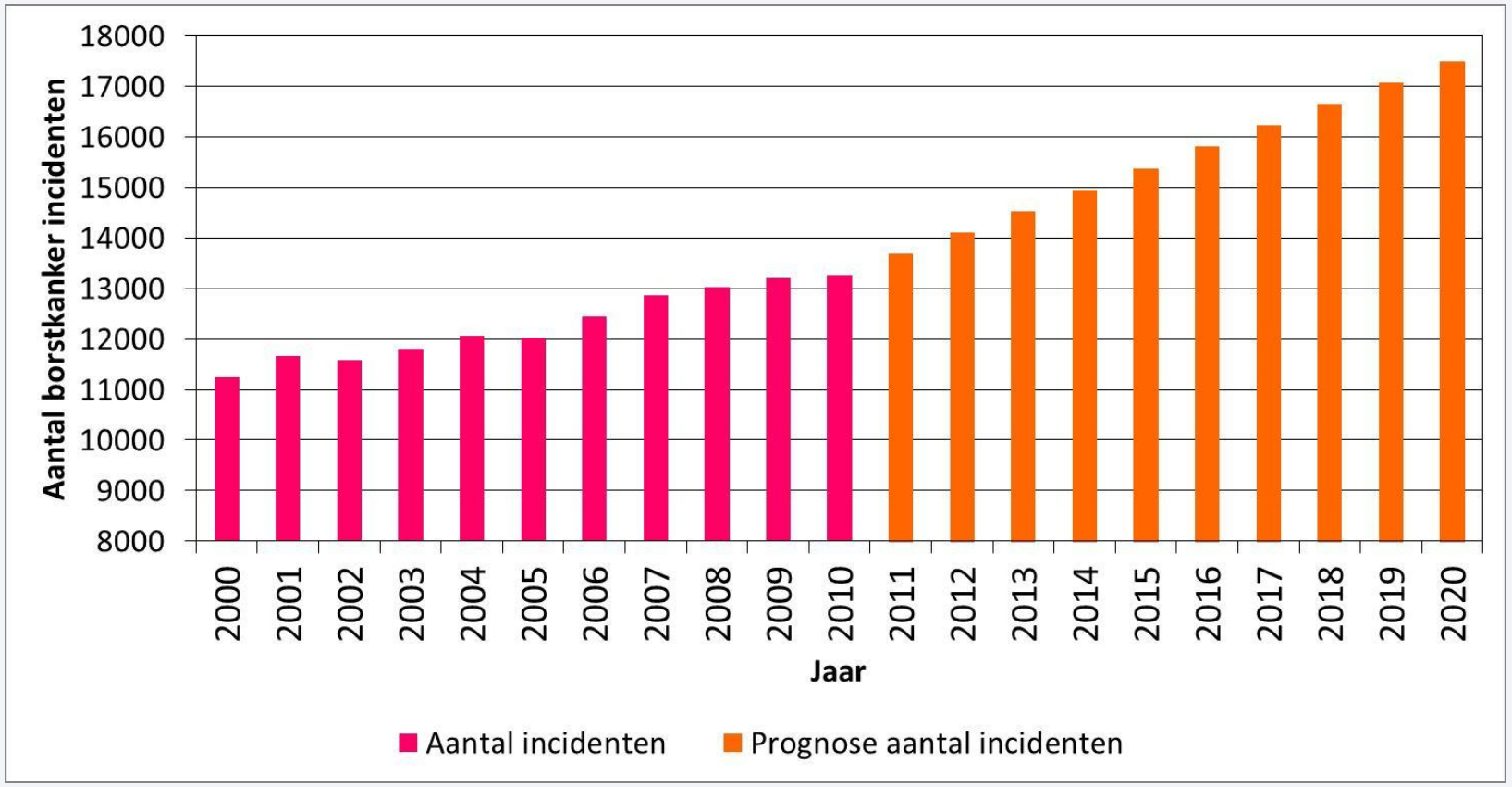
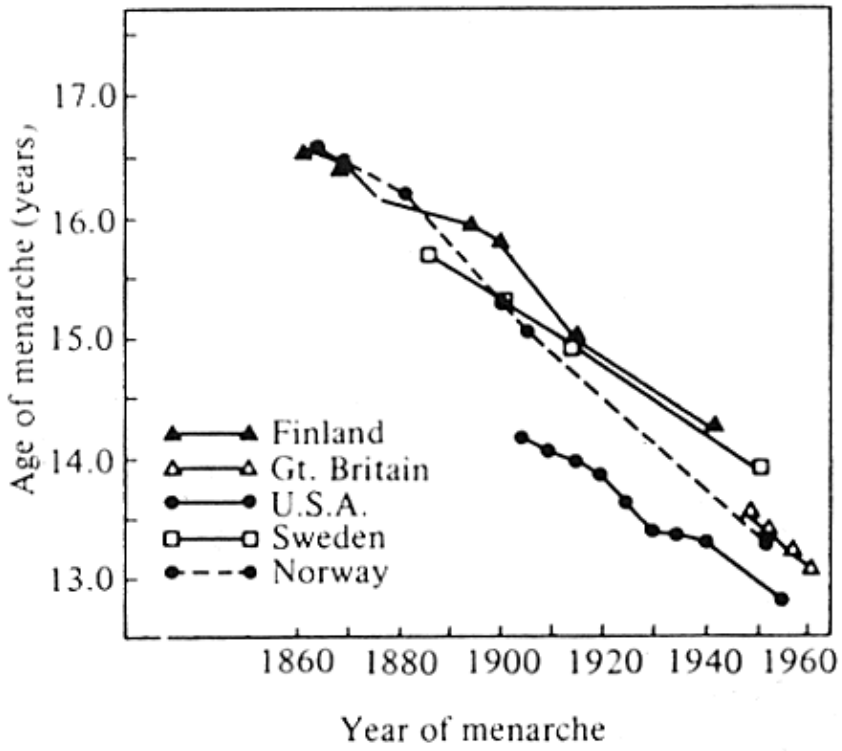
Hormonale invloed op de ongeboren baby en de gevolgen op lange termijn.

G. Devriendt


Aantal borstkanker incidenten
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
Jaar
Aantal incidenten
Prognose aantal incidenten

Menarche – Pubertas praecox

FIGURE 12–7
The decline in the average age of menarche in five Western industrial nations



(After Tanner, 1970 [594] copyright 1970 by John Wiley & Sons.)

Hormone disrupters xeno-oestrogenen:

- ✓ **HRT, pil**
- ✓ **insecticiden, pesticiden, herbiciden**
- ✓ **bisfenol A, ftalaten, ...**

26 JUNI 2008

Hormoonverstorende stoffen in Nederlands regenwater

In het Nederlandse regenwater zitten kunstmatige verbindingen die de werking van het vrouwelijke geslachtshormoon estradiol imiteren. Dat concluderen onderzoekers van TNO en onderzoeksinstituut RIKILT in de *Journal of Environmental Monitoring* uit onderzoek naar de kwaliteit van regenwater. In de regendruppels zitten weekmakers, vlamvertragers en synthetische muskusachtige geurstoffen uit parfums.

Dat muskachtige componenten uit parfums in regenwater zitten, dat had dr. Ruud Peters eigenlijk wel verwacht. 'We produceren ze, gebruiken ze en spoelen ze weg als we ons wassen. Het ligt voor de hand dat die stoffen in de atmosfeer komen. We hebben op vijftig plaatsen in Nederland regenwater onderzocht, en ontdekt dat de regendruppels in de Gelderse Vallei bijvoorbeeld de synthetische geurstof tonalide bevatten. Een fabriek in de regio die ze produceert is de bron. Overal in Nederland vinden we een andere synthetische geurstof, galaxolide. Die wordt in Nederland niet geproduceerd. De aanwezigheid in regenwater is het gevolg van het gebruik door onszelf.'

De concentratie parfumcomponenten in regenwater was echter beperkt, en bedroeg maximaal enkele nanogrammen per liter. Beduidend hoger was de concentratie weekmakers. Eén monster bevatte bijvoorbeeld een tiende milligram DIDP per liter. 'Dat was een uitschieter', erkent Peters. 'Maar we vonden opvallend veel weekmakers.'

Die stoffen worden toegevoegd aan kunststoffen om ze zacht en flexibel te maken. Ze zijn omstreden omdat ze in hoge doses de werking van het mannelijke geslachtshormoon verstoren. Omdat het lichaam ze vrij snel afbreekt is hun hormoonverstorende werking niet groot. Die vlieger gaat echter niet op voor de hardnekkige gebromeerde vlamvertragers, die de onderzoekers ook in regenwater aantroffen. In één monster liep de concentratie van de vlamvertrager HBCD, een verbinding die de werking van het schildklierhormoon kan verstoren, op tot twee microgram per liter.

Toxicoloog prof. Tinka Murk, verbonden aan de leerstoelgroep Toxicologie en Wageningen Imares, kijkt niet op van Peters' bevindingen. 'Vijf jaar geleden keken wij ook al naar hormoonverstorende stoffen in regenwater. We hebben toen bij een meting in het Westland meer pesticiden per liter in regendruppels gevonden dan in water uit de Rijn.'

In hoeverre de concentraties die Peters heeft gevonden gevaarlijk zijn voor mens en milieu, durft Murk niet te zeggen. 'Je zou de monsters ook moeten onderzoeken met bio-assays die de hormoonwerking van verbindingen en mengsels verklikken. Uit onderzoek dat onze groep in 2003 heeft gedaan weten we inmiddels dat Nederlands regenwater een vervrouwelijkende werking heeft, maar we zijn er nooit achter gekomen welke stoffen daarvoor precies verantwoordelijk zijn.

Pubertas praecox

Ziekte is idiopatisch?

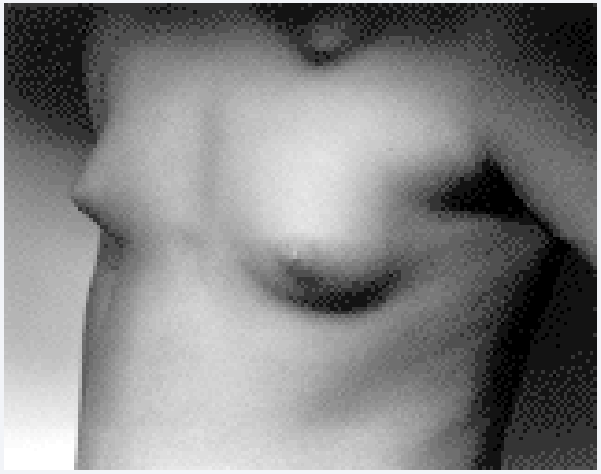
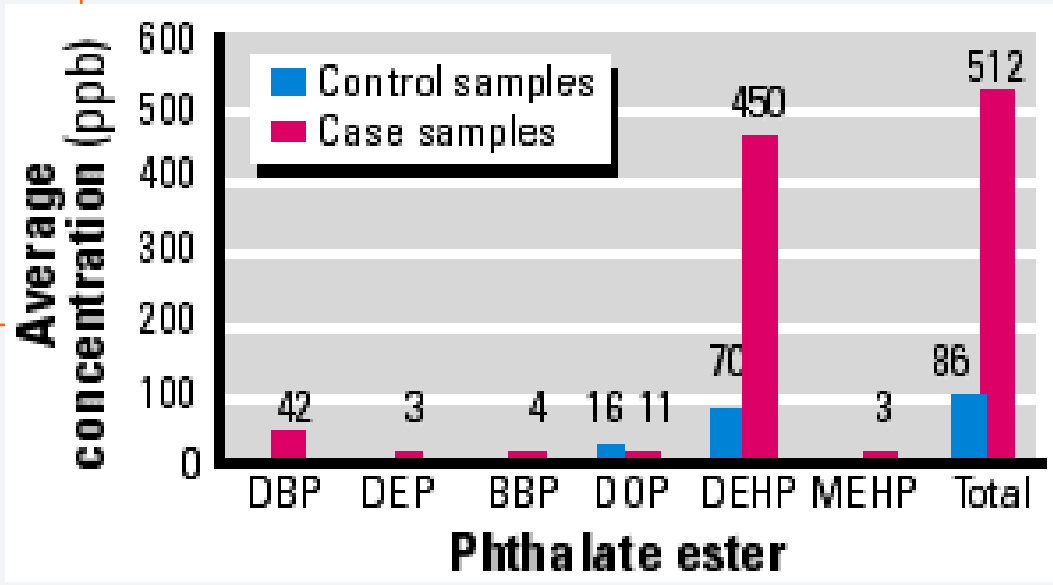


Figure 1. Twenty-three-month-old Puerto Rican girl with premature breast development (thelarche).

Identification of phthalate esters in the serum of young puerto rican girls with premature breast development

Environmental Health Perspectives v.108, n.9, Sep00
Ivelisse Colón, et al.
Department of Chemistry, University of Puerto Rico, San Juan, Puerto Rico
Pediatric Endocrinology and Diabetes Division, San Juan City Hospital, San Juan, Puerto Rico
Department of Pediatrics, University of Puerto Rico, School of Medicine, San Juan, Puerto Rico



Proc Natl Acad Sci U S A. 2005 May 10;102(19):7014-9. Epub 2005 May 2.

Estrogenic chemicals in plastic and oral contraceptives disrupt development of the fetal mouse prostate and urethra.

Timms BG, Howdeshell KL, Barton L, Bradley S, Richter CA, vom Saal FS.
Division of Basic Biomedical Sciences, University of South Dakota School of Medicine, Vermillion, SD 57069, USA.

Abstract

Exposure of human fetuses to man-made estrogenic chemicals can occur through several sources. For example, fetal exposure to ethinylestradiol occurs because each year approximately 3% of women taking oral contraceptives become pregnant. Exposure to the estrogenic chemical bisphenol A occurs through food and beverages because of significant leaching from polycarbonate plastic products and the lining of cans. We fed pregnant CD-1 mice ethinylestradiol (0.1 microg/kg per day) and bisphenol A (10 microg/kg per day), which are doses below the range of exposure by pregnant women. In male mouse fetuses, both ethinylestradiol and bisphenol A produced an increase in the number and size of dorsolateral prostate ducts and an overall increase in prostate duct volume. Histochemical staining of sections with antibodies to proliferating cell nuclear antigen and mouse keratin 5 indicated that these increases were due to a marked increase in proliferation of basal epithelial cells located in the primary ducts. The urethra was malformed in the colliculus region and was significantly constricted where it enters the bladder, which could contribute to urine flow disorders. These effects were identical to those caused by a similar dose (0.1 microg/kg per day) of the estrogenic drug diethylstilbestrol (DES), a known human developmental teratogen and carcinogen. In contrast, a 2,000-fold higher DES dose completely inhibited dorsolateral prostate duct formation, revealing opposite effects of high and low doses of estrogen.

Acceleration in the rate of proliferation of prostate epithelium during fetal life by small amounts of estrogenic chemicals could permanently disrupt cellular control systems and predispose the prostate to disease in adulthood.

PHTHALATES: risk factors for breast cancer

Phthalates are a family of synthetic chemicals used in a wide variety of consumer products including plastics, nail polish, perfumes, skin moisturizers, baby care products and toys, flavorings and solvents. These chemicals don't stay in the plastics they soften or in the countless other products in which they are used. Instead, they migrate into the air, into food and/or into people, including babies in their mother's wombs. Phthalates have been found in indoor air and dust, and in human urine, blood, and breast milk.

Rudel RA, Brody JG, Spengler JD,Vallarino J, Geno PW, Sun G, Yau A (2001).Methods to detect selected potential mammary carcinogens and endocrine disruptors in commercial and residential air and dust samples. Journal of Air andWasteManagement Association 51(4):499-513.

Kato K, SilvaMJ, Reidy JA,Hurtz D,Malek NA, Needham LL, Nakazawa H, Barr DB, Calafat AM(2003). Mono(2-ethyl-5-hydroxyhexyl) phthalate and mono-(2-ethyl-5-oxhexyl) phthalate as biomarkers for human exposure assessment to di-(2-ethylhexyl) phthalate. Environmental Health Perspectives 112: 327-330.Kang SC, Lee BM(2005). DNA methylation of estrogen receptor alpha gene by phthalates. Journal of Toxicology and Environmental Health Part A 68: 1995-2003.

Measurement of paraben concentrations in human breast tissue at serial locations across the breast from axilla to sternum

L. Barr et al.
Journal of Applied Toxicology
Volume 32, Issue 3, pages 219–232, March 2012

ABSTRACT

The concentrations of five esters of *p*-hydroxybenzoic acid (parabens) were measured using HPLC-MS/MS at four serial locations across the human breast from axilla to sternum using human breast tissue collected from 40 mastectomies for primary breast cancer in England between 2005 and 2008. One or more paraben esters were quantifiable in 158/160 (99%) of the tissue samples and in 96/160 (60%) all five esters were measured.

Proc Natl Acad Sci U S A. 2012 Sep 24.

Bisphenol A alters early oogenesis and follicle formation in the fetal ovary of the rhesus monkey.

Hunt PA, Lawson C, Gieske M, Murdoch B, Smith H, Marre A, Hassold T, Vandevoort CA.

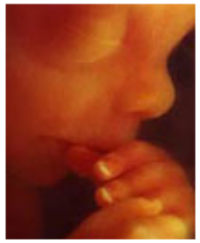
Source

School of Molecular Biosciences and Center for Reproductive Biology, Washington State University, Pullman, WA 99164.

Abstract

Widespread use of the endocrine disrupting chemical bisphenol A (BPA) in consumer products has resulted in nearly continuous human exposure. In rodents, low-dose exposures have been reported to adversely affect two distinct stages of oogenesis in the developing ovary: the events of prophase at the onset of meiosis in the fetal ovary and the formation of follicles in the perinatal ovary. Because these effects could influence the reproductive longevity and success of the exposed individual, we conducted studies in the rhesus monkey to determine whether BPA induces similar disturbances in the developing primate ovary. The routes and levels of human exposure are unclear; hence, two different exposure protocols were used: single daily oral doses and continuous exposure via subdermal implant. Our analyses of second trimester fetuses exposed at the time of meiotic onset suggest that, as in mice, BPA induces subtle disturbances in the prophase events that set the stage for chromosome segregation at the first meiotic division. Our analyses of third-trimester fetuses exposed to single daily oral doses during the time of follicle formation revealed an increase in multioocyte follicles analogous to that reported in rodents. However, two unique phenotypes were evident in continuously exposed animals: persistent unenclosed oocytes in the medullary region and small, nongrowing oocytes in secondary and antral follicles. Because effects on both stages of oogenesis were elicited using doses that yield circulating levels of BPA analogous to those reported in humans, these findings raise concerns for human reproductive health.

Participant: Baby #10
Found 136-183 of 395 tested chemicals



Baby #10's cord blood contained 136-183 of 395 industrial compounds, pollutants and other chemicals tested, including chemicals linked to brain and nervous system toxicity, immune system toxicity, and reproductive toxicity and fertility problems.

Summary of chemicals found in Baby #10

CHEMICAL FAMILY	LEVEL FOUND	HEALTH EFFECTS	EXPOSURE ROUTES
Chlorinated dioxins & furans	moderate	Immune system (including sensitization and allergies), Birth defects and developmental delays	Dietary sources, fatty meat, dairy and fish
Methylmercury	moderate		Dietary sources, particularly seafood
Organochlorine Pesticides (OCs)	low	Reproduction and fertility	Contaminated food and drinking water
Perfluorochemicals (PFCs)	moderate	Cancer, Birth defects and developmental delays, Endocrine system	Stain- and grease-proof coatings on food packaging, couches, carpets, pans
Polybrominated diphenyl ethers (PBDEs)	low	Reproduction and fertility, Brain and nervous system	Foam furniture, carpet padding, computers, televisions, contaminated house dust, food
Polychlorinated biphenyls (PCBs)	moderate	Brain and nervous system, Immune system (including sensitization and allergies)	Dietary sources, fatty meat, dairy and fish
Polychlorinated naphthalenes (PCNs)	low	Gastrointestinal (including liver)	Dietary sources, fatty meat, dairy and fish

ABOUT THIS PARTICIPANT:

The Red Cross collected umbilical cord blood from an anonymous newborn on this baby's day of birth, September 8, 2004, at a U.S. hospital.

Related links:

- Report executive summary

Location:
USA

Participant's groups:
In Utero/newborn

Study:
EWG/Commonweal Study #4, industrial chemicals and pesticides in cord blood

HEALTH & SAFETY CONCERNS:	chemicals found in this person
Brain and nervous system	126
Immune system (including sensitization and allergies)	118
Reproduction and fertility	33
Gastrointestinal (including liver)	26
Birth defects and developmental delays	8
Cancer	2
Biochemical effects	1
Hematologic (blood) system	1

Bisphenol A disrupts young brains, scientists report

2005- **Low doses of Bisphenol A (BPA), a packaging chemical, can damage the development of young brains, according to new scientific study.**

The research from a University of Cincinnati scientific team on the packaging chemical adds to the growing body of scientific evidence indicating that it should not be used for food contact materials.

BPA works by disrupting the important effects of estrogen in the developing brain, the University of Cincinnati team, headed by Scott Belcher, reported.

BPA shows negative effects in brain tissue "at surprisingly low doses". they say in two articles in the December 2005 edition of the journal Endocrinology.

"In the face of more than 100 studies published in peer-reviewed journals showing the detrimental effects of BPA, the chemical industry and federal regulatory agencies have resisted banning BPA from plastics used as food and beverage containers, despite the fact that plastics free of BPA and other toxic chemicals are available," Belcher stated.

Oestrogenen "vermannelijken" hersenen

10/01/2006

Oestrogenen vermannelijken de hersenen van de foetus. Een bepaald soort proteïne verhindert dat oestrogenen bij de vrouwelijke foetus hun weg vinden naar de hersenen. Dat blijkt uit een studie van de universiteit van Luik (ULg) en de Vrije Universiteit Brussel (VUB) bij muizen.
Tot nu toe was niet geweten of oestrogenen volledig afwezig zijn in het vrouwelijke brein. Er bestonden twee theorieën over.
De eerste theorie stelde dat de menselijke hersenen bij aanvang vrouwelijk zijn. Mannelijke foetussen produceren het hormoon testosteron. Dat wordt in de hersenen omgezet tot het hormoon oestrogeen. Oestrogeen heeft een vermannelijking van de hersenen tot gevolg, wat zowel psychologisch als gedragsmatige gevolgen heeft.
Dat zou komen omdat de alpha-foetoproteïne, een proteïne waarover nog niet veel geweten is maar waarvan bekend is dat ze oestrogenen kan vasthouden, bedoeld is om de vrouwelijke hersenen te vrijwaren van vermannelijking door de oestrogenen vast te houden en hen te beletten naar de hersenen te reizen.
De tweede theorie stelde daarentegen dat de alpha-foetoproteïne een actieve rol heeft in het transporteren van oestrogenen naar de hersenen en dat ze dus wel een rol spelen in de ontwikkeling van de vrouwelijke hersenen.
De studie die de ULg en de ULB op muizen uitvoerden, heeft aangetoond dat oestrogenen de hersenen effectief vermannelijken. De alpha-foetoproteïne beschermt de vrouwelijke hersenen wel degelijk tegen een vermannelijking door oestrogenen. De vrouwelijke muizen die genetisch werden ontdaan van de alpha-foetoproteïne, werden onvruchtbaar.
Mogelijk kan deze studie nuttig zijn voor het bestuderen van onvruchtbaarheid. Als is het nog niet zeker of de test bij mensen dezelfde resultaten zou opleveren, luidt het.

Pollution triggers bizarre behaviour in animals

03 September 04
Source: New Scientist

Hyperactive fish, stupid frogs, fearless mice and seagulls that fall over. It sounds like a weird animal circus, but this is no freak show. Animals around the world are increasingly behaving in bizarre ways, and the cause is environmental pollution.

The chemicals to blame are known as endocrine disruptors, and range from heavy metals such as lead to polychlorinated biphenyls (PCBs) and additives such as bisphenol A.

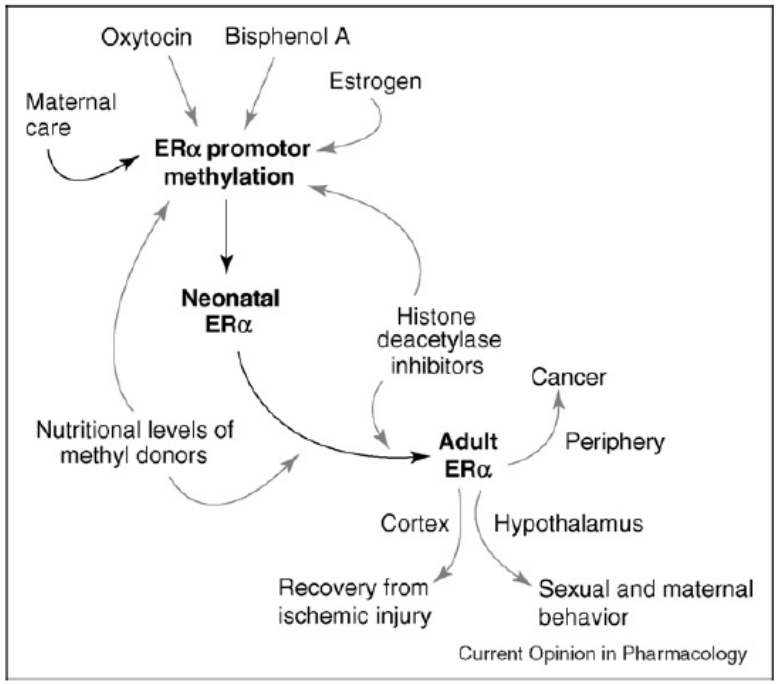
For decades, biologists have known that these chemicals can alter the behaviour of wild animals. And in recent years it has become clear that pollutants can cause gender-bending effects by altering animals' physiology, particularly their sexual organs.

But now two major reviews have revealed that the chemicals are having a much greater impact on animal behaviour than anyone suspected. **Low concentrations of these pollutants are changing both the social and mating behaviours of a raft of species.** This potentially poses a far greater threat to survival than, for example, falling sperm counts caused by higher chemical concentrations.

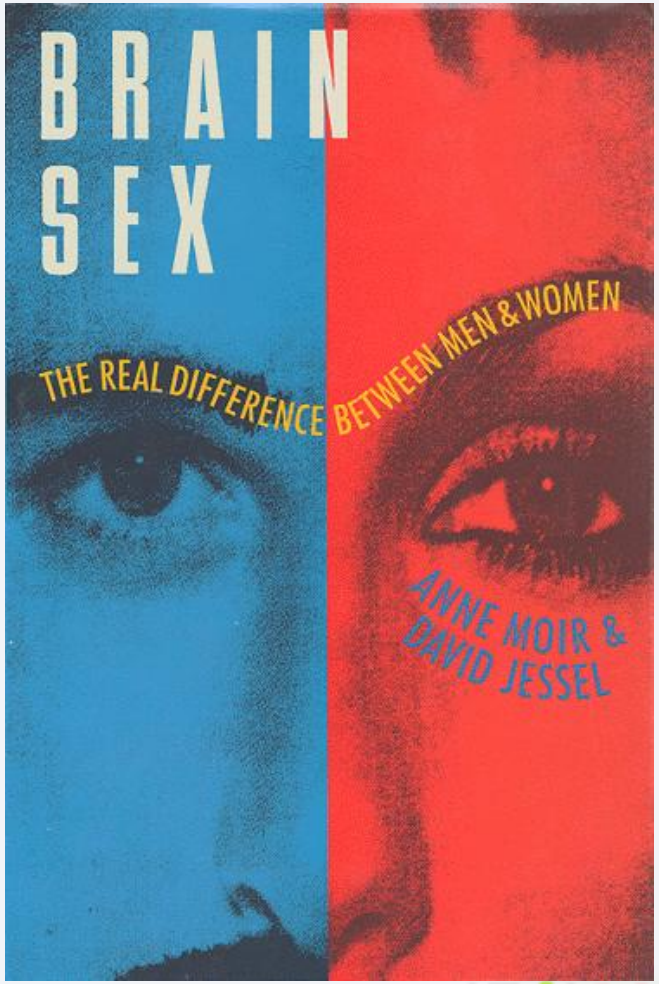
"Heritable" aspects of epigenetics

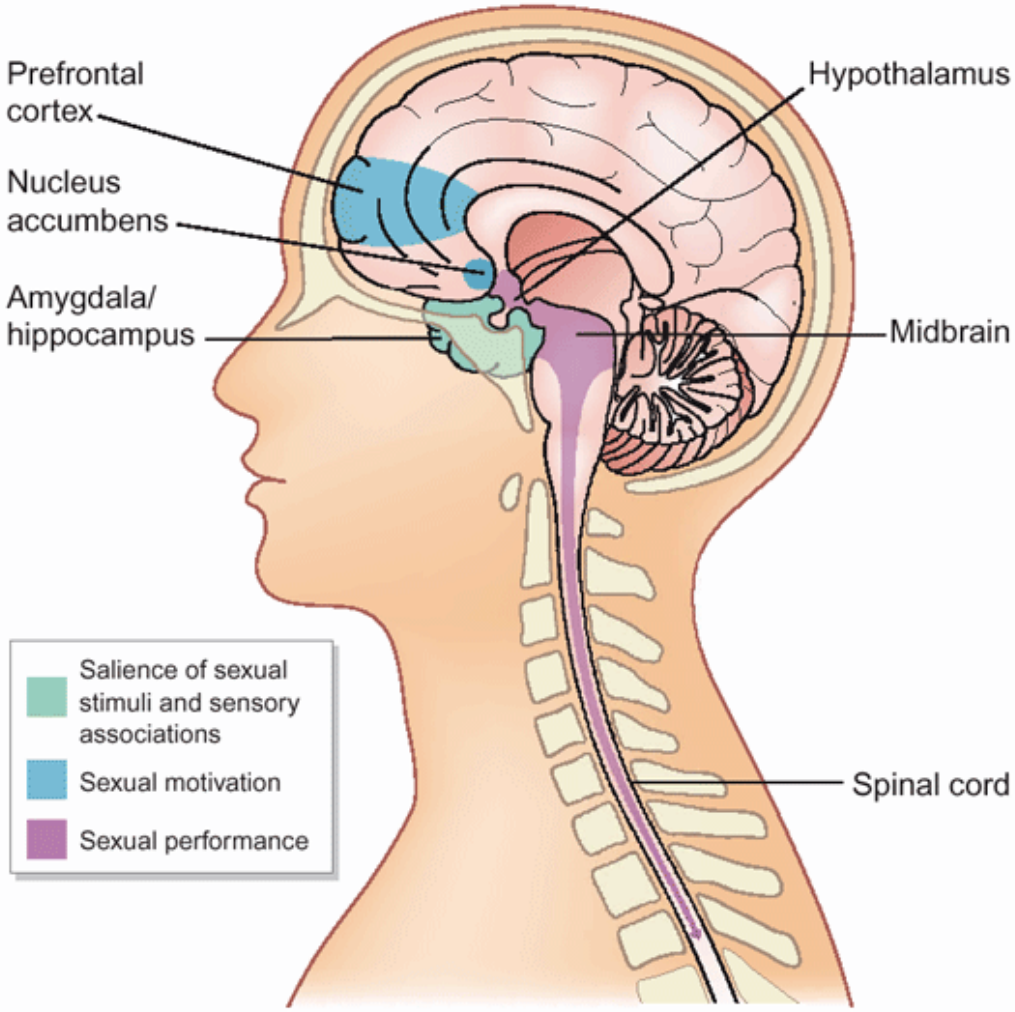
Meiotic heritance – Mental health

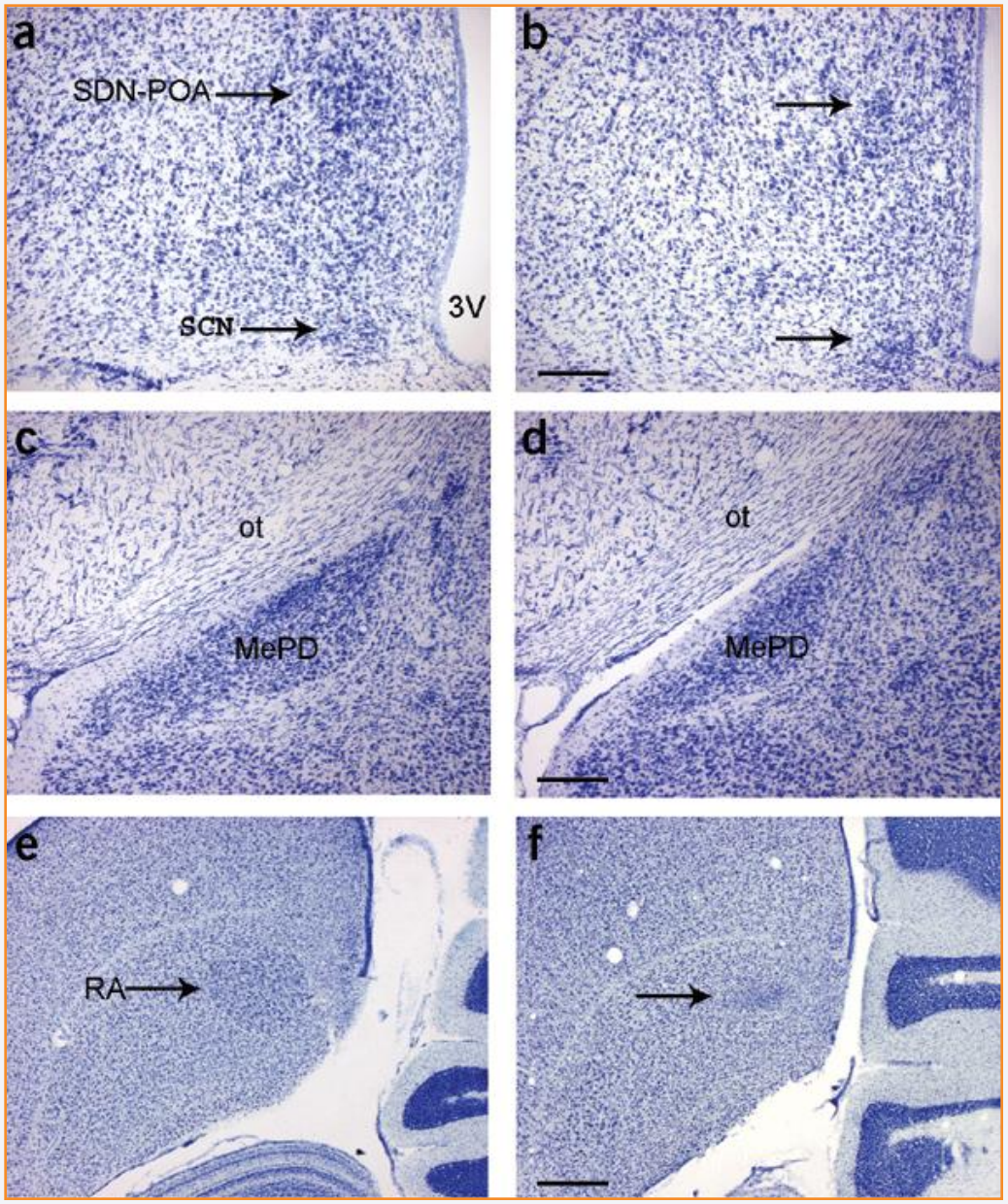
Memory - Behaviour - Neurodegeneration



Potential regulatory pathways of early environment influence on adult ERα expression. Maternal care has been demonstrated to alter site-specific ERα promotor methylation whereas neonatal oxytocin, bisphenol A, and estrogen treatment have been demonstrated to exert long-term influence on ERα expression with the role of DNA methylation yet to be elucidated. Gene expression in infancy and adulthood can be modified epigenetically through dietary intake of methyl donors such as folic acid and genistein or through administration of histone deacetylase inhibitors that promote reduced DNA methylation. Consequently, adult ERα expression has site-specific effects on health and behavior.

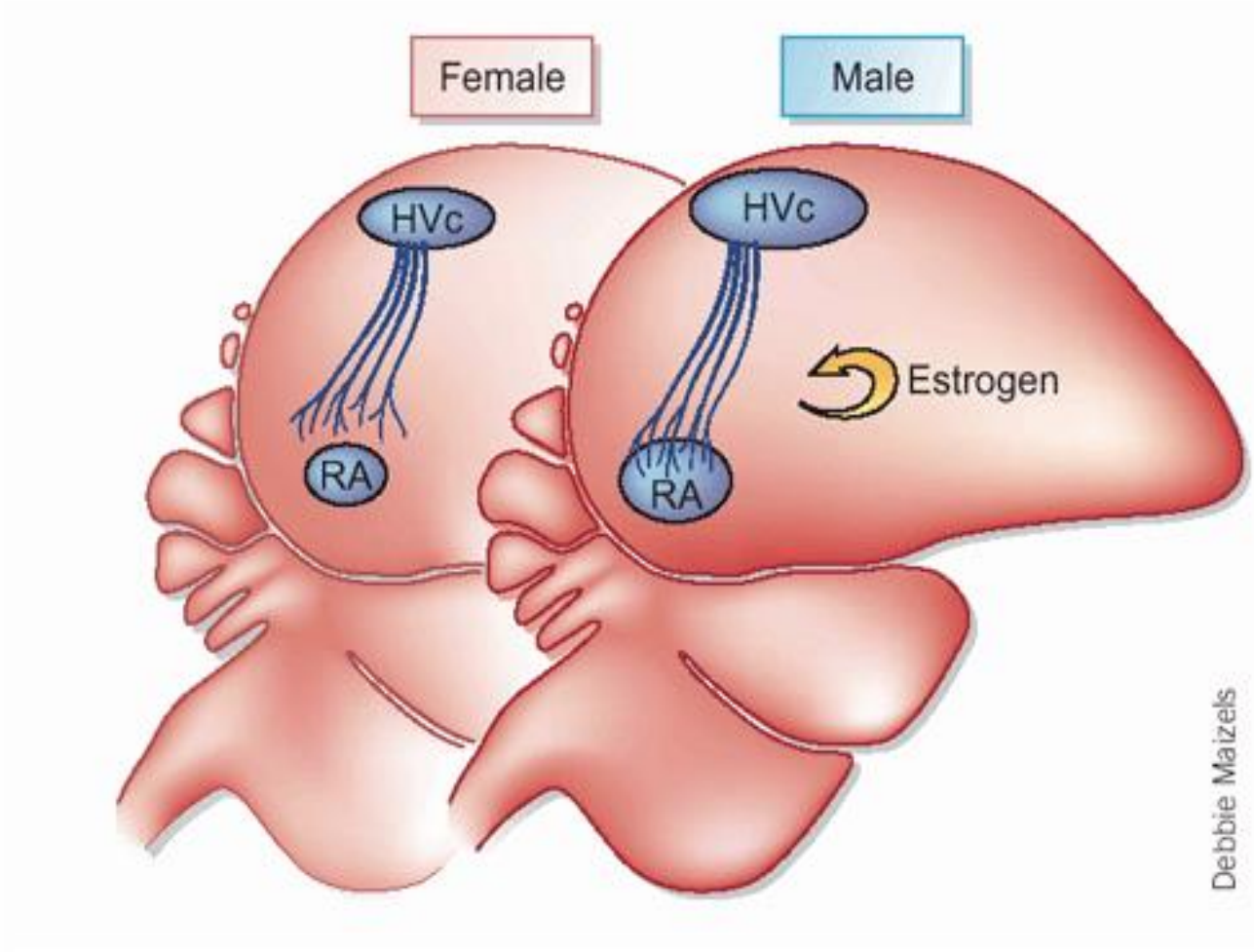



Prefrontal cortex
Nucleus accumbens
Amygdala/ hippocampus
Hypothalamus
Midbrain
Spinal cord
Salience of sexual stimuli and sensory associations
Sexual motivation
Sexual performance



Sexual dimorphisms in the brain.

(a,b) The sexually dimorphic nucleus of the preoptic area (SDN-POA) is larger in male rats (a) than in females (b) because the testes secrete testosterone during the perinatal sensitive period. After that time, testosterone has little effect on SDN-POA volume. (c,d) In contrast, the volume of the rat posterodorsal medial amygdala (MePD), which is about 1.5 times larger in males (c) than in females (d), retains its responsiveness to testosterone throughout life. (e,f) In zebra finches, the robustus archistriatum (RA) nucleus is crucial for song production and has a greater volume in males (e) than in females (f). Like the rat SDN-POA, exposure to steroid hormones early in life is essential for the RA to develop a masculine phenotype. For the RA, however, the steroids may not originate from the testes, but are rather synthesized locally in the brain itself. SCN, suprachiasmatic nucleus; 3V, third ventricle; ot, optic tract. All scale bars = 250 m.


Female
Male
HVc
HVc
RA
RA
Estrogen
Debbie Maizels

Sexual behavior activity tracks rapid changes in brain estrogen concentrations

Mélanie Taziaux, * Matthieu Keller, * Julie Bakker, and Jacques Balthazart

Center for Cellular and Molecular Neurobiology, University of Liège, B-4000 Liège, Belgium

Brain estrogen production can be regulated within minutes by changes in aromatase (estrogen synthase) activity as a result of calcium-dependent phosphorylations of the enzyme. To determine the effects of rapid changes in estrogen availability on male copulatory behavior, we mimicked in male mice the rapid upregulation and downregulation of brain estrogen concentration that should occur after inactivation or activation of aromatase activity. **Increases or decreases in brain estrogen concentrations are followed within minutes by corresponding changes in male sexual behavior.**

Gender-related behavior in women exposed prenatally to diethylstilbestrol

Retha R. Newbold
National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709 USA
Abstract

Accumulating evidence in experimental animals over the past three decades suggests that mammalian brain development and differentiation of the central nervous system are influenced by perinatal exposure to sex hormones. Hence, changes in human behavioral patterns may be associated with prenatal exposure to estrogenic substances such as diethylstilbestrol (DES). This paper reviews relevant studies from a series of laboratories and finds that no clear-cut differences can be demonstrated to date between unexposed and DES-exposed women in gender-related behavior, although the physical and psychological impact of the problems associated with exposure to DES are well documented. If both prenatal and postnatal influences such as social, economic, and environmental factors are taken into consideration, individual variation is more apparent than differences in gender-related behavior between unexposed and DES-exposed women. In summary, gender-related behavior is determined by a complex array of interacting factors, and prenatal influences are only one of many developmental events.

"Sexual Orientation and Adolescents".
American Academy of Pediatrics Clinical Report. 2007
"Sexual orientation probably is not determined by any one factor but by a combination of genetic, hormonal, and environmental influences"

"Genetic and Environmental Effects on Same-sex Sexual Behaviour:
*A Population Study of Twins in Sweden". Archives of Sexual Behavior (Archives of Sexual Behavior) **39** (1): 75–80*
Långström, Niklas; Qazi Rahman, Eva Carlström, Paul Lichtenstein. (2008).

Fetal exposure to prescription drugs and adult sexual orientation

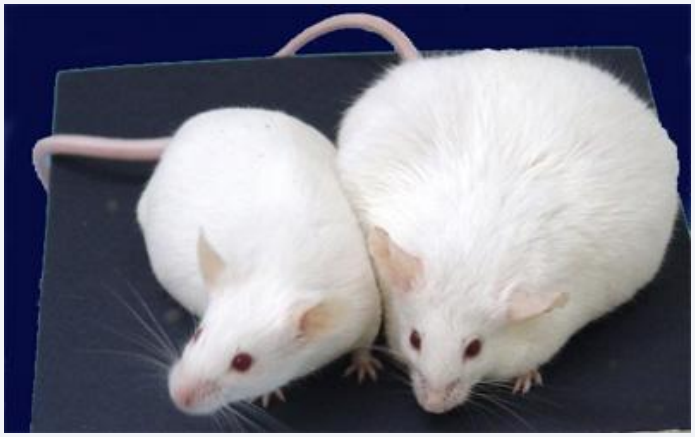
LEE ELLIS & JILL HELLBERG / Personality and Individual Differences v.38, i.1, 1jan2005
Division of Social Science, Minot State University, 500 University Avenue, Minot, ND 58707, USA
Received 7 July 2003; Revised 1 March 2004; accepted 10 April 2004. Available online 9 June 2004.

Abstract

This study was undertaken to determine if prenatal exposure to therapeutic drugs contributes to variations in sexual orientation. Especially suspect were drugs that could affect the delicate balance of sex hormone levels that appear to guide the sexual differentiation of the fetal brain. The recollections of 5102 mothers concerning their use of therapeutic drugs during pregnancy were linked to reports of the sexual orientation of their offspring (as provided by either the offspring themselves or by their mothers). About 14% of the mothers recalled having taken at least one of 19 prescription drugs (or classes of drugs) during their pregnancy. Regarding male offspring, little evidence was found that prenatal exposure to any of these medications was associated with variations in sexual orientation. However, even after controlling for age, education, and self-rated recall ability of the mothers, exposure to two types of drugs was significantly related to sexual orientation among female offspring. One type consisted of amphetamine-based diet pills and the other was comprised of synthetic thyroid medications. A month-by-month analysis **revealed that during the first trimester consumption of all prescription drugs was unusually high for mothers of female homosexual offspring**. Prescription medications that affect the mother's and/or the female fetuses' developing immune system may alter the feminization/demasculinization of the brain in ways that cause variations in the offspring's adult sexual orientation.

Low doses, big effects: Scientists seek 'fundamental changes' in testing, regulation of hormone-like chemicals

Small doses can have big health effects. That is a main finding of a new report, three years in the making, published Wednesday by a team of 12 scientists who study hormone-altering chemicals. Dozens of substances that can mimic or block hormones are found in the environment, the food supply and consumer products, including plastics, pesticides and cosmetics. One of the biggest controversies is whether the tiny doses that most people are exposed to are harmful. Researchers led by Tufts University's Laura Vandenberg concluded after examining hundreds of studies that health effects "are remarkably common" when people or animals are exposed to low doses. "Fundamental changes in chemical testing are needed to protect human health," they wrote.



Retha Newbold

At a small dose of 1 part per billion, an estrogenic drug called DES causes obesity. But at 1,000 ppb it causes weight loss. The drug was given to pregnant women in the 1940s through 1970 to prevent miscarriage, and it caused cancer and other health effects in their offspring

Environ Health Perspect

Exposure to phthalates and phenols during pregnancy and offspring size at birth.

Bisfenol A verhoogt geboortegewicht bij baby's.

Een studie van de Inserm toont aan dat 96% van de zwangere vrouwen in Bretagne en de streken van Nancy en Poitiers besmet is met ftalaten en fenolen en dat er een omgekeerd verband bestaat tussen 2,5-DCP en een rechtstreeks verband tussen BP3 en het gewicht van mannelijke pasgeborenen. Die stoffen gaan immers doorheen de placentabarrière.

Abstract

Sept 2011

Claire Philippat, Marion Mortamais, Cécile Chevrier, Claire Petit, Antonia M. Calafat, Xiaoyun Ye, Manori J. Silva, Christian Brambilla, Isabelle Pin, Marie-Aline Charles, Sylvaine Cordier, Rémy Slama

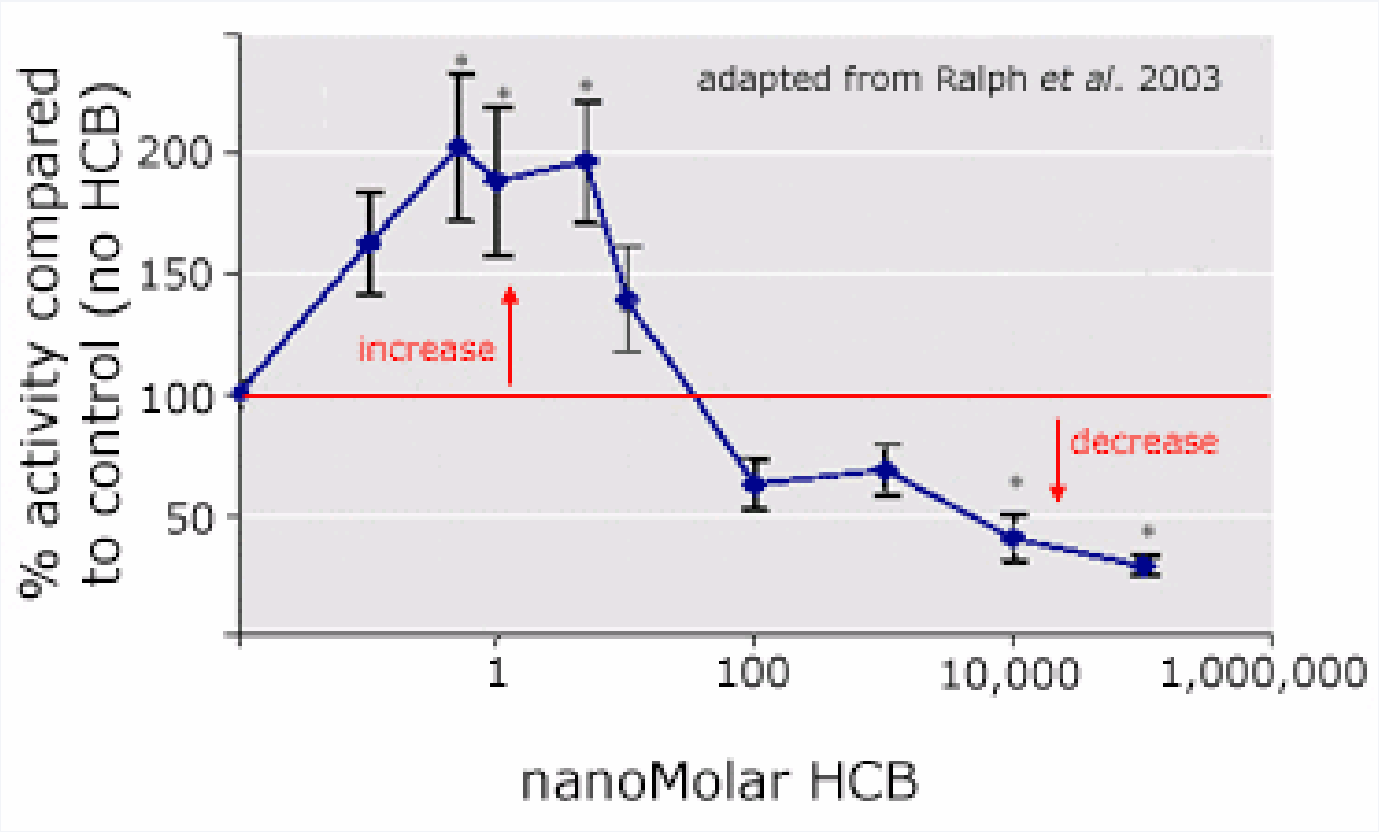
Background: Data concerning the effects of prenatal exposures to phthalates and phenols on fetal growth are limited in humans. Previous findings suggest possible effects of some phenols on male birthweight.

Objectives: Our aim was to assess the relationships between prenatal exposures to phthalates and phenols and fetal growth among male newborns.

Methods: We conducted a case-control study on male malformations of the genitalia nested in two French mother-child cohorts with recruitment between 2002 and 2006. We measured, in maternal urinary samples collected between 6 and 30 gestational weeks, the concentrations (µg/l) of 9 phenol (n=191 pregnant women) and 11 phthalate metabolites (n=287). Weight, length and head circumference at birth were collected from maternity records. Statistical analyses were corrected for the over-sampling of malformation cases.

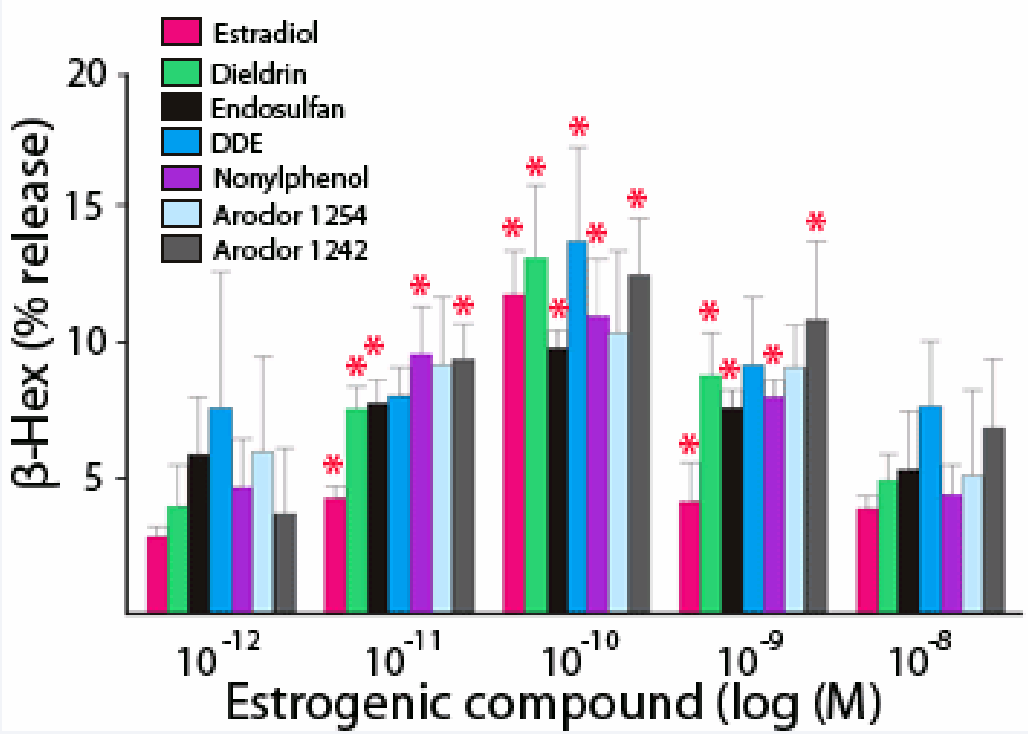
Results: Adjusted birthweight decreased by 77 g (95% confidence interval (CI), -129; -25) and by 49 g (95% CI, -86; -13) in association with a 1-unit increase ln-transformed 2,4-dichlorophenol (DCP) and 2,5-DCP urinary concentrations, respectively. Benzophenone-3 (BP3) ln-transformed concentrations were positively associated with weight (+ 26 g, 95% CI, -2; 54) and head circumference at birth (+ 0.1 cm, 95% CI, 0.0; 0.2). Head circumference increased by 0.3 cm (95% CI, 0.0; 0.7) in association with a 1-unit increase in ln-transformed BPA concentration. For phthalate metabolites there was no evidence of monotonic associations with birthweight.

Conclusions: Consistent with findings of a previous study, we observed evidence of an inverse association of 2,5-DCP and a positive association of BP3 with male birthweight.



At doses far beneath the current EPA safe level, Takano *et al*. found that the phthalate DEHP increases the immune response of mice to a common allergen. Clinical scores of an allergic reaction were strongest at intermediate doses(4 and 20 µg). A dose of 100 µg (yellow line) was no different than the control (purplish blue line).

Narita *et al*. report that a key step in immune reactions, the release of histamine and cytokines by mast cells, is exacerbated by very low levels of environmental contaminants, similar to the effect of estradiol. These experiments, done in cell culture, used levels of the contaminants well within the range of human exposure. The peak response was seen at approximately 0.1 parts per billion (10-10 molar). By the time the dose rose to 10 parts per billion (10-8 molar), the response disappeared. This experiment was done with mouse and human cells in culture.



Bioaccumulatie

Welshons, WV, KA Thayer, BM Judy, JA Taylor, EM Curran and FS vom Saal. 2003.

Large effects from small exposures. I. Mechanisms for endocrine disrupting chemicals with estrogenic activity.

Environmental Health Perspectives 111:994-1006.

Wozniak, AL, NN Bulayeva and CS Watson. 2005.

Xenoestrogens at Picomolar to Nanomolar Concentrations Trigger Membrane Estrogen Receptor-alpha-Mediated Ca++ Fluxes and Prolactin Release in GH3/B6.

Pituitary Tumor Cells. Environmental Health Perspectives 113:431-439.

Serum dioxin-like activity is associated with reproductive parameters in young men from the general flemish population

*Willem Dhooge,1 Nicolas van Larebeke,2 Gudrun Koppen,3 Vera Nelen,4 Greet Schoeters,3 Robert Vlietinck,5 Jean-Marc Kaufman,1 and Frank Comhaire,1 for the Flemish Environment and Health Study Group**

1Department of Endocrinology, University Hospital Ghent, Belgium; 2Study Centre for Carcinogenesis and Primary Prevention of Cancer, Department of Radiotherapy, Nuclear Medicine and Experimental Cancerology, University Hospital Ghent, Belgium; 3Flemish Institute of Technological Research (VITO), Centre of Expertise in Environmental Toxicology, Mol, Belgium; 4Provincial Institute for Hygiene, Antwerp, Belgium; 5Department of Human Heredity, Catholic University of Leuven, Leuven, Belgium

BACKGROUND: 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and some related environmental contaminants are aryl hydrocarbon receptor (AhR) ligands that exert reproductive and developmental toxicity in laboratory animals. In humans, fertility-related effects are less documented.

OBJECTIVE: The aim of this study was to investigate the relationship between dioxin-like biological activity in serum and parameters of reproductive status in men from the general population 5 months after a polychlorinated biphenyl and dioxin food-contamination episode in Belgium.

DESIGN: In the framework of the cross-sectional Flemish Environment and Health Study (FLEHS), we recruited 101 men 20–40 years of age and evaluated sperm parameters, measured sex hormones, and gathered information on a number of lifestyle factors. In addition, we determined the AhR-mediated

enzymatic response elicited by individual serum samples and expressed it as TCDD equivalent concentrations (CALUX-TEQs) using an established transactivation assay.

RESULTS: Age ($p = 0.04$) and the frequency of fish ($p = 0.02$) and egg ($p = 0.001$) consumption were independent positive determinants of serum dioxin-like activity. After correcting for possible confounders, we found that a 2-fold increase in CALUX-TEQ > 16 pg/L was associated with a 7.1% and 6.8% (both $p = 0.04$) decrease in total and free testosterone, respectively. We also observed a more pronounced drop in semen volume of 16.0% ($p = 0.03$), whereas sperm concentration rose by 25.2% ($p = 0.07$). No relationship was found with total sperm count or sperm morphology.

CONCLUSIONS: These data suggest an interaction of dioxin-like compounds with the secretory function of the seminal vesicles or prostate, possibly indirectly through an effect on testosterone secretion, at levels not affecting spermatogenesis as such.

Environ Health Perspect 114:1670–1676 (2006).

Environmental neurotoxicology

Biologic markers in immunotoxicology

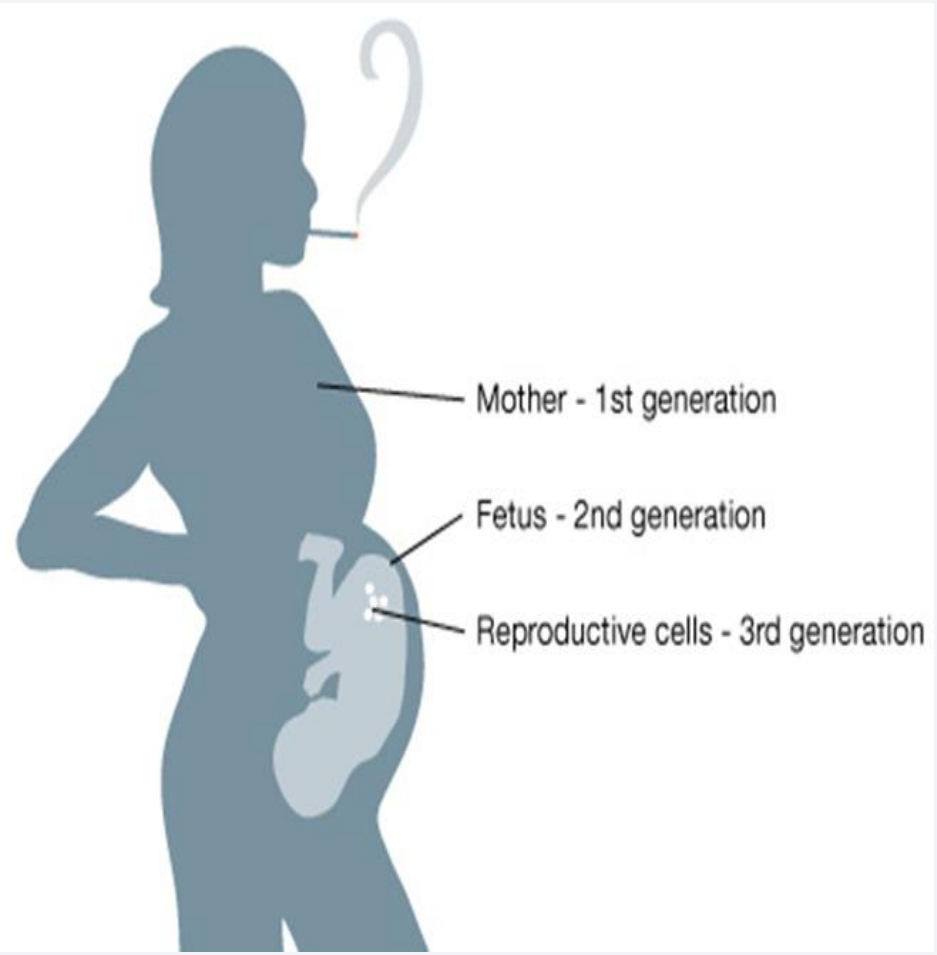
2 volumes published by National Academy of Sciences 1990

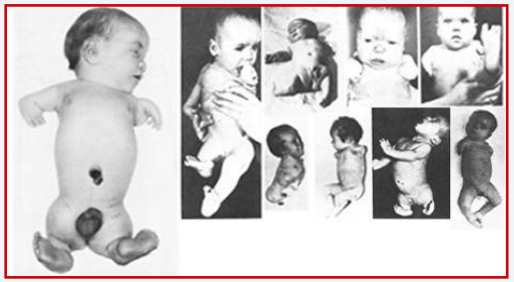
Results:

Functional changes results from low chemical exposure.

Effects multiply when an individual is exposed to more than one agent.

2 miljoen vrouwen kregen DES voorgeschreven in V.S. en Europa gedurende de periode 1948-1971 tegen dreigende miskramen.



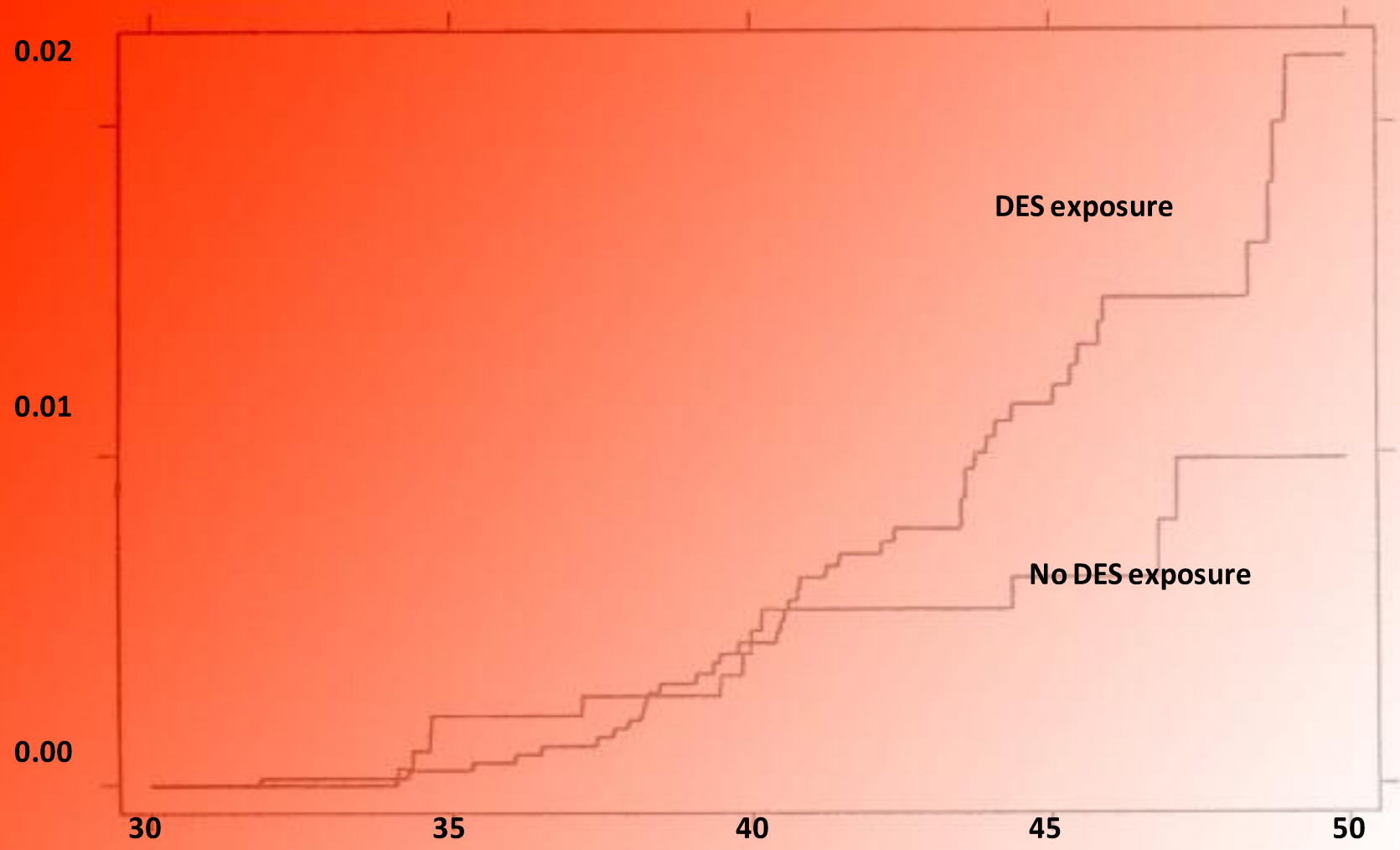


DES hormoon

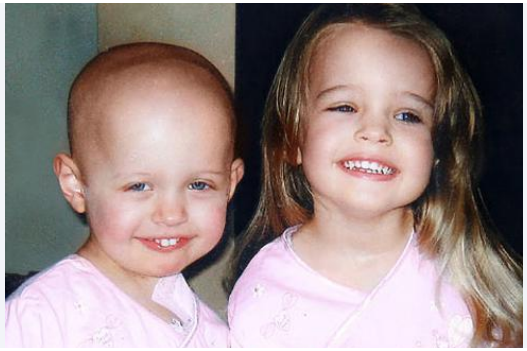
- **Malignancy**
- **Cervical dysplasia**
- **Congenital anatomic abnormalities**
- **Infertility**
- **Spontaneous abortion**
- **Other adverse effects**

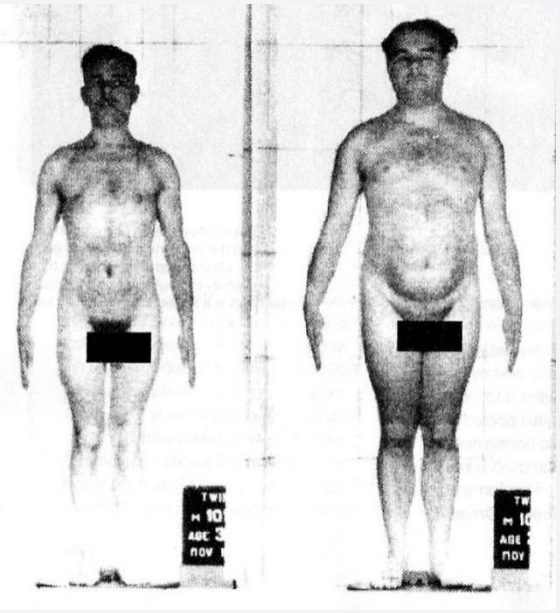
3rd generation

Cumulative hazard plots of breast cancer incidence in DES-exposed and non-exposed women under age 50



Leukemia, RA, MS in identical twins





This image is of 28-year-old identical twins, one with schizophrenia and the other well. It therefore clearly illustrates two points: (1) schizophrenia is a brain disease with measurable structural and functional abnormalities in the brain; and (2) it is not a purely genetic disease, and other biological factors play a role in its etiology.

SCHIZOPHRENIA IN IDENTICAL TWINS

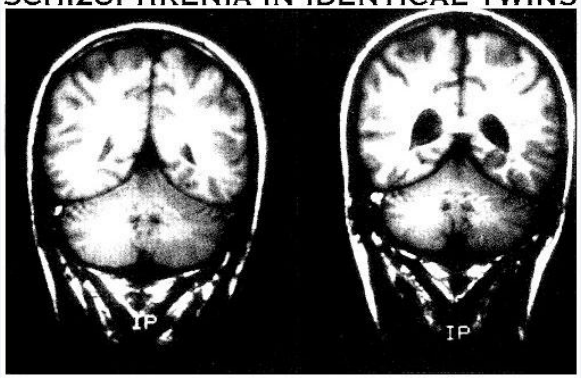
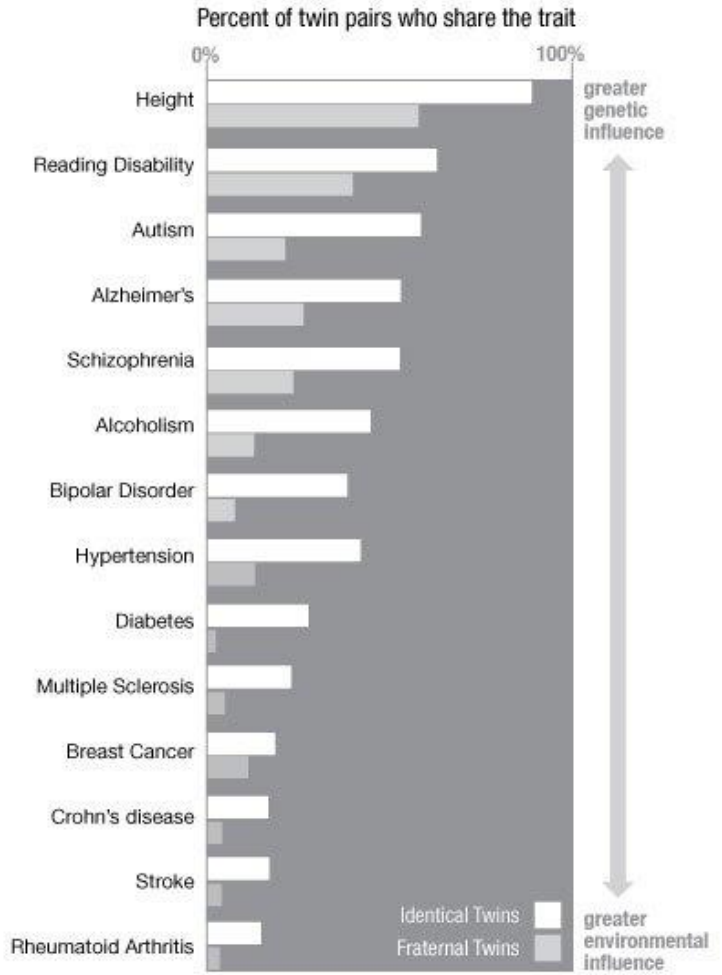
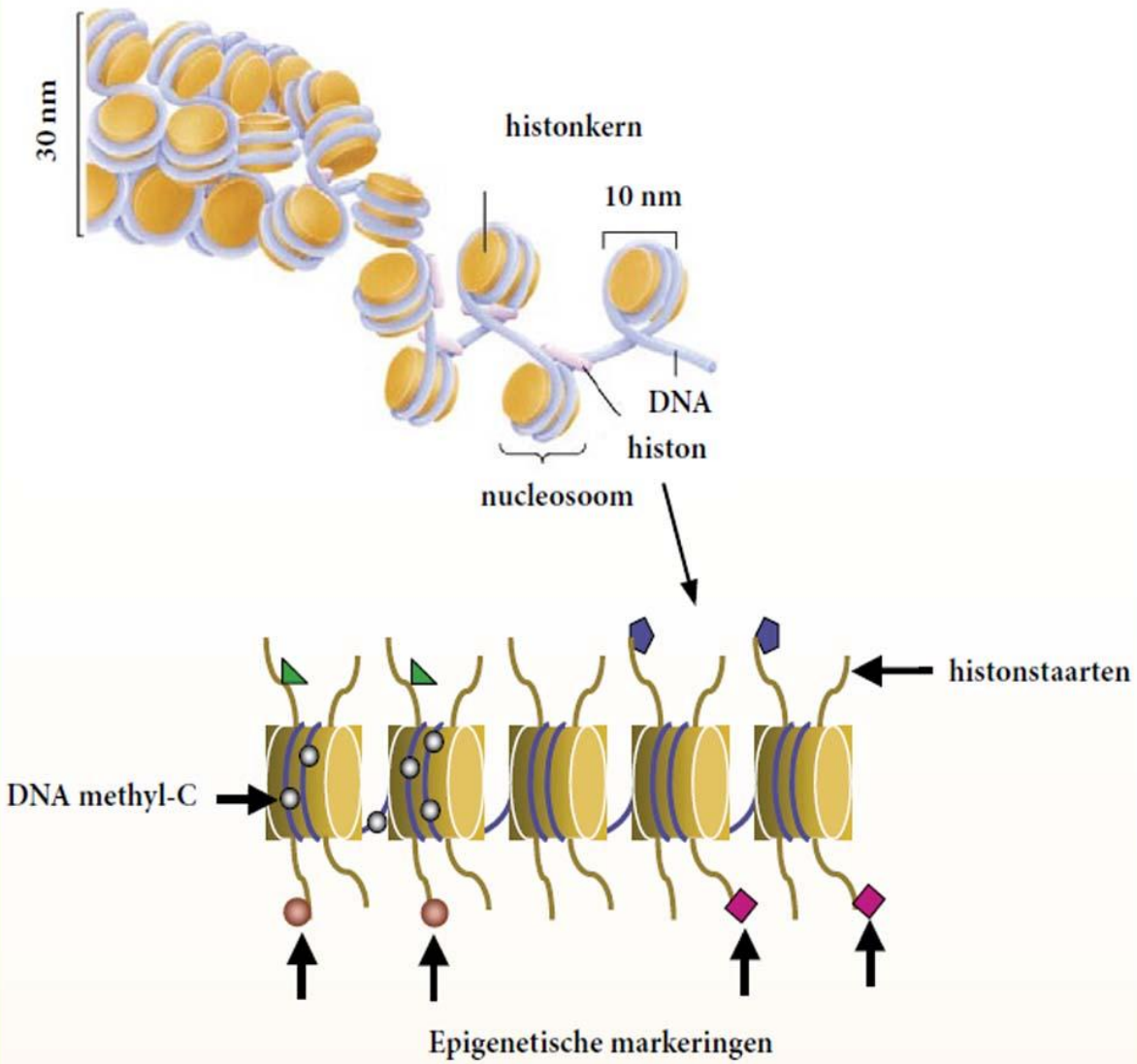


Photo courtesy of Drs. E. Fuller Torrey and Daniel Weinberger.

MRI scans of 28-year-old male identical twins showing the enlarged brain ventricles in the twin with schizophrenia (right) compared to his well brother (left).

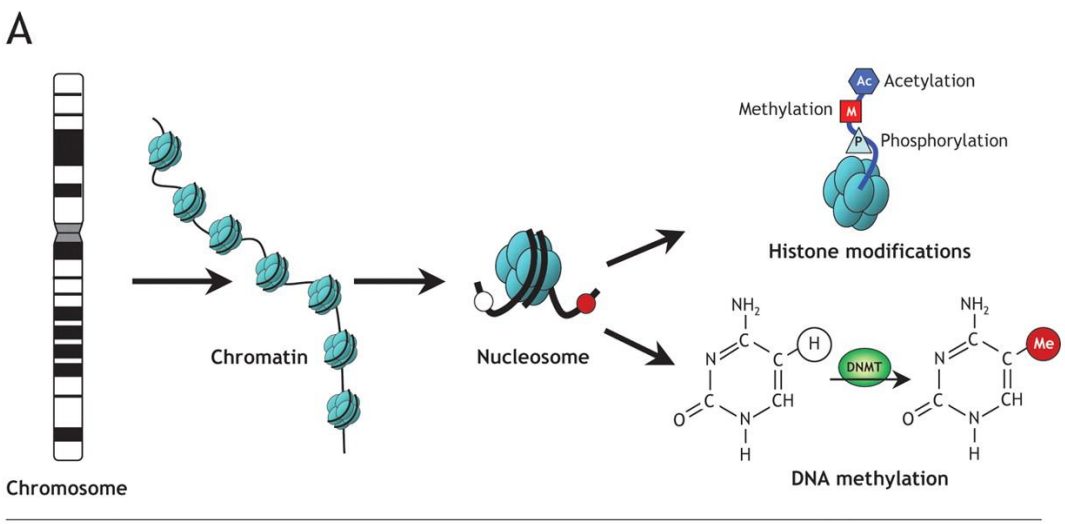


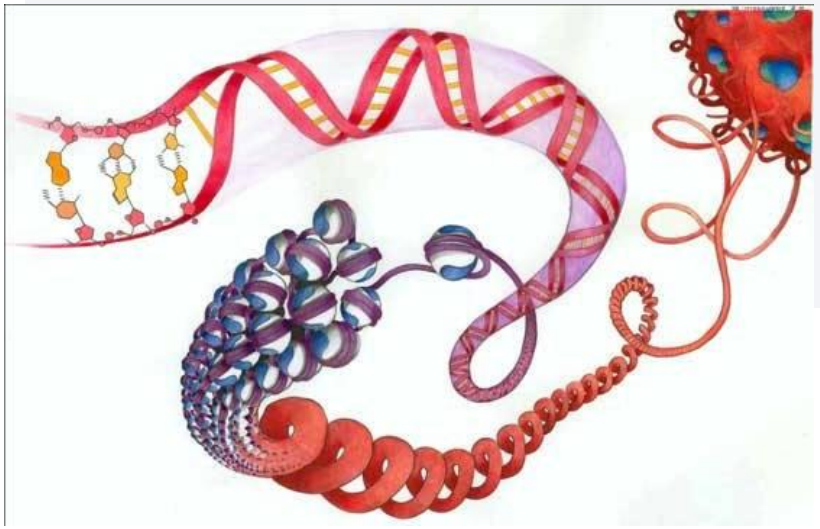
NUCLEOSOMEN EN HISTONEN

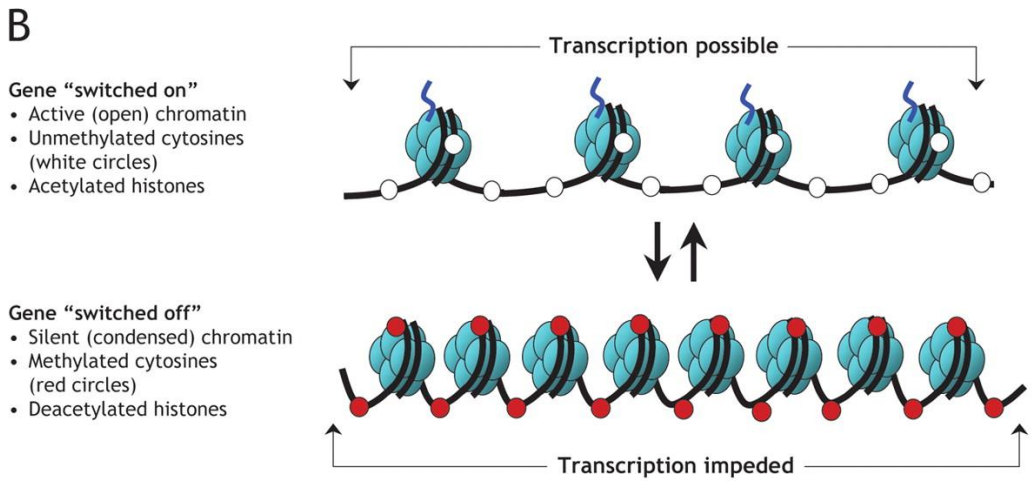


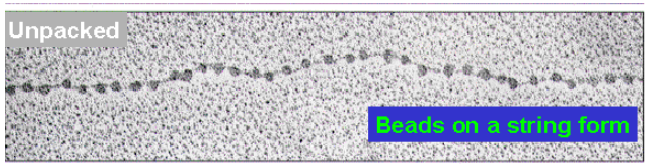
Het DNA is in de verpakte vorm (nucleosoom) niet af te lezen. Moleculen aan de staarten van histonen die uit de nucleosomen steken, bepalen of een gen wel of niet wordt afgelezen.

From genetics to epigenetics

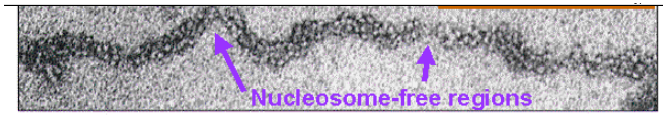




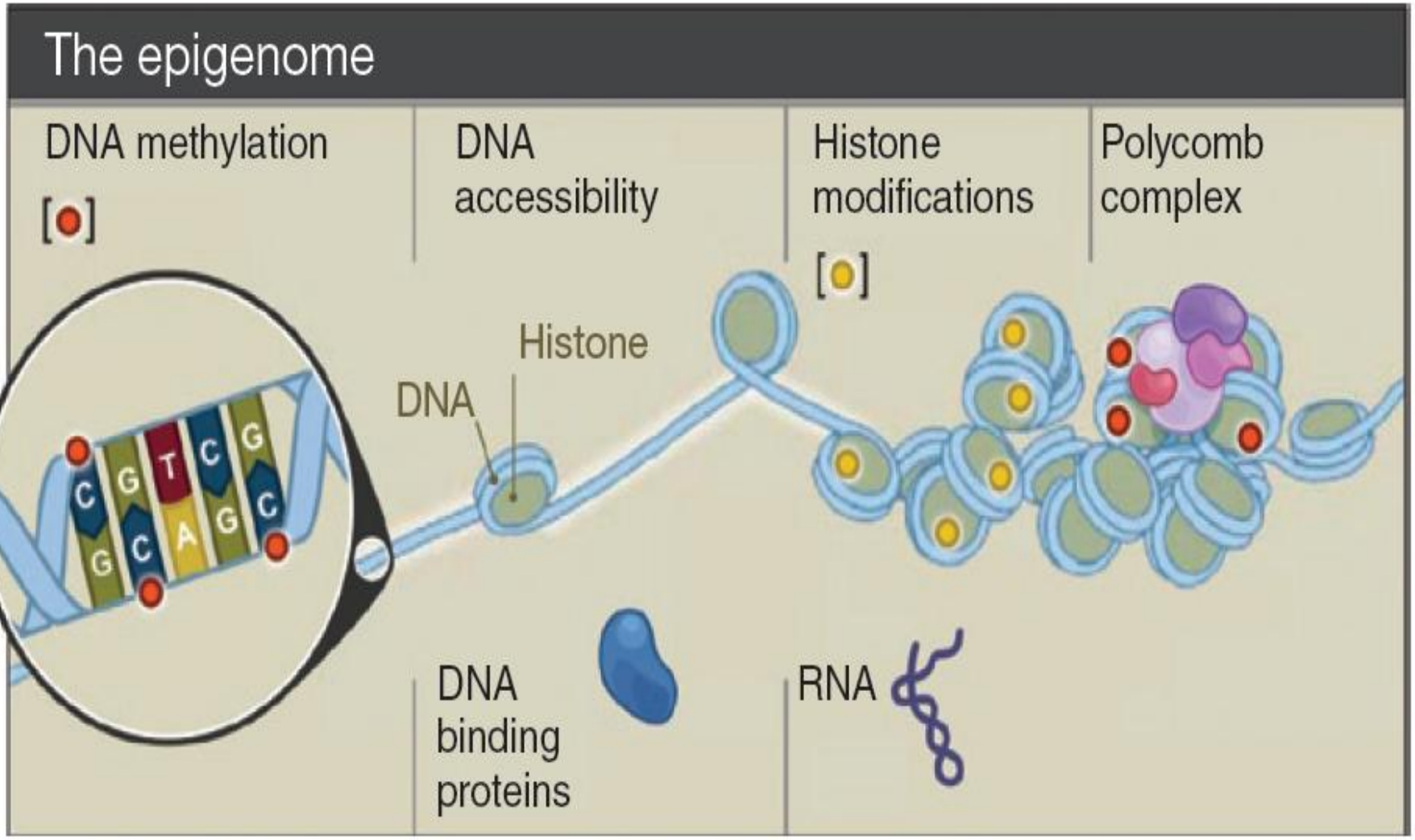




Beads on a string – active - relaxed



Solenoid fiber – inactive - silenced


The epigenome
DNA methylation
DNA accessibility
Histone modifications
Polycomb complex
Histone
DNA
DNA binding proteins
RNA
B. Wong

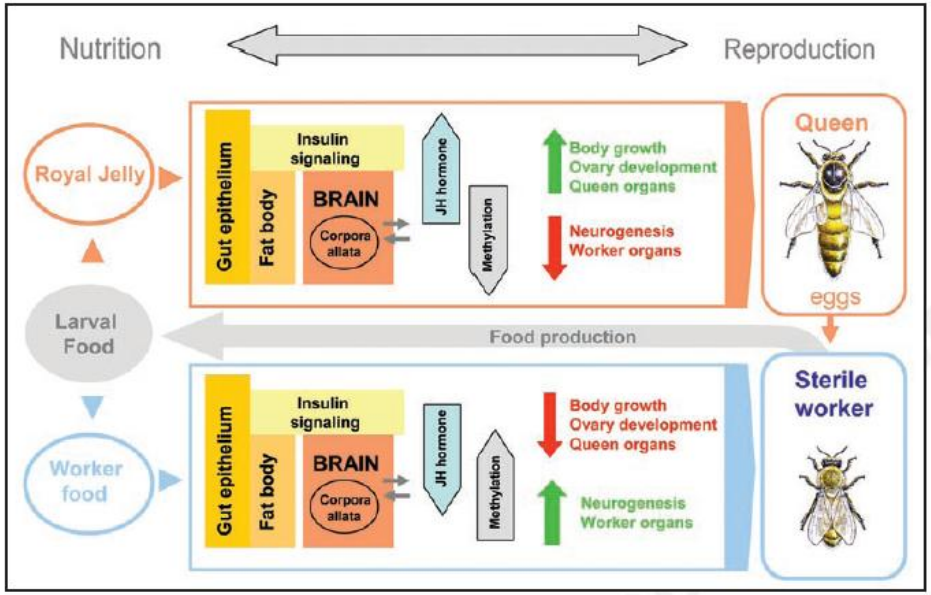
"Heritable" aspects of epigenetics

Meiotic heritance – Diet

Queen vs. Sterile worker

Point of View

Epigenetic integration of environmental and genomic signals in honey bees



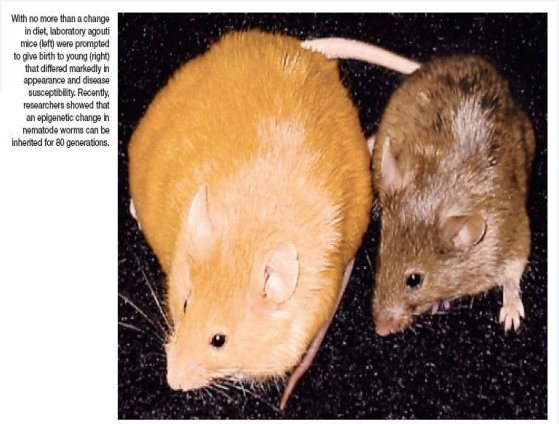
Royalactin induces queen differentiation in honeybees

478 | NATURE | VOL 473 | 26 MAY 2011

Masaki Kamakura[1]

“Heritable” aspects of epigenetics

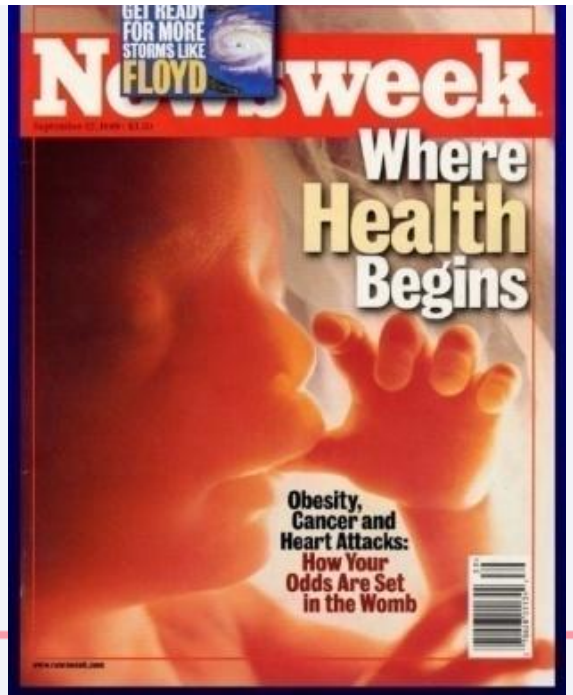
Environmental exposure


With no more than a change in diet, laboratory agouti mice (left) were prompted to give birth to young (right) that differed markedly in appearance and disease susceptibility. Recently, researchers showed that an epigenetic change in nematode worms can be inherited for 80 generations.

Agouti model: R. Waterland and R. Jirtle

Germ cells carry the epigenetic benefits of grandmother’s diet

Craig A. Cooney*
Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock, AR 72205



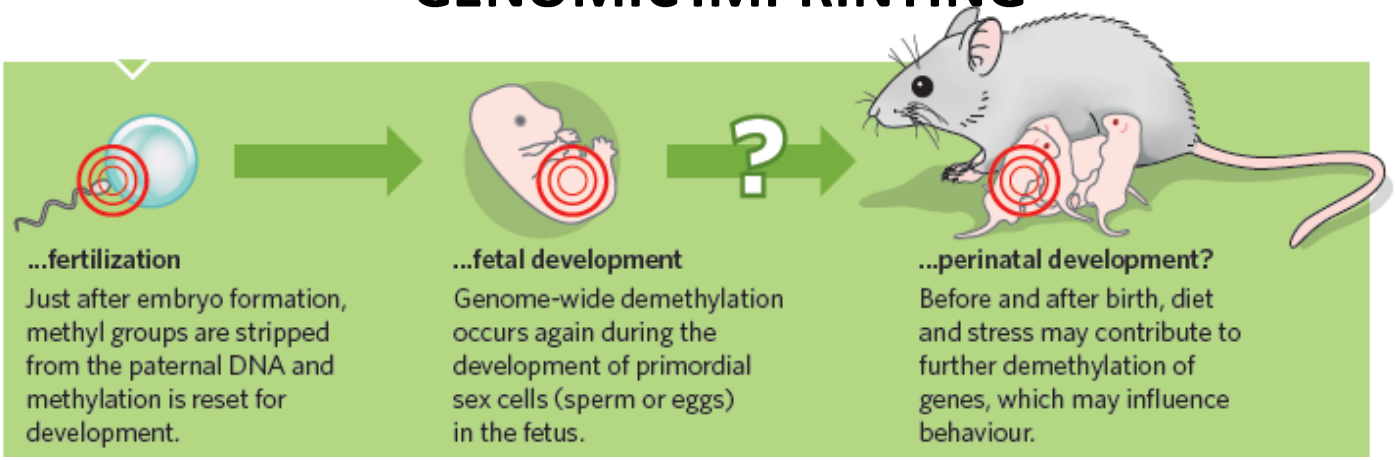
Maternal supplements with genistein, zinc, methionine, betaine, choline, folate B_{12}

Lower risk of cancer, diabetes, obesity , CVD and prolonged life

“Heritable” aspects of epigenetics

Transgenerational

GENOMIC IMPRINTING



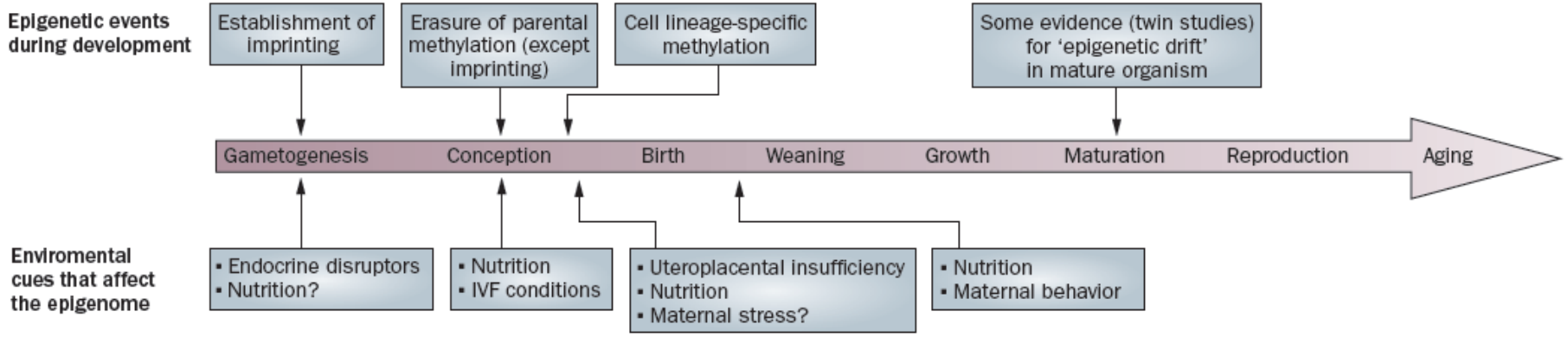
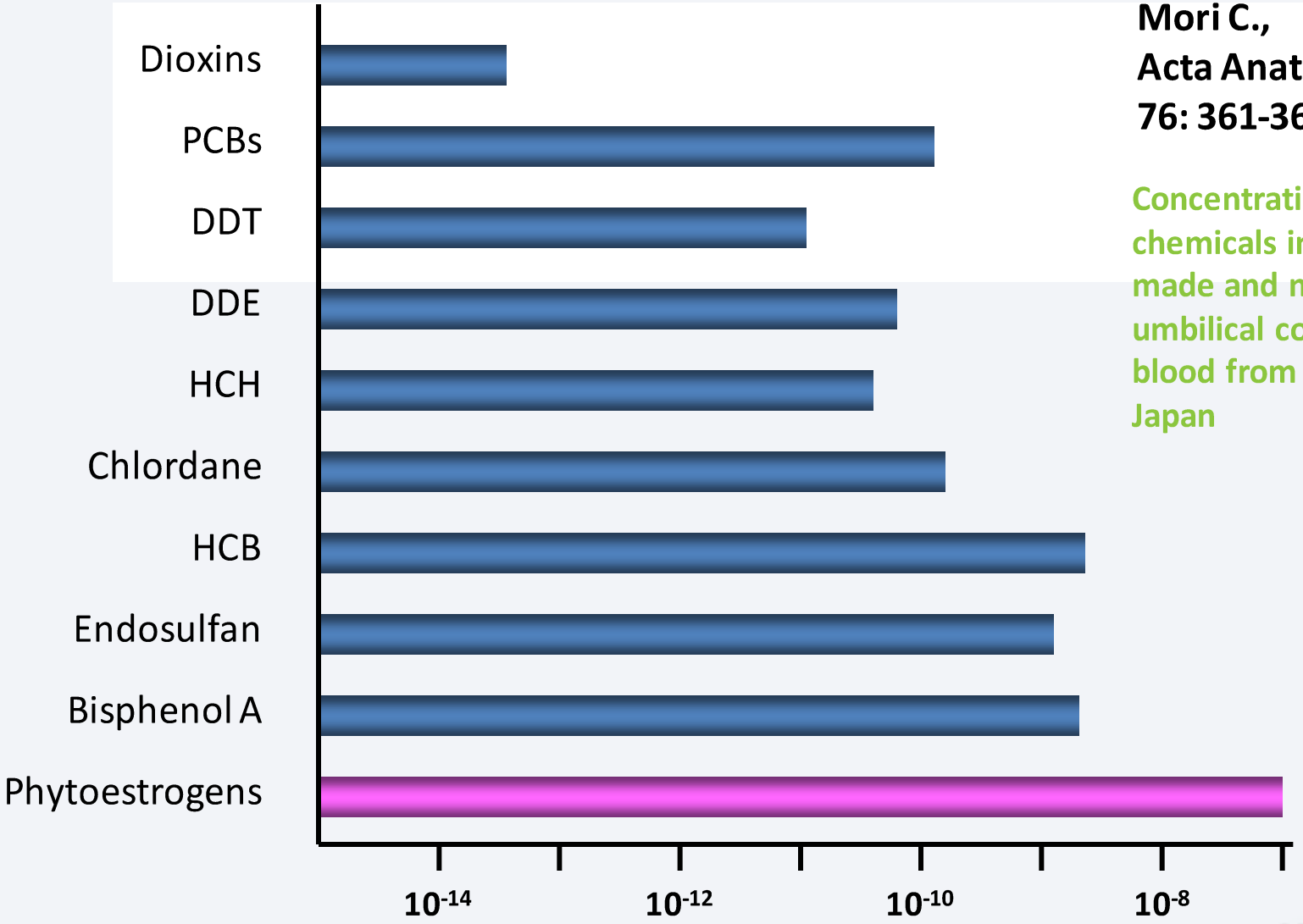


Figure 2 | Environmental sensitivity of the epigenome throughout life. The top row indicates normal reprogramming of the epigenome during gametogenesis, fertilization and development. The bottom row indicates the environmental cues that affect the epigenome and have late-life consequences, and the stages of life at which they act. Sensitivity of the epigenome to the environment (represented by shading of the arrow) is likely to decrease during life as growth slows. Abbreviation: IVF, *in vitro* fertilization.

“Heritable” aspects of epigenetics

Meiotic heritance – Environmental exposure



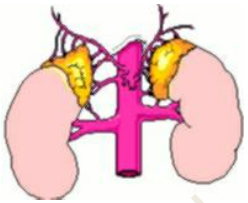
Mori C.,
Acta Anat. Nippon.
76: 361-368 (2001)

Concentration of chemicals including man-made and natural in umbilical cords/cord blood from newborns in Japan

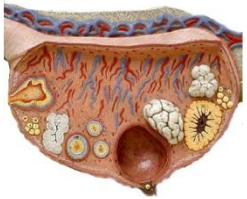
Methylatie:

- Detoxificatie lever: fase II
- Synthese van fosfatidylcholine
- Aanmaak neurotransmitters: adrenaline, acetylcholine, melatonine
- Synthese van aminozuren, omegavetzuren, creatine, fosfolipiden, carnitine
- Herstel DNA
- Regulatie van DNA-expressie (kanker)

HYPER-ESTROGENISM



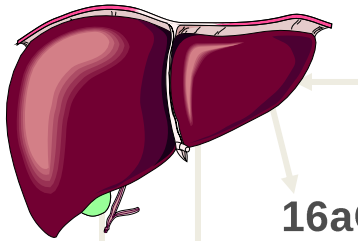
Adrenals



Ovaries

Androgens

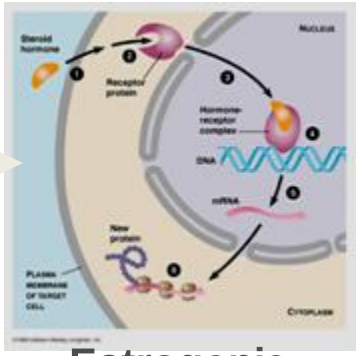
Aromatase



Estrogens

Transport

SHBG



Estrogenic Effects

16aOH-E genotoxic

4OH-E → 3,4 quinone genotoxic

oxydation

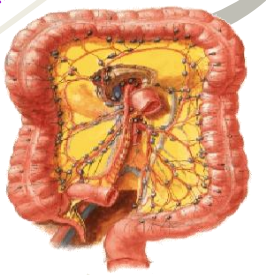
2OH-E

Methylation

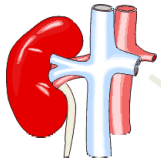
4-MethoxyE

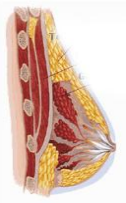
2-MethoxyE anticancer

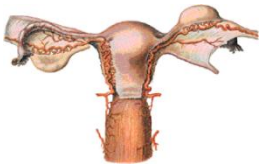
glucuronidation-sulfatation-methylation

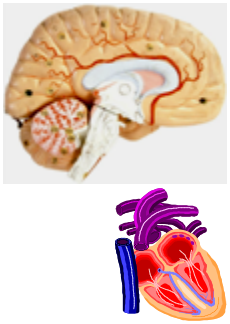


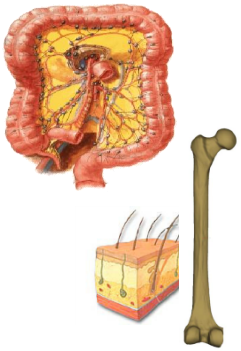
Deconjugation











Catechol quinones of estrogens in the initiation of breast, prostate, and other human cancers: keynote lecture.

Estrogens can be converted to electrophilic metabolites, particularly the catechol estrogen-3,4-quinones, estrone (estradiol)-3,4-quinone [E(1)(E(2))-3,4-Q], which react with DNA to form depurinating adducts. These adducts are released from DNA to generate apurinic sites. Error-prone repair of this damage leads to the mutations that initiate breast, prostate, and other types of cancer. The reaction of E(1)(E(2))-3,4-Q with DNA forms the depurinating adducts 4-hydroxyE(1)(E(2))-1-N3adenine [4-OHE(1)(E(2))-1-N3Ade] and 4-OHE(1)(E(2))-1-N7guanine(Gua). These two adducts constitute >99% of the total DNA adducts formed. The E(1)(E(2))-2,3-Q forms small amounts of the depurinating 2-OHE(1)(E(2))-6-N3Ade adducts. Reaction of the quinones with DNA occurs more abundantly when estrogen metabolism is unbalanced. Such an imbalance is the result of overexpression of estrogen-activating enzymes and/or deficient expression of deactivating (protective) enzymes. Excessive formation of E(1)(E(2))-3,4-Q is the result of this imbalance. Oxidation of catechols to semiquinones and quinones is a mechanism of tumor initiation not only for endogenous estrogens, but also for synthetic estrogens such as hexestrol and diethylstilbestrol, a human carcinogen. This mechanism is also involved in the initiation of leukemia by benzene, rat olfactory tumors by naphthalene, and neurodegenerative diseases such as Parkinson's disease by dopamine. In fact, dopamine quinone reacts with DNA similarly to the E(1)(E(2))-3,4-Q, forming analogous depurinating N3Ade and N7Gua adducts. The depurinating adducts that migrate from cells and can be found in body fluids can also serve as biomarkers of cancer risk. In fact, a higher level of estrogen-DNA adducts has been found in the urine of men with prostate cancer and in women with breast cancer compared to healthy controls. This unifying mechanism of the origin of cancer and other diseases suggests preventive strategies based on the level of depurinating DNA adducts that generate the first critical step in the initiation of diseases.

Ann N Y Acad Sci. 2006 Nov;1089:286-301

Proc. Natl. Acad. Sci. USA

Vol. 94, pp. 10937–10942, September 1997

Medical Sciences

Epigenetic information levels

DNA methylation & chromatin silencing in cancer

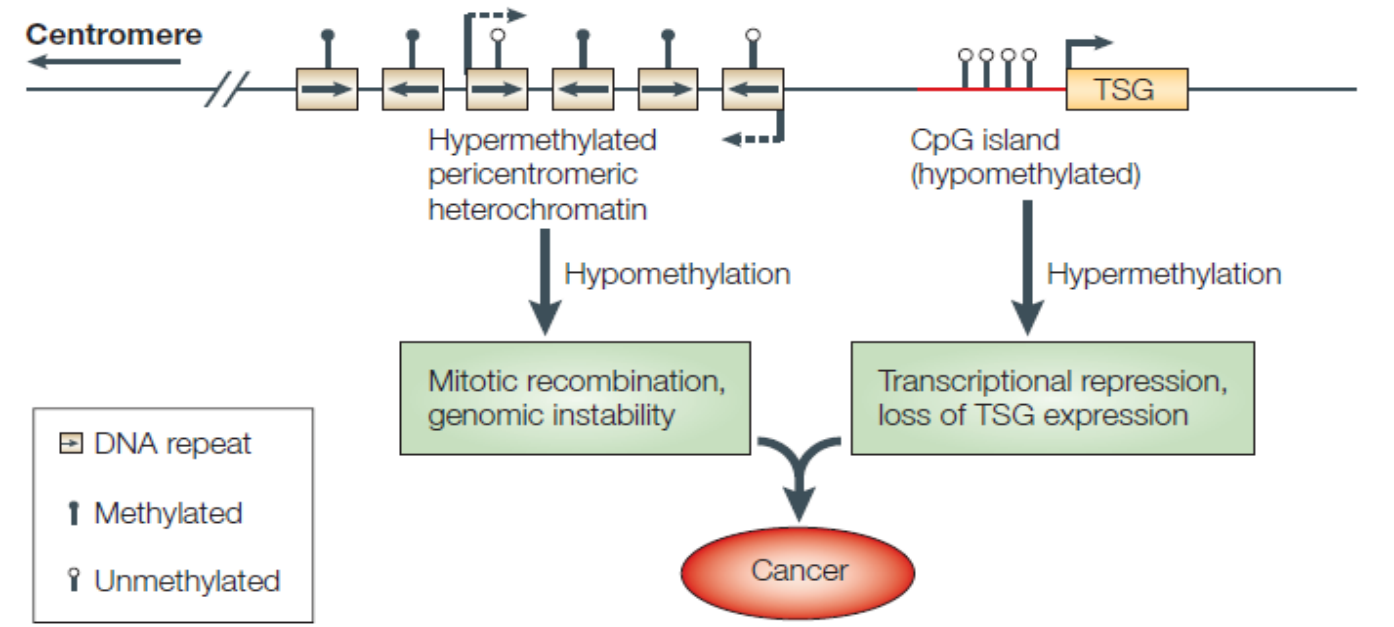


Figure 1 | **DNA methylation and cancer.** The diagram shows a representative region of genomic DNA in a normal cell. The region shown contains repeat-rich, hypermethylated pericentromeric heterochromatin and an actively transcribed tumour suppressor gene (TSG) associated with a hypomethylated CpG island (indicated in red). In tumour cells, repeat-rich heterochromatin becomes hypomethylated and this contributes to genomic instability, a hallmark of tumour cells, through increased mitotic recombination events. *De novo* methylation of CpG islands also occurs in cancer cells, and can result in the transcriptional silencing of growth-regulatory genes. These changes in methylation are early events in tumorigenesis.

Biology of Sex Differences 2012

Oral contraceptives modify DNA methylation and monocyte-derived macrophage function

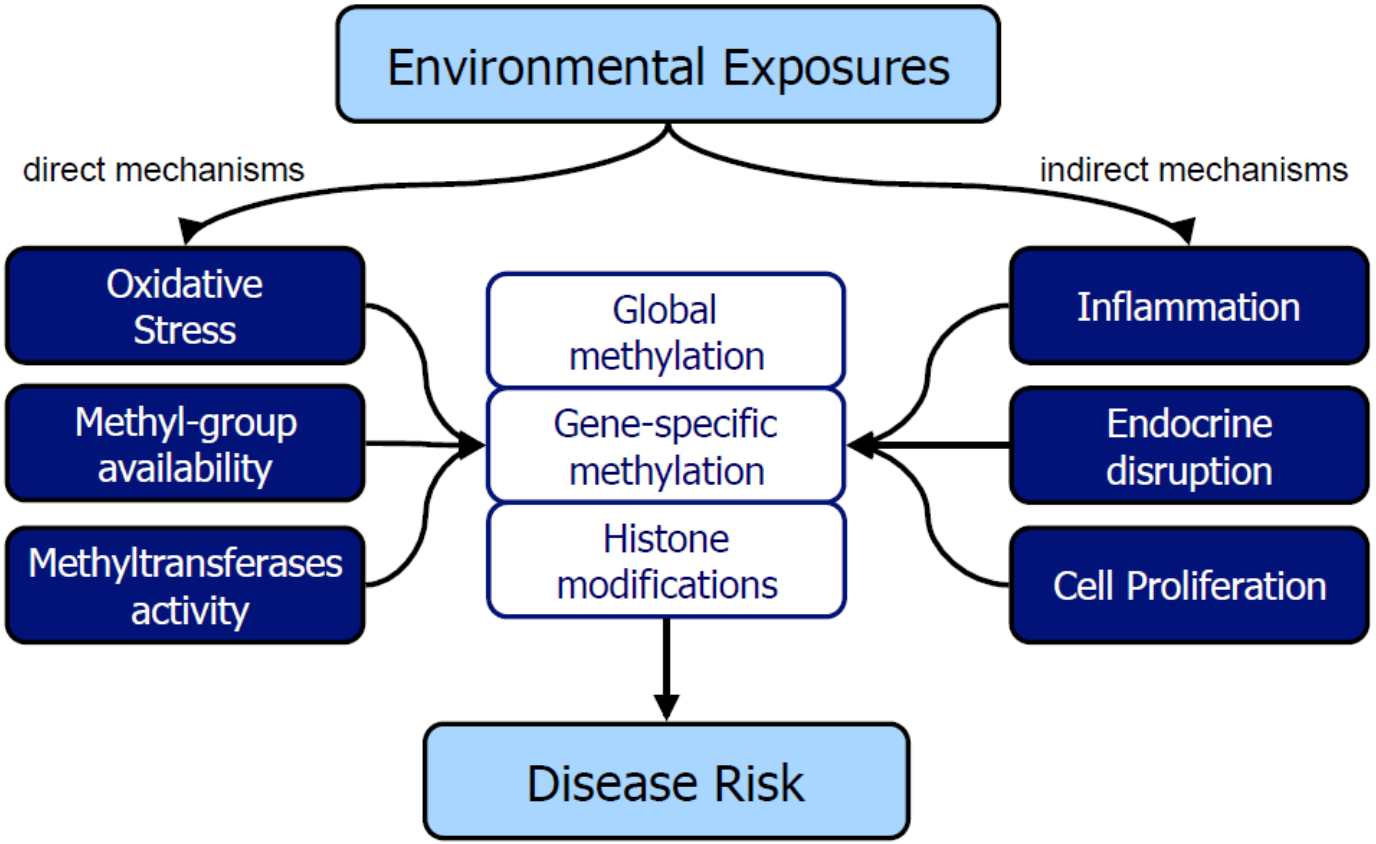
Ilaria Campesi et al.

Conclusions:

OC use induced many changes in hematological and plasmatic markers, modifying hormonal levels, endothelial function, inflammation index and some redox state parameters, producing a perturbation of the internal milieu that impacted macrophagic function.

In fact, different levels of estrogen receptor expression and release of TNFa were observed in macrophages derived from OC users. Some of the above activities were linked to the androgenic properties of progestin. Even though it is not known whether these effects are reversible, the results indicate that to avoid potential skewing of results only a single type of OC should be used during a single clinical trial.

A Conceptual Model for Environmental Epigenetics



Adapted from Baccarelli & Bollati, Curr Opin Pediatr 2009

"Heritable" aspects of epigenetics

Meiotic heritance – Mental health

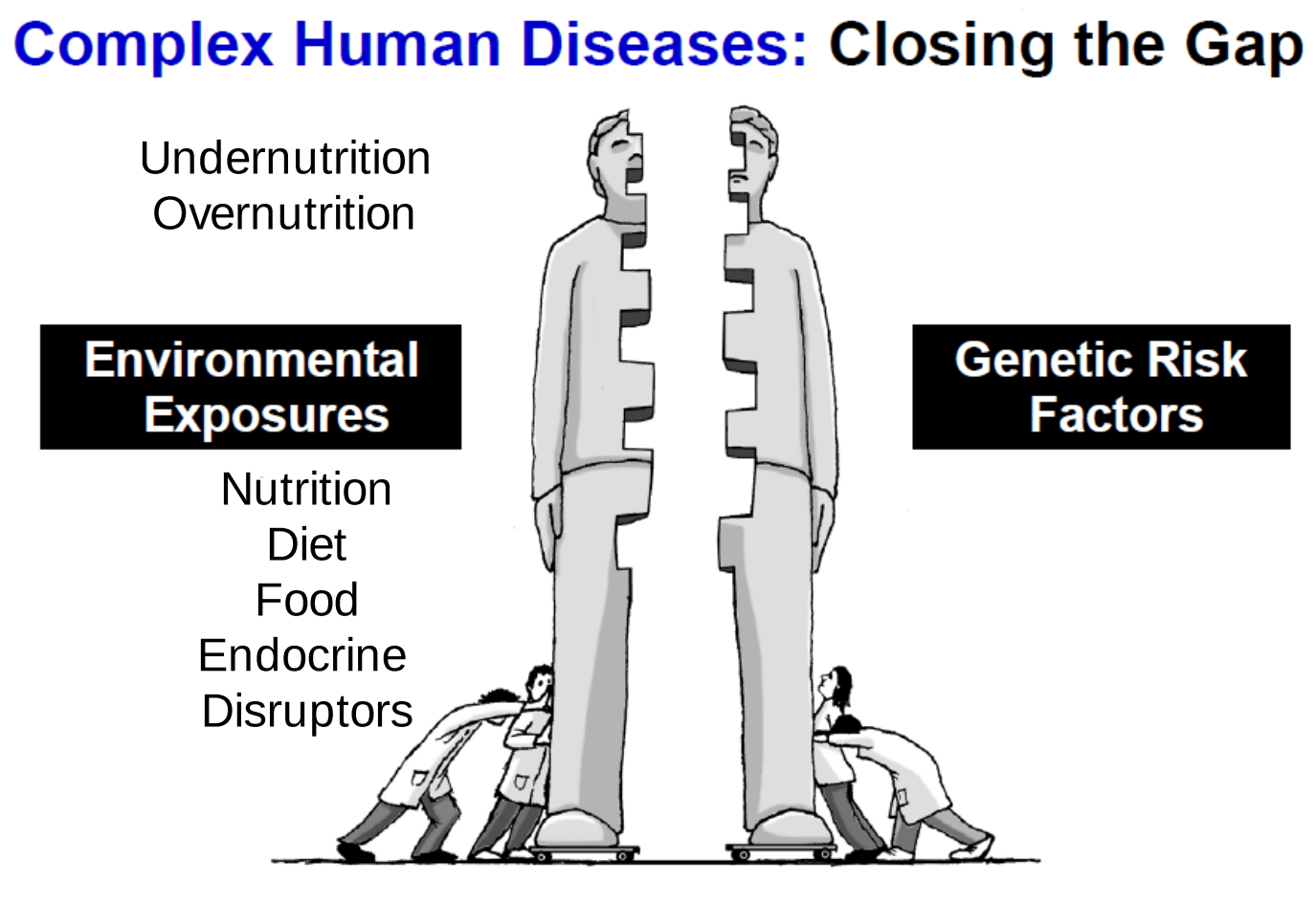
Cognition, memory & neuroplasticity

Epigenetic Mechanisms : Critical Contributors to Long-Term Memory Formation
Farah D. Lubin, Swati Gupta, R. Ryley Parrish, Nicola M. Grissom and Robin L. Davis
Neuroscientist 2011 17: 616
DOI: 10.1177/1073858411386967

Table 2. Examples of studies in which the regulation of chromatin remodeling enzymes has been observed with neurological disorders

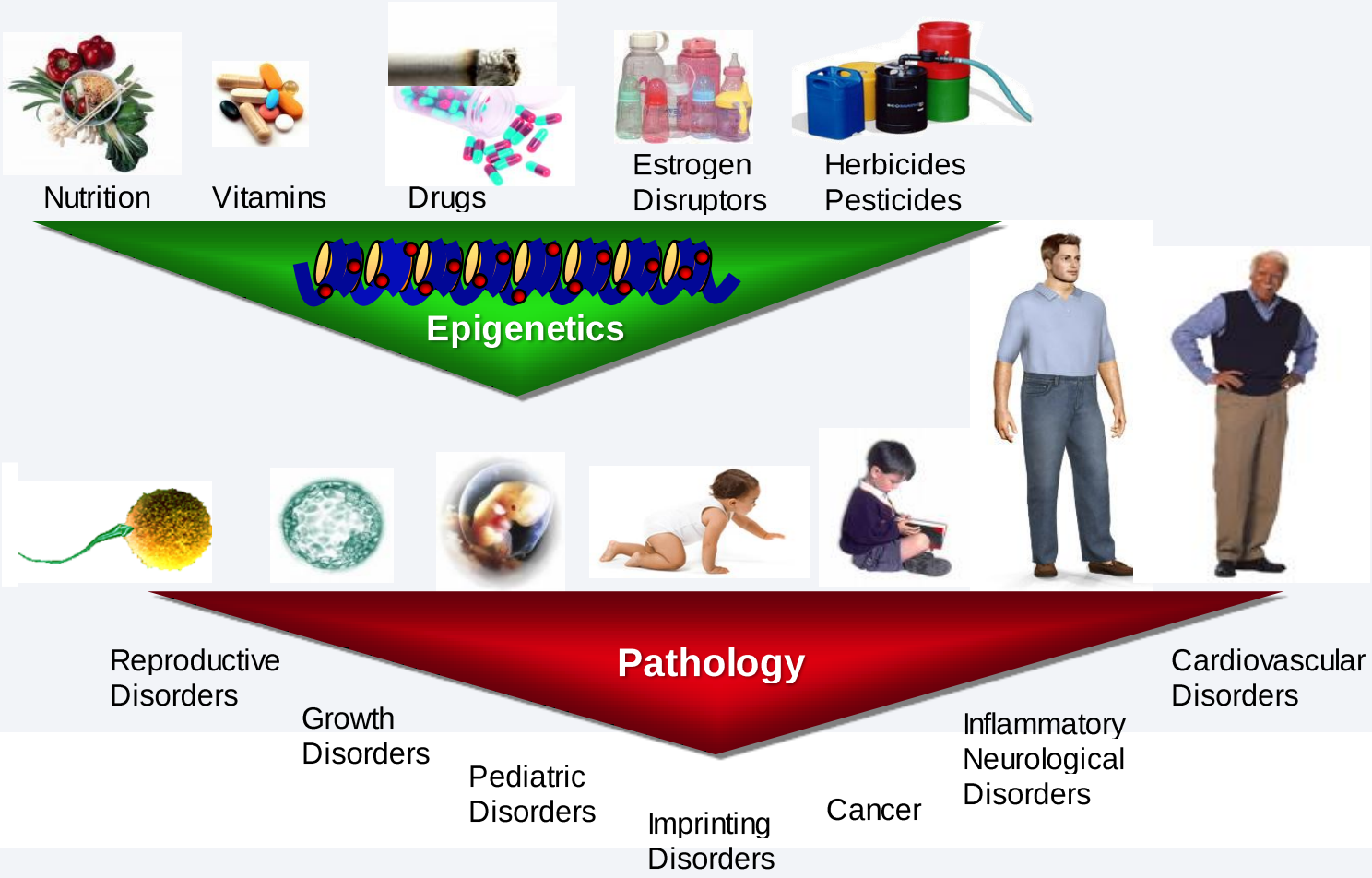
Associated Disorder	Epigenetic Modification	Associated Gene	HDI/DNA Demethylating Agents	References
Alzheimer disease	Histone acetylation ↓ DNA methylation ↑	NEP APP	Sodium 4-phenylbutyrate 5-Azadeoxycytidine?	Chen and others 2009; Ricobaraza and others 2009; Tohgi and others 1999
Anxiety	Histone acetylation ↓ DNA methylation ↑	GR NGFI-A	Trichostatin-A L-methionine	Lupien and others 2009; Weaver and others 2006
Autism	Histone acetylation ↓	*Reelin* *MeCP2*	Valproic acid Trichostatin-A	Hendriksen and others 2001
Depression	Histone acetylation ↓	BDNF	Sodium butyrate	Schroeder and others 2007; Tsankova and others 2006
Epilepsy	Histone acetylation ↓	BDNF GluR2; GRIA2	Valproic acid	Hsieh and others 2004; Huang and others 2002; Jessberger and others 2007
Fragile X syndrome	DNA methylation ↑	FMR1	5-Azadeoxycytidine	Chiurazzi and others 1998; Chiurazzi and others 1999
Schizophrenia	DNA methylation ↑ Histone acetylation ↓	*Reelin* *GAD1*	5-Azadeoxycytidine? Zebularine	Chen and others 2002; Huang and Akbarian 2007; Huang and others 2007; Roth and others 2009
Substance abuse	Histone acetylation ↓	c-Fos BDNF Cdk5	Sodium sutyrate	Kumar and others 2005; Pandey and others 2008

From genetics to epigenetics



“Heritable” aspects of epigenetics

Meiotic heritance – Environmental exposure



Carcinogen induced tumor model

Joseph Huang, Christoph Plass, Clarissa Gerhauser
German Cancer Research Center Heidelberg

Current Drug Targets,* 2011, *12

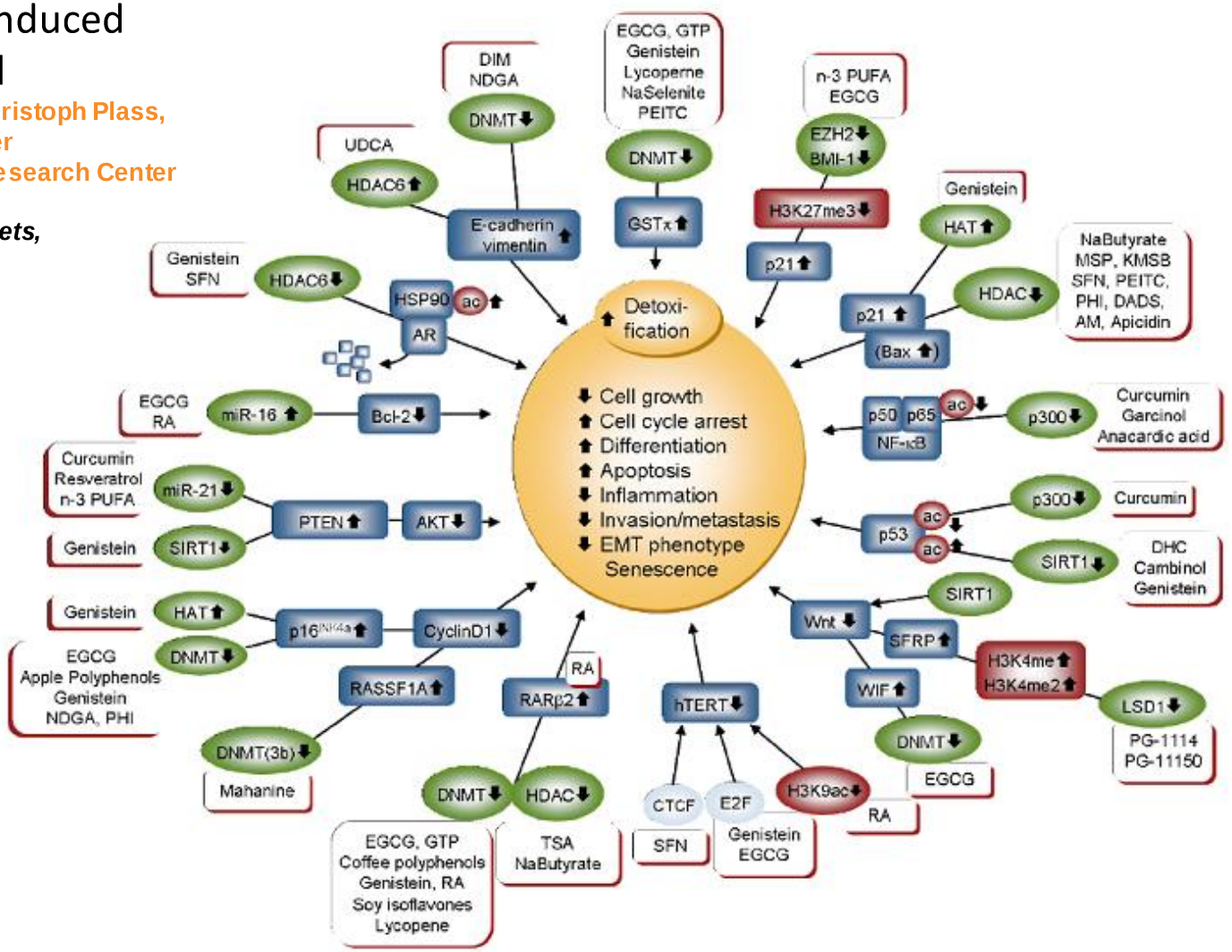


Fig. Overview of epigenetic mechanisms targeted by chemopreventive agents, and their influence on pathways and mechanisms controlling tumor growth.

Abbreviations: AM, allyl-mercaptan; BMI-1, B-cell-specific Moloney murine leukemia virus integration site 1 (histone lysine methyltransferase); DADS, diallyldisulfide; DHC, dihydrocoumarin; DIM, diindolylmethane; EGCG, epigallocatechin gallate; EZH2, enhancer of zeste 2 (histone lysine methyltransferase); GTP, green tea polyphenols; HAT, histone acetyl transferase (e.g. p300); KMSB, α-keto-γ-methylselenobutyrate; MSP, β-methylselenopyruvate; NDGA, nordihydroguaiaretic acid; PEITC, phenethyl isothiocyanate; PHI, phenhexyl isothiocyanate; n-3 PUFA, n-3 polyunsaturated fatty acids; RA, retinoic acid; SITR1, Silent information regulator 1 (NAD^+-dependent histone deacetylase class III); SFN, sulforaphane; SFRP, secreted frizzled-related protein; TSA, trichostatin A; UDCA, ursodeoxycholic acid ; WIF, Wnt-inhibitory factor.

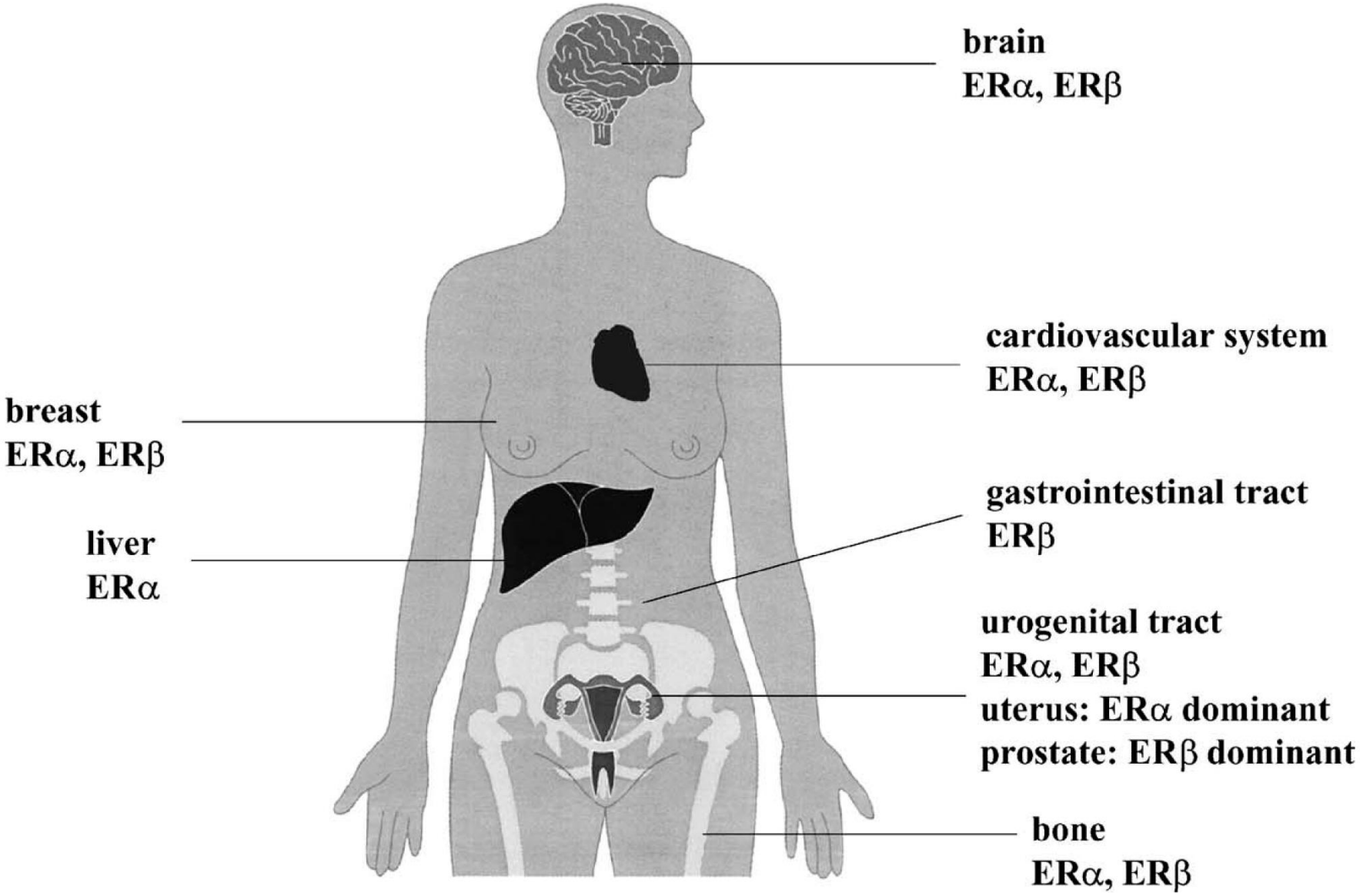


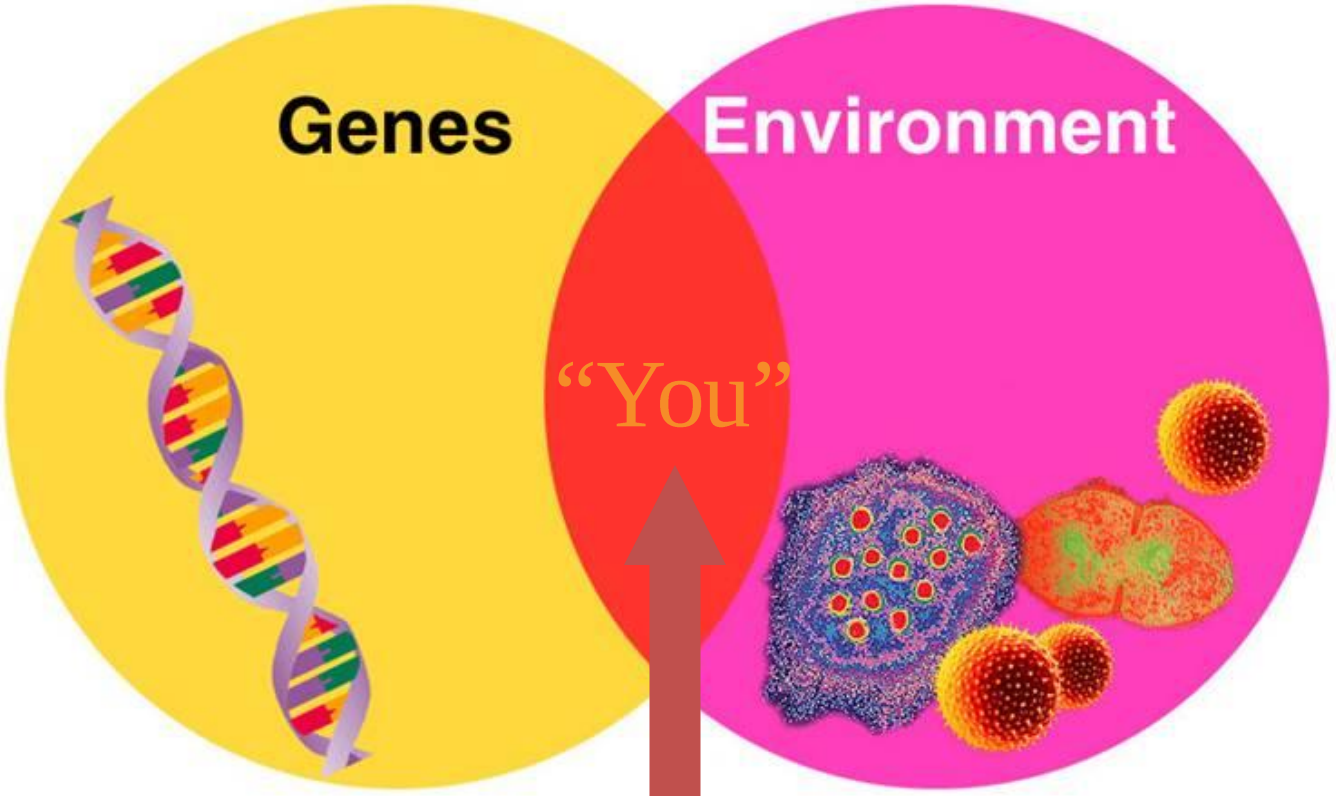
Fig. Distribution of ERα and ERβ in the human body. Adapted from [34].

Abnormal transmethylation/transsulfuration metabolism and DNA hypomethylation among parents of children with autism.

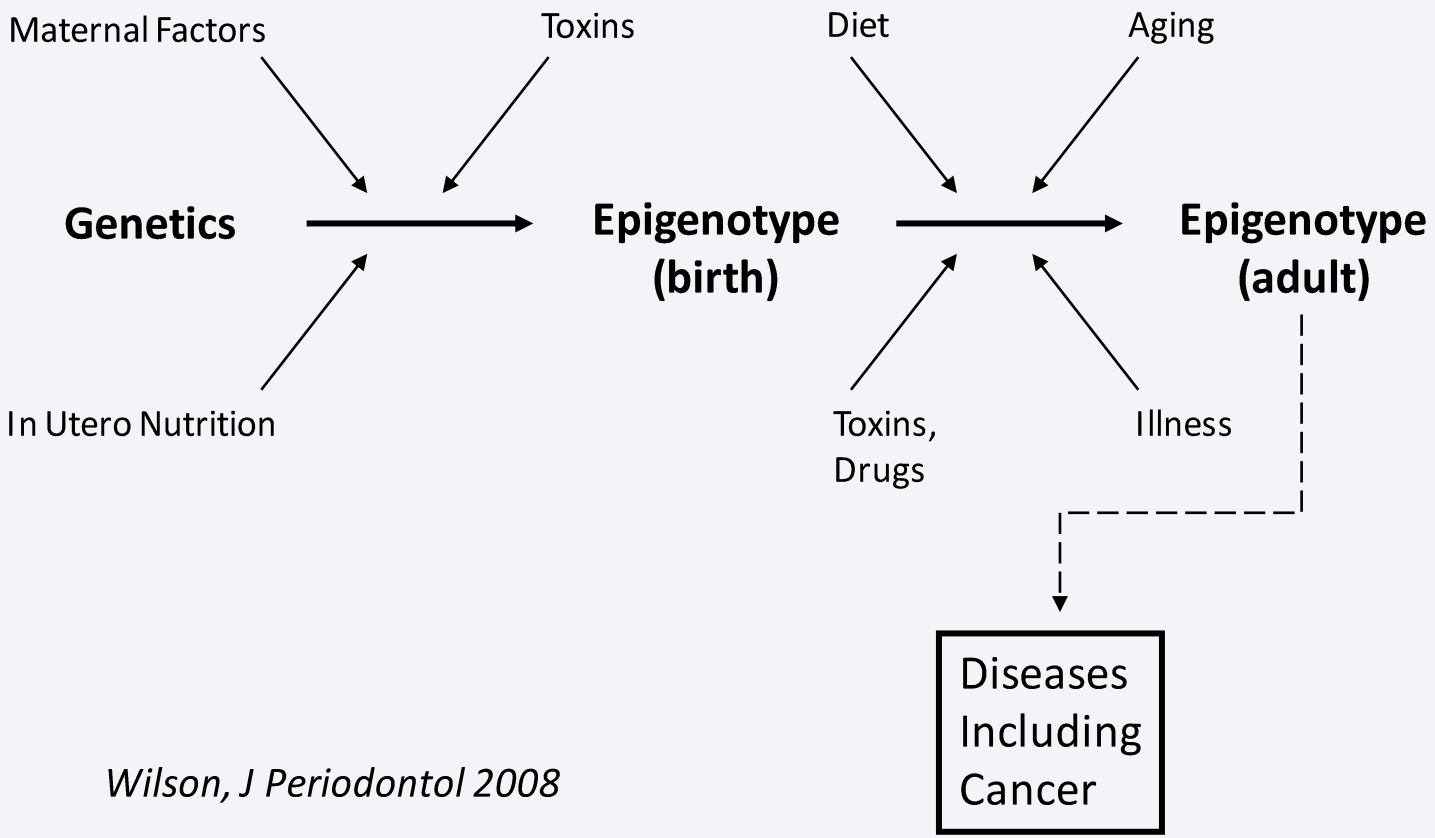
J Autism Dev Disord. 2008 Nov;38(10):1966-75. James SJ, et al.
Department of Pediatrics, University of Arkansas for Medical Sciences, J Autism Dev Disord. 2008

ABSTRACT

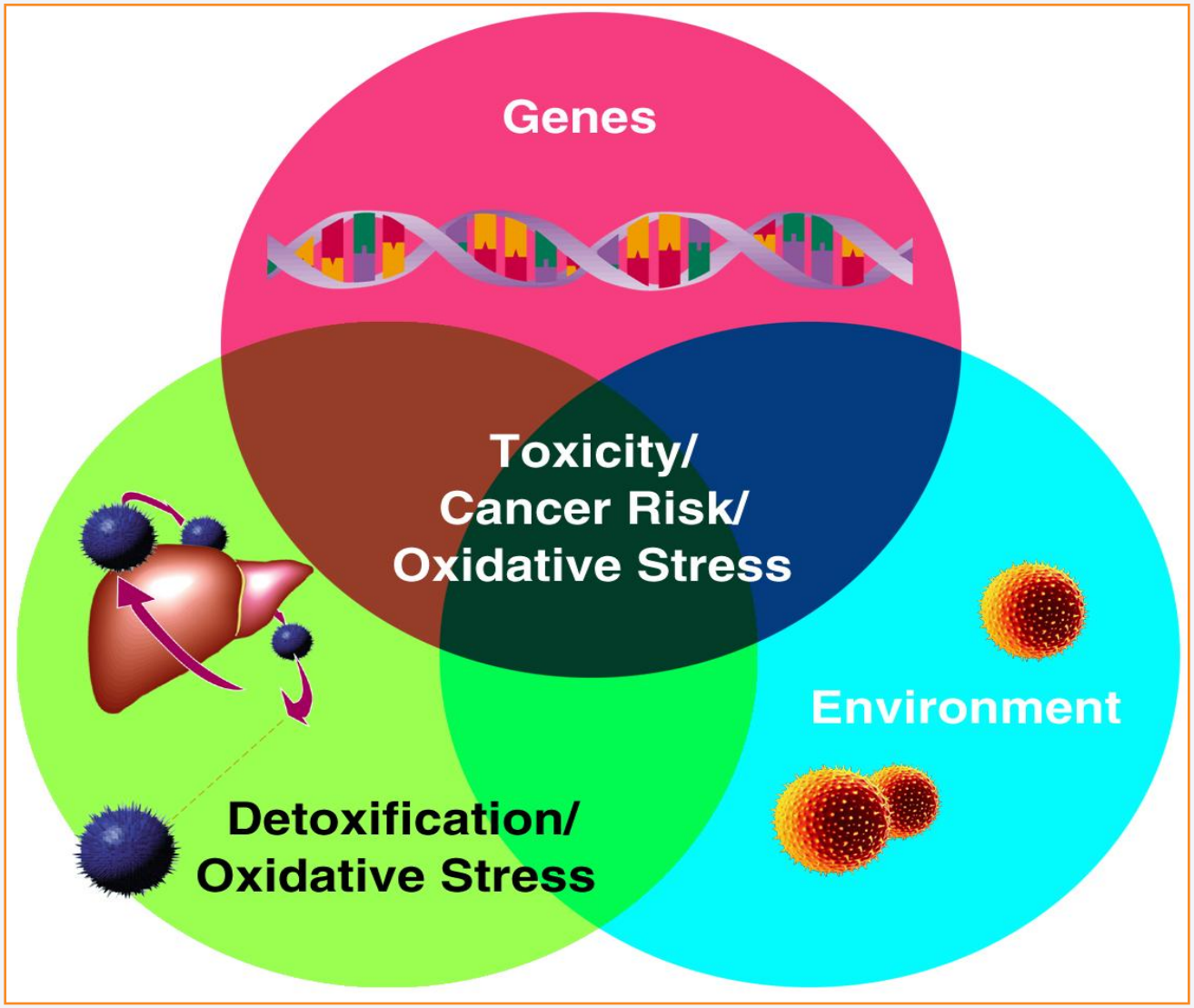
An integrated metabolic profile reflects the combined influence of genetic, epigenetic, and environmental factors that affect the candidate pathway of interest. Recent evidence suggests that some autistic children may have reduced detoxification capacity and may be under chronic oxidative stress. Based on reports of abnormal methionine and glutathione metabolism in autistic children, it was of interest to examine the same metabolic profile in the parents. The results indicated that parents share similar metabolic deficits in methylation capacity and glutathione-dependent antioxidant/detoxification capacity observed in many autistic children. Studies are underway to determine whether the abnormal profile in parents reflects linked genetic polymorphisms in these pathways or whether it simply reflects the chronic stress of coping with an autistic child.


Genes
Environment
"You"
"Phenotype"

Unlike the genetic sequence, the epigenetic signature is dynamic and changes in response to various environmental stimuli



Wilson, J Periodontol 2008


Genes
Toxicity/
Cancer Risk/
Oxidative Stress
Environment
Detoxification/
Oxidative Stress

Chemical sensitivity: breaking the paralyzing paradigm: how knowledge of chemical sensitivity enhances the treatment of chronic disease

Rogers, Sherry, M.D., Internal Medicine World Report, 1992;7(8):13-41"

There are environmental triggers for many diseases that are currently treated with drugs. Glomerulonephritis from hydrocarbons from auto exhaust, some endocrinopathies, impaired taste and hearing, muscular atrophy, nausea and abdominal pain, acne, impaired hepatic enzymes, blood disorders, lethargy, myocarditis, cardiac arrhythmias, hypercholesterolemia, enteropathies and inability to concentrate due to indoor pesticides are a few examples. Home paints have been shown to induce atrial fibrillation. There are a variety of other examples given. The author notes that usually the answers are not straightforward and sometimes there may be a combination of chemicals, molds and foods that are causing the sensitivity problems.

The author notes a variety of individuality with regard to target- organ predilection; for example, 2,000 people were exposed to 4-PC in a new carpet at the Environmental Protection Agency, only 126 developed symptoms, and there were more than a dozen different complaints. Just as symptoms from any one chemical are diverse, likewise there are causes found for one disease entity that can be just as unique. In this type of approach, a diagnostic label is not as important as the diagnostic process of finding the cause.

The author feels that chemical sensitivities in severe cases cannot be dealt with until nutrient deficiencies have been rectified.

It is the integrity of the xenobiotic detoxification system that is critical to the manifestation of the illness.

Toxic chemicals released by industries
2013: 6,752,498 tons

Toxic chemical release - sources and methods

Facts:

Each and every second 310 Kg of toxic chemicals are released into our air, land, and water by industrial facilities around the world.

This amounts to approximately 10 million tons (over 21 billion pounds) of toxic chemicals released into our environment by industries each year.

Of these, over 2 million tons (over 4.5 billion pounds) per year are recognized carcinogens. This amounts to about 65 Kg each second.

Definition:
toxic chemicals: substances that can cause severe illness, poisoning, birth defects, disease, or death when ingested, inhaled, or absorbed by living organisms.

“the hidden life of garbage“

Het milieu zit in ons

G. Devriendt