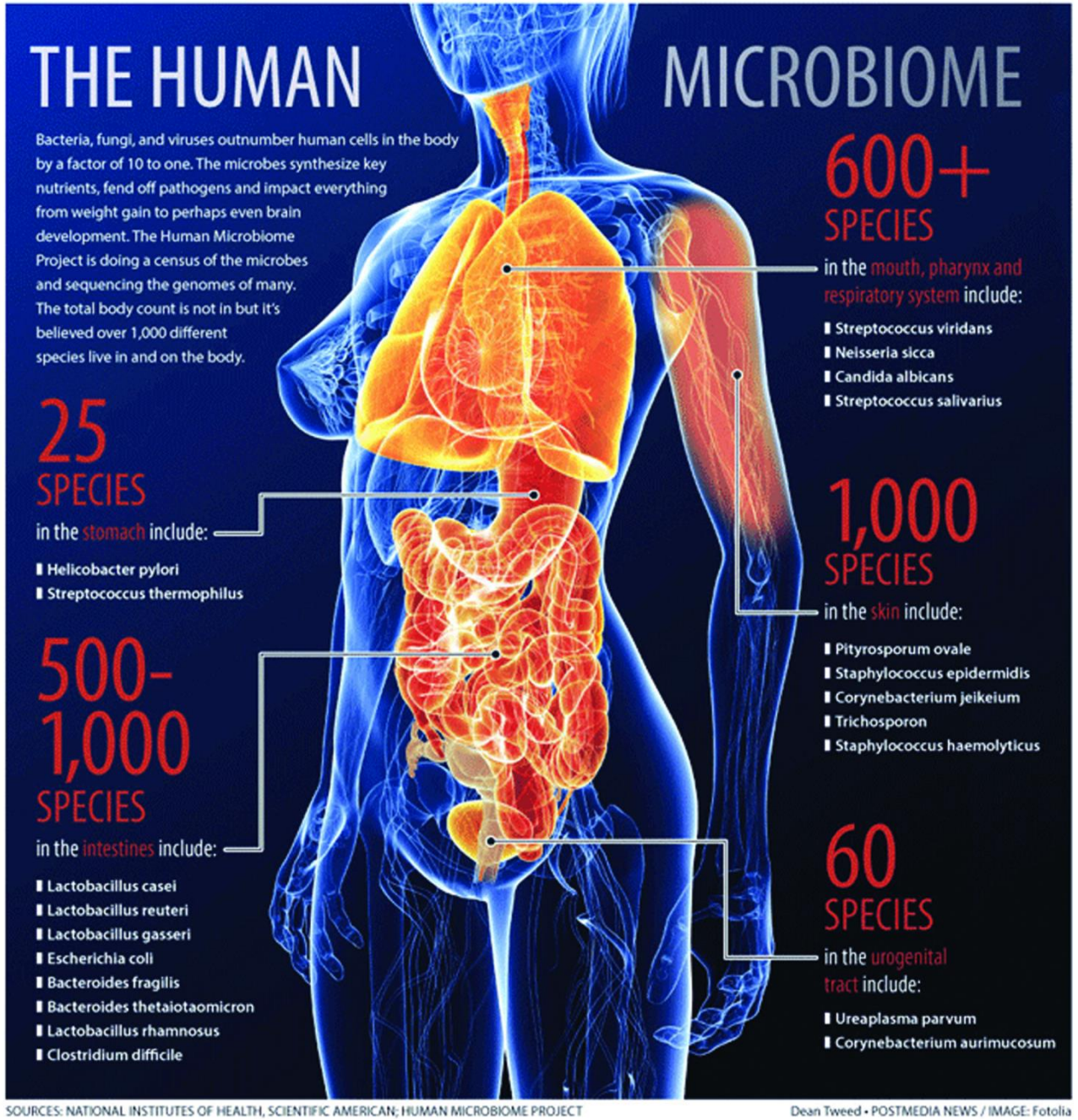
- *One-gene--One-enzyme & One-gene–One-disease* theories proven wrong
- The closer we look at mechanistic first causes, the more our research points to **systemic** processes and interdependencies



http://thescienceofreality.tumblr.com/post/89016282567/biovisual-genetics-vs-epigenetics-from-hidden\

Openness and Interdependencies

- Human body has 30 trillion cells of its own, hosts more than 100 trillion bacterial and fungal cells
- *"The welfare of a person's microbiome, the collective term for resident bacteria, plays a critical role in health and the last seventy years has seen a progressive weakening of these crucial organism"*
- **Missing Microbes: How Killing Bacteria Creates Modern Plagues. Martin Blaser Oneworld Publications 2014**
  http://www.villagemagazine.ie/index.php/2014/12/biome/



We are NOT the *being* of Clockwork Man

- Modern ‘man’ wrongly conceptualized after the spiritually infused machine
  - wherein environment is thought largely in terms of lifestyle choices (our moral fortitude)
  - wherein bodily nature is thought primarily in terms of the inanimate machine – of atomistic mechanism or simple systems - especially in relation to hereditary matter, which is bifurcated from environment

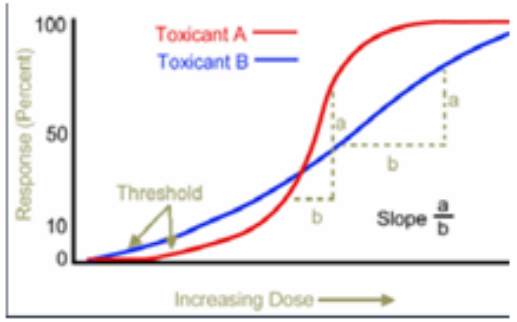
E.V. Odle’s *The Clockwork Man* 1923

Mechanistic Reductionism encoded into 20th century environmental law and cost-benefit-analyses

- TSCA did not require DNA testing for mutagenesis and excluded from review over 60,000 chemicals at time of passage.
- Delaney Provision limited
- US Regulatory regimes are cost-benefit rather than precautionary
- Lab testing relies on limited exposures when testing toxicity, often 48 hours
  - Fail to address bio-accumulation and chemical synergies
  - Ignore endocrine system and immunological effects
  - Fail to address long term health and reproductive effects

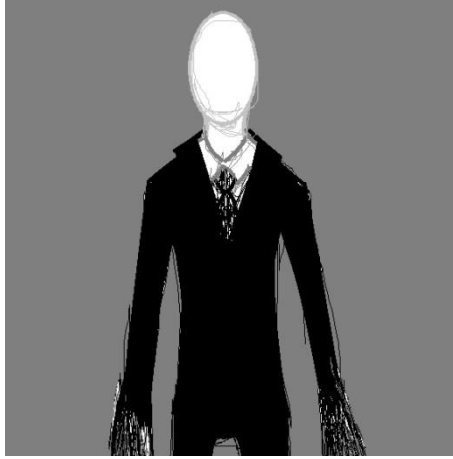
Toxicity Measurements and Endpoints

- Median Lethal Dose or Concentration (LD_{50} or LC_{50})
- Often used to compare toxicity
- Only measures lethality
- Best for acute exposure
- BUT tells nothing about the slope or variation in response



Research on dose-response relationships used to test chemical safety often focus on median lethal dose or concentration under short-term exposure. Slide Credit Beth Polidoro "Introduction to Toxicology" Instructional Lecture

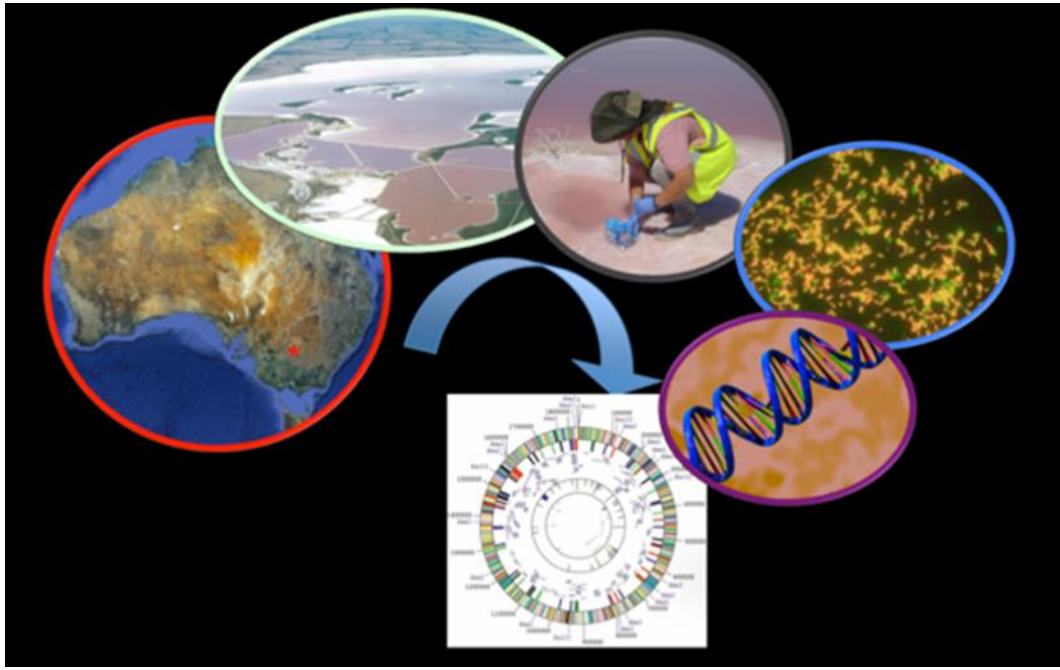
Limits of Reference Man “Norming”



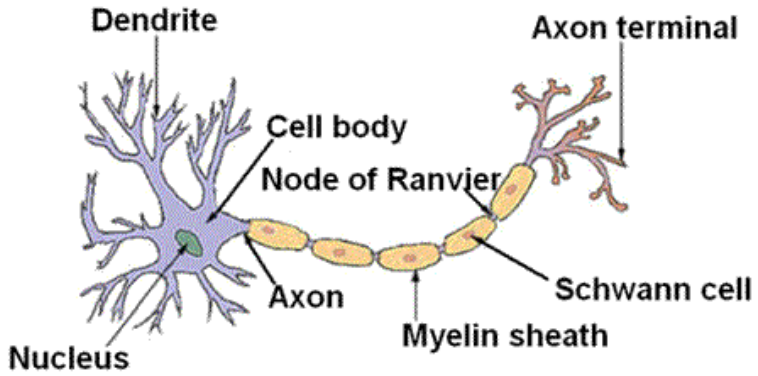
- Embryos not included : Illustrated by the registration for chlorpyrifos currently under review
  - “EPA's assessment relies on a model developed by Dow. The model tries to determine at which point exposure will inhibit the necessary enzyme for nerve function by 10 percent. That sets a "safe" limit for chlorpyrifos levels that EPA can then use to guide restrictions on the pesticide's label.
  - But the model doesn't take into account the neurological impacts to fetuses, said Jennifer Sass, a senior scientist with the Natural Resources Defense Council.
  - "It's not that the model is so bad inherently, it's that it misses the mark," Sass said. EPA should have included the epidemiological studies in the model. "Protecting the mother from 10 percent [of enzyme inhibition] is not protecting the fetus, we know that for sure," she added.
  - **Stecker, Tiffany (2015, May 6) Greens, industry clash as EPA assesses widely used farm chemical . Greenwire.** http://www.eenews.net/stories/1060018095

New Technologies, New Imaginaries

- Failure of atomistic mechanism
- New paradigm of inquiry emphasizing systems openness and interdependencies
- From genetic inheritance to the role of the environment in shaping genomic expression
- Autism and Genetic Mosaicism as Case Examples



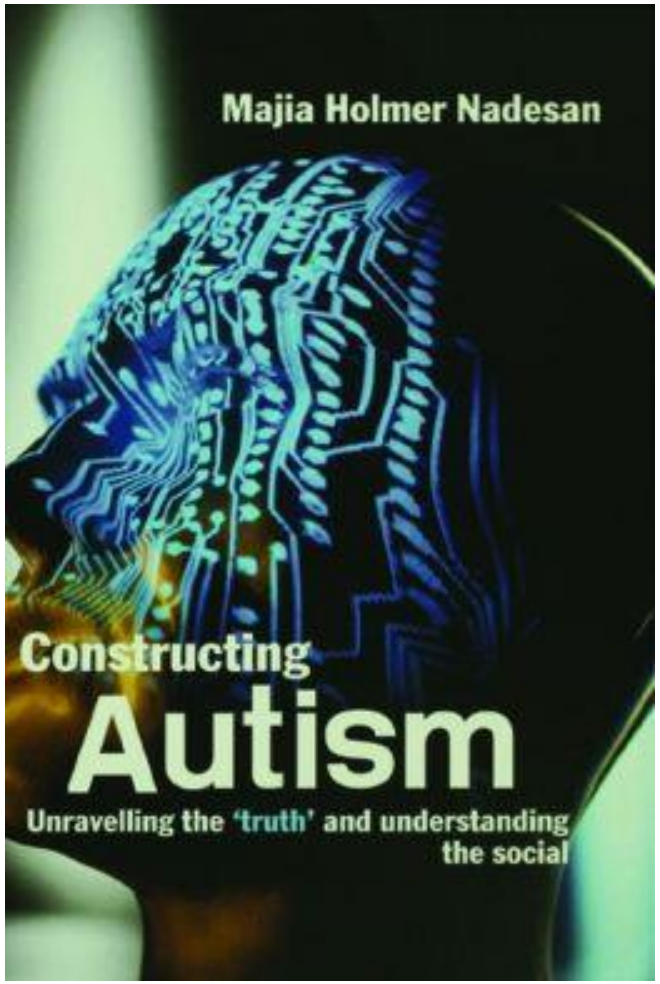
Neurological Disease Incidents Rising in Adults and Children



- Autism now 1 in 50 School-aged children (6-17)
- Friday, March 29th, 2013 The U.S. Centers for Disease Control and Prevention (CDC) and Health Resources and Services Administration released a report titled "Changes in Prevalence of Parent-reported Autism Spectrum Disorder in School-aged U.S. Children: 2007 to 2011–2012". The report presents data on the prevalence of diagnosed autism spectrum disorder (ASD) as reported by parents of school-aged children ages 6–17 years in 2011–2012. Data was drawn from the 2007 and 2011–2012 National Survey of Children's Health, which comprises independent, nationally representative telephone surveys of households with children.Last year, the CDC's Autism and Developmental Disabilities Monitoring Network estimated that 1 in 88 children had been identified with ASD. The CDC now estimates that in 2011–2012, about 1 in 50 school-aged children, or 2 percent of children ages 6–17 years have some form of the disorder. Since the average school bus holds 50–55 children, that means, statistically speaking, on average there is one child with parent-reported ASD on every school bus in America.http://www.nimh.nih.gov/news/science-news/2013/prevalence-of-parent-reported-autism.shtml
- http://www.calautism.org/tag/autism-statistics/

Autism Research: From Atomistic First Causes to Environmental Interdependencies and Vulnerabilities

- **1979-2000:** Autism viewed as rare, untreatable disorder caused by a few defective gene alleles. Science searched for neural phenotypes and hereditary autistic genotypes
  - Models of genetic causation in autism are complicated by uncertainties posed by the lack of *consistently replicable* genetic markers despite over two decades of research.
  - As Landrigan, Lambertini, and Birnbaum (2012) explain: "no single [genetic] anomaly predominates," with the exception of Fragile X syndrome.
- **Today: Environmental Gene Interactions and Embryonic Development Susceptibilities**



From Genetics to Genomics, from Alleles to SNVs…

- **GENETICS:** Genetic Paradigm: Focused on alleles and rare mutations in families with high rates of autism. **FEW REPLICABLE FINDINGS.**

- **GENOMICS Entire genomes and SNVs**: SNVs are rare single-letter mutations, also called single nucleotide variations, or SNVs. (O'Roak, 2012; Sanders, 2012; Singer, 2012).

- People diagnosed with autism have more SNVs than their parents or unaffected siblings. Could environment cause SNVs implicated in disease?

…from Genomics to "Environmental Genomics"

- ***Autism: no consistently replicable alleles or particular SNVS but increase in overall frequency of SNVs ARE LINKED.***

- ***Are environmental factors to blame?***
  - ***"It's time to start looking for the environmental culprits responsible for the remarkable increase in the rate of autism in California…. Funding for studying genetic causes of autism is 10 to 20 times higher than funding for environmental causes, she said. "It's very off-balance."***Irva Hertz-Picciotto, epidemiology UC Davis who has worked on pesticides and VOCs (cited in Cone, 2009)

- **Environmental research foci include gene-environment interactions:**
  - Environmentally-induced genetic and epigenetic damage
  - Studies of how genetic susceptibilities (e.g., mutations in mitochondrial DNA or DNA coding glutathoine) increase susceptibilities to environmental toxins

Medical Hypothesis: “Do environmental risk factors contribute to de novo mutations contributing to autism?”

Kinney, D. K., Barch, D. H., Chayka, B., Napoleon, S., Munir, K. M. (2010) Environmental risk factors for autism: Do they help cause do novo genetic mutations that contribute to the disorder? *Medical Hypotheses*, 74, 102-106.

- Recent research has discovered that a number of genetic risk factors for autism are *de novo* mutations. Advanced parental age at the time of conception is associated with increased risk for both autism and de novo mutations. We investigated the hypothesis that *other* environmental factors associated with increased risk for autism might also be mutagenic and contribute to autism by causing de novo mutations. A survey of the research literature identified 9 environmental factors for which increased pre-conceptual exposure appears to be associated with increased risk for autism. Five of these factors – mercury, cadmium, nickel, trichloroethylene, and vinyl chloride – are established mutagens. Another four – including residence in regions that are urbanized, located at higher latitudes, or experience high levels of precipitation – are associated with decreased sun exposure and increased risk for vitamin D deficiency. Vitamin D plays important roles in repairing DNA damage and protecting against oxidative stress – a key cause of DNA damage. Factors associated with vitamin D deficiency will thus contribute to higher mutation rates and impaired repair of DNA. We note how de novo mutations may also help explain why the concordance rate for autism is so markedly higher in monozygotic than dizygotic twins. De novo mutations may also explain in part why the prevalence of autism is so remarkably high, given the evidence for a strong role of genetic factors and the low fertility of individuals with autism – and resultant selection pressure against autism susceptibility genes.

Neal, B. et al (2012, May 10). Patterns and rates of exonic *de novo* mutations in autism spectrum disorders Nature 485, 242–245 (10 May 2012) doi:10.1038/nature11011

- Autism spectrum disorders (ASD) are believed to have genetic and environmental origins, yet in only a modest fraction of individuals can specific causes be identified[1, 2]. To identify further genetic risk factors, here we assess the role of *de novo* mutations in ASD by sequencing the exomes of ASD cases and their parents (*n* = 175 trios). Fewer than half of the cases (46.3%) carry a missense or nonsense *de novo* variant, and the overall rate of mutation is only modestly higher than the expected rate. In contrast, the proteins encoded by genes that harboured *de novo* missense or nonsense mutations showed a higher degree of connectivity among themselves and to previous ASD genes[3] as indexed by protein-protein interaction screens. The small increase in the rate of *de novo* events, when taken together with the protein interaction results, are consistent with an important but limited role for *de novo* point mutations in ASD, similar to that documented for *de novo* copy number variants. Genetic models incorporating these data indicate that most of the observed *de novo* events are unconnected to ASD; those that do confer risk are distributed across many genes and are incompletely penetrant (that is, not necessarily sufficient for disease). Our results support polygenic models in which spontaneous coding mutations in any of a large number of genes increases risk by 5- to 20-fold. Despite the challenge posed by such models, results from *de novo* events and a large parallel case–control study provide strong evidence in favour of *CHD8* and *KATNAL2* as genuine autism risk factors.

Kong, A. et al (2012, August 22) Rate of *de novo* mutations and the importance of father's age to disease risk Augustine Kong, et al Nature 488, 471–475 doi:10.1038/nature11396

[ABSTRACT excerpted]…We show that in our samples, with an average father's age of 29.7, the average *de novo* mutation rate is 1.20×10^{-8} per nucleotide per generation. Most notably, the diversity in mutation rate of single nucleotide polymorphisms is dominated by the age of the father at conception of the child. The effect is an increase of about two mutations per year. An exponential model estimates paternal mutations doubling every 16.5 years. After accounting for random Poisson variation, father's age is estimated to explain nearly all of the remaining variation in the *de novo* mutation counts. These observations shed light on the importance of the father's age on the risk of diseases such as schizophrenia and autism….

Genetic Susceptibilities and Cascading Environmental Effects

- **MICRODELETIONS** in **mitochondrial DNA** and in DNA regulating **synaptic development** (such as SCN2A) and **oxytocin** than family members (Sebat et al., 2007; Smith, Spence, & Flodman, 2009)

- DNA regulating glutathione, neurological anti-oxidant, illustrates how genes confer susceptibility for autism. Low-levels of intracellular glutathione found in autistic children (Theoharides et al., 2012; Bowers et al., 2011).
  - Variation in genes involved in counterbalancing oxidative stress may contribute to autism

Environmental Factors that can increase mutations, epigenetic changes – such as methylation – and endocrine effects: Research Focus on CHEMICALS

- Landrigan's (2012) review points to a number of chemical exposures linked to autism, IQ deficits, dyslexia, and ADHD:
  - organophosphate insecticide chlorpyrifos (Eskenazi et al 2007pesticides; London et al., 2012)
  - phthalates (Miodovnik et al, 2011).
  - lead (Jusko et al., 2008),
  - methylmercury (Oken et al., 2008),
  - polychlorinated biphenyls (Winneke, 2011),
  - arsenic (Wasserman et al., 2007),
  - manganese (Khan et al., 2011),
  - polycyclic aromatic hydrocarbons (Perera et al., 2009),
  - bisphenol A (Braun et al., 2011),
  - brominated flame retardants (Herbstman et al., 2010)
  - perfluorinated compounds (Stein and Savitz, 2011)
  - Glyphosate, otherwise known as Round-Up (Samsel and Seneff, 2013).

Subtle (Endocrine) Effects: From “the dose makes the poison” to “the timing makes the poison”*

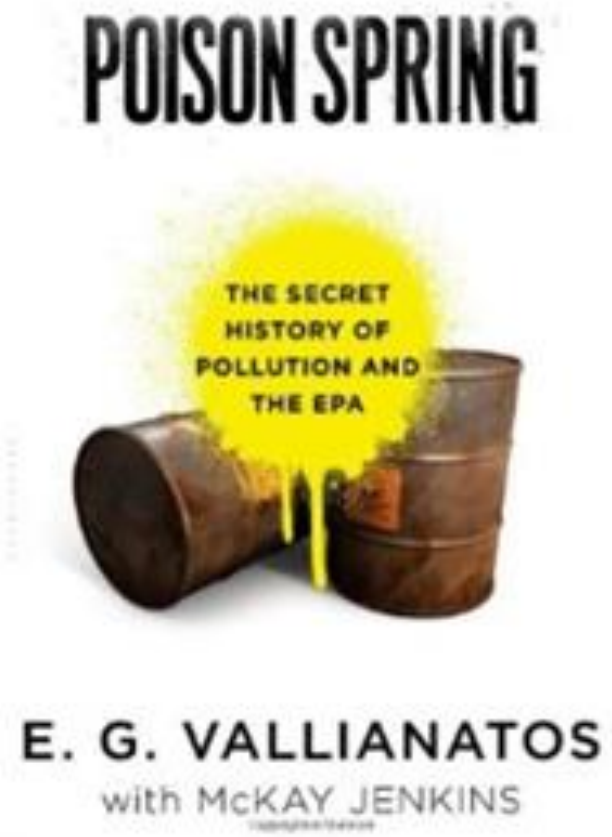
- **Reference man is a fallacy:** “Essentially what happens is during pregnancy there are certain sensitive periods where the fetus is very vulnerable to a range of small molecules – from things like plasticizers, prescription drugs, environmental pesticides and other things...And some of these small molecules essentially alter normal development. It’s not really well known why, but it’s an experimental observation, especially in boys and especially in the reproductive system.” Andrey Rzhetsky, a professor of genetic medicine and human genetics at the University of Chicago (cited in Grush, 2014)

- *Vogel, Sarah A. (2008) From 'The Dose Makes the Poison' to 'The Timing Makes the Poison': Conceptualizing Risk inthe Synthetic Age. Environmental History, Vol. 13, No. 4 (Oct., 2008), pp. 667-673

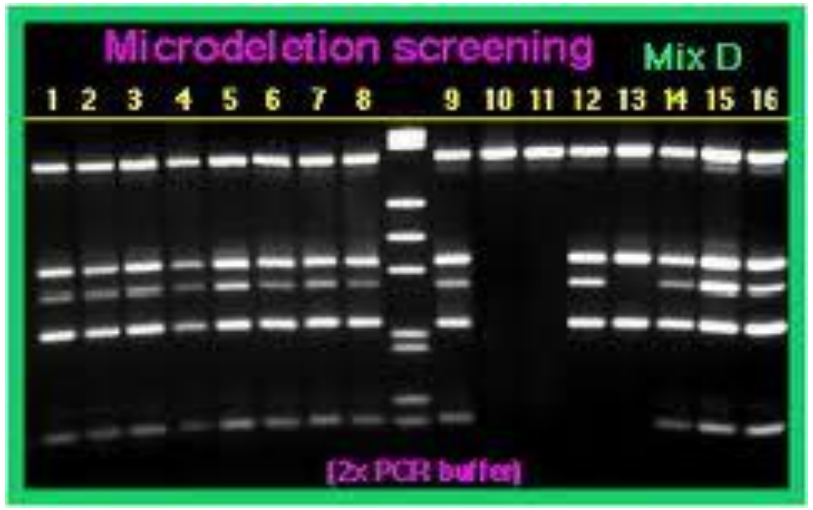
Atomistic Mechanism and Chemical Approval

- **Chemicals approved using short-term laboratory tests**:
  - 3-4 day trials
  - 1 chemical – 1 trial (no synergistic effects)
  - Laboratory animals, often fish
  - Toxicity and dose-response curves (no endocrine effects)
  - No long-term reproductive effects
  - Labs charged with fraud by ex-employees

- **Few studies of other exposures (elements such as lead and ionizing and non-ionizing radiation)**



Autism Genotype Looks Like Trans-Generational Effects of Ionizing Radiation described by UNSCEAR and BEAR

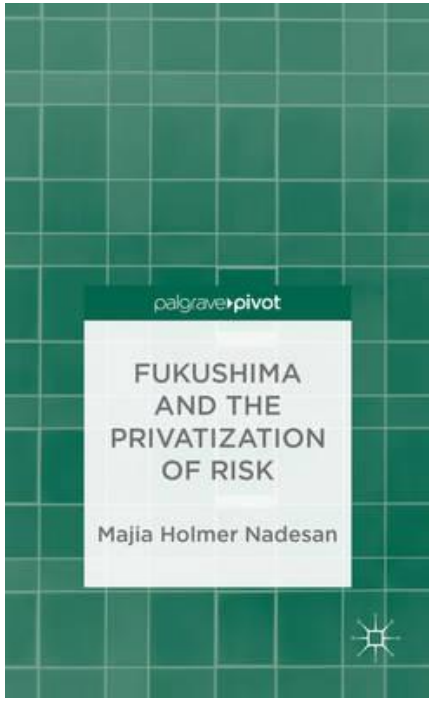


Both characterized by point mutations, especially micro-deletions, leading to genomic instabilities

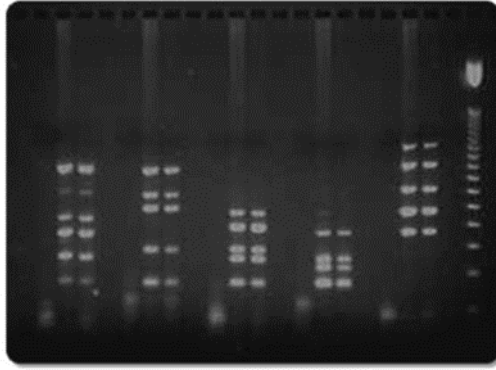
Both characterized as multi-system developmental anomalies

Both characterized by defective mitochondrial DNA

No research studying convergence



Trans-Generational Effects of Ionizing Radiation include multi-system developmental anomalies



PCR for Y - microdeletion

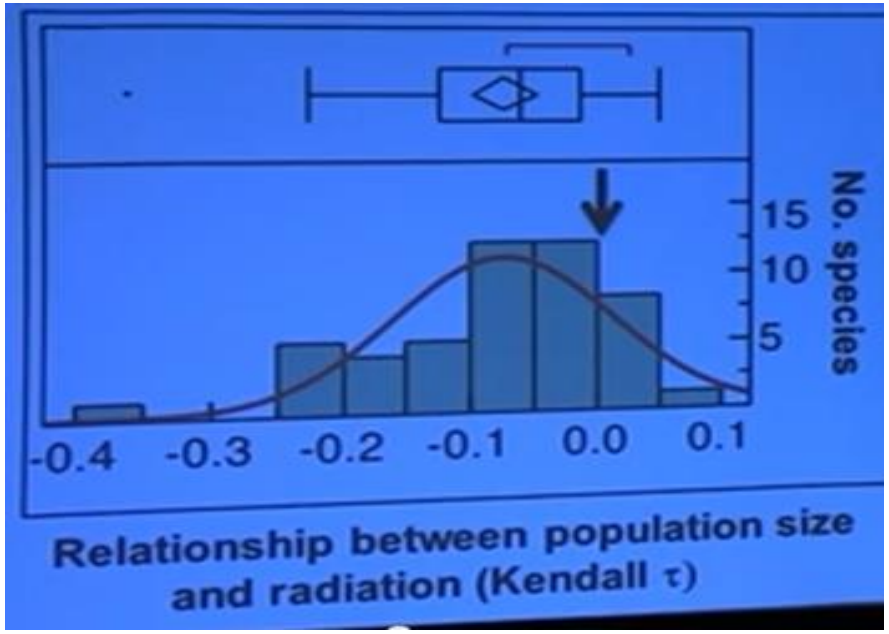
Transgenerational Effects of Ionizing Radiation include increased instability of repeat-DNA sequences (Dubrova, et. Al. 2000). UNSCEAR Concepts for Genetic Risks from Ionizing Radiation:

- Most radiation-induced mutations are DNA deletions, often encompassing multiple genes, but only a small proportion of the induced deletions is compatible with offspring viability;
- The viability-compatible deletions induced in germ cells are more likely to manifest themselves as multi-system developmental anomalies rather than as single gene disorders. (Sankaranarayanan et al 2005)

Radiation Health Risks: From BEAR to Fukushima

1956 The *Biological Effects of Atomic Radiation: A Report to the Public from a Study by The National Academies of Science* (BEAR) warned of transgenerational mutations. Findings were shared with the US public in *The New York Times* June 13, 1956.

Timothy Mousseau (2014, August) "***Contrary to governmental reports, there is now an abundance of information demonstrating consequences (i.e., injury) to individuals, populations, species, and the ecosystem function stemming from the low dose radiation due to the Chernobyl and Fukushima disasters***" (chart to right; see also Moller et al., 2011)



Creation of Regulatory Structure Around "Adequate Protection"

- **EPA AND NRC promise only "adequately protective" against radionuclides from the nuclear fuel cycle (EPA)**
  - EPA (August 2010) "Radiation Protection at the EPA: The First Thirty Years" EPA 402-B-00-001. http://www.epa.gov/radiation/docs/402-b-00-001.pdf

- Their models of excess risk often focus exclusively on increased cancer risks, while failing to acknowledge range of diseases caused and/or exacerbated **by chronic exposure to *DNA damaging*, *epigenetically altering, and free radical producing* ionizing radiation**

Conclusions

Precautionary Principle

- **Legacy of mechanistic atomism LIMITS understanding YET UNDERPINS REGULATORY STRUCTURE**
- **Red Flags and Hubris**
- **Catastrophic Risk?**

Systems Approach

- **Solution:** ***The catastrophic risks engineered into our technological system potentially threaten the long-term integrity of our being and demand a systems-based precautionary approach to managing new and existing technologies***

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Images not referenced on slides

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Final Thoughts and Questions

- ***What follows are some reflections and extensions on issues raised throughout the presentation.***

Stem Cells, Ionizing Radiation and Genomic Instability

Harfouche, G., & Martin, MT. (2010, Apr-Jun) Response of normal stem cells to ionizing radiation: a balance between homeostasis and genomic stability. Mutation Research 2010 Apr-Jun;704(1-3):167-74. doi: 10.1016/j.mrrev.2010.01.007. Epub 2010 Feb 1.

- **Abstract**
- http://www.ncbi.nlm.nih.gov/pubmed/20117235
- Stem cells have been described in most adult tissues, where they play a key role in maintaining tissue homeostasis. As they self-renew throughout life, accumulating genetic anomalies can compromise their genomic integrity and potentially give rise to cancer.
- Stem cells (SCs) may thus be a major target of radiation carcinogenesis. In addition, unrepaired genotoxic damage may cause cell death and stem cell pool depletion, impairing lineage functionality and accelerating aging.
- Developments in SC biology enabled the characterization of the responses of stem cells to genotoxic stress and their role in tissue damage. We here examine how these cells react to ionizing radiation (IR), and more specifically their radiosensitivity, stress signaling and DNA repair.
- We first review embryonic SCs, as a paradigm of primitive pluripotent cells, then three adult tissues, bone marrow, skin and intestine, capable of long-term regeneration and at high risk for acute radiation syndromes and long-term carcinogenesis. We discuss IR disruption of the fine balance between maintenance of tissue homeostasis and genomic stability. We show that stem cell radiosensitivity does not follow a unique model, but differs notably according to the turnover rates of the tissues.

Stem Cell Mutation Increased by Chronic Inflammation, Ionizing Radiation

- Chronic inflammation: Houghton JM, Stoicov C, Nomura S, *et al*. Gastric cancer originating from bone marrow-derived cells. Science 2004; 306:1568-1571.

- Sokolov, Mykyta, and Ronald Neumann. “Lessons Learned about Human Stem Cell Responses to Ionizing Radiation Exposures: A Long Road Still Ahead of Us.” International Journal of Molecular Sciences 14.8 (2013): 15695–15723. PMC. Web. 13 May 2015
- Although the details of human stem cells (hSC) response to genotoxic stresses , especially ionizing radiation in particular, are not fully understood because of the scarcity of the hSC within the human body, problems of in vitro isolation, challenges with establishing continuous cultures, among other issues. However, human embryonic stem cells have been found to undergo apoptosis at levels exceeding low-dose range in a dose-dependent relationship. In their review, Sokolov & Neumann write: “it is plausible that IR exposures shift the delicate balance between pro-survival and pro-death choices in stressed hESC cultures in favor of the latter, even though the marked heterogeneity of hESC cultures observed earlier may explain why some subpopulations of hESC survive after genotoxic stress whereas others within the same cultures die [18,21].

Vulnerabilities: Rising Neurological Disorders

- Pritchard C, Mayers, A, Baldwin D. Changing patterns of neurological mortality in the 10 major developed countries 1979-2010. Public Health, 2013. Abstract from PubMed citation here

- The lead author, C. Pritchard, was interviewed in the May 10, 2013 *Science Daily* article, "Brain Diseases Affecting More People and Starting Earlier Than Ever Before" here. This is Dr. Pritchard's response to a question about the cause of increased incidents of neurological disease:

    - *When asked what he thought caused the increases he replied,* "This has to be speculative but it cannot be genetic because the period is too short. Whilst there will be some influence of more elderly people, it does not account for the earlier onset; the differences between countries nor the fact that more women have been affected, as their lives have changed more than men's over the period, all indicates multiple environmental factors.
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    - Considering the changes over the last 30 years -- the explosion in electronic devices, rises in background non-ionising radiation- PC's, micro waves, TV's, mobile phones; road and air transport up four-fold increasing background petro-chemical pollution; chemical additives to food etc. There is no one factor rather the likely interaction between all these environmental triggers, reflecting changes in other conditions.
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    - For example, whilst cancer deaths are down substantially, cancer incidence continues to rise; levels of asthma are un-precedented; the fall in male sperm counts -- the rise of auto-immune diseases -- all point to life-style and environmental influences. These `statistics' are about real people and families, and we need to recognise that there is an `epidemic' that clearly is influenced by environmental and societal changes."

Endocrine Disruptors and Systemic Inflammation

- E Campioli[1,2], D B Martinez-Arguelles[1,2] and V Papadopoulos (2014) ***In utero* exposure to the endocrine disruptor di-(2-ethylhexyl) phthalate promotes local adipose and systemic inflammation in adult male offspring** *Nutrition & Diabetes* (2014) **4**, e115; doi:10.1038/nutd.2014.13

- **Abstract**
- **Background::** Di-(2-ethylhexyl) phthalate (DEHP) is a plasticizer used to increase the flexibility of polyvinyl chloride. DEHP and its active metabolite mono-(2-ethylhexyl) phthalate are detected in many biological fluids during fetal and postnatal life. In rodent models, *in utero* DEHP exposure has been shown to alter sexual organ development, decrease testosterone and aldosterone production, increase body and epididymal adipose tissue weight, and raise serum lipids and glucose levels in male offspring.
- **Objectives::** The objective of this study is to characterize the effects of *in utero* DEHP exposure on adipose tissue development and function in male offspring.
- **Methods::** Sprague–Dawley pregnant dams were gavaged 1, 20, 50 or 300 mg DEHP per kg per day from gestational day 14 until birth.
- **Results::** Global gene expression analyses of postnatal day 60 male offspring that were exposed *in utero* to 300 mg DEHP per kg per day revealed increased expression of immune response and inflammation markers, and increased expression of differentiation pathway genes in the epididymal whole-adipose tissue and isolated stromal vascular fraction. C-reactive protein and tumor necrosis factor (TNF) serum levels were increased in the 300 mg DEHP *in utero*-exposed offspring. TNF levels in adipose tissue homogenates were increased in the 50 and 300 mg DEHP *in utero*-exposed offspring. Immunofluorescence studies revealed focal macrophage infiltration in whole-adipose tissue confirmed by increased CD163 tissue content.

Role of De Novo Mutations in Genetic Disease

Veltman, J. A., & Brunner, H. G. (2012) De novo mutations in human genetic disease. Nat Rev Genet. 2012 Jul 18;13(8):565-75. doi: 10.1038/nrg3241.

- New mutations have long been known to cause genetic disease, but their true contribution to the disease burden can only now be determined using family-based whole-genome or whole-exome sequencing approaches. In this Review we discuss recent findings suggesting that de novo mutations play a prominent part in rare and common forms of neurodevelopmental diseases, including intellectual disability, autism and schizophrenia. De novo mutations provide a mechanism by which early-onset reproductively lethal diseases remain frequent in the population. These mutations, although individually rare, may capture a significant part of the heritability for complex genetic diseases that is not detectable by genome-wide association studies. http://www.ncbi.nlm.nih.gov/pubmed/22805709

De Novo Mutations and Autism

- Sanders SJ, Murtha MT, Gupta AR, Murdoch JD, Raubeson MJ, et al. (2012) De novo mutations revealed by whole-exome sequencing are strongly associated with autism. Nature 485: 237–241. doi: 10.1038/nature10945 View Article
- *SCN2A* (sodium channel, voltage-gated, type II, α subunit),
- Here we show, using whole-exome sequencing of 928 individuals, including 200 phenotypically discordant sibling pairs, that highly disruptive (nonsense and splice-site) *de novo* mutations in brain-expressed genes are associated with autism spectrum disorders and carry large effects. On the basis of mutation rates in unaffected individuals, we demonstrate that multiple independent *de novo* single nucleotide variants in the same gene among unrelated probands reliably identifies risk alleles, providing a clear path forward for gene discovery. Among a total of 279 identified *de novo* coding mutations, there is a single instance in probands, and none in siblings, in which two independent nonsense variants disrupt the same gene, *SCN2A* (sodium channel, voltage-gated, type II, α subunit), a result that is highly unlikely by chance.

Volatile Organic Compounds (VOCs) and Autism

- Raz R, et al. Autism spectrum disorder and particulate matter air pollution before, during, and after pregnancy: a nested case–control analysis within the Nurses' Health Study II Cohort. Environ Health Perspect 123(3):264–270 (2015); doi: 10.1289/ehp.1408133.
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- Kalkbrenner AE, et al. Perinatal exposure to hazardous air pollutants and autism spectrum disorders at age 8. Epidemiology 21(5):631–641 (2010); doi: 10.1097/EDE.0b013e3181e65d76.
- Roberts AL, et al. Perinatal air pollutant exposures and autism spectrum disorder in the children of Nurses' Health Study II participants. Environ Health Perspect 121(8):978–984 (2013); doi: 10.1289/ehp.1206187.
- Volk HE, et al. Residential proximity to freeways and autism in the CHARGE study. Environ Health Perspect 119(6):873–877 (2010); doi: 10.1289/ehp.1002835.
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- von Ehrenstein OS, et al. *In utero* exposure to toxic air pollutants and risk of childhood autism. Epidemiology 25(6):851–858 (2014); doi: 10.1097/EDE.0000000000000150.
- Yanosky JD, et al. Predicting chronic fine and coarse particulate exposures using spatiotemporal models for the northeastern and midwestern United States. Environ Health Perspect 117(4):522–529 (2009); doi: 10.1289/ehp.11692.
- Allen JL, et al. Early postnatal exposure to ultrafine particulate matter air pollution: persistent ventriculomegaly, neurochemical disruption, and glial activation preferentially in male mice. Environ Health Perspect 122(9):939–945 (2014); doi: 10.1289/ehp.1307984.