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Grandjean P.

A Silent Pandemic

Industrial Chemicals Are Impairing The Brain Development of Children Worldwide

For immediate release: Tuesday, November 7, 2006

Landrigan Ph

THE LANCET
Volume 368, Issue 9553, 16 December 2006-22 December 2006, Pages 2167-2178

Developmental neurotoxicity of industrial chemicals

P Grandjean, PJ Landrigan

Neurodevelopmental disorders such as autism, attention deficit disorder, mental retardation, and cerebral palsy are common, costly, and can cause lifelong disability. Their causes are mostly unknown. A few industrial chemicals (eg, lead, methylmercury, polychlorinated biphenyls [PCBs], arsenic, and toluene) are recognised causes of neurodevelopmental disorders and subclinical brain dysfunction. Exposure to these chemicals during early fetal development can cause brain injury at doses much lower than those affecting adult brain function. Recognition of these risks has led to evidence-based programmes of prevention, such as elimination of lead additives in petrol. Although these prevention campaigns are highly successful, most were initiated only after substantial delays. Another 200 chemicals are known to cause clinical neurotoxic effects in adults. Despite an absence of systematic testing, many additional chemicals have been shown to be neurotoxic in laboratory models. The toxic effects of such chemicals in the developing human brain are not known and they are not regulated to protect children. The two main impediments to prevention of neurodevelopmental deficits of chemical origin are the great gaps in testing chemicals for developmental neurotoxicity and the high level of proof required for regulation. New, precautionary approaches that recognise the unique vulnerability of the developing brain are needed for testing and control of chemicals.

Strong Association of De Novo Copy Number Mutations with Autism

Jonathan Sebat *et al.*

Science **316**, 445 (2007);

We tested the hypothesis that de novo copy number variation (CNV) is associated with autism spectrum disorders (ASDs). We performed comparative genomic hybridization (CGH) on the genomic DNA of patients and unaffected subjects to detect copy number variants not present in their respective parents. Candidate genomic regions were validated by higher-resolution CGH, paternity testing, cytogenetics, fluorescence in situ hybridization, and microsatellite genotyping. Confirmed de novo CNVs were significantly associated with autism ($P = 0.0005$). Such CNVs were identified in 12 out of 118 (10%) of patients with sporadic autism, in 2 out of 77 (3%) of patients with an affected first-degree relative, and in 2 out of 196 (1%) of controls. Most de novo CNVs were smaller than microscopic resolution. Affected genomic regions were highly heterogeneous and included mutations of single genes. These findings establish de novo germline mutation as a more significant risk factor for ASD than previously recognized.

Science

AAAS

Rare Structural Variants Disrupt Multiple Genes in Neurodevelopmental Pathways in Schizophrenia

Science

AAAS

Tom Walsh *et al.*

Science **320**, 539 (2008);

Schizophrenia is a devastating neurodevelopmental disorder whose genetic influences remain elusive. We hypothesize that individually rare structural variants contribute to the illness. Microdeletions and microduplications >100 kilobases were identified by microarray comparative genomic hybridization of genomic DNA from 150 individuals with schizophrenia and 268 ancestry-matched controls. All variants were validated by high-resolution platforms. Novel deletions and duplications of genes were present in 5% of controls versus 15% of cases and 20% of young-onset cases, both highly significant differences. The association was independently replicated in patients with childhood-onset schizophrenia as compared with their parents. Mutations in cases disrupted genes disproportionately from signaling networks controlling neurodevelopment, including neuregulin and glutamate pathways. These results suggest that multiple, individually rare mutations altering genes in neurodevelopmental pathways contribute to schizophrenia.

Published in final edited form as:
Neurosci Biobehav Rev. 2008 October ; 32(8): 1519–1532. doi:10.1016/j.neubiorev.2008.06.004.

PRENATAL STRESS AND RISK FOR AUTISM

Dennis K. Kinney, Ph.D.[a,b,*], Kerim M. Munir, M.D., M.P.H., D.Sc.[b,c], David J. Crowley[a], and Andrea M. Miller[a]

This paper reviews several converging lines of research that suggest that prenatal exposure to environmental stress may increase risk for Autistic Disorder (AD). We first discuss studies finding that prenatal exposure to stressful life events is associated with significantly increased risk of AD, as well as other disorders, such as schizophrenia and depression. We then review evidence from animal and huma… resemble the defi… such as learning … neuroinflammato… role for prenatal s… fetal brain develo… AD, including po… prevention progra…

Prenatal exposure to stressful life events is associated with significantly increased risk of Autistic Disorders (AD), as well as other disorders, such as **schizophrenia** and **depression**..

Prenatal stress can produce both
(a) abnormal postnatal behaviors that resemble the defining **symptoms of AD**, and
(b) other abnormalities that have elevated rates in AD, such as **learning deficits, seizure disorders, perinatal complications, immunologic and neuroinflammatory anomalies, and low postnatal tolerance for stress**

nature neuroscience

Nature Neuroscience **7**, 847 - 854 (2004)
Published online: 27 June 2004 | Corrected online: 27 July 2004 | doi:10.1038/nn1276

Epigenetic programming by maternal behavior

Ian C G Weaver[1,2], Nadia Cervoni[3], Frances A Champagne[1,2], Ana C D'Alessio[3], Shakti Sharma[4], Jonathan R Seckl[5], Sergiy Dymov[3], Moshe Szyf[6,2] & Michael J Meaney[1,2]

Here we report that increased pup licking and grooming (LG) and arched-back nursing (ABN) by rat mothers altered the offspring epigenome at a glucocorticoid receptor (GR) gene promoter in the hippocampus. Offspring of mothers that showed high levels of LG and ABN were found to have differences in DNA methylation, as compared to offspring of 'low-LG-ABN' mothers. These differences emerged over the first week of life, were reversed with cross-fostering, persisted into adulthood and were associated with altered histone acetylation and transcription factor (NGFI-A) binding to the GR promoter. Central infusion of a histone deacetylase inhibitor removed the group differences in histone acetylation, DNA methylation, NGFI-A binding, GR expression and hypothalamic-pituitary-adrenal (HPA) responses to stress, suggesting a causal relation among epigenomic state, GR expression and the maternal effect on stress responses in the offspring. Thus we show that an epigenomic state of a gene can be established through behavioral programming, and it is potentially reversible.

Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ. **Epigenetic programming by maternal behavior.** Nat Neurosci. 2004 Aug;7(8):847-54.

The **fifth** key word is **phylogeny**

The chimpanzee DNA is for 98.77% identical to the human .

On average, a gene encoding a protein in a man differs from its chimpanzee ortholog by only two aa substitutions

.. almost one third of human genes has exactly the same protein translation as their orthologs in chimpanzee

We are quite stable (for millions of years) both genetically and phenotypically

Species ***phylogeny***

Evo

From the Tree of the Life Website, University of Arizona

Orangutan *Gorilla* ***Chimpanzee*** ***Human***




Sanger Institute

Chimpanzee-human divergence

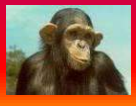
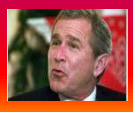
Evo

6-8 million years

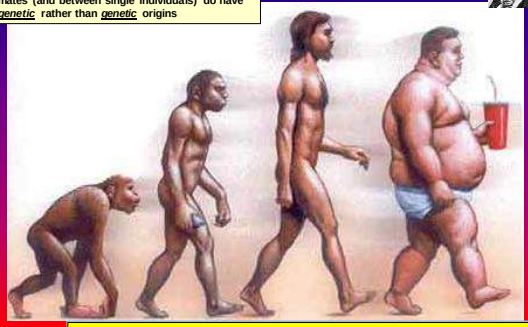
Chimpanzees *Humans*

Hominids or hominins

Brain: a *rapidly evolving Organ*..

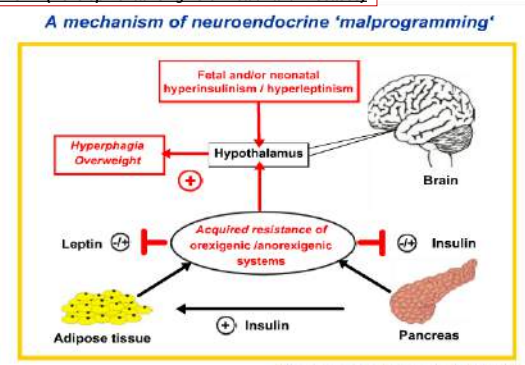



We can already summarize all this by saying that the **main phenotypic (in particular behavioural) differences between *Homo sapiens* and the other primates (and between single individuals) do have *epigenetic* rather than *genetic* origins**



Which also means that the **main variations in our phenotype** (both physiological and pathological) have their origin in ***fetal programming*** and are **induced** by the altogether changing ***environment*** and **modulated** by the ***epigenome*** …

The **sixth key word** is (*epigenetic-phenotypical*) ***mismatch***
→ ***DOHA (Developmental Origins of Health and Diseases)***



Dutch famine *versus* Leningrad Siege

Roseboom TJ et al. ***Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview*** Twin Res. (2001);4(5):293-8

Stanner SA, Yudkin JS ***Fetal programming and the Leningrad Siege study*** Twin Res.(2001); 4(5):287-92

Foetal programming implies that during critical periods of prenatal growth, **permanent changes in metabolism** and/or structures may result from adverse intrauterine conditions… Anyway, such **(epigenetic) changes** are **potentially adaptive: in case of a rapid change** between the **information** that the child Receives before and after birth.. the **responses are mismatched and disease risk** increases **(→ chronic diseases)**

EPIGENOME ROADMAP
A *Nature* special issue
nature.com/epigenomeroadmap

Sperm carry not only DNA to the ovum but a wide variety of RNAs

GENETICS versus ***EPIGENETICS***

The *epigenetics revolution* hit in the early 2000s, when scientists began reporting **that environmental factors** — everything from *neglectful mothering* and *child abuse* to a *high-fat diet* and *air pollution* — can **influence the addition or removal of chemical tags on DNA** that turn genes on and off… particularly in the **very first stages of life (*fetal programming*)**

The idea of an environmentally responsive genome still stirs debate …

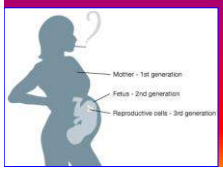
Yet the notion that epigenetic marks are transmitted across generations is even more provocative.

But **the most amazing discoveries**, that impose a radical revision of the dominant models

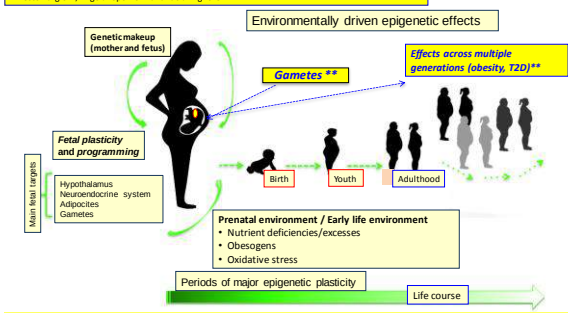
- both in the biomedical field
- and in evolutionary biology (neo-Darwinian model)

do concern the **transgenerational transmission of acquired characteristics by epigenetic adaptive, targeted modifications of the genome of the gametes**

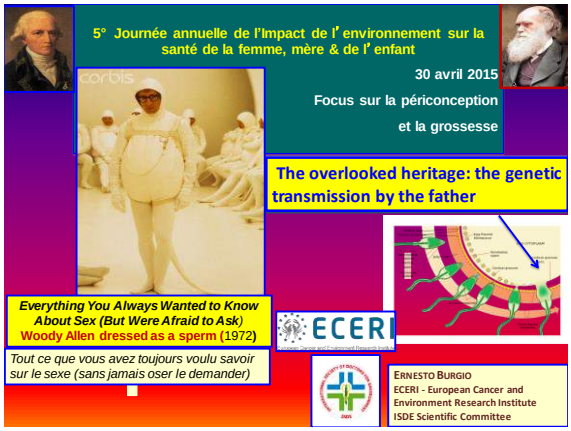
(probably transmitted to the gametes by ***microRNAs*** or ***exosomes***)



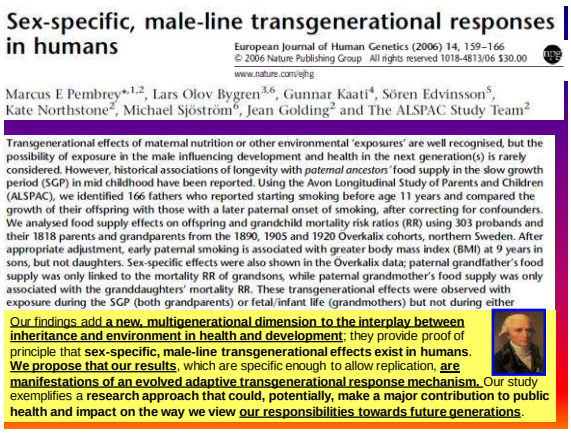
OBESITY AND DIABETES: FROM GENETICS TO EPIGENETICS – Molecular Reports 2014
Ernesto Burgio[1,2], Angela Lopomo[3,4] and Lucia Migliore[1]

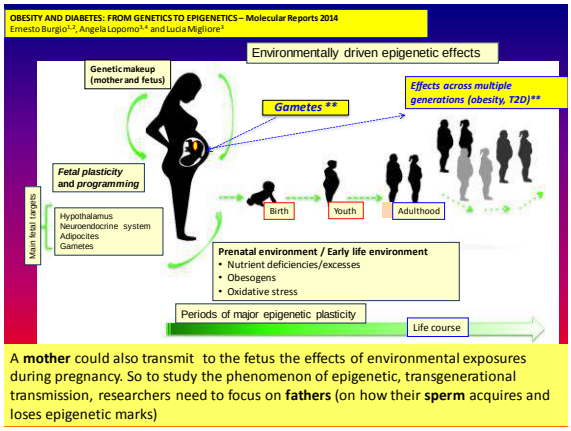


A **mother** could also transmit to the fetus the effects of environmental exposures during pregnancy. So to study the phenomenon of epigenetic, transgenerational transmission, researchers need to focus on **fathers** (on how their **sperm** acquires and loses epigenetic marks)


5° Journée annuelle de l'Impact de l'environnement sur la santé de la femme, mère & de l'enfant
30 avril 2015
Focus sur la périconception
et la grossesse
The overlooked heritage: the genetic transmission by the father
Everything You Always Wanted to Know About Sex (But Were Afraid to Ask)
Woody Allen dressed as a sperm (1972)
Tout ce que vous avez toujours voulu savoir sur le sexe (sans jamais oser le demander)
ECERI
Ernesto Burgio
ECERI - European Cancer and Environment Research Institute
ISDE Scientific Committee


nature
International weekly journal of science
Published online 1 November 2002 | Nature | doi:10.1038/news021028-9
News
Cardiovascular and diabetes mortality determined by nutrition during parents' and grandparents' slow growth period
Effects of nutrition could be carried down generations.
Grandfathers who overeat might ruin their grandchildren's health, say Swedish researchers. The study suggests that diet, which does not change genes, can nevertheless influence future generations.
Gunnar Kaati and his team at the University of Umeå collected health histories of 300 Swedes born between 1890 and 1920. Crop records showed how much they were eating just before puberty. Grandchildren of well-fed grandfathers were four times as likely to die from diabetes..
A nutrition-linked mechanism through the male line influenced the risk for cardiovascular and diabetes mellitus mortality.
(Odds Ratio 4.1, 95% confidence interval 1.33-12.93, P=0.01).


Sex-specific, male-line transgenerational responses in humans
European Journal of Human Genetics (2006) 14, 159–166
© 2006 Nature Publishing Group All rights reserved 1018-4813/06 $30.00
www.nature.com/ejhg
Marcus E Pembrey*,1,2, Lars Olov Bygren3,6, Gunnar Kaati4, Sören Edvinsson5, Kate Northstone2, Michael Sjöström6, Jean Golding2 and The ALSPAC Study Team2
Transgenerational effects of maternal nutrition or other environmental 'exposures' are well recognised, but the possibility of exposure in the male influencing development and health in the next generation(s) is rarely considered. However, historical associations of longevity with paternal ancestors' food supply in the slow growth period (SGP) in mid childhood have been reported. Using the Avon Longitudinal Study of Parents and Children (ALSPAC), we identified 166 fathers who reported starting smoking before age 11 years and compared the growth of their offspring with those with a later paternal onset of smoking, after correcting for confounders. We analysed food supply effects on offspring and grandchild mortality risk ratios (RR) using 303 probands and their 1818 parents and grandparents from the 1890, 1905 and 1920 Överkalix cohorts, northern Sweden. After appropriate adjustment, early paternal smoking is associated with greater body mass index (BMI) at 9 years in sons, but not daughters. Sex-specific effects were also shown in the Överkalix data; paternal grandfather's food supply was only linked to the mortality RR of grandsons, while paternal grandmother's food supply was only associated with the granddaughters' mortality RR. These transgenerational effects were observed with exposure during the SGP (both grandparents) or fetal/infant life (grandmothers) but not during either
Our findings add a new, multigenerational dimension to the interplay between inheritance and environment in health and development; they provide proof of principle that sex-specific, male-line transgenerational effects exist in humans. We propose that our results, which are specific enough to allow replication, are manifestations of an evolved adaptive transgenerational response mechanism. Our study exemplifies a research approach that could, potentially, make a major contribution to public health and impact on the way we view our responsibilities towards future generations.



A **mother** could also transmit to the fetus the effects of environmental exposures during pregnancy. So to study the phenomenon of epigenetic, transgenerational transmission, researchers need to focus on **fathers** (on how their **sperm** acquires and loses epigenetic marks)

Similar work in Britain reported in 2005 that **fathers who had started smoking before the age of 11 had an increased risk of having boys of above average weight**

When Pembrey, Bygren and Golding **looked at the sons of those 166 early smokers**, it turned out that the boys had significantly **higher body mass indexes** than other boys by age 9. That means the **sons of men who smoke in prepuberty will be at higher risk for obesity and other health problems well into adulthood …**

Pembrey, Bygren, Golding and their colleagues concluded in the *European Journal of Human Genetics* paper. In other words, you can change your epigenetics even when you make a dumb decision at 10 years old. **If you start smoking then, you may have made not only a medical mistake but a catastrophic genetic mistake.**

Sperm signatures

- Yet many scientists remained sceptical. Epidemiological studies are often messy, and it is impossible to rule out all confounding variables.
- In the past few years, however, several **studies in rodents have supported** these observations and begun to attribute the **transmission of various traits to changes in sperm.**

Epigenetics
Volume 7, Issue 5, 2012

Twenty-eight microRNAs were found to be differentially expressed in the sperm from **male smokers** vs. **non-smokers**

Smoking induces differential miRNA expression in human spermatozoa: A potential transgenerational epigenetic concern?

Recent work has suggested that environmental chemicals, including those contained in cigarette smoke, can have adverse effects on the exposed individuals as well as their future progeny. The mechanisms underlying transmission of environmentally induced phenotypes through the germ line are not well understood. However, a predominant process appears to be the establishment of permanent heritable epigenetic alterations, and a number of studies have implicated microRNAs in such processes. Here, we show that cigarette smoke induces specific differences in the spermatozoal microRNA conte predor cell de pheno

The mechanisms underlying transmission of environmentally induced phenotypes through the germ line are not well understood. However, a predominant process appears to be **the establishment of permanent heritable epigenetic alterations, and a number of studies have implicated microRNAs** in such processes.
Here, we show that **cigarette smoke induces specific differences in the spermatozoal microRNA** content of human smokers compared with non-smokers, and that **these altered microRNAs appear to predominantly mediate pathways vital for healthy sperm and normal embryo development**, particularly cell death and apoptosis.

Behavioral/Cognitive
The Journal of Neuroscience, May 22, 2013 • 33(21):9003–9012 • 9003

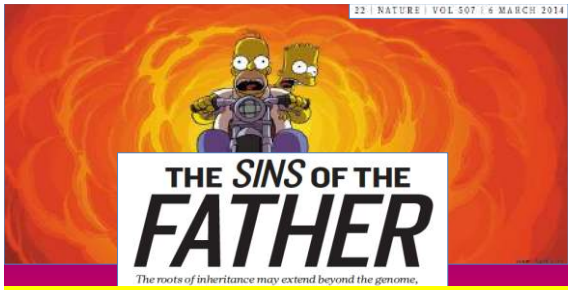
Paternal Stress Exposure Alters Sperm MicroRNA Content and Reprograms Offspring HPA Stress Axis Regulation

Ali B. Rodgers, Christopher P. Morgan, Stefanie L. Bronson, Sonia Revello, and Tracy L. Bale

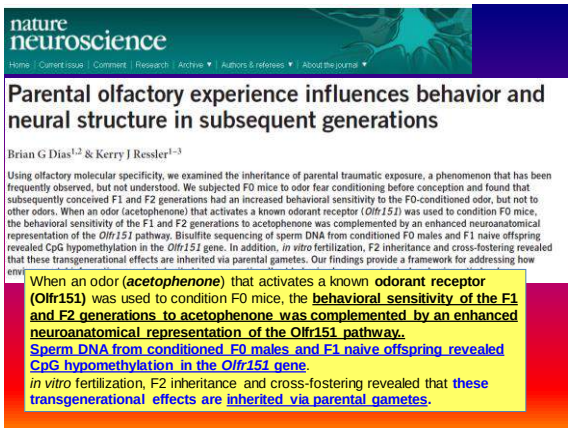
Neuropsychiatric disease frequently presents with an underlying hyporeactivity or hyperreactivity of the HPA stress axis, suggesting an exceptional vulnerability of this circuitry to external perturbations. Parental lifetime exposures to environmental challenges are associated with increased offspring neuropsychiatric disease risk, and likely contribute to stress dysregulation. While maternal influences have been extensively examined, much less is known regarding the specific role of paternal factors. To investigate the potential mechanisms by which paternal stress may contribute to offspring hypothalamic–pituitary–adrenal (HPA) axis dysregulation, we exposed mice to 6 weeks of chronic stress before breeding. As epidemiological studies support variation in paternal germ cell susceptibility to reprogramming across the lifespan, male stress exposure occurred either throughout puberty or in adulthood. Remarkably, offspring of sires from both paternal stress groups displayed significantly reduced HPA stress axis responsivity. Gene-set enrichment analyses in offspring stress regulating brain regions, the paraventricular nucleus (PVN) and the bed nucleus of stria terminalis, revealed global pattern changes in transcription suggestive of epigenetic reprogramming and consistent with altered offspring stress responsivity, including increased expression of glucocorticoid-responsive genes in the PVN. In examining potential epigenetic mechanisms of germ cell transmission, we found robust changes in sperm microRNA (miR) content, where nine

Neuropsychiatric disease frequently presents with an underlying hyporeactivity or hyperreactivity of the HPA stress axis, suggesting an **exceptional vulnerability of this circuitry** to external perturbations. **Parental lifetime exposures to environmental challenges are associated with increased offspring neuropsychiatric disease risk**, and likely contribute to **stress dysregulation**. While **maternal influences** have been extensively examined .. **to investigate the potential mechanisms by which paternal stress may contribute to offspring hypothalamic-pituitary-adrenal (HPA) axis dysregulation, we exposed mice to 6 weeks of chronic stress before breeding.**

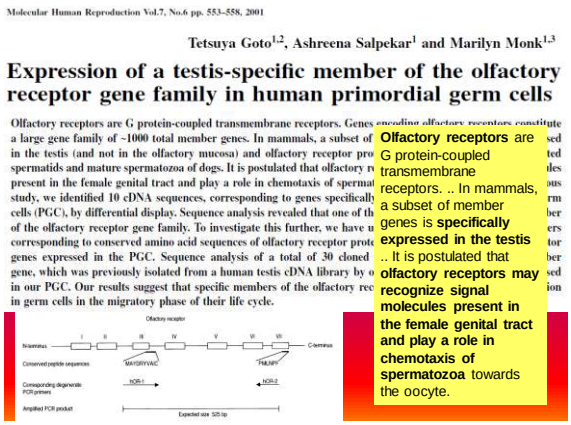
Remarkably, **offspring from both paternal stress groups displayed significantly reduced HPA stress axis responsivity**…In examining **epigenetic mechanisms of germ cell transmission, we found robust changes in sperm microRNA (miR)..**



When Brian Dias became a father last October, he was, like any new parent, **mindful of the enormous responsibility** that lay before him... But, unlike most new parents, **Dias was also aware of the influence of his past experiences — not to mention those of his parents, his grandparents and beyond, whether they smoked, endured famine or fought in a war.** As a postdoc he had spent much of the two years before studying these kinds of questions in mice: **specifically, he looked at how fear associated with a particular smell affects the animals and leaves an imprint on the brains of their descendants.**



When an odor (***acetophenone***) that activates a known **odorant receptor (Olfr151)** was used to condition F0 mice, the **behavioral sensitivity of the F1 and F2 generations to acetophenone was complemented by an enhanced neuroanatomical representation of the Olfr151 pathway..**
Sperm DNA from conditioned F0 males and F1 naive offspring revealed CpG hypomethylation in the *Olfr151* gene.
in vitro fertilization, F2 inheritance and cross-fostering revealed that **these transgenerational effects are inherited via parental gametes**.



Olfactory receptors are G protein-coupled transmembrane receptors. .. In mammals, a subset of member genes is **specifically expressed in the testis** .. It is postulated that **olfactory receptors may recognize signal molecules present in the female genital tract and play a role in chemotaxis of spermatozoa** towards the oocyte.

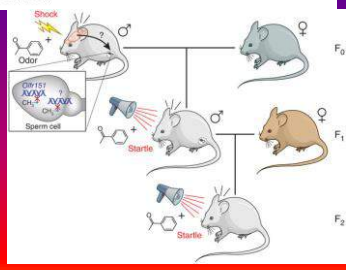
Lamarck revisited: epigenetic inheritance of ancestral odor fear conditioning

Nature Neuroscience 17, 2–4 (2014)

Moshe Szyf

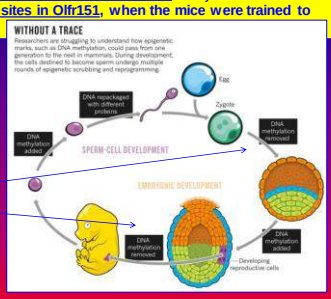
A study shows that when mice are taught to fear an odor, both their offspring and the next generation are born fearing it. The gene for an olfactory receptor activated by the odor is specifically demethylated in the germ line and the olfactory circuits for detecting the odor are enhanced.

A study shows that **when mice are taught to fear an odor, both their offspring and the next generation are born fearing it.**
The **gene for an olfactory receptor activated by the odor is specifically demethylated in the germ line** and **the olfactory circuits for detecting the odor are enhanced**



Because a **molecular target, a specific olfactory receptor gene, is known**, the authors were able to examine **epigenetic marks at this locus**. They found that there were **differentially demethylated sites in Olfr151, when the mice were trained to fear acetophenone.**

Even more surprising is the fact that this **methylation signature in sperm is transferred to the F1 and F2 generations**, indicating that **it escapes both the post-fertilization and primordial germ cell erasures** of DNA methylation



But creating an epigenetic mark in the sperm is only the first step.
To pass down through multiple generations, the signal needs to survive multiple rounds of rigorous epigenetic reprogramming.

frontiers in GENETICS
May 2014 | Volume 5 | Article 133 | 1
OPINION ARTICLE
published: 15 May 2014
doi: 10.3389/fgene.2014.00133

Molecular mechanisms for the inheritance of acquired characteristics—exosomes, microRNA shuttling, fear and stress: Lamarck resurrected?

John Smythies[1], Lawrence Edelstein[2] and Vilayanur Ramachandran[1]*

[1] Department of Psychology, Center for Brain and Cognition, University of California, San Diego, La Jolla, CA, USA
[2] Medimark Corporation, Del Mar, CA, USA
*Correspondence: jsmythies@ucsd.edu

This paper will explore two possible molecular mechanisms, based on microRNAs and exosomes, which may contribute to the inheritance of acquired characteristics. It will not be concerned directly with other mechanisms proposed in this field, such as the epigenetic reprogramming of the developing germ line, including epimutations, which may be responsible for some instances of inheritance. Stringer et al. (2013) have recently reviewed the Byzantine complexity of this field (also see Dias and Ressler, 2014). We propose to explore two additional (non-competitive) fields presented in the form of two hypotheses. The first involves short range exosome signaling and the second involves long range exosome signaling.

This paper will **explore two possible molecular mechanisms, based on microRNAs and exosomes**, which may contribute to the **inheritance of acquired characteristics**.

It will **not be concerned directly with other mechanisms proposed in this field,** such as the **epigenetic reprogramming of the developing germ line**..

We propose to explore two additional hypotheses. The first involves **short range exosome signaling** and the second involves **long range exosome signaling.**

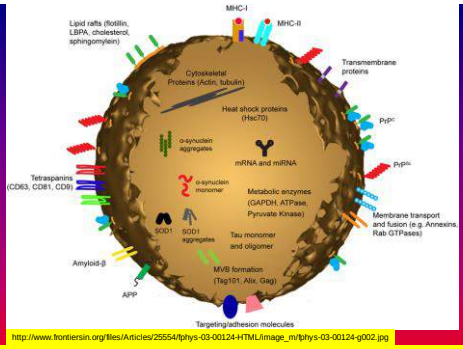
HYPOTHESIS 1

SHORT RANGE EXOSOME SIGNALING

We suggest that parental stress up-regulates the production of the microRNAs specified above in the epididymis, via activation of the HPA axis. Other chemical signals, generated by such factors as tobacco usage and insulin resistance, may also modulate microRNA expression. Subsequently, these microRNAs are shuttled by exosomes to the sperm and conveyed to the ovum. Here, they may epigenetically up-regulate the sensitivity of the developing HPA system in the developing embryo during the formation of the HPA axis. The fact that the top-predicted target of the microRNAs detected by Rodgers et al. (2013) was a DNA methyltransferase may be significant in this context. Consequently, when the adult offspring is stressed, it would exhibit behaviors associated with having an HPA system with a lowered threshold for activation. This reaction would in turn lower the threshold for expression of particular stress-evoked miRNAs in its own epididymis and sperm, owing to a repeat of the mechanism described above.

Sperm carry not only DNA to the ovum but a **wide variety of RNAs**. These include mRNAs, microRNAs and piRNAs playing a **major role in embryo development** by regulating the expression of various genes. **These microRNAs reach the developing sperm in the epididymis, where they are transported by exosomes from the epididymal epithelium ..**

We suggest that **parental stress up-regulates the production of the microRNAs specified above in the epididymis, via activation of the HPA axis.** Other chemical signals, generated by such factors **tobacco usage and insulin resistance, may also modulate microRNA expression**. Subsequently, **these microRNAs are shuttled by exosomes to the sperm and conveyed to the ovum**. Here, they may **epigenetically up-regulate the sensitivity of the developing HPA system in the developing embryo during the formation of the HPA axis**.



http://www.frontiersin.org/files/Articles/25554/fphys-03-00124-HTML/image_m/fphys-03-00124-g002.jpg

Exosomes are small membrane bound **vesicles containing mRNA and miRNA**, and a vast array of different proteins depending on their host cell...Scientists that are actively researching **the role that exosomes may play in cell-to-cell signaling, hypothesize that delivery of their cargo RNA molecules can explain many biological effects**

Journal of Andrology, Vol. 33, No. 3, May/June 2012

Effects of the Exposure to Mobile Phones on Male Reproduction: A Review of the Literature

SANDRO LA VIGNERA, ROSITA A. CONDORELLI, ENZO VICARI, ROSARIO D'AGATA, AND ALDO E. CALOGERO

From the Section of Endocrinology, Andrology, and Internal Medicine and Master in Andrological, Human Reproduction, and Biotechnology Sciences, Department of Internal Medicine and Systemic Diseases, University of Catania, Catania, Italy.

ABSTRACT: The use of mobile phones is now widespread. A great debate exists about the possible damage that the radiofrequency electromagnetic radiation (RF-EMR) emitted by mobile phones exerts on different organs and apparatuses. The aim of this article was to review the existing literature exploring the effects of RF-EMR on the male reproductive function in experimental animals and humans. Studies have been conducted in rats, mice, and rabbits using a similar design based upon mobile phone RF exposure for variable lengths of one has explored the effects of RF-EMR directly on spermatozoa and the other has evaluated the sperm parameters in men using or not using mobile phones. The results showed that human spermatozoa exposed to RF-EMR have decreased motility, morphometric abnormalities, and increased oxidative stress, whereas men using mobile phones have decreased sperm concentration, decreased motility (particularly rapid progressive motility), normal morphology, and decreased viability. These abnormalities seem to be directly related

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WI-FI PRODUCED BY YOUR PC
the radiated signal exceeds 13 V / m

Exposure to RF-EMW can induce alterations in many sub-cellular mechanisms

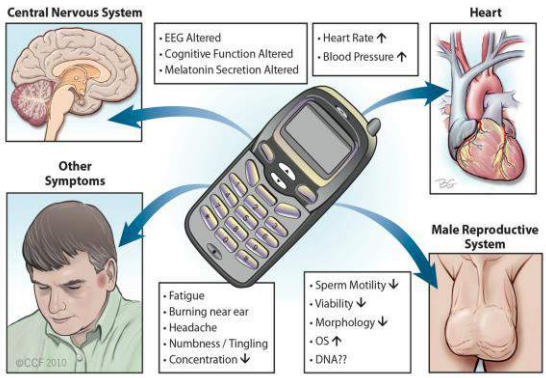
Changed plasma membrane potential and calcium efflux with resultant **calcium depletion** leads to **decrease in the activity of protein kinase C (PKC).** This decrease leads to **alteration in many enzymes, ion pumps, channels and proteins as well as inducing apoptosis**.

RF-EMW also induce ROS production through disturbance of the mitochondrial membrane bound NADH oxidase. ROS has impact on PKC, histone kinase, heat shock protein, DNA and apoptosis.

Heat shock proteins (HSPs) increase in response to electromagnetic radiation and ROS. HSPs slows the metabolism of the sperm and impairs the blood testis barrier interfering with apoptosis of damaged and transformed sperm.

Genotoxic effect of RF-EMW on sperm is either through ROS production or through direct clastogenic chromatin breaking effect.

Hamada JL et al. ***Cell Phones and their Impact on Male Fertility: Fact or Fiction***
The Open Reproductive Science Journal, 2011, 5, 125-137



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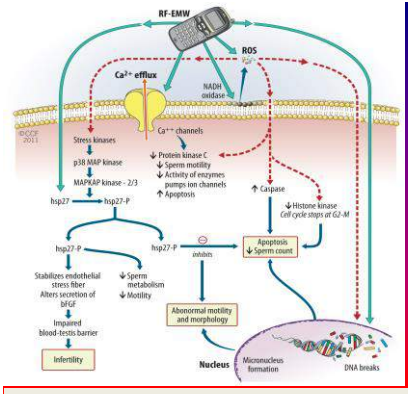

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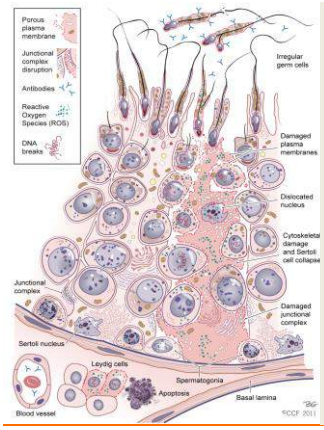
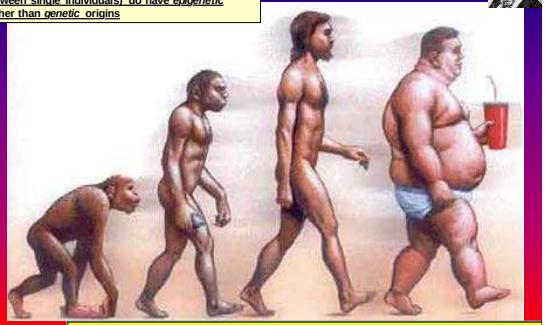


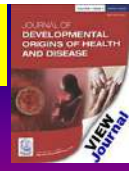
Cross sectional view of **testicular tissue** showing various effects of **cell phone RF-EMW** on cellular components of the testis.
In sperm: a) plasma membrane becomes leaky and porous due to EMW induced electroporation,
b) **cytoplasmic mitochondria generate excess ROS** resulting in ***oxidative stress***
c) **nuclear DNA and chromatin undergo breaks and damage**.
In **Sertoli cells**: a) **damage to plasma membrane tight junctional complexes** compromises the **integrity of BTB (Blood testis Barrier)** and increases its permeability resulting in exposure of sperm antigens to immune system and formation of ASA (Antisperm ABs),
b) **damage to cytoskeleton** results in cell collapse with
c) production of excess **ROS**, and
d) **dislocation of nucleus** to a more central position.
In **Leydig cells**: a) plasma membrane sustains damage with
b) **excessive cytoplasmic ROS generation**, and c) **nuclear DNA damage resulting in apoptosis**.

We can summarize all this by saying that the **main phenotypic (in particular behavioural) differences between *Homo sapiens* and the other primates (and between single individuals) do have *epigenetic* rather than *genetic* origins**



Which also means that the **main variations in our phenotype** (both physiological and pathological) have their origin in ***fetal programming*** and are **induced** by the altogether changing ***environment*** and **modulated** by the ***epigenome*** …

Eventually, during the last years, the ***fetal programming mismatch theory*** has been transformed **from a theory essentially useful to explain the pathogenic mechanisms causing certain diseases of adulthood, into the key-model theory of the embryo-fetal origins of adult diseases (DOHA-Developmental Origins of Health and Diseases)**



Obesogens

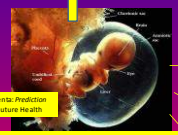
Multiorgan Effects of Endocrine Disruptors

Pesticides

In Vitro Fertilization

Materno Fetal Stress

Obesity/Metabolic Syndrome/Diabetes 2



Cardiovascular Diseases

Ipertension

Asthma and allergies

Lung Development

Developmental Time Windows of Vulnerability

Reproductive Diseases/Dysfunctions

Semen Abnormalities

CANCER

DOHAD

Neurobehavioral Deficits and Diseases

Psychiatric Diseases

A **new scientific truth** does not triumph by **convincing its opponents** and making them see the light, but rather because its **opponents eventually die,** and a **new generation grows up** that is familiar with it.
Max Planck (1858 - 1947)

Une **nouvelle vérité scientifique ne triomphe pas en convainquant** ses **adversaires** et en leur faisant voir la lumière, **mais plutôt parce que ses opposants meurent et qu'ils sont remplacés par une nouvelle génération** pour qui elle est familière
Max Planck (1858 - 1947)