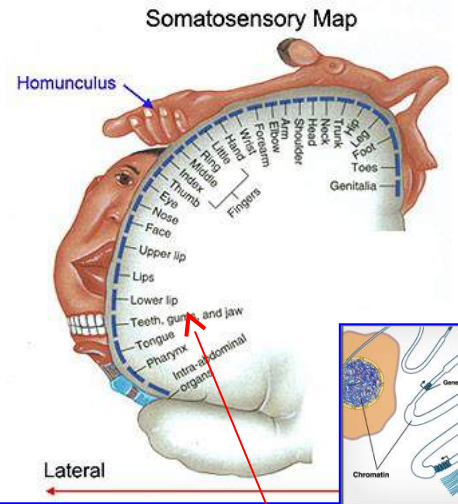
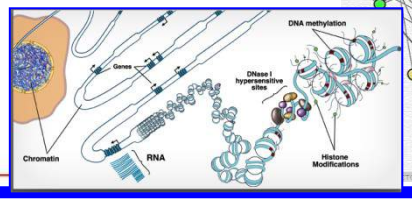
MOVIMENTO DI LOTTA PER LA SALUTE

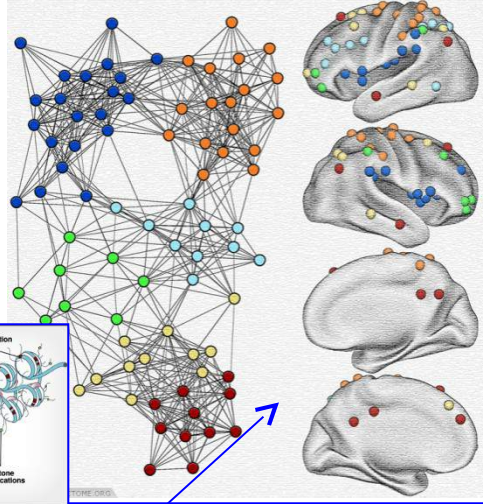
Medicina Democratica O.N.L.U.S.

VIII CONGRESSO NAZIONALE

FIRENZE 19-21 NOVEMBRE 2015

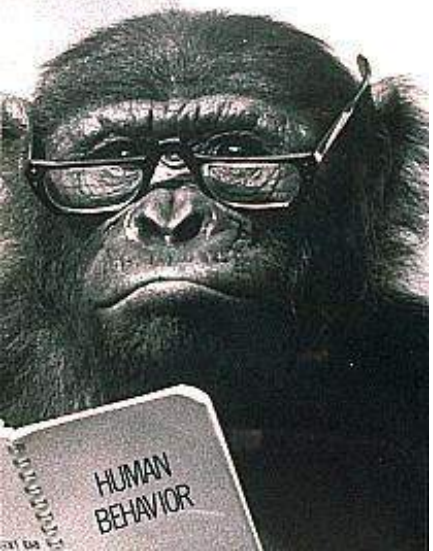




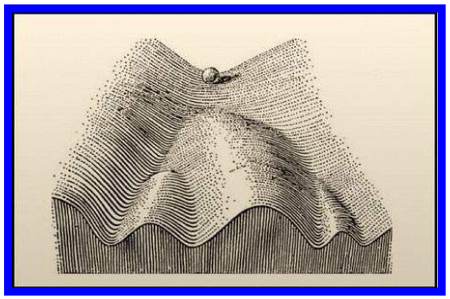


From GENETICS to EPIGENETICS

La transizione epidemiologica del XX secolo: dalla genetica all'epigenetica



ECERI
European Cancer and Environment Research Institute



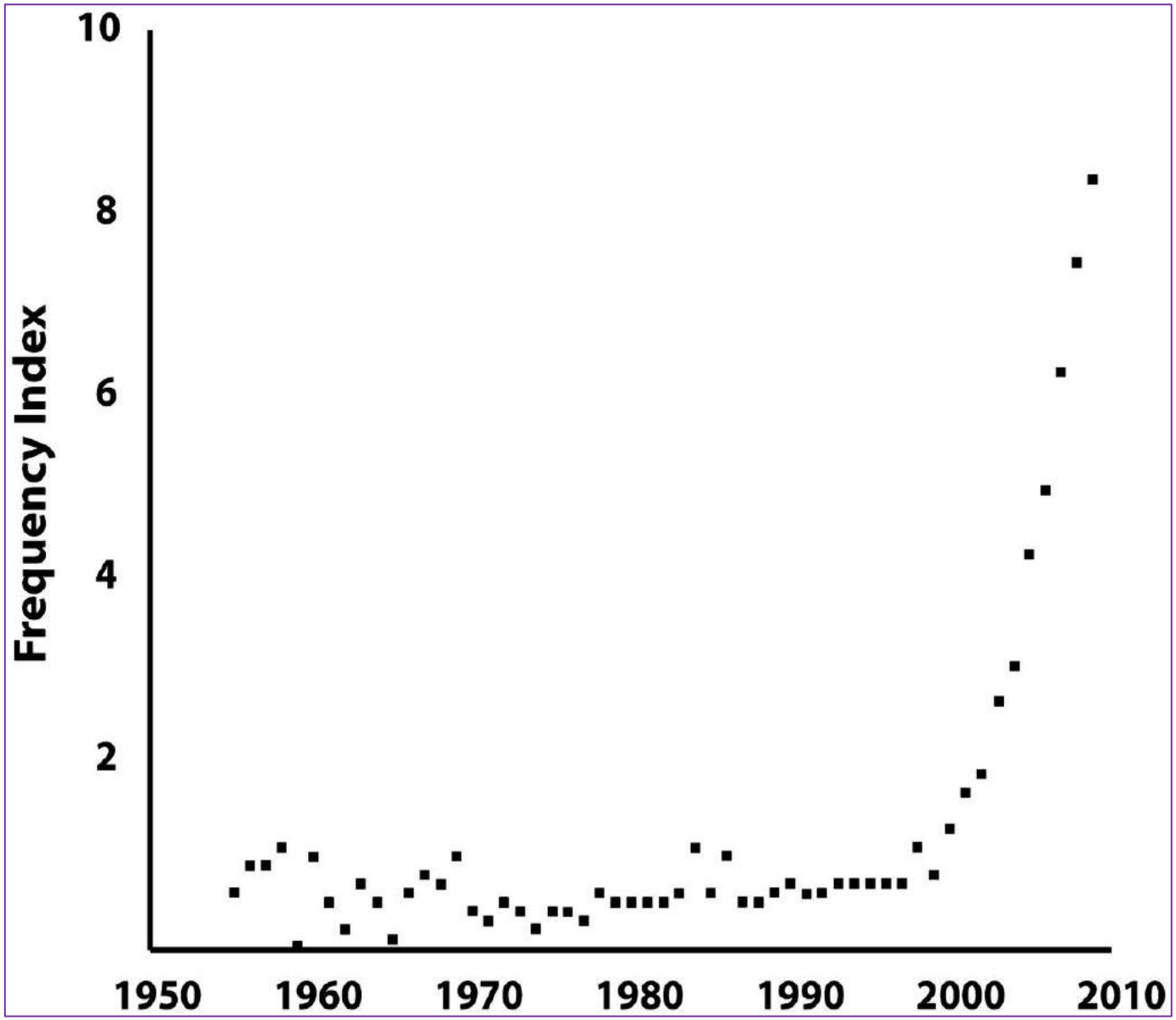
INTERNATIONAL SOCIETY OF DOCTORS FOR ENVIRONMENT
ISDE

ERNESTO BURGIO
ISDE Scientific Committee
ECERI - European Cancer and Environment Research Institute

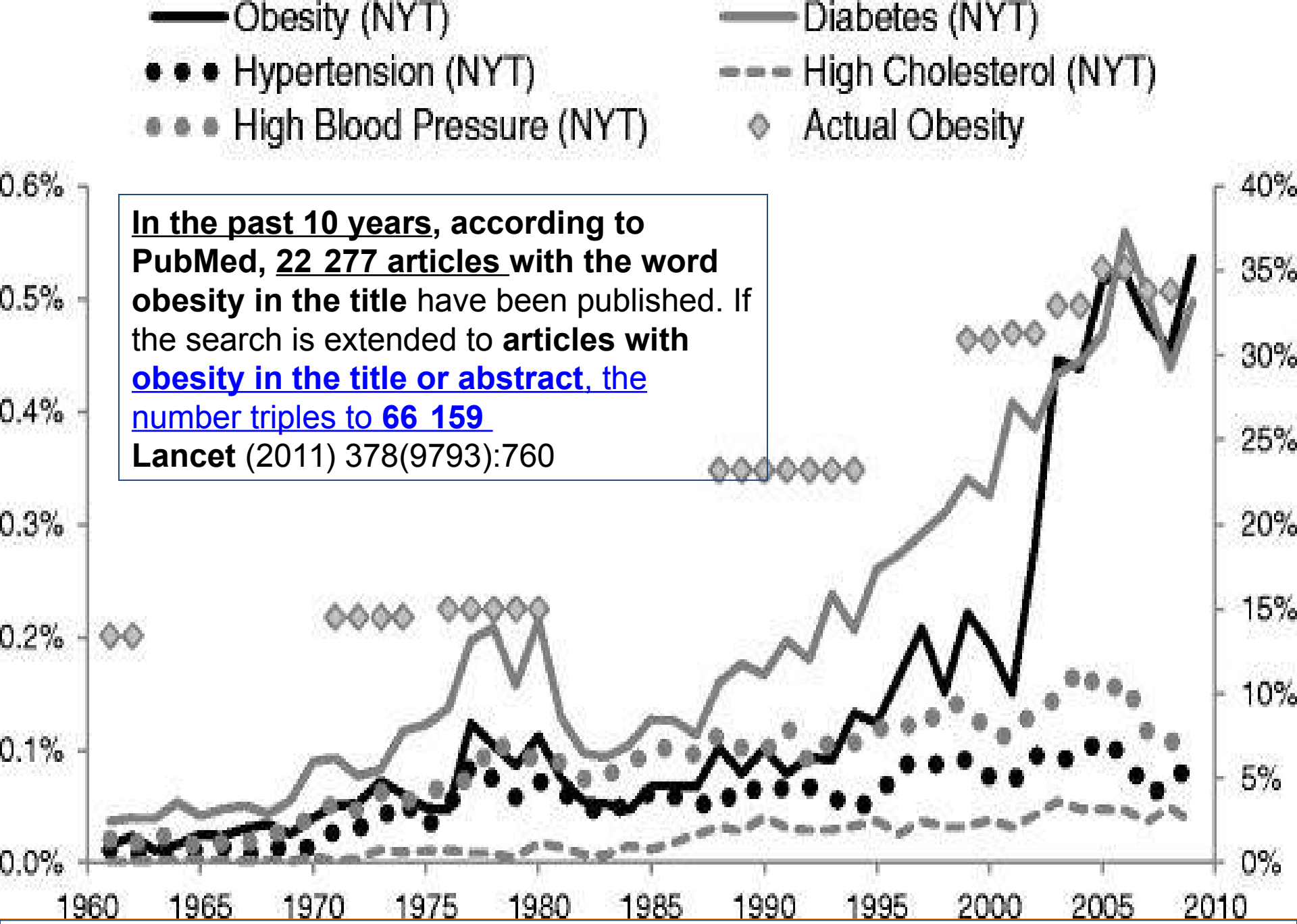
Foreword 1

Relative frequency of articles with epigenetic or epigenetics in their title

David Haig Int. J. Epidemiol. 2012;41:13-16

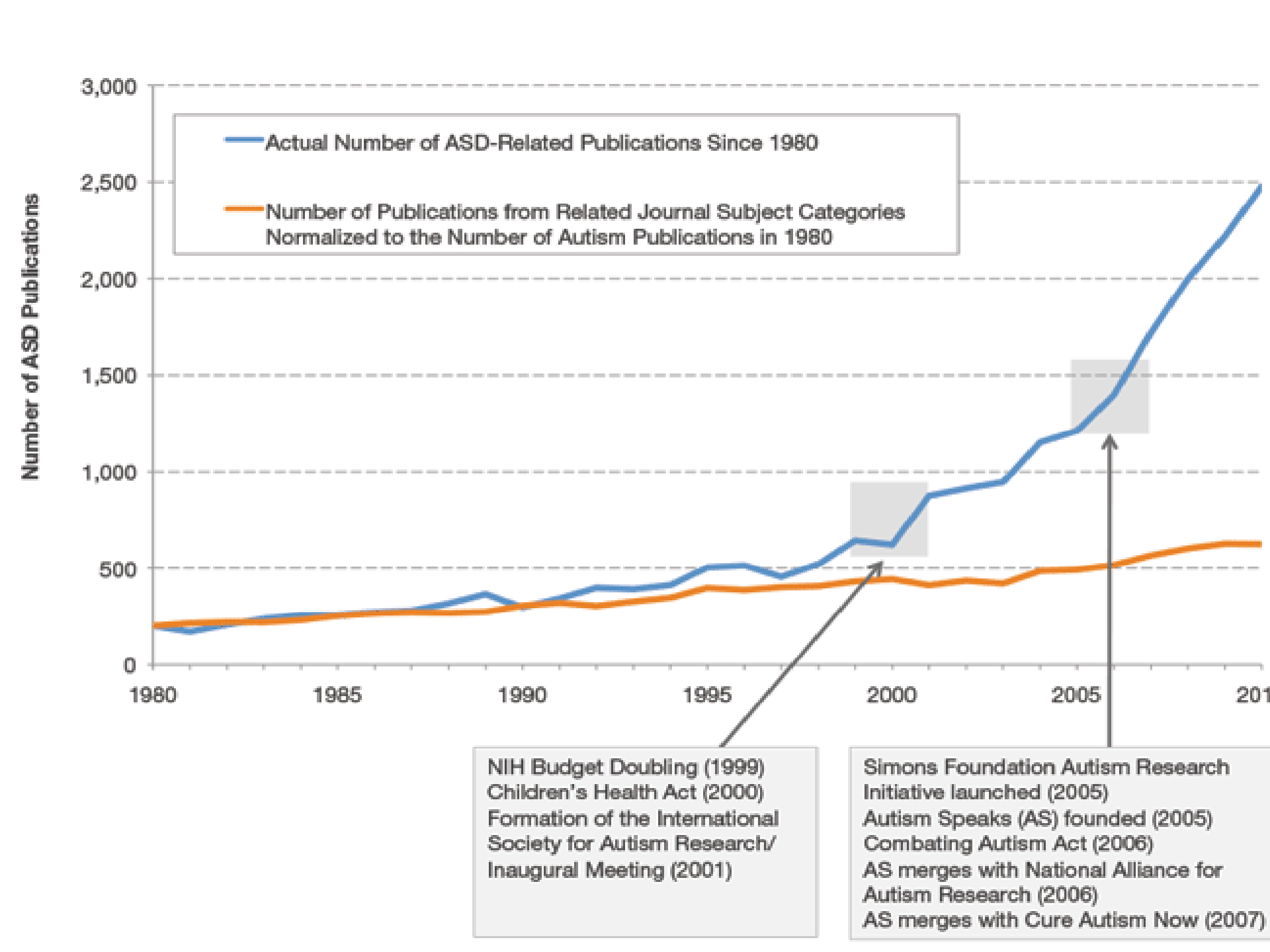


International Journal of Epidemiology

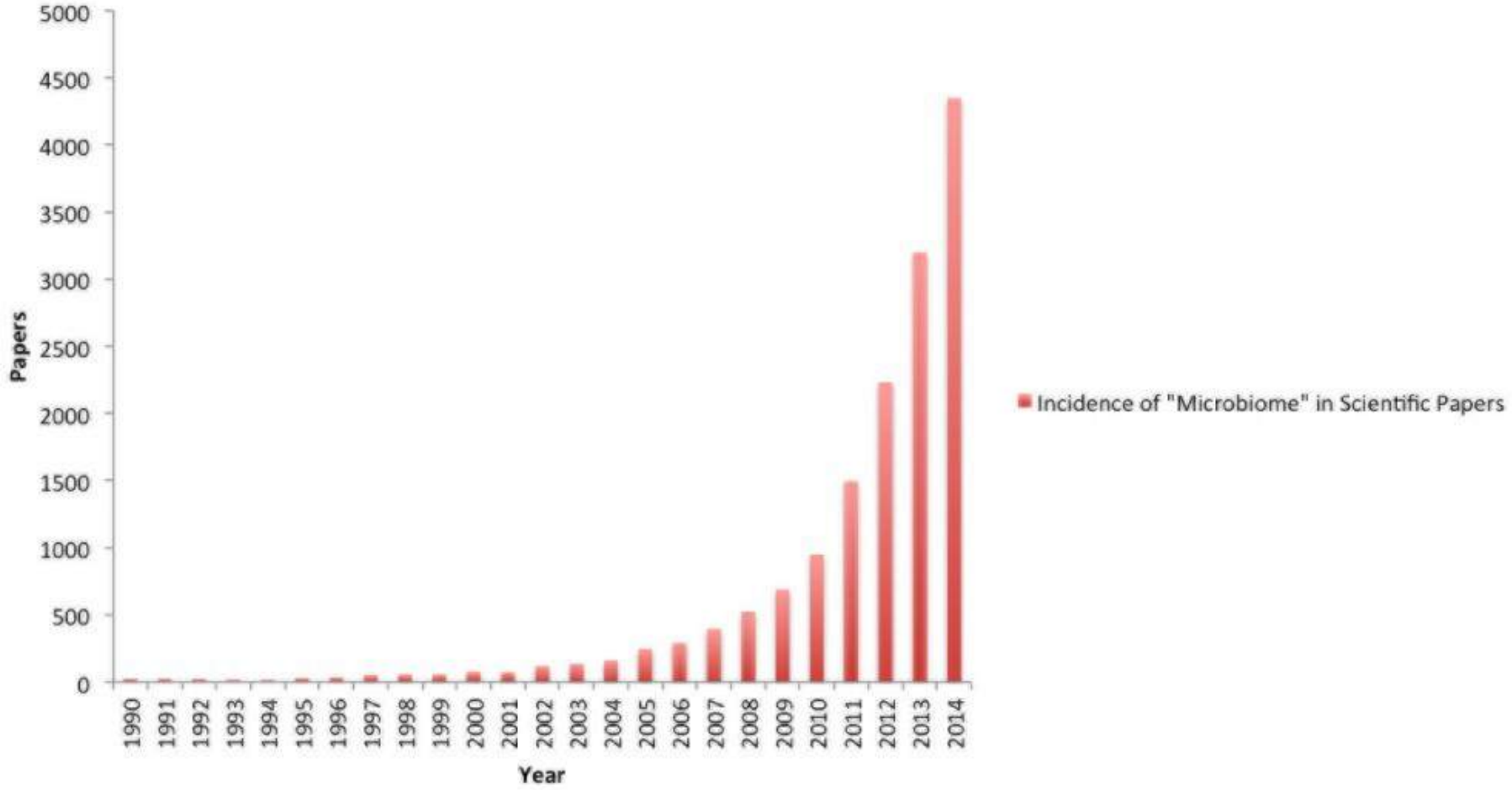


In the past 10 years, according to PubMed, 22 277 articles with the word obesity in the title have been published. If the search is extended to **articles with obesity in the title or abstract**, the number triples to **66 159**
Lancet (2011) 378(9793):760

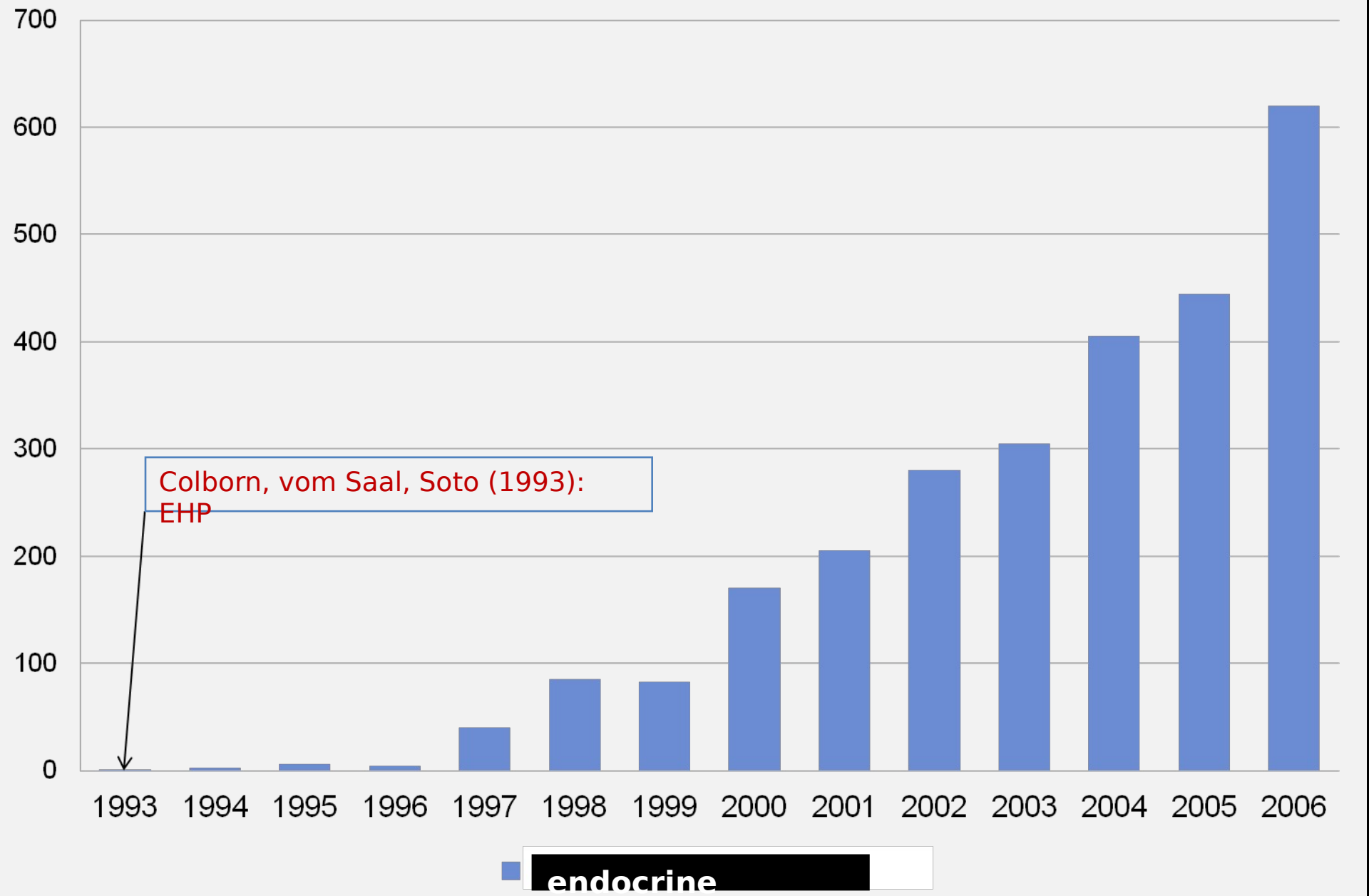
Number of *New York Times* articles mentioning obesity and related comorbidities


Number of ASD Publications
3,000
2,500
2,000
1,500
1,000
500
0
1980
1985
1990
1995
2000
2005
Actual Number of ASD-Related Publications Since 1980
Number of Publications from Related Journal Subject Categories Normalized to the Number of Autism Publications in 1980
NIH Budget Doubling (1999)
Children's Health Act (2000)
Formation of the International Society for Autism Research/ Inaugural Meeting (2001)
Simons Foundation Autism Research Initiative launched (2005)
Autism Speaks (AS) founded (2005)
Combating Autism Act (2006)
AS merges with National Alliance for Autism Research (2006)
AS merges with Cure Autism Now (2007)

*A quick search for "**Microbiome**" in **scienctific journals online** demonstrates how significantly this field of research has been **growing over the past ten years***



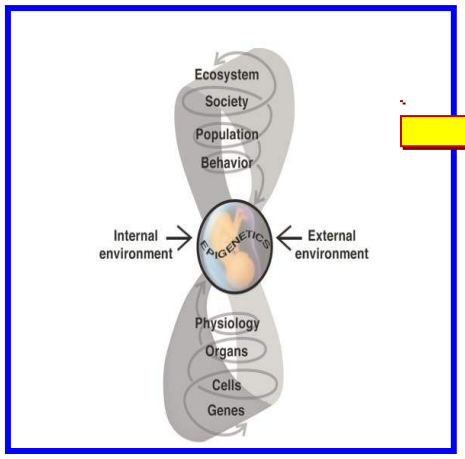
Published papers about endocrine disruptors between 1993 and november 2006 (Gies)



etal programming

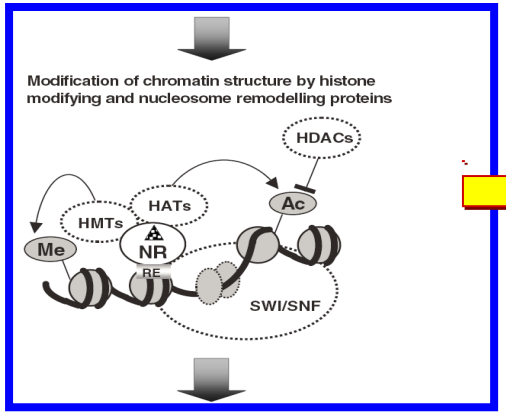
Ontogeny

3



4

Developmental Plastici

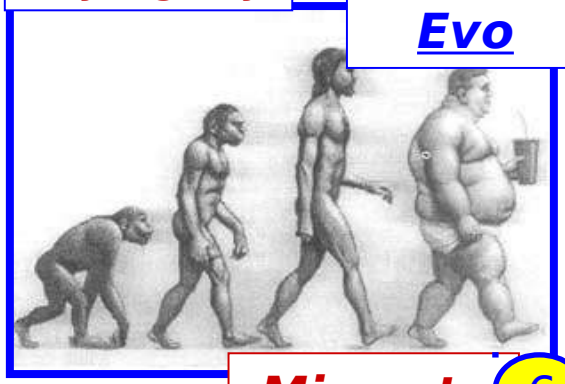


Evolutionary Medicine

5

Phylogeny

Devo-Evo

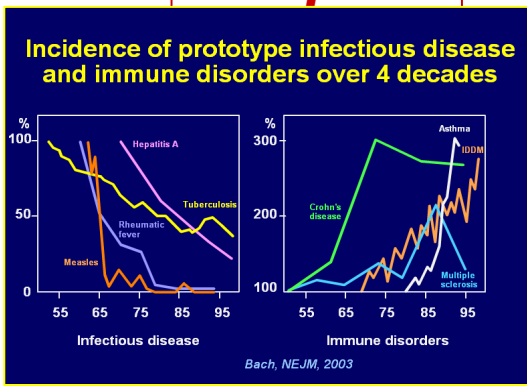


Mismatc

6

7

XX Century Epidemiologic Transition

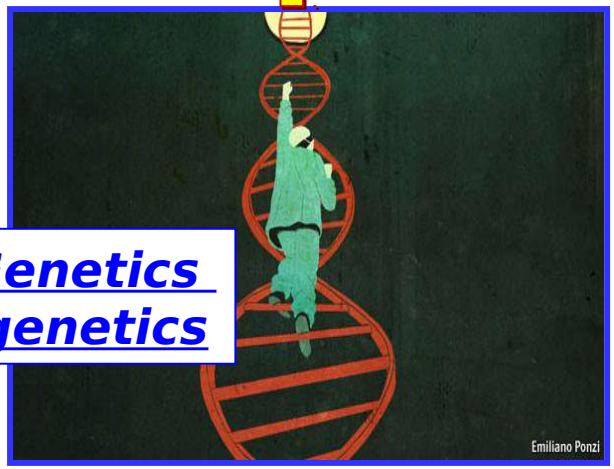


2

Environment

1

From Genetics to Epigenetics



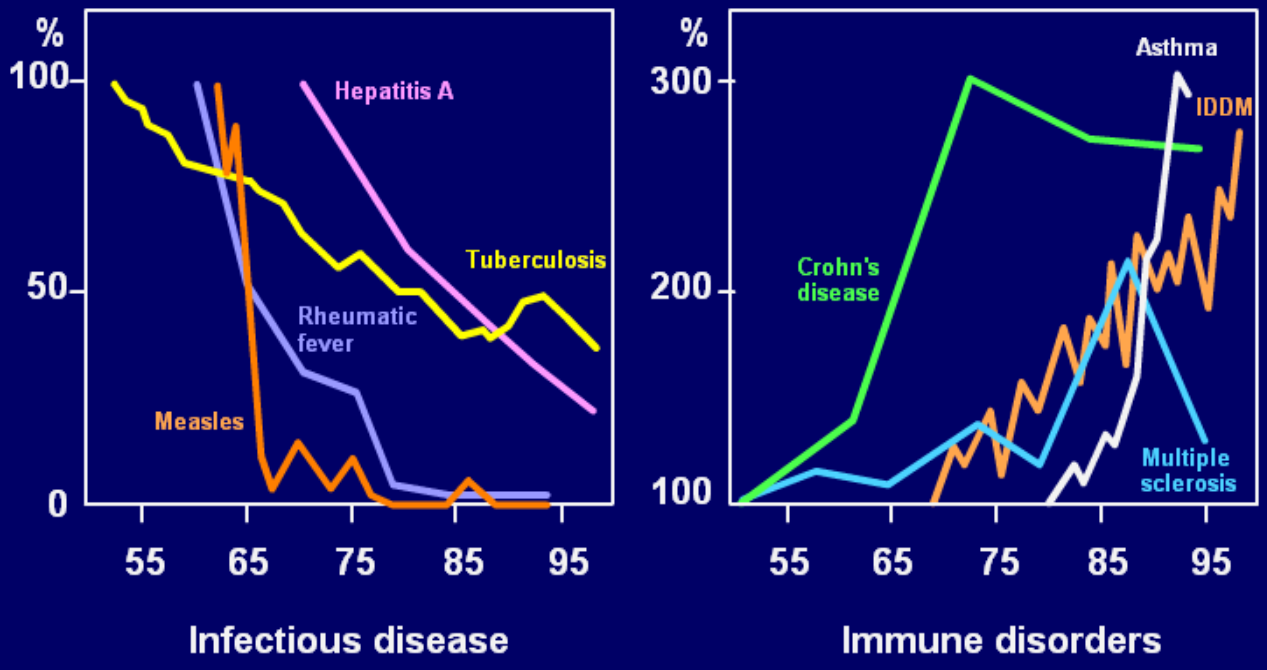
Is there a Project ?

La transizione epidemiologica del XX secolo: dalla genetica all'epigenetica

ERNESTO BURGIO
ISDE Scientific Committee
ECERI - European Cancer and Environment

Le septième mot clé: La ***transition épidémiologique*** du XX siècle

Incidence of prototype infectious disease and immune disorders over 4 decades



Bach, NEJM, 2003

Pandemie d'obésité, **syndrome métabolique**
diabète II

Allergies
maladies
auto-immunes
(diabète de type I, maladie coeliaque),

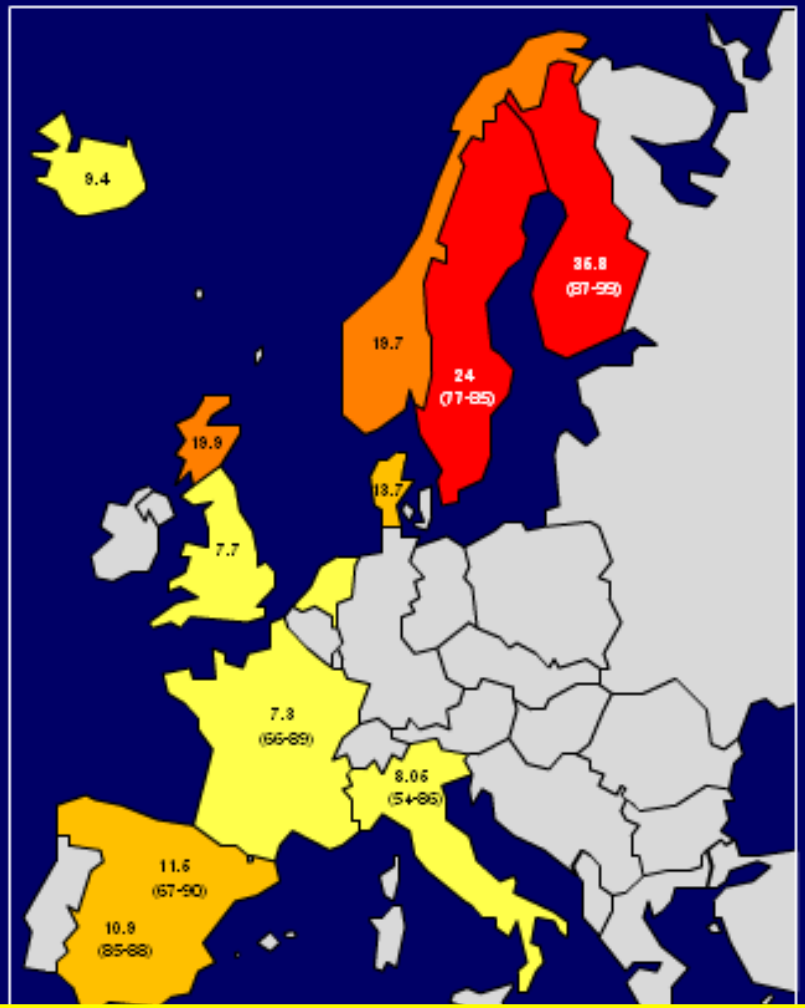
Athérosclérose

Troubles du **neurodéveloppement**
neurodegeneratives

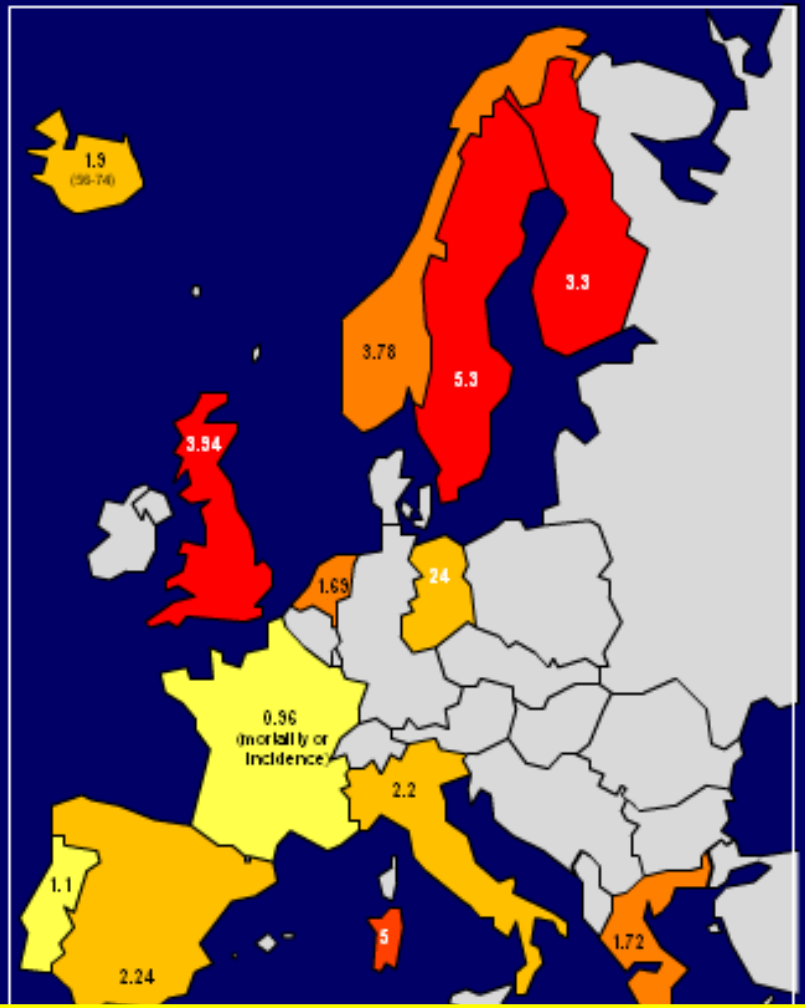
Cancer.

This is **a graph** taken from a famous article published **10 years ago on NEJM, showing the rapid decrease of the infectious/acute diseases** and the **simultaneous increase of the chronic/inflammatory diseases** in the North of the World (***Hygiene Hypothesis ?***)

Incidence of IDDM
(per 100,000)



Incidence of multiple sclerosis
(per 100,000)



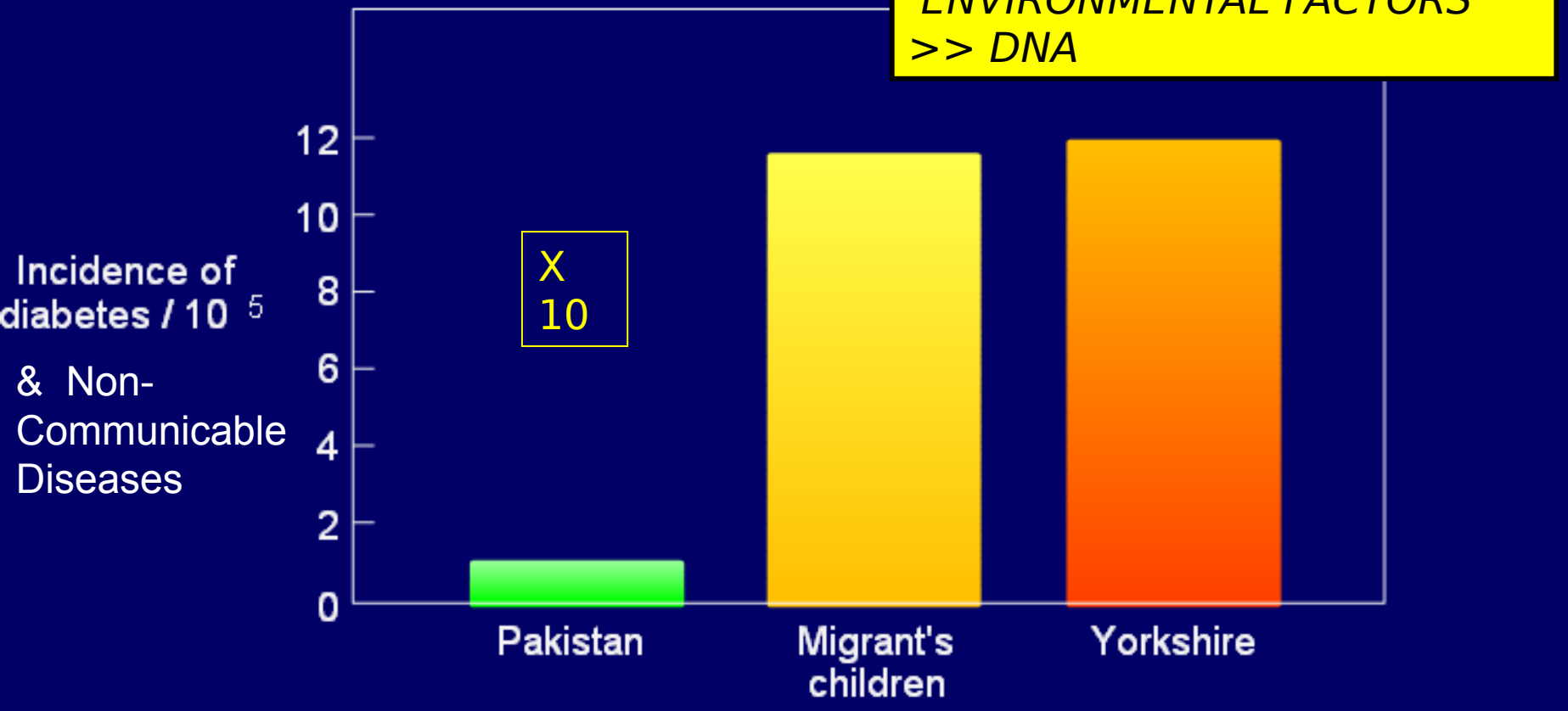
This is a figure taken from the same article, showing the presence

of a **South → North Gradient** concerning this **epidemiological transition**

TIPE I DIABETES

IDDM incidence in children of migrants from Pakistan to Yorkshire

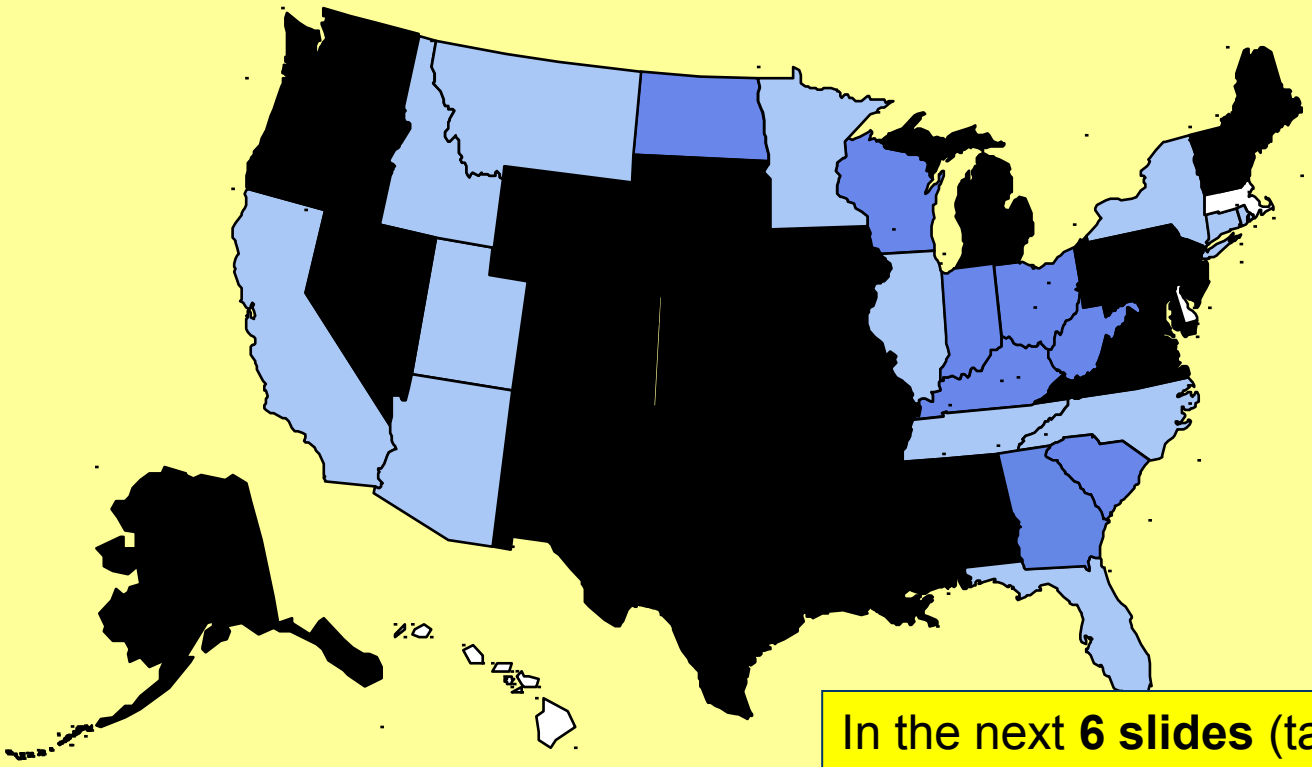
ENVIRONMENTAL FACTORS >> DNA



Here we see that **environment and lifestyles** have, in this epidemiological transition, **a much greater role that the DNA**: migrants from the South to the North will soon get sick of the typical, **chronic "*Non-Communicable Diseases*"**

Obesity Trends* Among U.S. Adults 1985

(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)

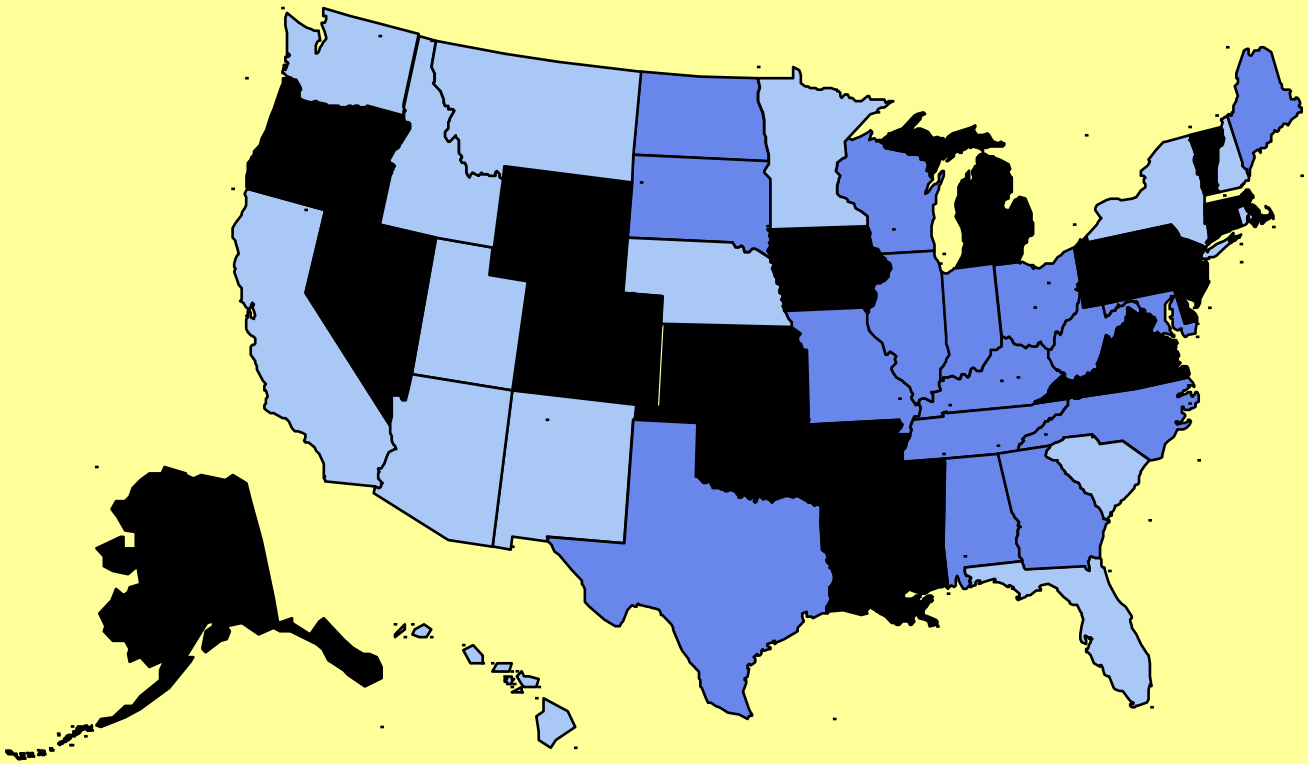


In the next **6 slides** (taken from **JAMA**) we'll follow, **in quick succession**, the dramatic, **TRULY EPIDEMIC SPREAD**

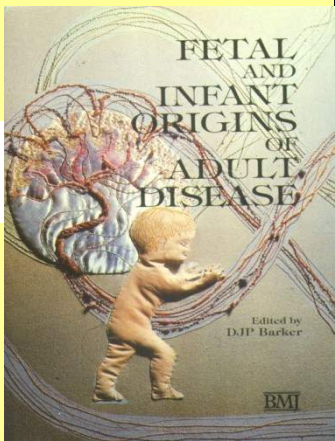
Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

Obesity Trends* Among U.S. Adults 1987

(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)

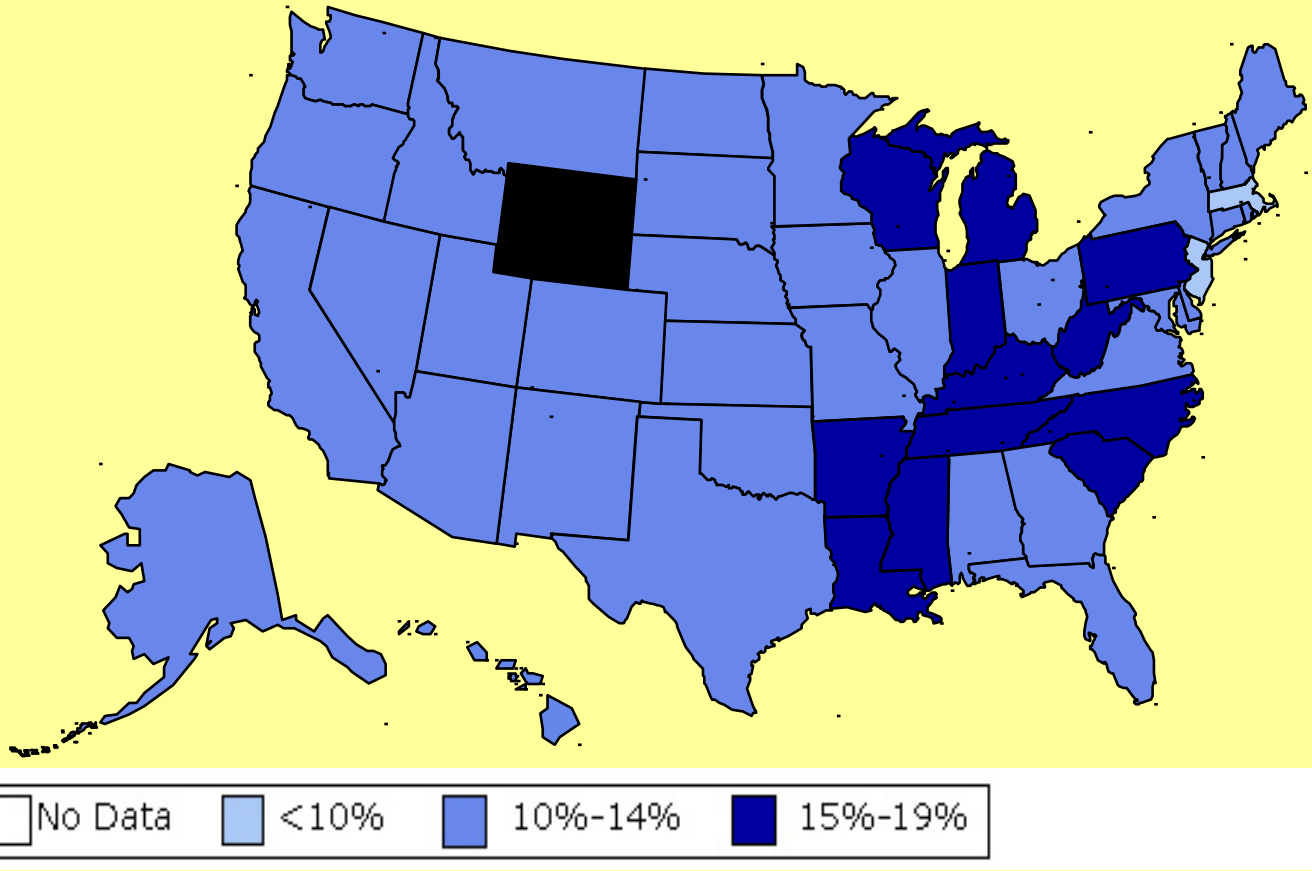


Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

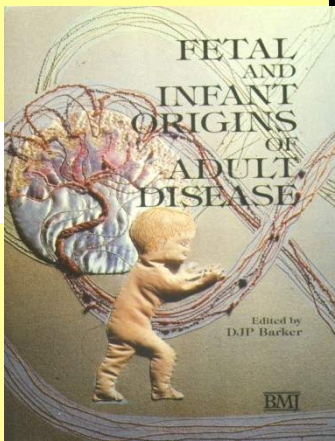


Obesity Trends* Among U.S. Adults 1993

(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)

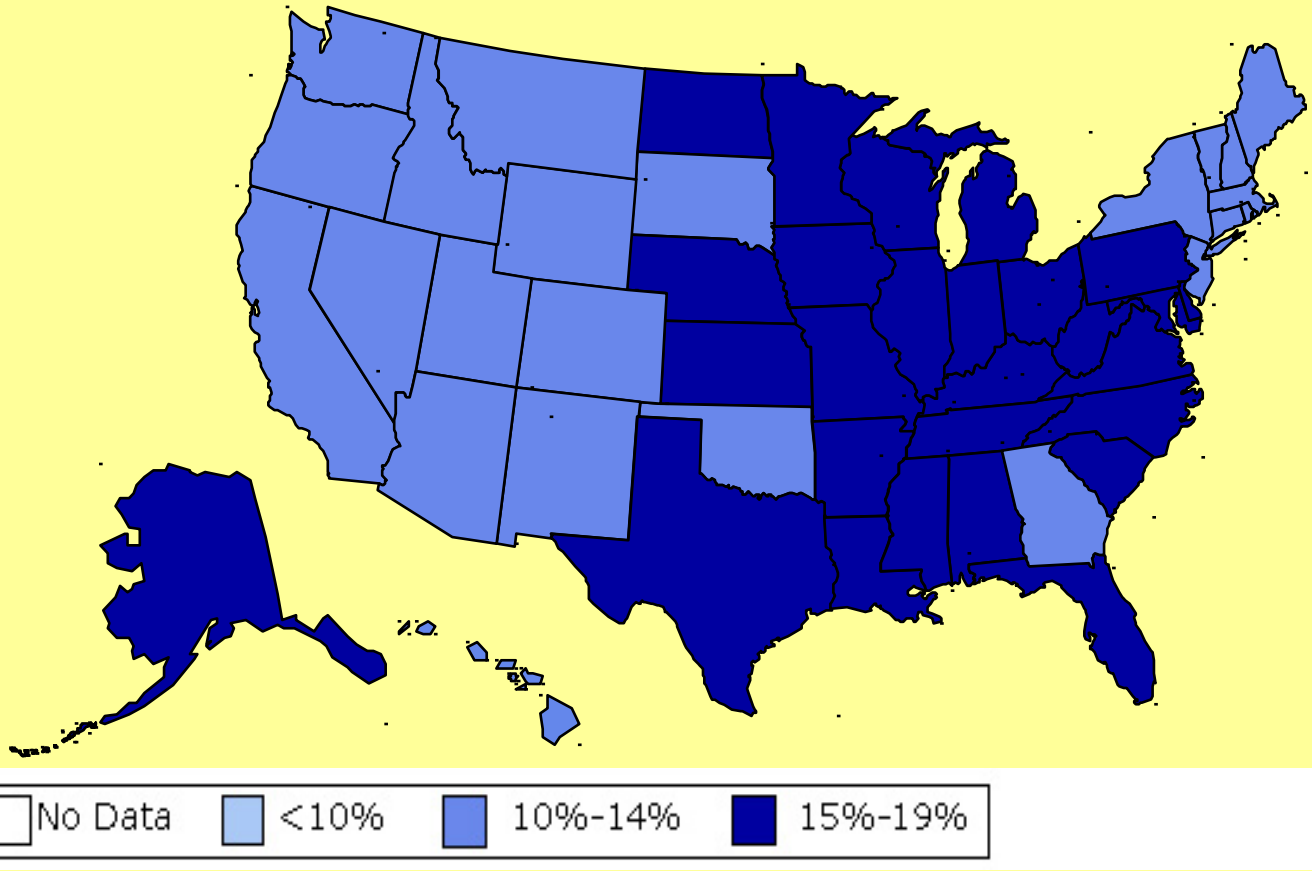


Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

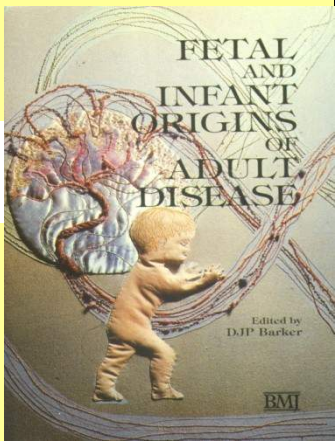


Obesity Trends* Among U.S. Adults 1995

(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)

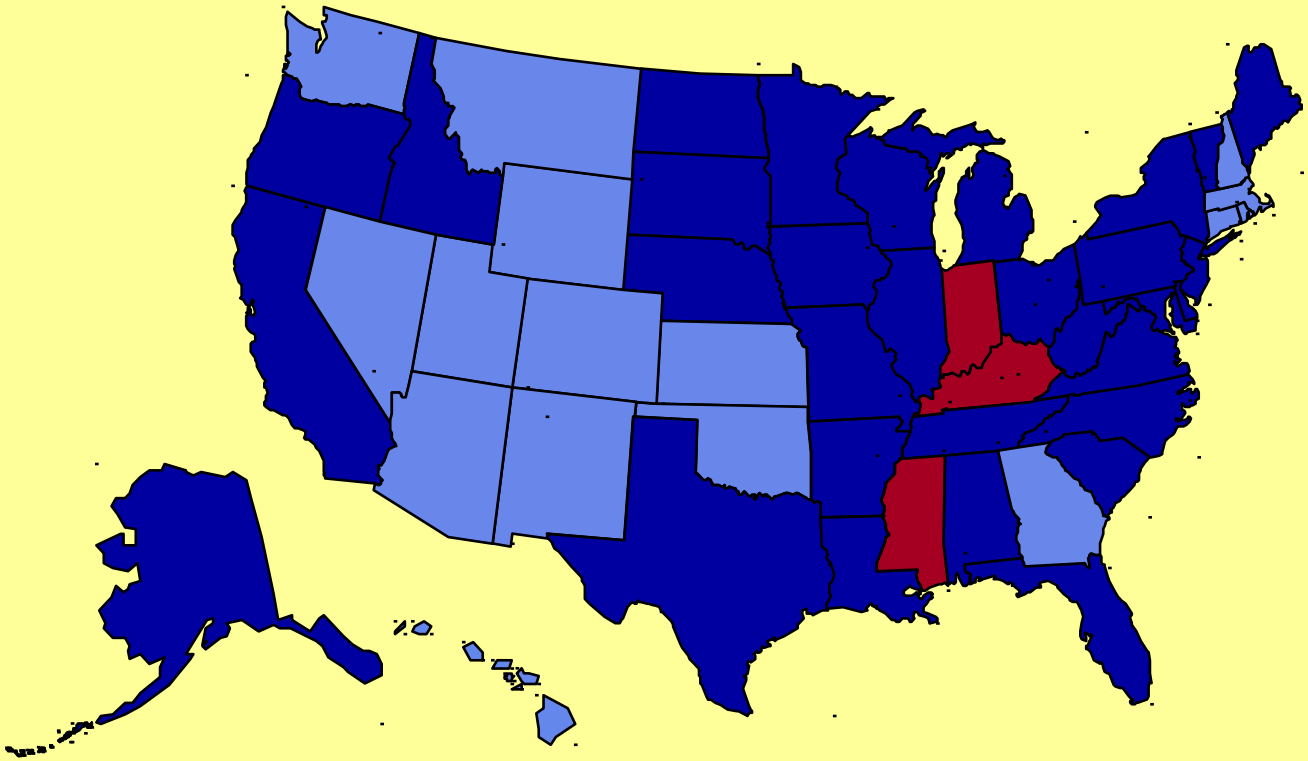


Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

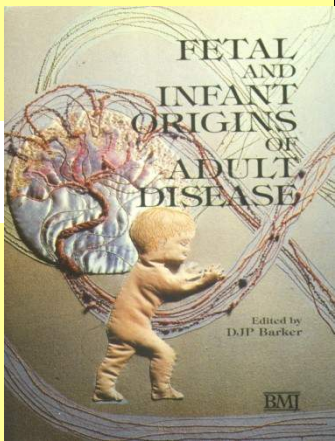


Obesity Trends* Among U.S. Adults 1997

(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)

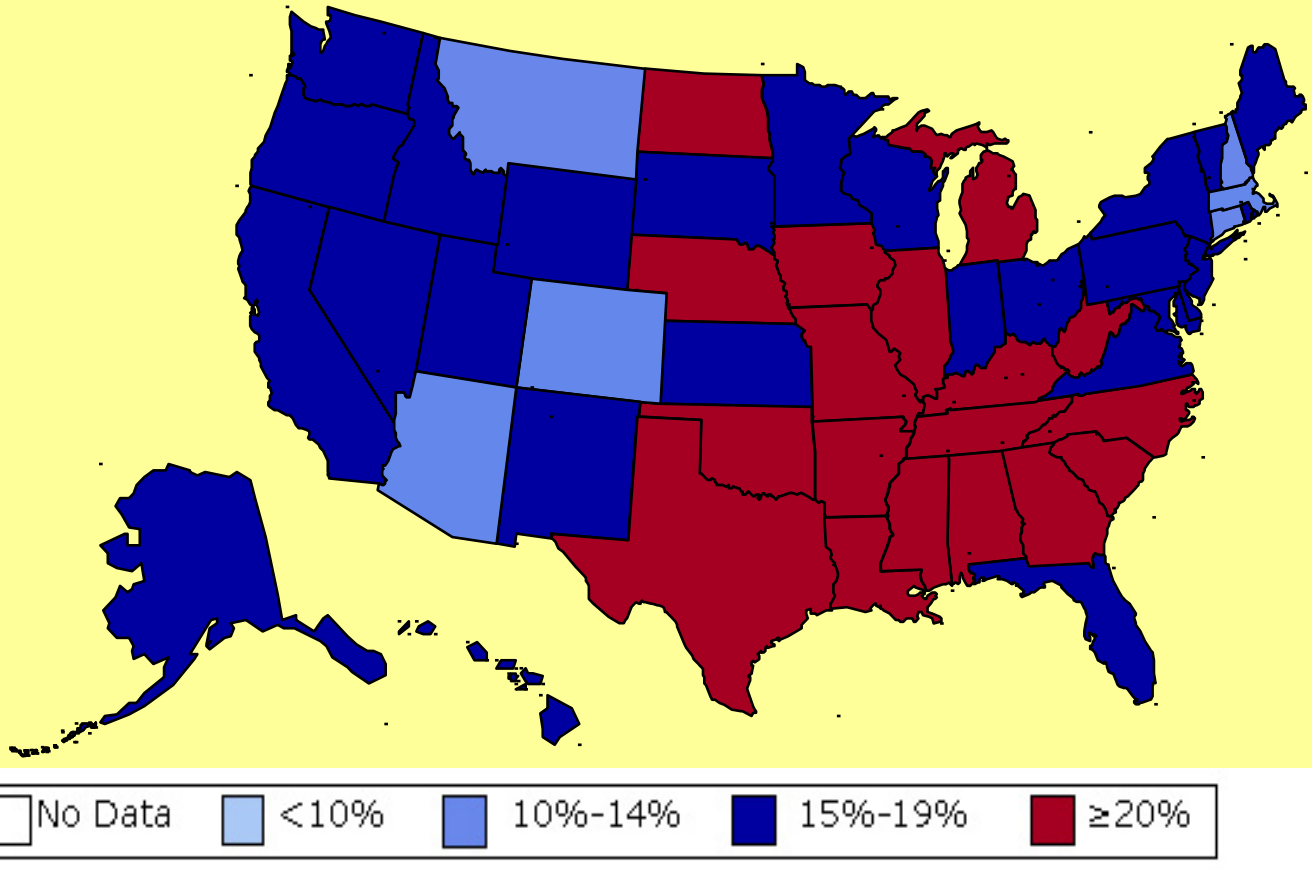


Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

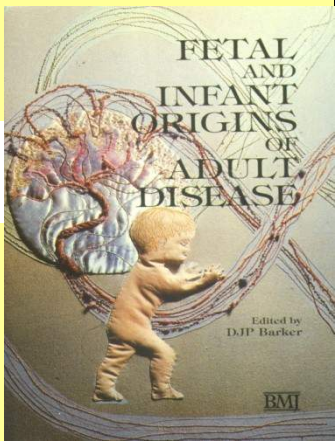


Obesity Trends* Among U.S. Adults 1999

(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)

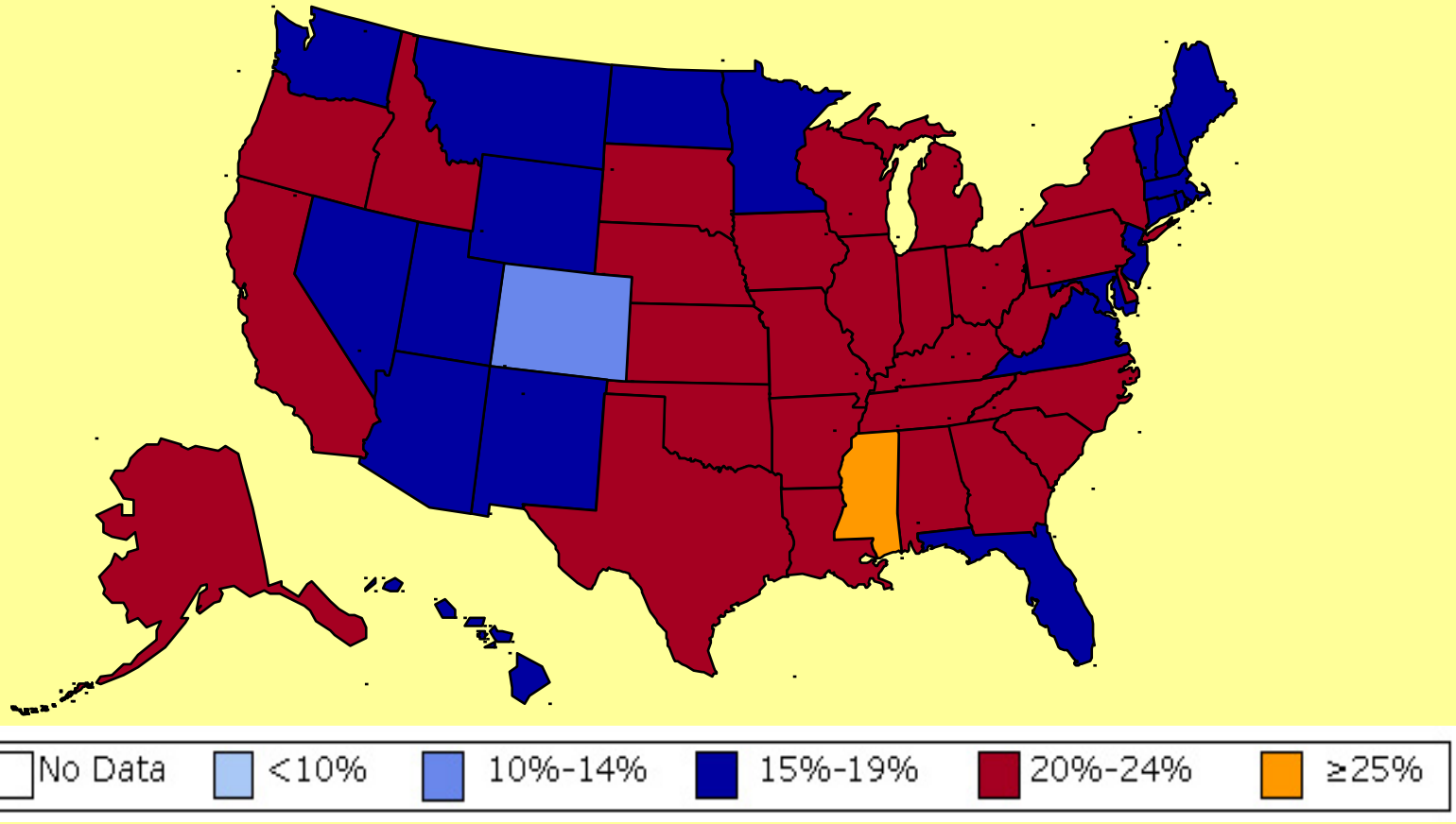


Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10



Obesity Trends* Among U.S. Adults 2001

(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)



Source: Mokdad A H, et al. *J*

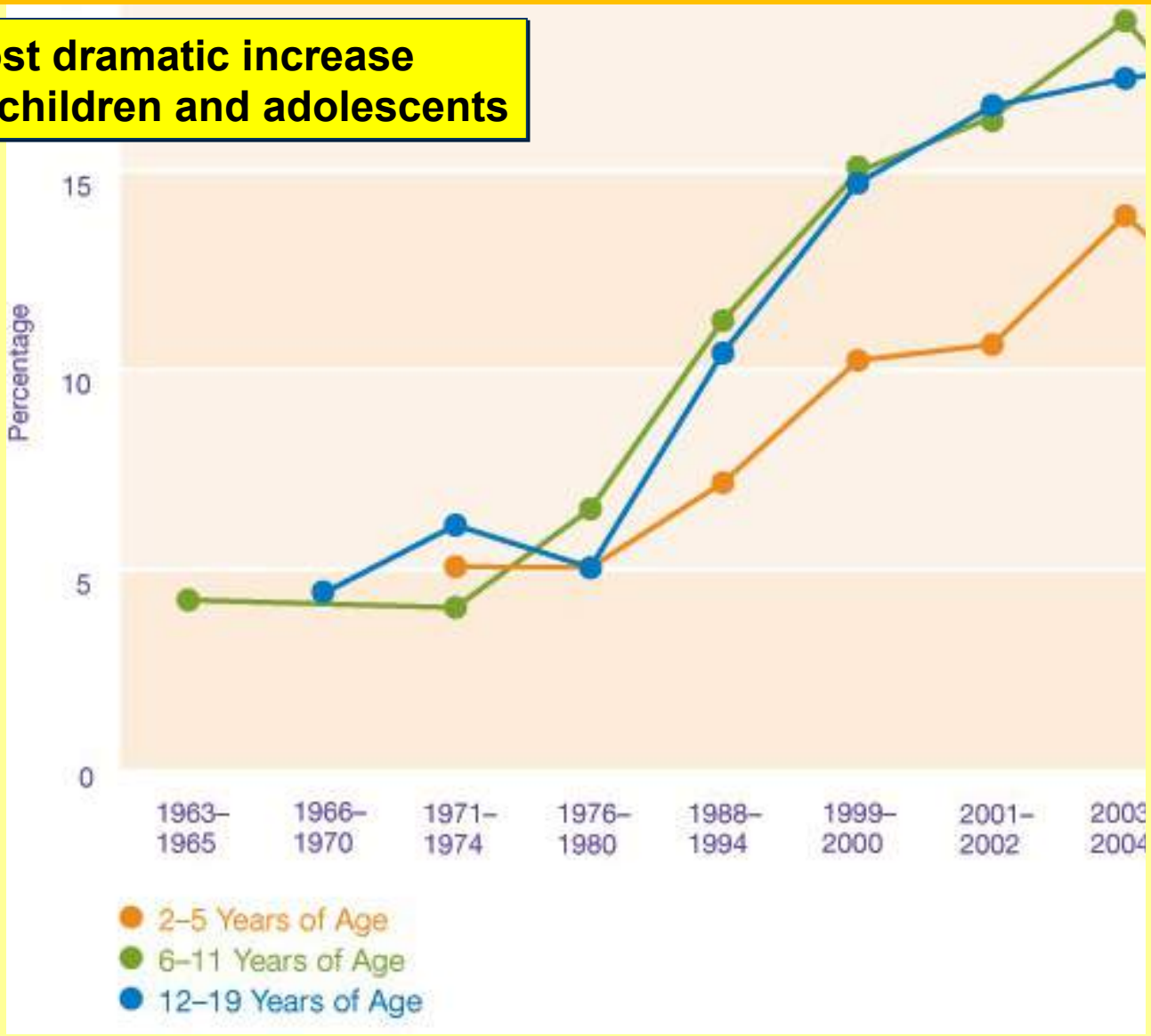
Today the situation has **further deteriorated:**
65% of Americans are overweight, **35%** morbidly obese

The Childhood Obesity Epidemic

Matthew W. Gillman, MD, SM

Yet the **most dramatic increase concerns children and adolescents**

BMI >95th %'ile



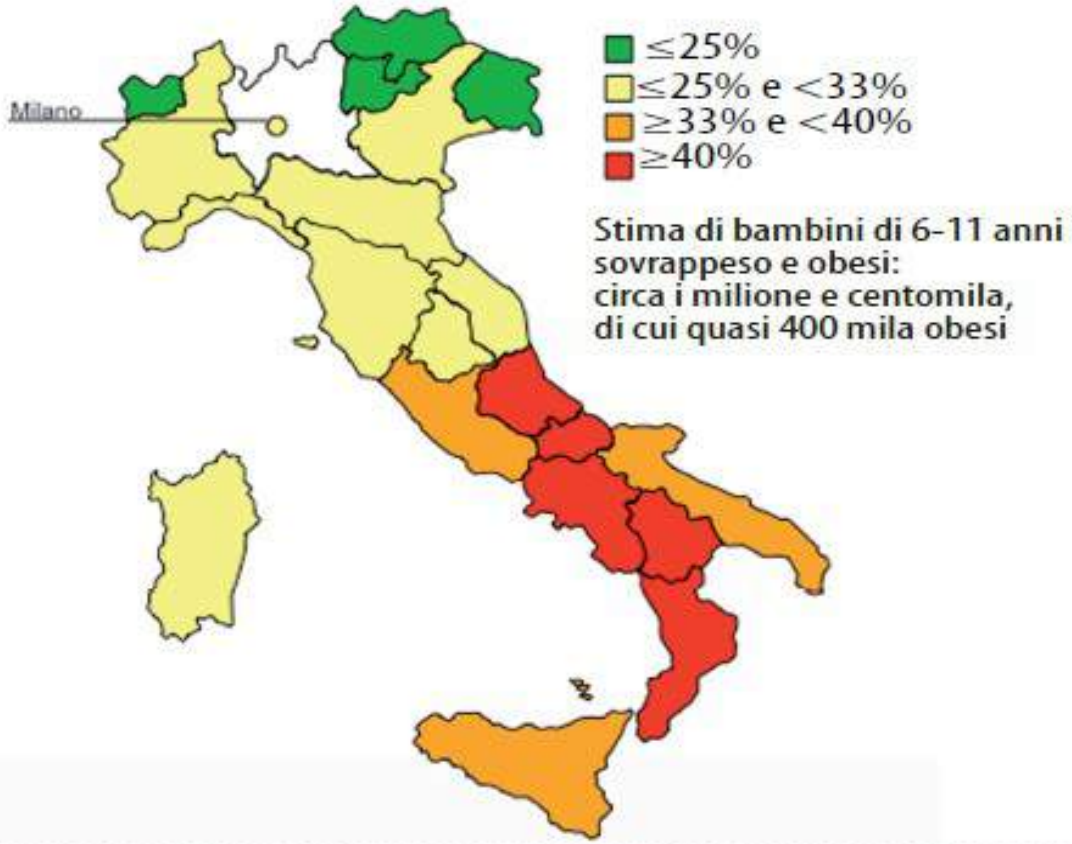
US DHHS, 2001; Hedley et al., 2004; Ogden et al., 2006, 2008

<u>in the 70s</u> childhood obesity virtually did not exist (it was associated with **rare genetic syndromes**): since then the increase has been **rapid and relentless**

FIGURA 1

SOVRAPPESO+OBESITÀ PER REGIONE, BAMBINI DI 8-9 ANNI DELLA 3A PRIMARIA

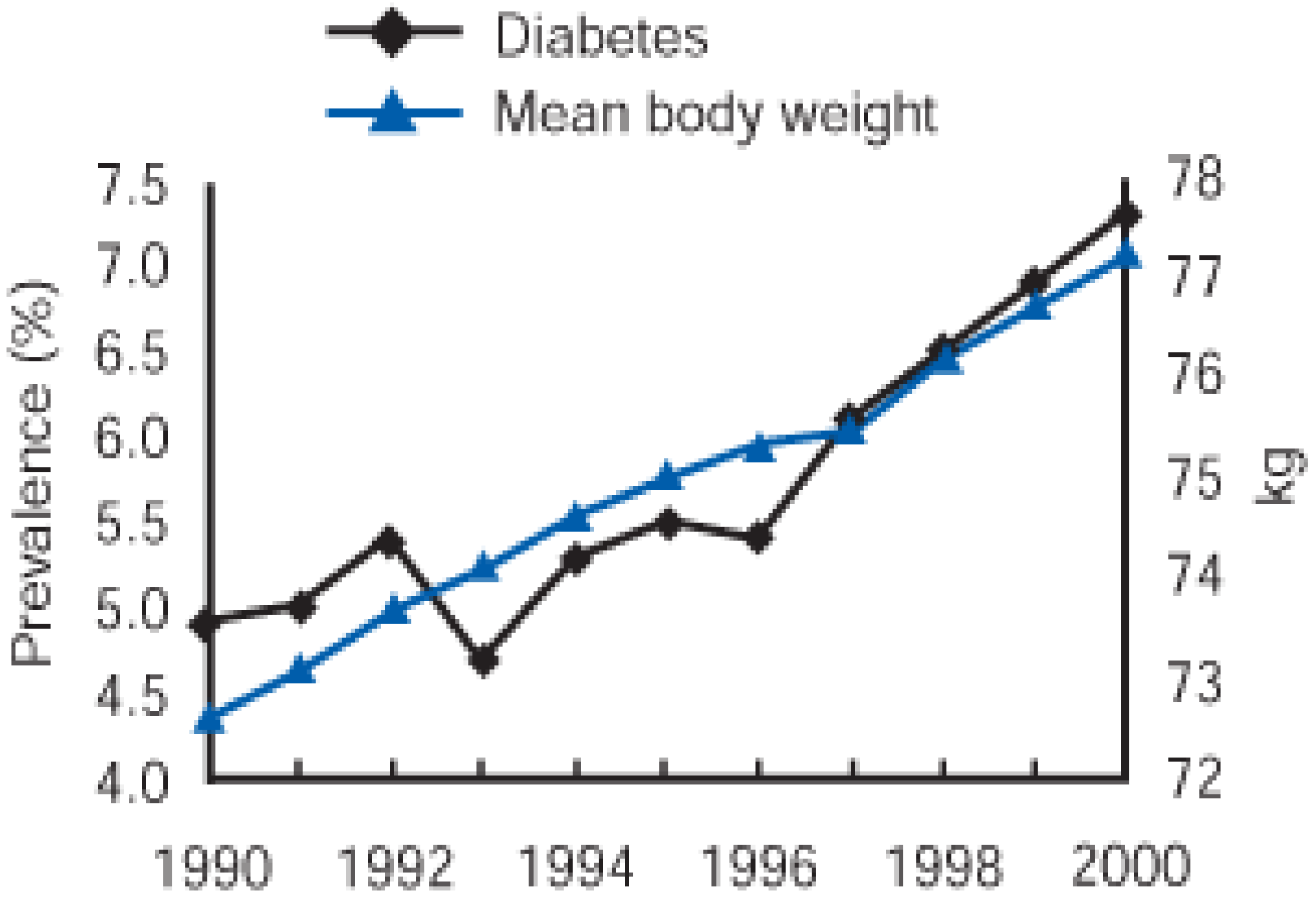
OKKIO ALLA SALUTE 2010



NOTA: è opportuno sottolineare che l'obesità infantile era un **evento raro fino a pochi anni fa** e generalmente **associata a sindromi**

In Italia il fenomeno ha proporzioni preoccupanti tra i bambini dai 6 ai 12 anni che presentavano un tasso di obesità del **7%** tra il 1976 e il 1980, del 12% tra 1988 e 1994 e del **15%** nel 2000. I dati più aggiornati (Istituto Superiore di Sanità), hanno rivelato una **spiccata variabilità interregionale**: le regioni in cui l'incremento è più netto sono quelle **meridionali**

The most serious consequence of the epidemic of obesity is **the association with many chronic diseases**: first of all with **diabetes 2** (today affecting 180 million people)



… with a **constant anticipation of the age of onset …**

Executive Healthcare Management
www.executivehm.com

autism the great modern health concern

Autism spectrum disorders (**ASDs**) are a group of developmental disabilities that can cause significant social, communication and behavioral challenges. People with **ASDs** handle information in their brain differently than other people. **ASDs** are "spectrum disorders." That means **ASDs** affect each person in different ways, and can range from very mild to severe. There are three different types of **ASDs**: **Autistic Disorder** (also called "classic" autism), **Asperger Syndrome** and **Pervasive Developmental Disorder** – Not Otherwise Specified (PDD-NOS; also called "atypical autism")

1980 1 : 15

Autistic Disorder

What most people think of when hearing the word "autism." People with autistic disorder usually have significant language delays, social and communication challenges and unusual behaviors and interests.

Asperger Syndrome

Usually have some milder symptoms of autistic disorder. They might have social challenges and unusual behaviors and interests. However, typically do not have problems with language or intellectual disability.

Pervasive Developmental Disorder

The symptoms might cause only social and comm… challenges. People with PDD-NOS usually have f… milder symptoms than those with autistic disorder.

2002 1 : 1

2006 1 : 1

~~1 in 150~~ children in the US have an AS…

2014 1 : 68 !?

meaning

1% of the population of children aged 3-17 have an ASD

with

ASDs 4 to 7 times more likely to occur in BOYS than in GIRLS

2008 1 :

There is no medical test to diagnose ASDs, doctors look at the child's behavior and development to make a diagnosis.

About half of parents of children with ASD notice their child's unusual behaviors by age 18 months

about four-fifths notice by age 24 months

2014 1 :

A person with an ASD might: Not respond to their name by 12 months | Avoid eye contact and want to be alone | Have delayed speech and language skills | Repeat words or phrases over and over (echolalia) | Give unrelated answers to questions | Get upset by minor changes

ASDs are the fastest-growing developmental disability **1,148%** growth rate with **10-17%** annual growth

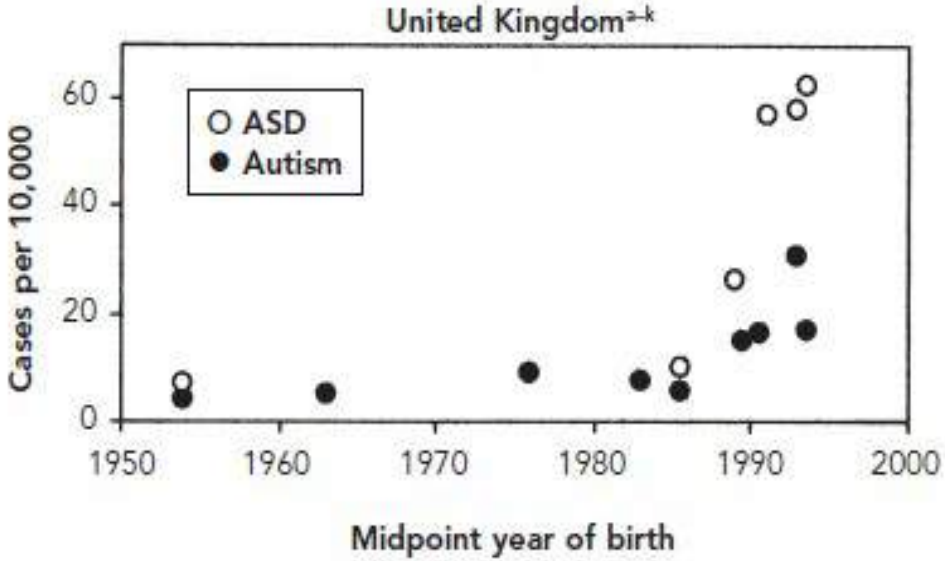
Reports of autism cases per 1,000 children

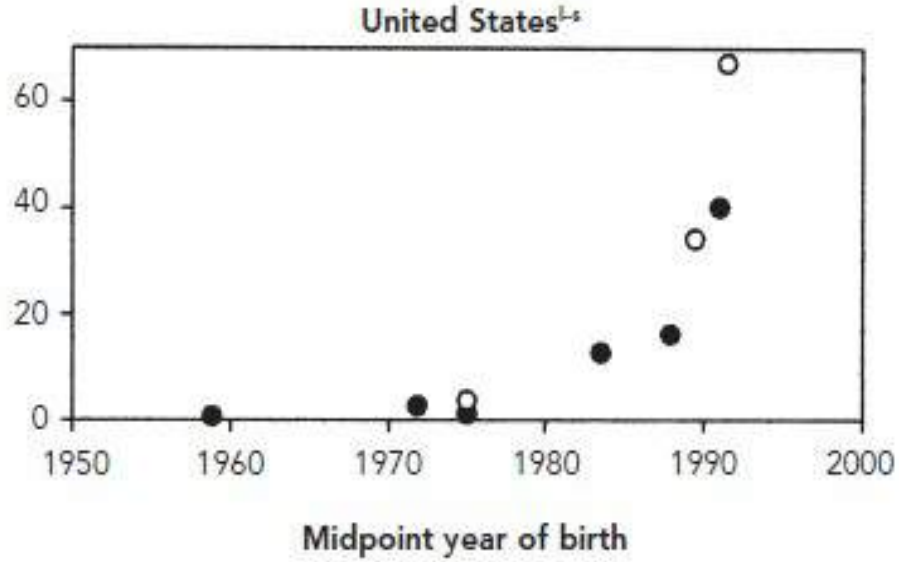
Lifetime cost to care for an individual with an ASD
Estimated from recent studies

$3.2m with **$4,110–$6,200** per year of medical expenditures for an individual with an ASD than one without

http://arstechnica.com/science/2012/04/new-autism-studies-find-new-mutations-many-genes-behind-the-disorder/

Figure 1. Reported prevalence of autism and autistic spectrum disorders (ASDs), by midpoint year of birth, United Kingdom and United States, 1954–1994





NOTE: These graphs show prevalence estimates from 11 U.K. and 8 U.S. studies. For studies with survey populations spanning a range of birth years, the midpoint of the birth year range is used.

[a]Lotter 1966[35]

[b]Wing and Gould 1979[42]

[c]Deb and Prasad 1994[82]

[d]Webb et al. 1997[89]

[e]Taylor et al. 1999[20]

[k]Baird et al. 2000[78]

[l]Treffert 1970[36]

[m]Ritvo et al. 1989[53]

[n]Burd et al. 1987[45]

[o]California Department of Developmental Services 2003[2]

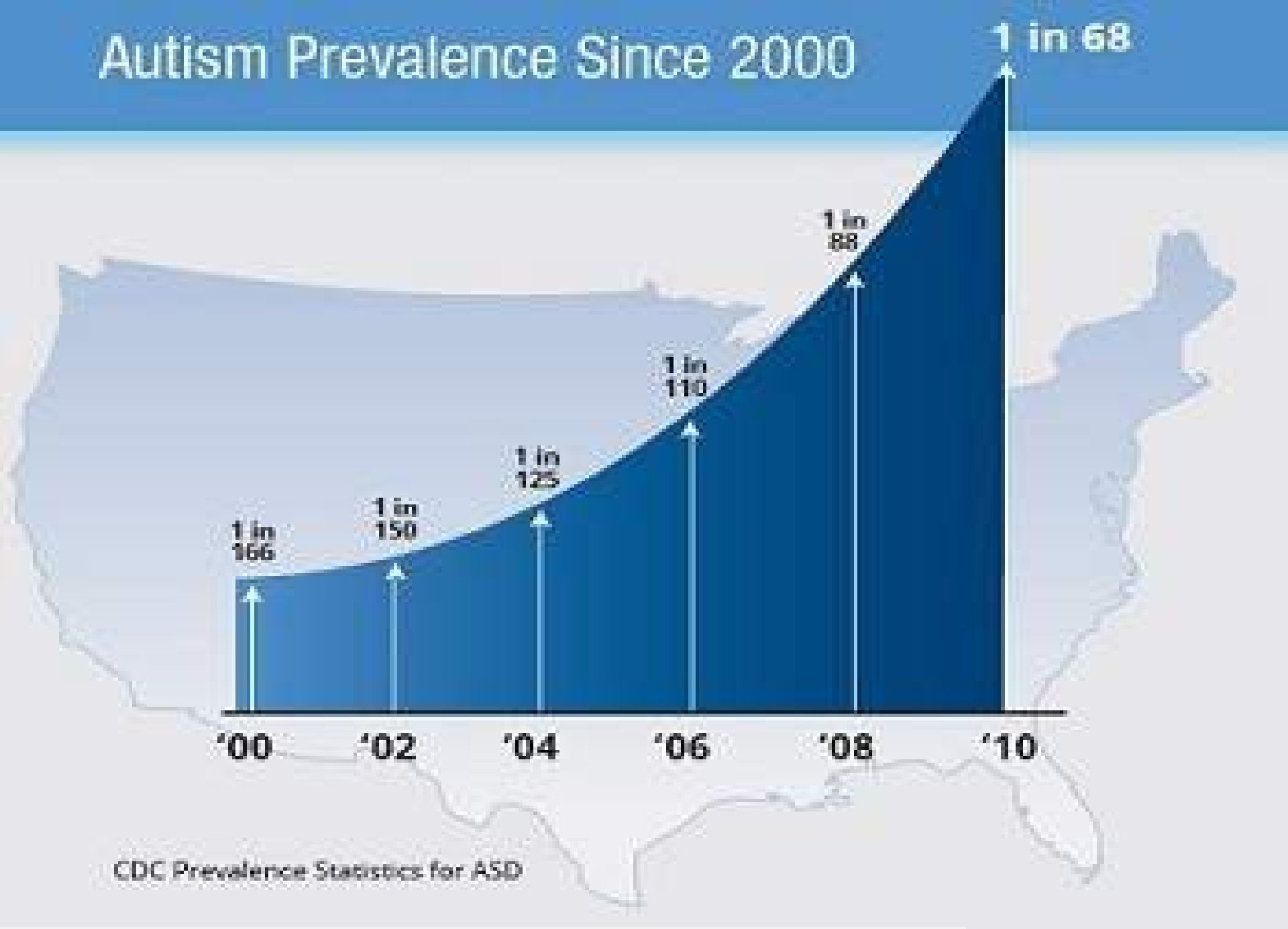
AUTISME
(ASD :Autism Spectrum Disorders)

ASD is the fastest-growing developmental disorder in the world,

the prevalence of diagnosis having increased by 600% over the last 20 years

New diagnosed cases (**inci**
15,580 in 1992
to 163.773 in 2003

The estimated **prevalence**
of 8-12 cases/1000 children (2012)



http://www.autismconsortium.org/blog/detail/cdc-releases-new-prevalence-numbers-of-

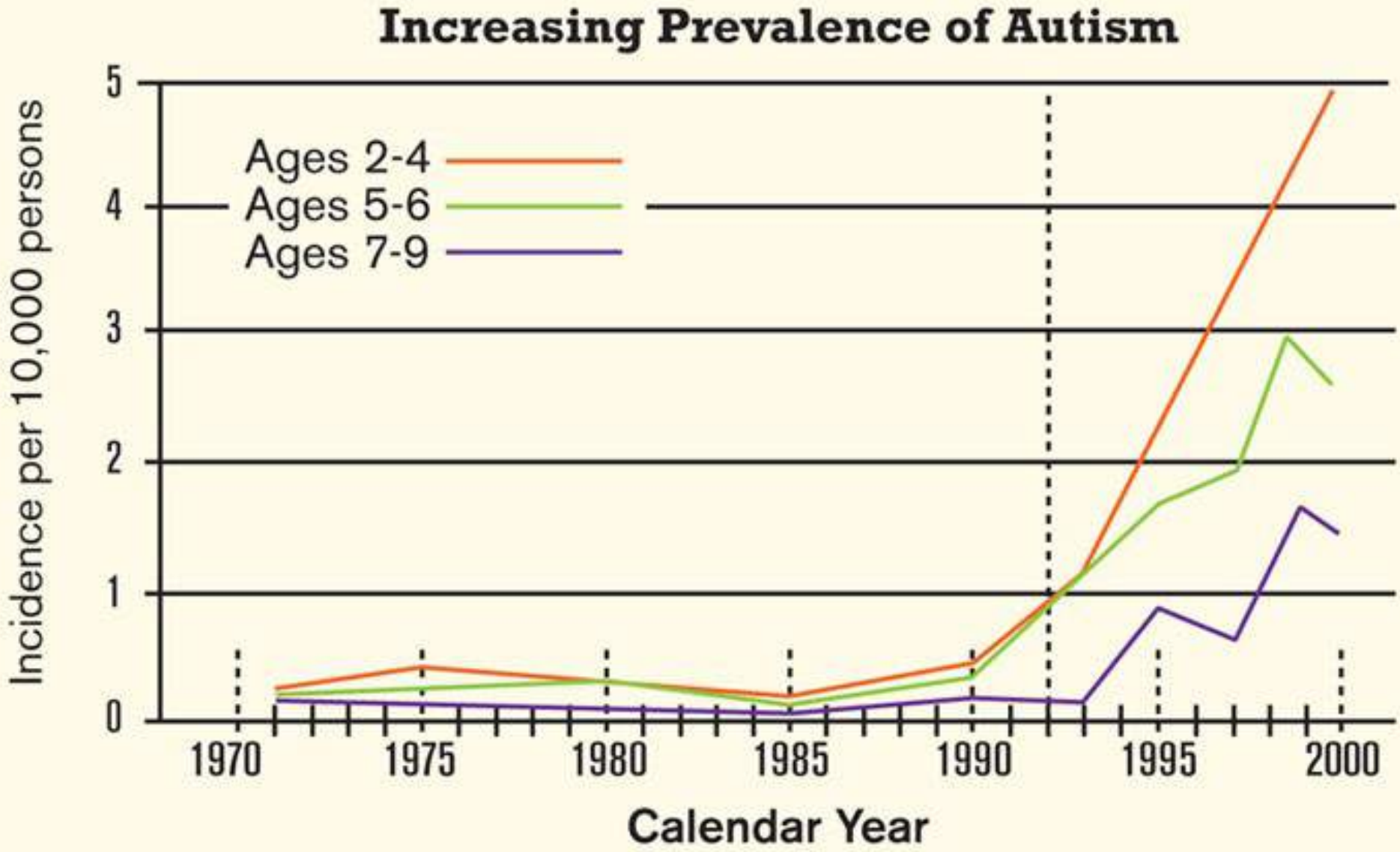


FIGURE 1. Incidence of autism by age and calendar year[89]

Il 17% dei bambini US < 18°a. ha un disturbo dello sviluppo, per lo più a carico del SN

Disturbi dell'apprendimento

ADHD

Disordini dello spettro autistico

Ritardo mentale

Problemi comportamentali

Analoghe sono le cifre europee

Il cervello è un organo prezioso e vulnerabile e, poiché il suo funzionamento ottimale dipende dalla sua integrità, anche danni limitati possono avere conseguenze serie (Grandjean 2006)

Grandjean P.

A Silent Pandemic

Industrial Chemicals Are Impairing The Brain Development of Children Worldwide

For immediate release: Tuesday, November 7, 2006

Landrigan P

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.

Neurobehavioural effects of developmental toxicity

Philippe Grandjean, Philip J Landrigan

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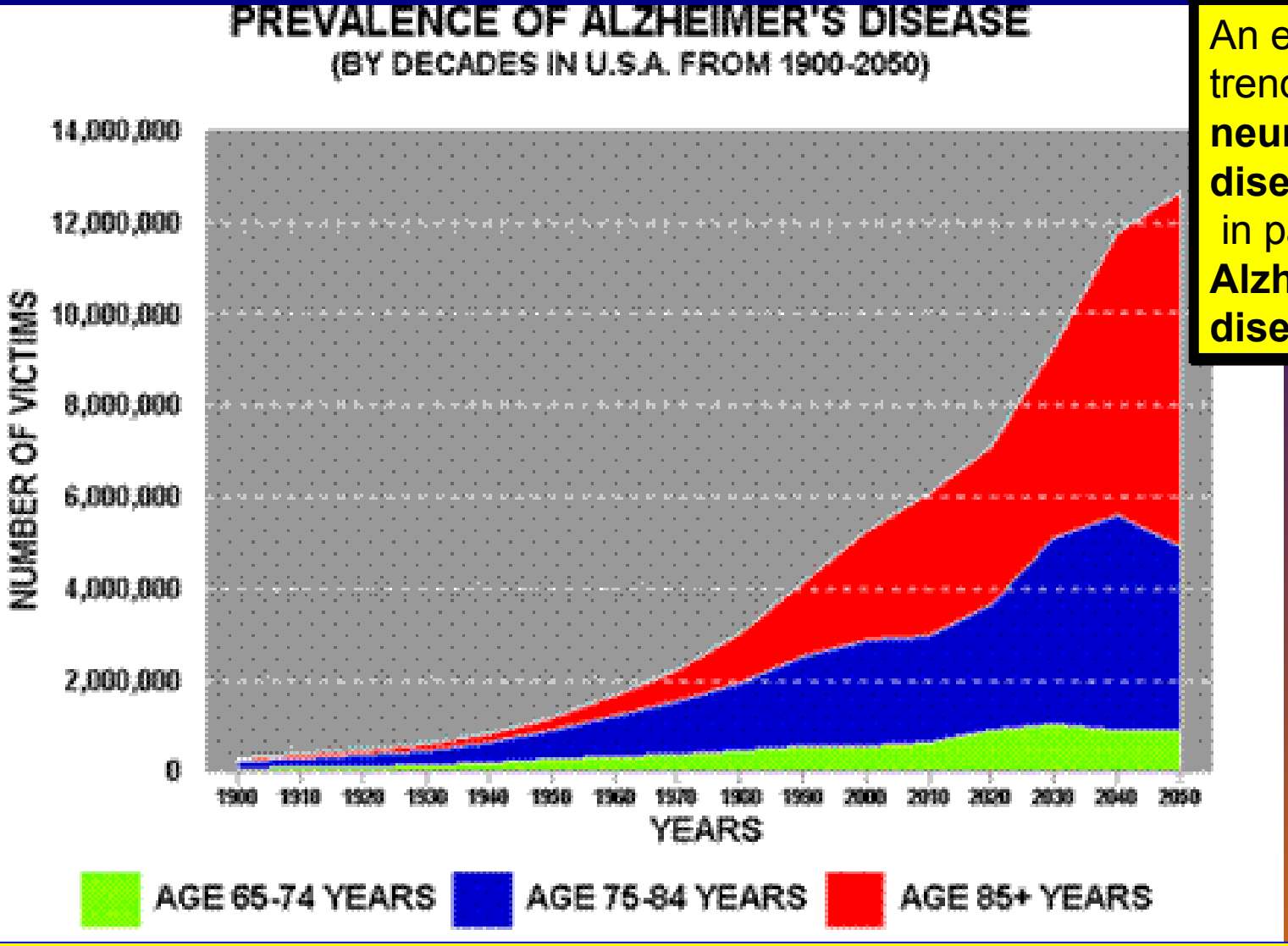
Neurodevelopmental disabilities, including autism, attention-deficit hyperactivity disorder, dyslexia, and other cognitive impairments, affect millions of children worldwide, and some diagnoses seem to be increasing in frequency. Industrial chemicals that injure the developing brain are among the known causes for this rise in prevalence. In 2006, we did a systematic review and identified five industrial chemicals as developmental neurotoxicants: lead, methylmercury, polychlorinated biphenyls, arsenic, and toluene. Since 2006, epidemiological studies have documented six additional developmental neurotoxicants—manganese, fluoride, chlorpyrifos, dichlorodiphenyltrichloroethane, tetrachloroethylene, and the polybrominated diphenyl ethers. We postulate that even more neurotoxicants remain undiscovered. To control the pandemic of developmental neurotoxicity, we propose a global prevention strategy. Untested chemicals should not be presumed to be safe to brain development, and chemicals in existing use and all new chemicals must therefore be tested for developmental neurotoxicity. To coordinate these efforts and to accelerate translation of science into prevention, we propose the urgent formation of a new international clearinghouse.

Since 2006, epidemiological studies have documented **six additional developmental neurotoxicants — manganese, fluoride, chlorpyrifos, tetrachloroethylene, dichlorodiphenyltrichloroethane,, and the polybrominated diphenyl ethers.**
We postulate that even more neurotoxicants remain undiscovered



An equally dramatic trend show **neurodegenerative diseases** and in particular **Alzheimer's disease**

Since 2000 there has been a **66% increase in Alzheimer's diagnoses**.
6th leading cause of death in the United States.
5.4 million Americans are living with the disease.
15-20 million more Americans will be diagnosed by 2040

Type 1 diabetes

Organ specific **autoimmune** disease

- **85% of patients have islet cell antibodies at presentation**
- Beta cell destruction takes place over a prolonged period of time
- **Diabetes develops when 80% of beta cells have been destroyed**

Genetics

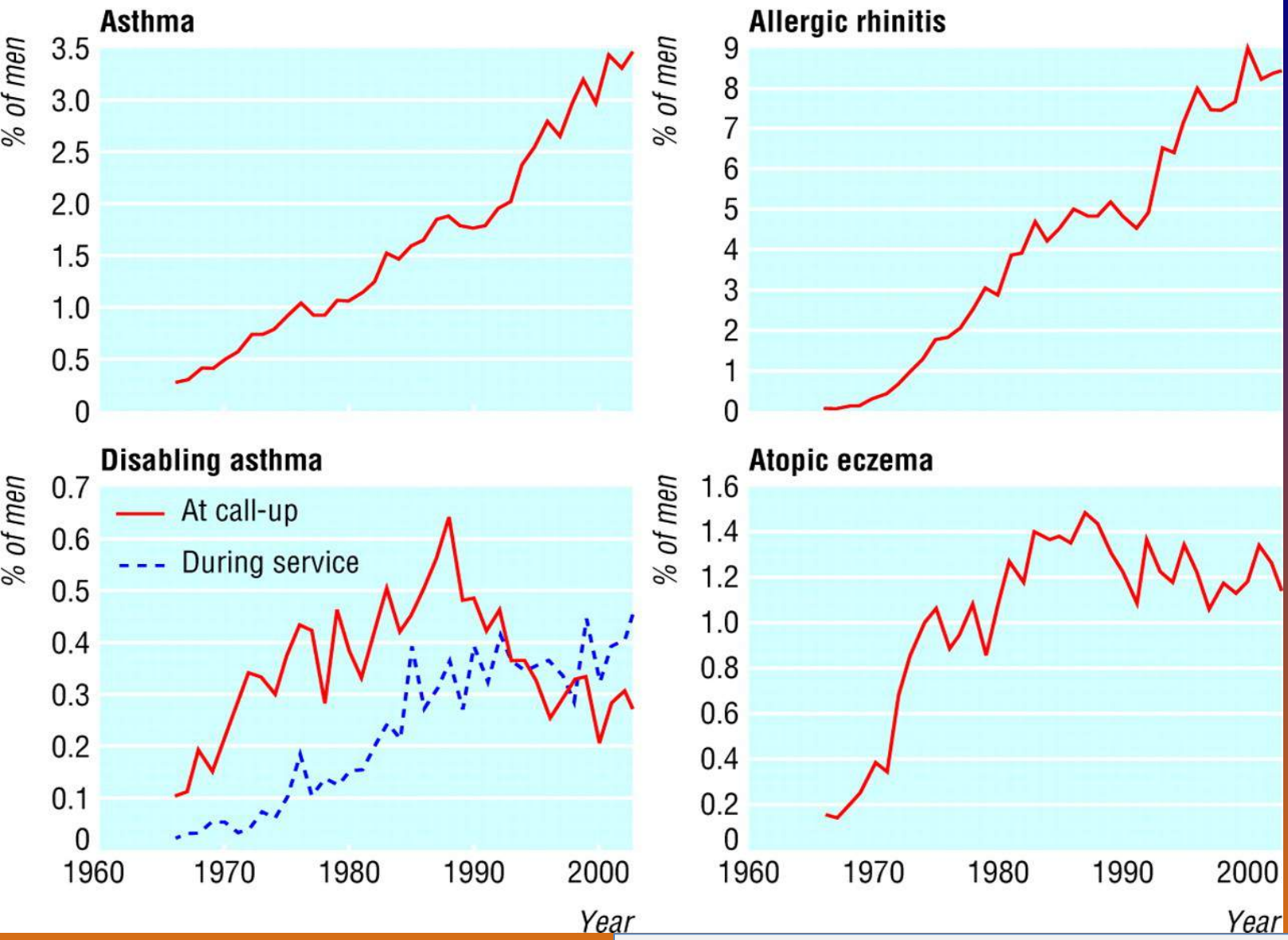
- **Up to 98% of patients are HLA DR3 or HLA DR4**
- Even stronger association with DQ alleles (**HLA-DQB1**)
- **Concordance rate in monozygotic twins only 30%**

Increasing Incidence

- **Incidence doubling every 30 years**
- **The incidence is rising particularly quickly in children under the age of 5**

Enteroviruses

- ***Coxsackie B virus*** cultured from the pancreas of one diabetic child. The virus caused diabetes when injected into mice.
- 30% of newly diagnosed diabetic patients and 5% of controls have IgM antibodies to ***Coxsackie B virus.***
- 27% of newly diagnosed diabetic children and 5% of controls have ***enteroviral RNA*** in serum at diagnosis.
- 51% of pre-diabetic children have evidence of ***enteroviral infection*** in the 6 months **before autoantibody seroconversion** compared with 28% in controls

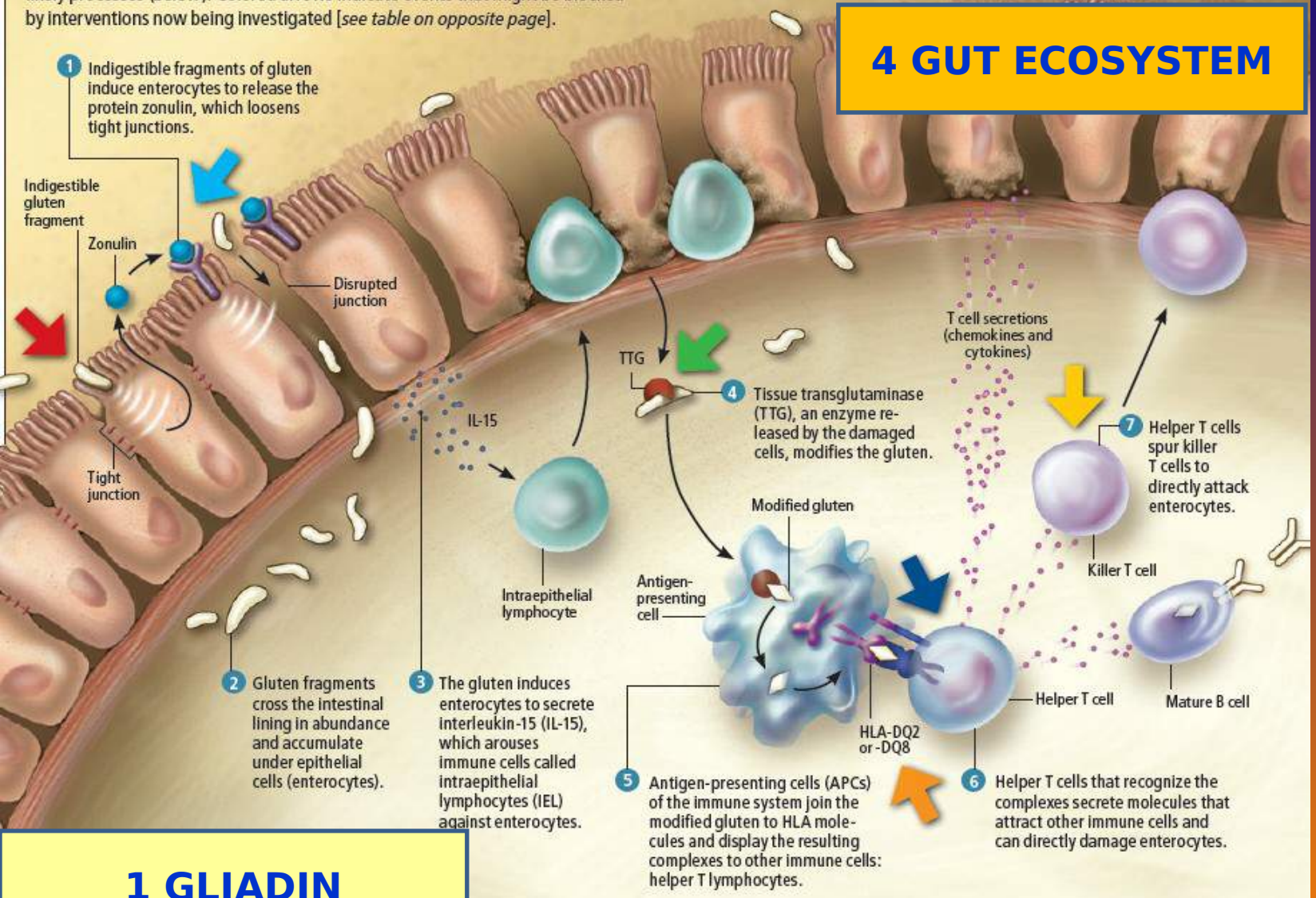


Trends in prevalence of asthma and allergy in Finnish young men
http://www.bmj.com/content/330/7501/1186

The ***prevalence*** of **asthma increased 12-fold between 1966 (0.29%) and 2003 (3.45%),** showing a continuous rising trend ... **The average annual increment** in prevalence during this period **was 0.1%.** By contrast, **the trends for indicators of disabling asthma turned downwards in 1989**

THE INSIDE STORY

Investigators do not know every detail of how the immune system wreaks havoc with the intestinal lining of celiac patients, but they have identified a number of likely processes (*below*). Colored arrows indicate events that might be blocked by interventions now being investigated [*see table on opposite page*].



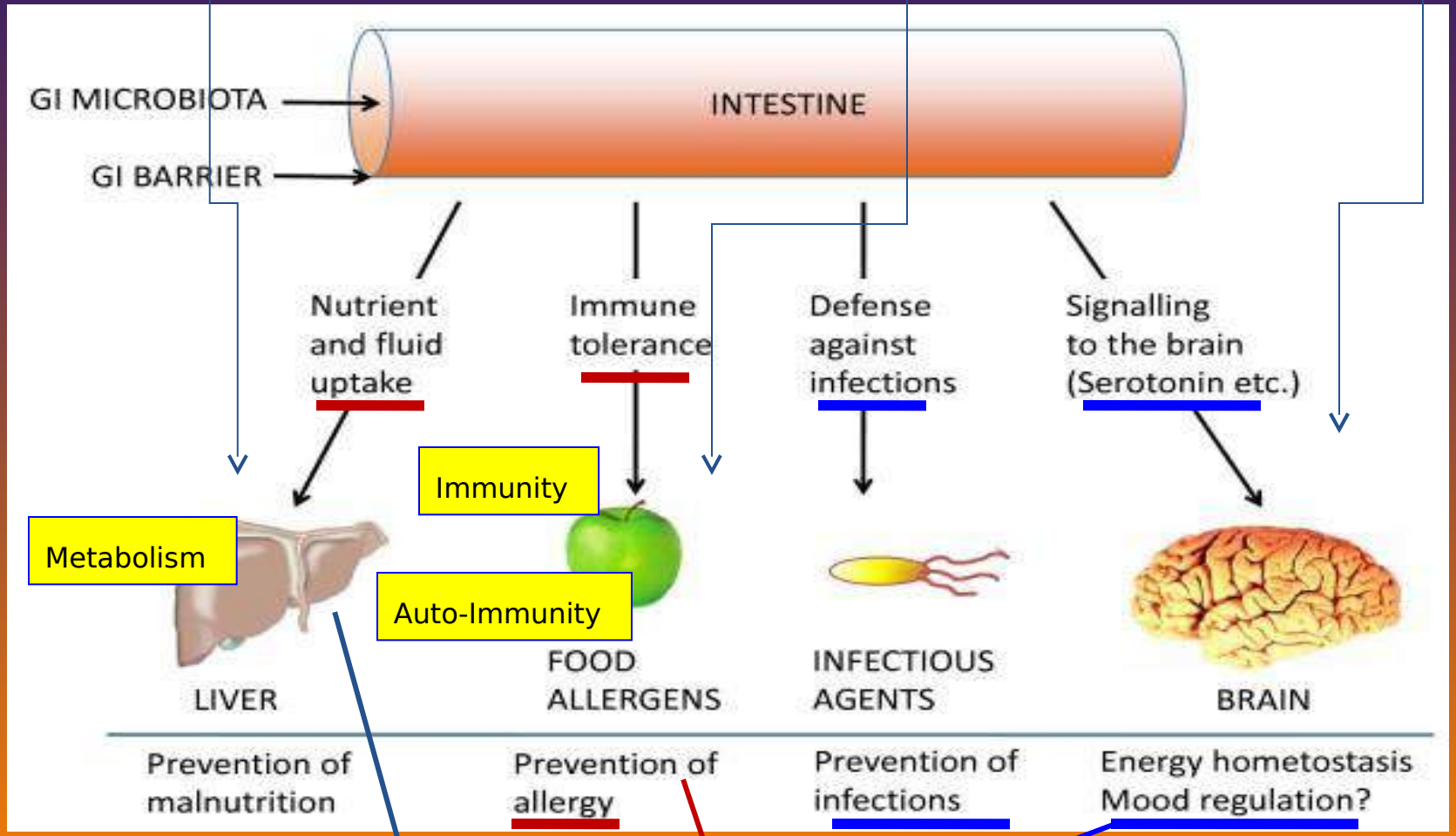
3 GUT PERMEABILITY

4 GUT ECOSYSTEM

1 GLIADIN

2 DQ2 – DQ8

The *dysbiosis* impacts on health: the *microbiome* a main epigenetic factor in development



IBDs-Metabolic Syndrome-Atherosclerosis-Depression…

No one likes to talk about a **CANCER PANDEMIC**.. But we must not forget that today, practically all over the North of the world, **one person out of two is likely to have a cancer** ..

CANCER RESEARCH UK

Science Update blog

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Men's cancer risk is climbing: what can we do about it?

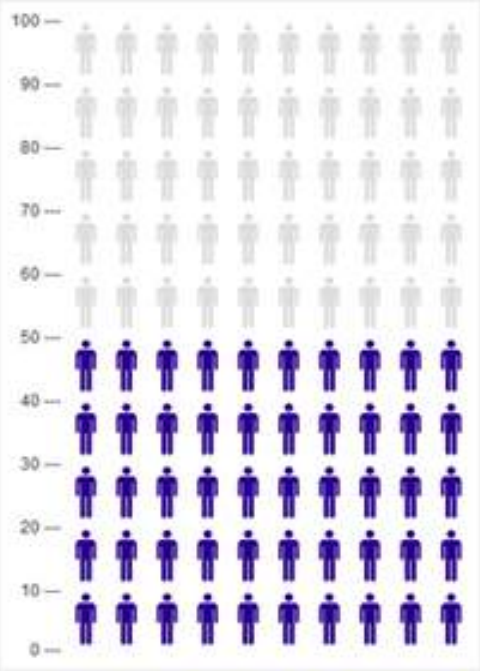
Posted on December 19, 2012 by Oliver Childs

A boy born in 2027 in the UK will have a **one in two** chance of developing cancer over the course of his lifetime, according to new figures we released today.

In other words, 50 in every 100 UK men in the future are likely to hear the words "you have cancer" at some point in their lifetime. However you say it, that's clearly not a positive headline.

But crucially, this increasing lifetime risk of cancer is balanced by another powerful force – that of increasing survival rates. Against a backdrop of increasing cancer risk over the past 40 years, **survival rates have doubled in the UK**.

This is thanks to our greatest weapon against cancer – research, be it new treatments or new ways to prevent people getting cancer in the first place.



If current trends continue, half of UK men born in 2027 will

Il rischio di ammalarsi di tumore

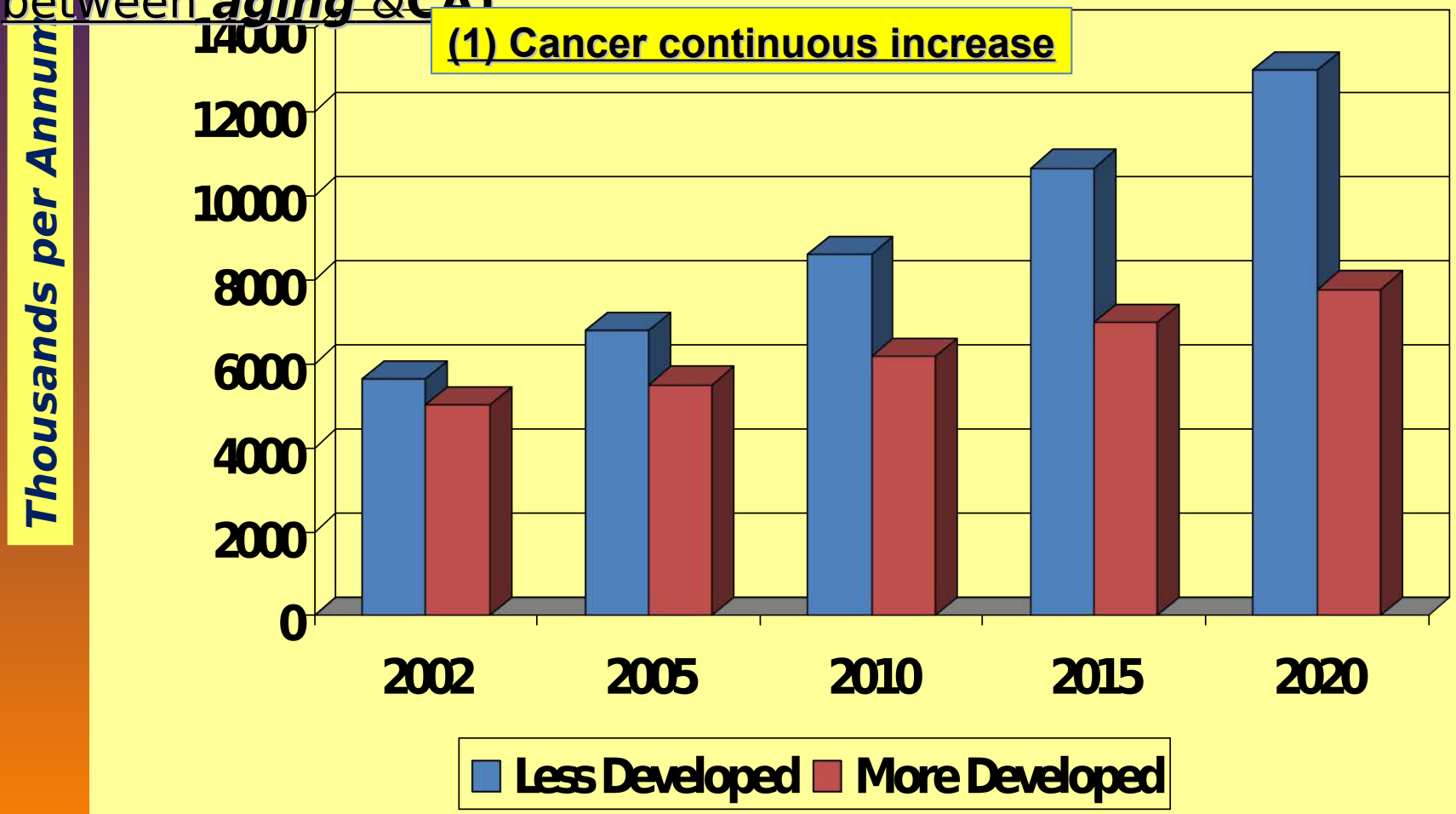
The risk of developing cancer

RISCHIO CUMULATIVO
OGNI QUANTE PERSONE UNA È DESTINATA AD AMMALARSI O MORIRE DI CANCRO?

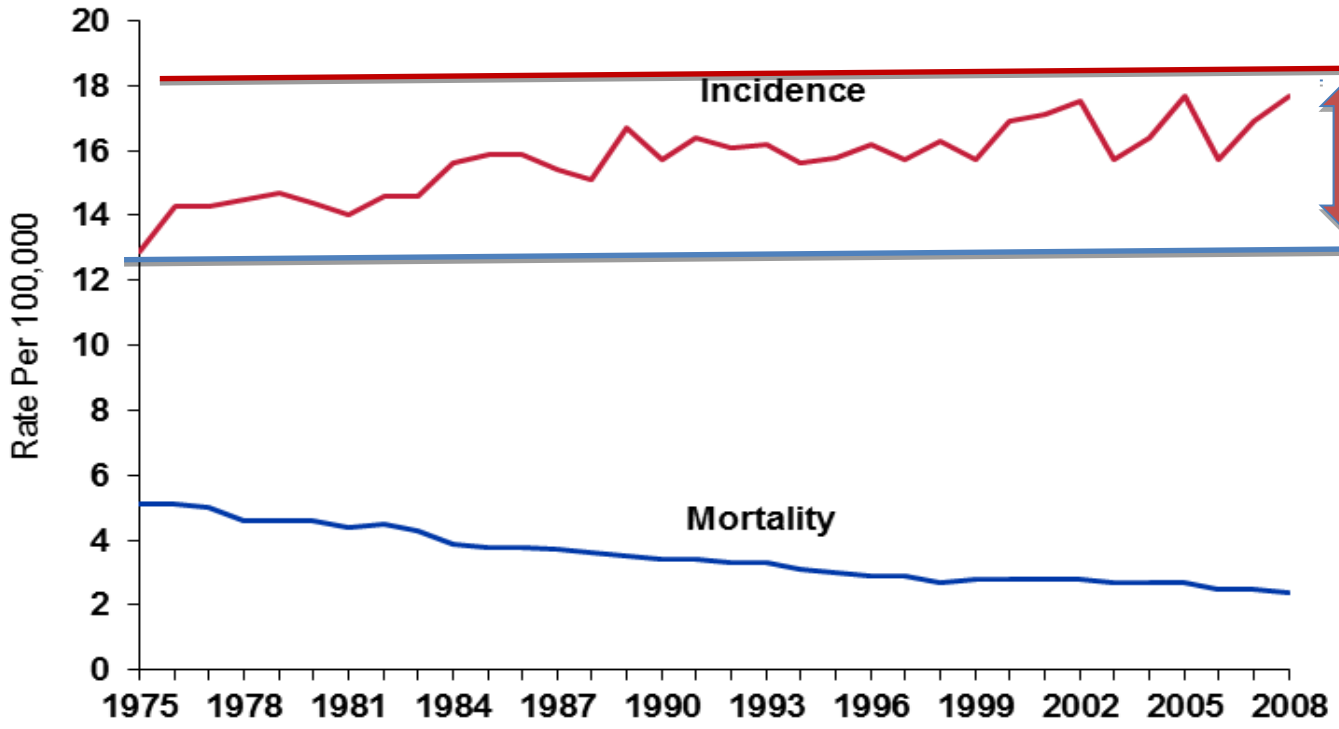
	UOMINI		DONNE	
	INCIDENZA	MORTALITÀ	INCIDENZA	MORTALITÀ
Totale (escluso epiteliomi della cute)	2	3	2	6
Prostata	7	33		
Mammella	614		8	33
Cute non melanomi	8		14	
Polmone	9	10	40	48
Colon Retto	11	26	17	46
Vescica	20	55	122	336
Stomaco	26	38	53	81

Complessivamente, in media,
1 uomo su 2 e 1 donna su 2 saranno colpiti da tumore nel corso della vita
1 uomo su 3 e 1 donna su 6 ne moriranno

the **significant increase** in the **Less Developed Countries** & **in young people all over the world** demonstrates the limits of the SMT (→**necessary link** between ***aging*** &**CA**)



Cancer Incidence and Death Rates* in Children 0-19 Years, 1975-2008

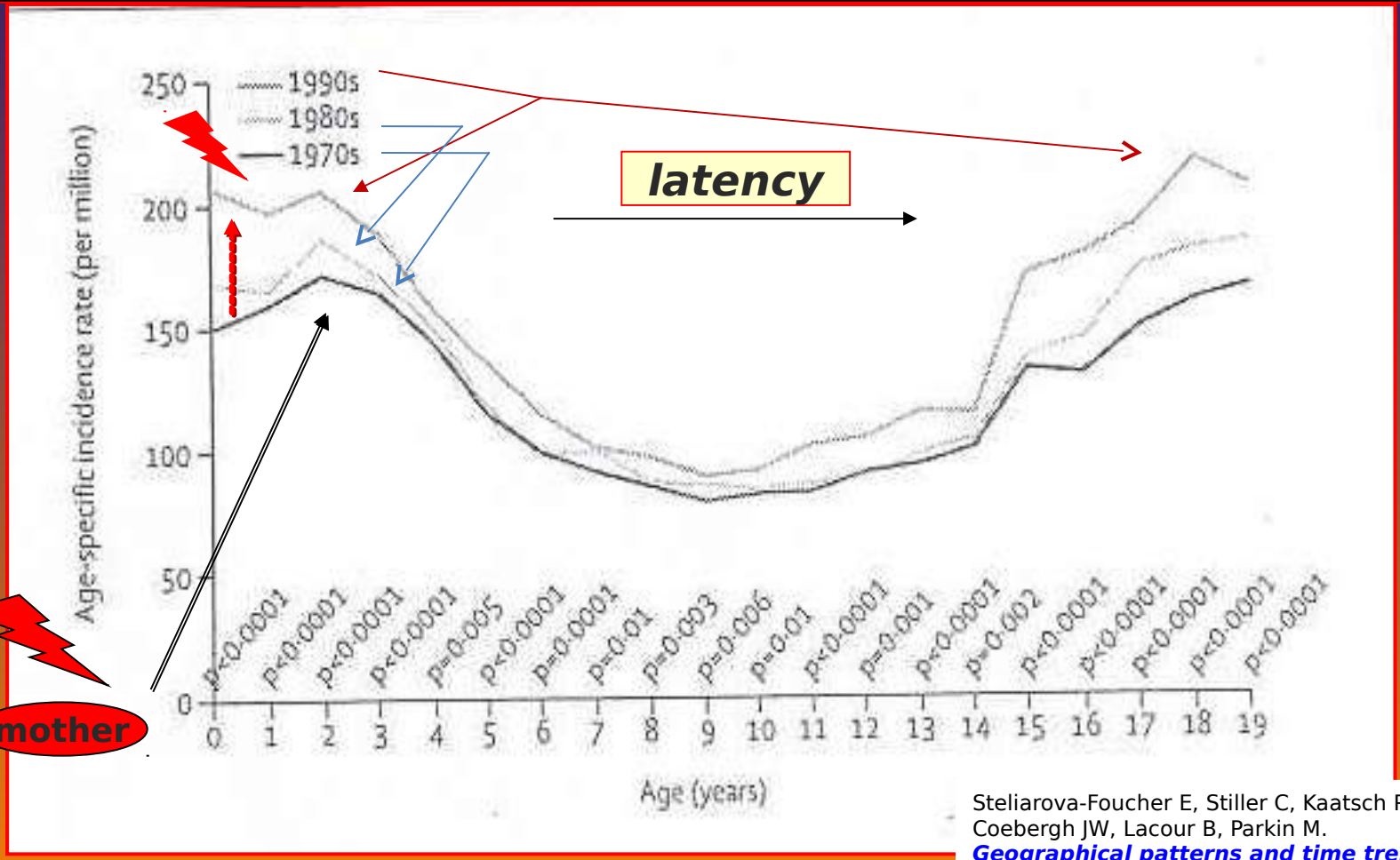


*Age-adjusted to the 2000 Standard population.
Source: Incidence - Surveillance, Epidemiology, and End Results Program, 1975-2008, Delay-adjusted incidence database. National Cancer Institute, 2011. Mortality – National Center for Health Statistics, 2011.

We should always consider the **epidemiological data in the medium and long term**, not to be deceived by the inevitable fluctuations. It's evident that the **incidence rates have increased dramatically over the past 30 years in the US, from 130 to 170-180 new cases/year per million** inhabitants (to demonstrate the importance of these data, **it is useful to remember that a very similar increase occurred in Europe in the same period)**

A first draft of the report, published on ***the Lancet*** in **2004**, demonstrated an **annual increase of 1-1,5% for all cancers** (with more marked increases in **lymphomas**, **soft tissue sarcomas**, **tumours of the nervous system...**) . But the **most troubling was the increase - almost the double** - for all cancers **in the very first year of life (apparently due to transplacental or even trans-generational exposure)**

http://www-dep.iarc.fr/accis.h



Steliarova-Foucher E, Stiller C, Kaatsch P, Berrino F, Coebergh JW, Lacour B, Parkin M.
Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS project): an epidemiological study.
Lancet. 2004 Dec 11-17;364(9451):2097-105

Fetal programming

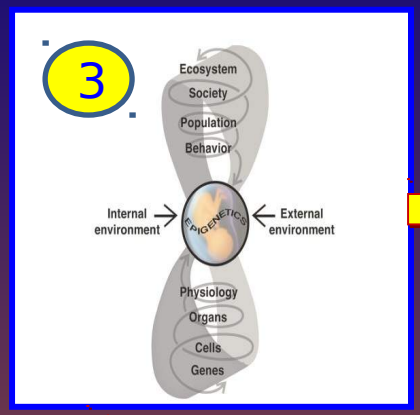
Ontogenesis

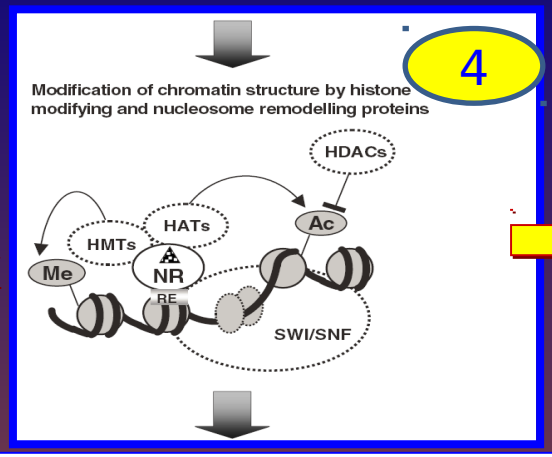
Epigenetic versus *genetic* origins of health and diseases: the 7 key words

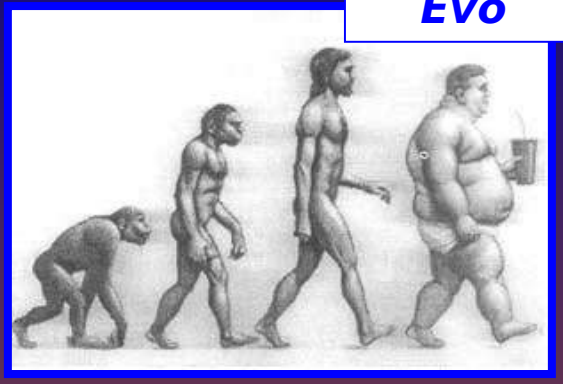
Evolutionary Medicine

Phylogenesis

Devo-Evo







Developmental Plasticity

6 **Mismatch/DOHA**

2

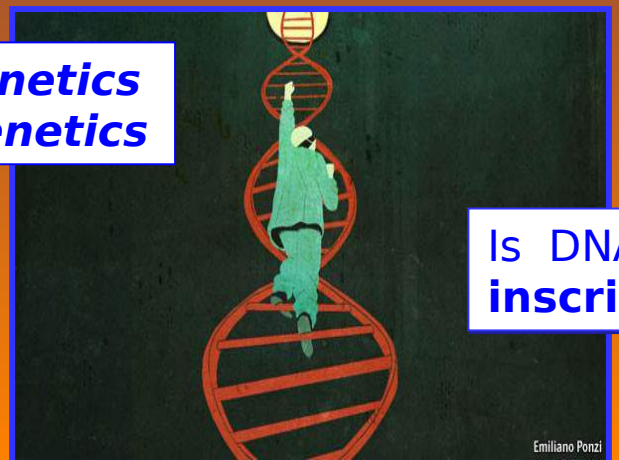
Environment

At this point, **having quickly mapped out the dramatic *epidemiological transition* underway**, we can briefly examine **the other 6 key words** ..

7 ***XX Century Epidemiologic Transition***

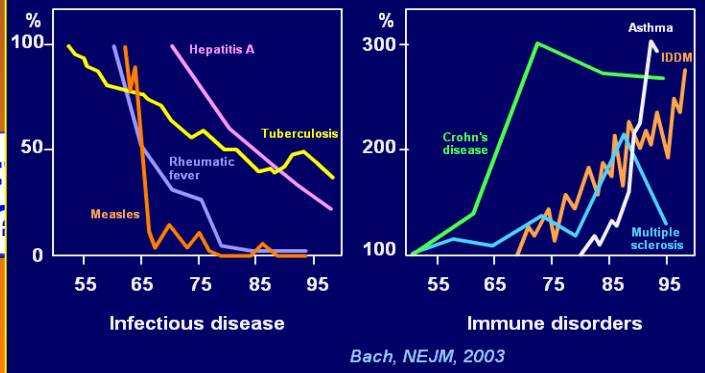
1

rom Genetics o Epigenetics



Is DNA a sort of **Projec inscribed in our cells**?

Incidence of prototype infectious disease and immune disorders over 4 decades

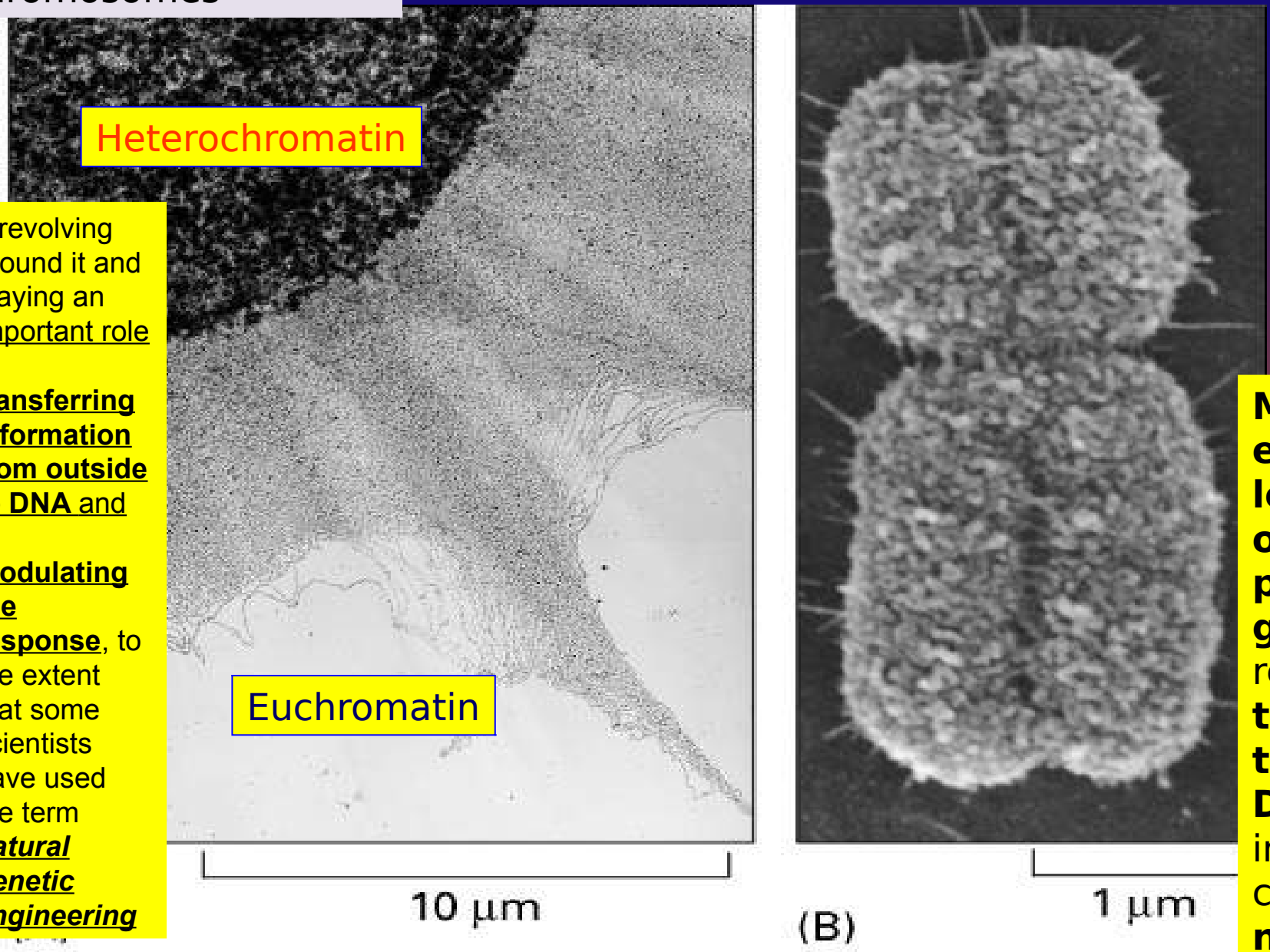


Bach, NEJM, 2003

Interphase chromosomes

What's Epigenetics ?

c chromosome



...revolving around it and playing an important role in **transferring information from outside to DNA** and in **modulating the response**, to the extent that some scientists have used the term ***natural genetic engineering***

Multiple levels of packing are required **to fit the DNA** into the cell **nucleus**

Figure 4–21. Molecular Biology of the Cell, 4th Edition.

DNA double helix (2-nm diameter)

Histones

"Beads on a string"

Nucleosome (10-nm diameter)

Nuclear DNA is **normally tightly wrapped around histones**

ht helical fiber (30-nm diameter)

Supercoil (200-nm diameter)

Metaphase chromosome

700 nm

Euchromatin

Multiple levels of packing are required **to fit the DNA** into the cell **nucleus**

Heterochromatin

Campbell NE et al (Eds): Biology: Concepts & Connections 4th Edition, 2003

nature biotechnology

COMMENTARY

Le **Dogme Central de Crick**: *Une fois l'information a pénétré dans une protéine ne peut pas sortir à nouveau* (***one direction-linear flow of information***)

EPIGENESIS AND COMPLEXITY

The coming Kuhnian revolution in biology

Richard C. Strohman

The Watson-Crick era, which began as a narrowly defined and proper theory and paradigm of the gene, has mistakenly evolved into a revived and thoroughly molecular form of genetic determinism.

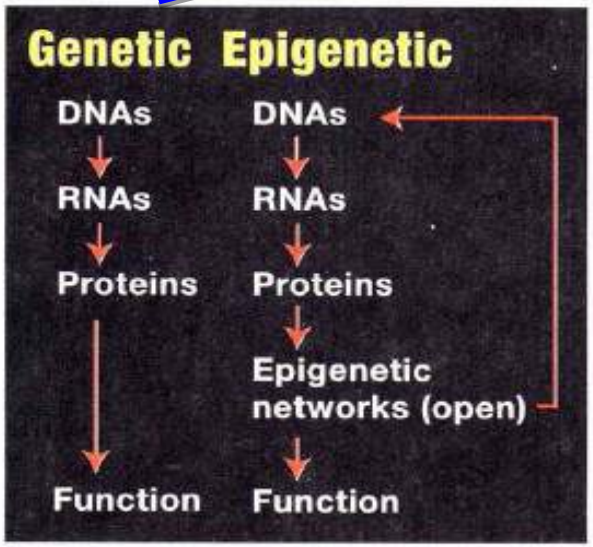


Figure 1. Genetic and epigenetic theories of information processing.

Pour citer le biologiste moléculaire Richard C. Strohmann : l'ère de **Watson et Crick**, qui a commencé comme une **théorie du gène a évolué à tort dans une théorie et le paradigme de la vie**: c'est a dire, dans une **forme revivifiée et soigneusement moléculaire du déterminisme génétique**

Science

AAAS

ScienceInsider

Breaking news and analysis from the world of science policy

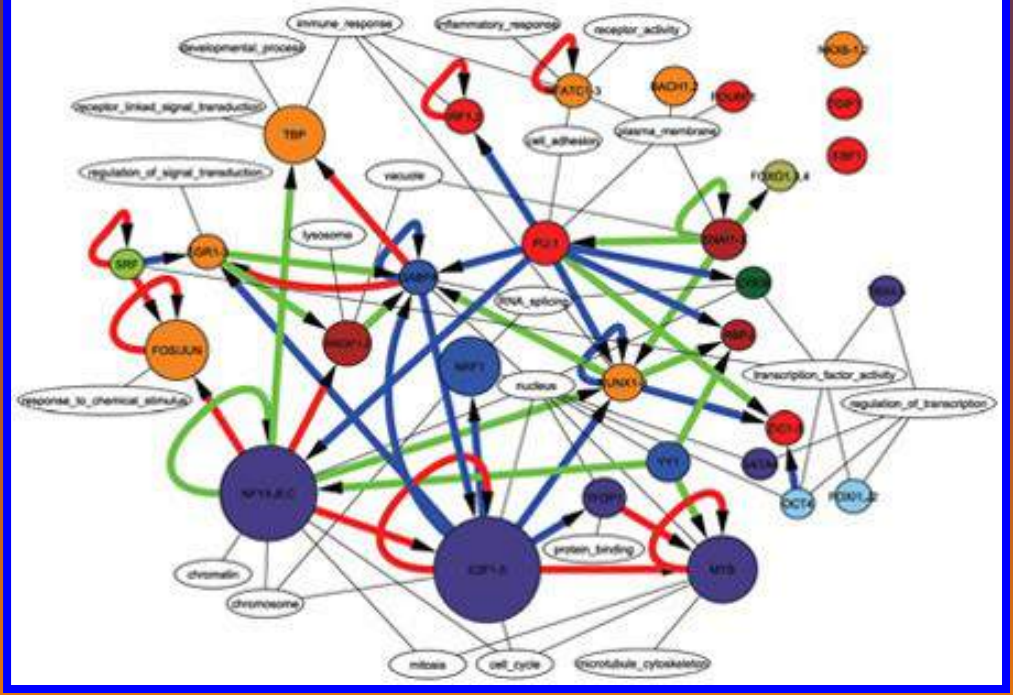
From directing **the fate of stem cells to determining how.. we grow**, **the genes in our body act in complex networks..** the whole ***Genome*** is a Complex and **highly**

….Genes Know How to Network…BUT…

n R. , April 2001 ***Beyond genetic inism***

sequences! and ***proteins***

http://news.sciencemag.org/sciencenow/2009/04/21-03.html



IN FACT Genes need to be told to switch "off" and "on":

- **Genes need to be told** how much **expression (protein) is required** and where.
- **Genes need to be regulated** – this **regulation is not performed by DNA** but by many other controls arranged in a **complex network**
- *DNA* has been called the ***Book of Life*** by the *Human Genome Project* scientists, but many other biologists consider **DNA to be simply a random collection of words from which a meaningful story of life may be assembled…**
- **In order to assemble that meaningful story, a living cell uses a second informational system. (…) The key concept here is that these**

Epigenetic Regulation, a mechanism that

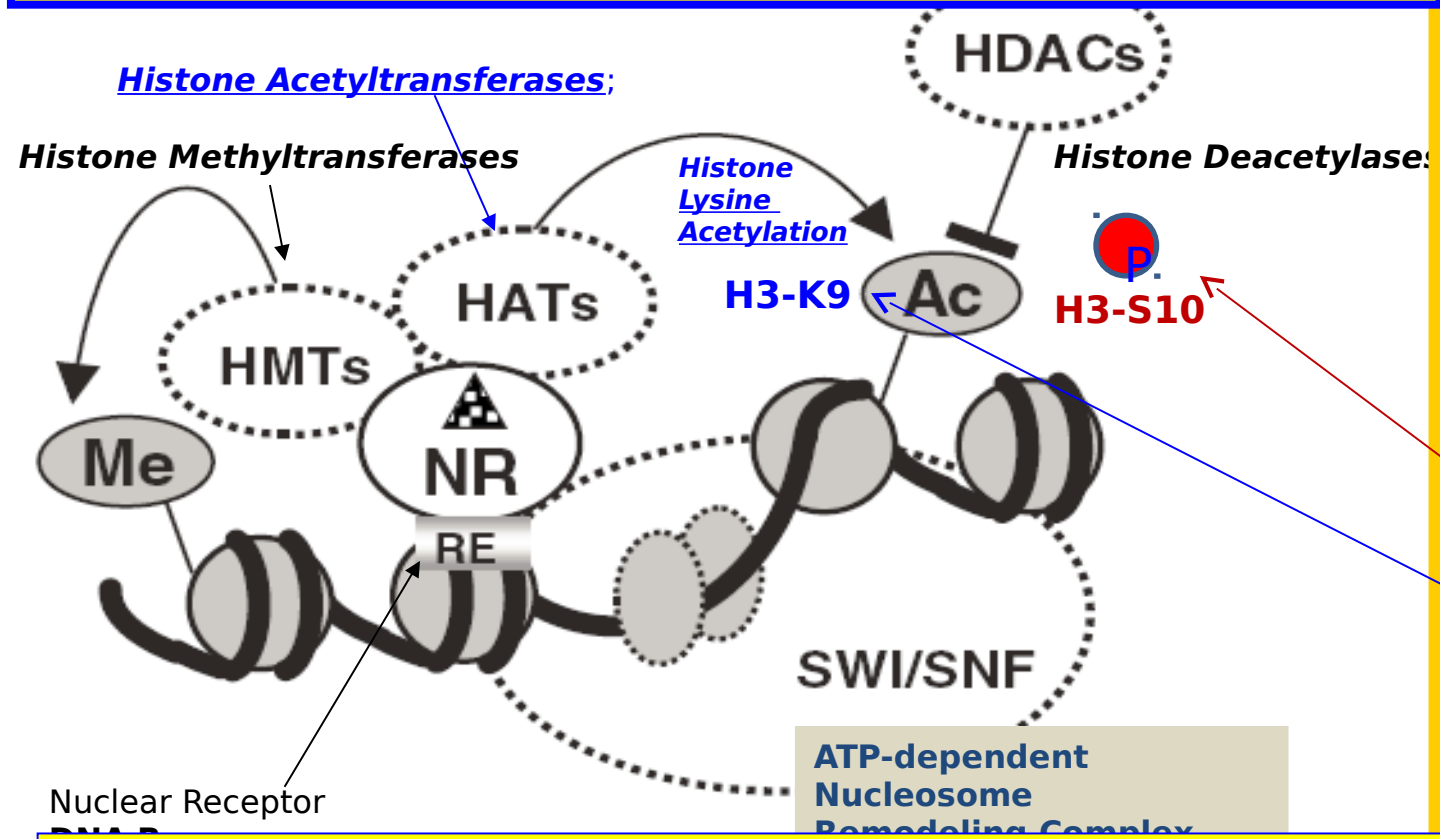
allows the genome to integrate

- ***intrinsic*** **with**
- ***environmental*** **signals**

Rudolf Jaenisch Whitehead Institute

The "***meeting-point***" between the **information** coming from the **environment** and the information encoded in the **DNA (*hardware*)** is the ***epigenome (software)***: ***mimetic molecules (EDCs)*** and other ***pollutants*** or ***danger-signals*** **induce the epigenome to change**

Many toxicants cause rapid alterations in gene expression by **activating protein kinase signaling cascades.**



The resulting **rapid, defensive alterations in gene activity require the transmission of a signal directly to the histones** present in the **chromatin of stress response genes**:

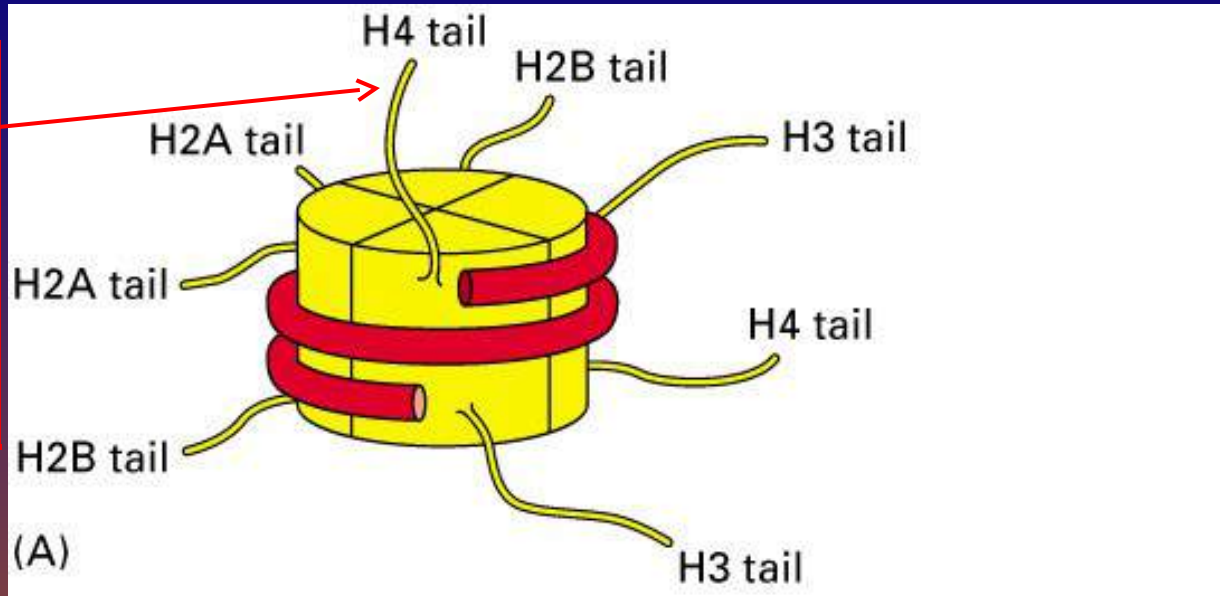
within minutes of exposure the

phorylation erine 10 of histone H3 and the

Chromatin itself is the direct target of many toxicants * … toxicant-induced perturbations in chromatin structure may precipitate adverse effects.. Forcing genome to change

The **Histone tails** are a **critical determinant** of chromatin structure

1



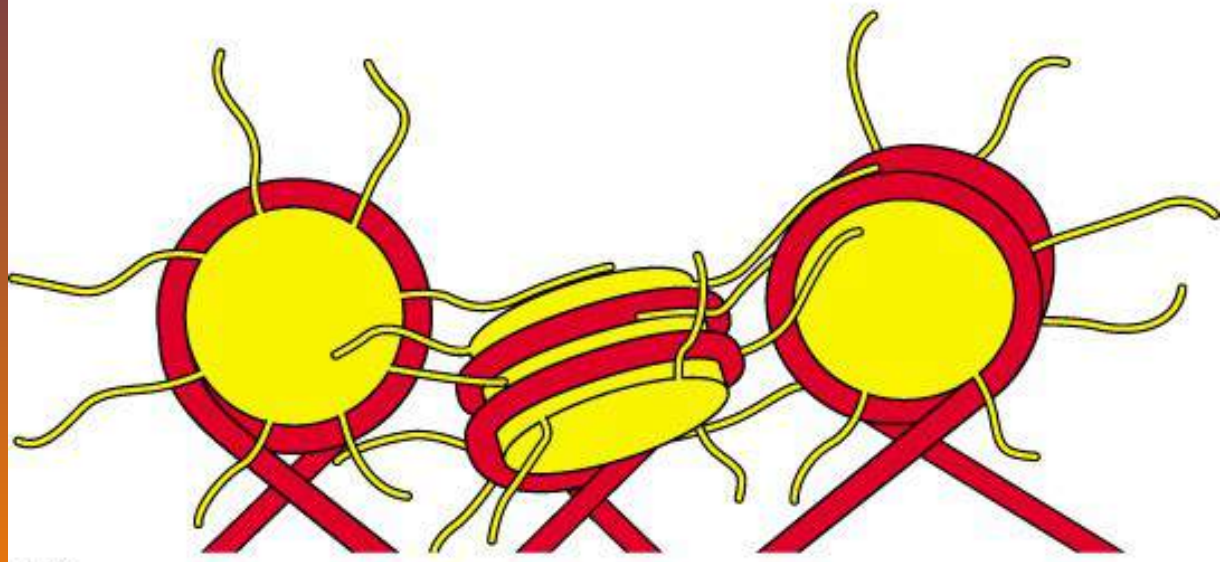


Figure 4–32. Molecular Biology of the Cell, 4th Edition.

Histone Tails are subject to a variety of **covalent modifications**

Histone Code" hypothesis: **modifications of the Histone tails** act as marks **read by other proteins** to control the **expression** or **replication** of chromosomal regions

E.g. generally, ***Histone Acetylation*** *is associated with* ***transcriptionally active genes***

Deacetylation is associated with

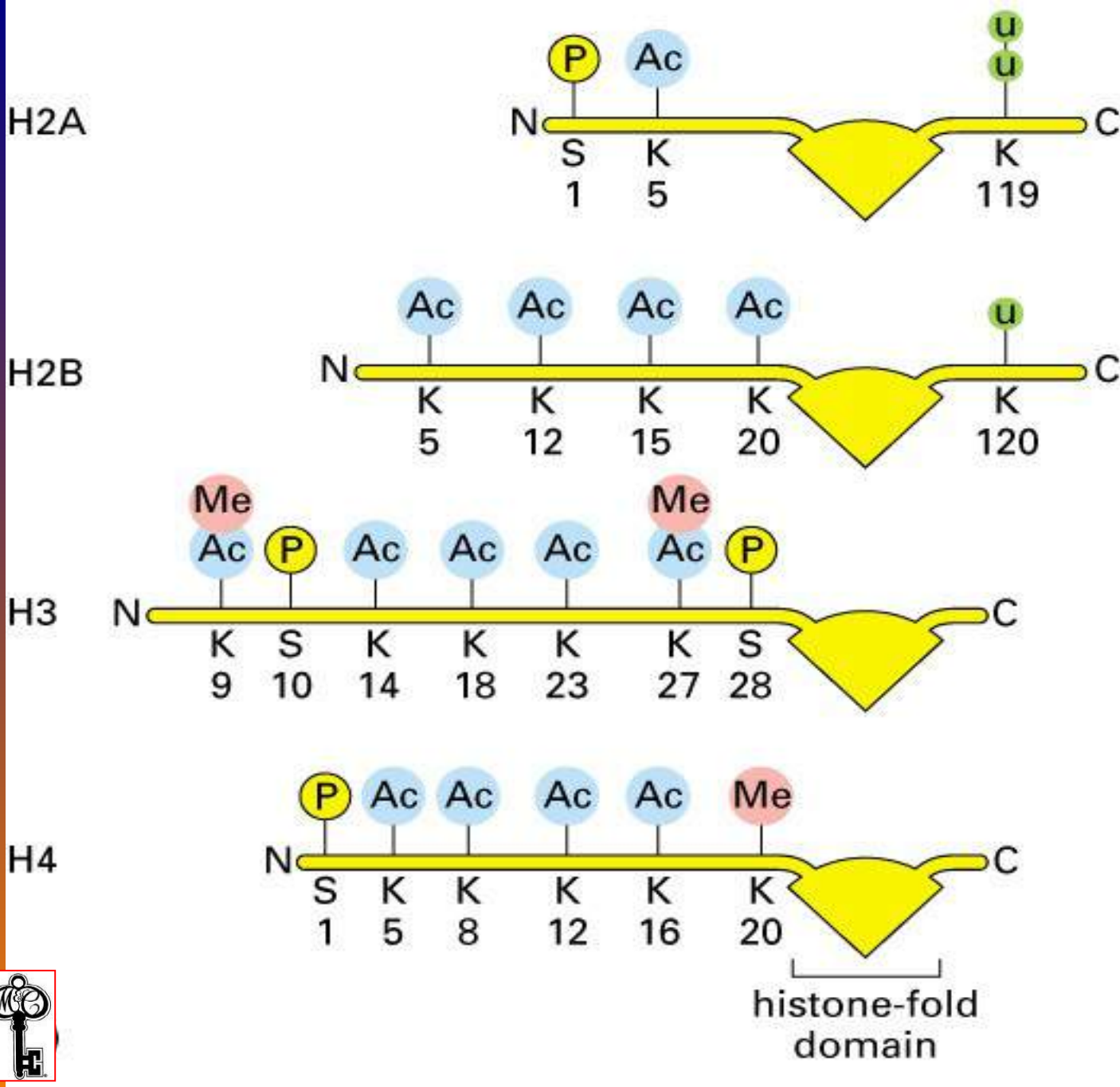


Figure 4–35 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

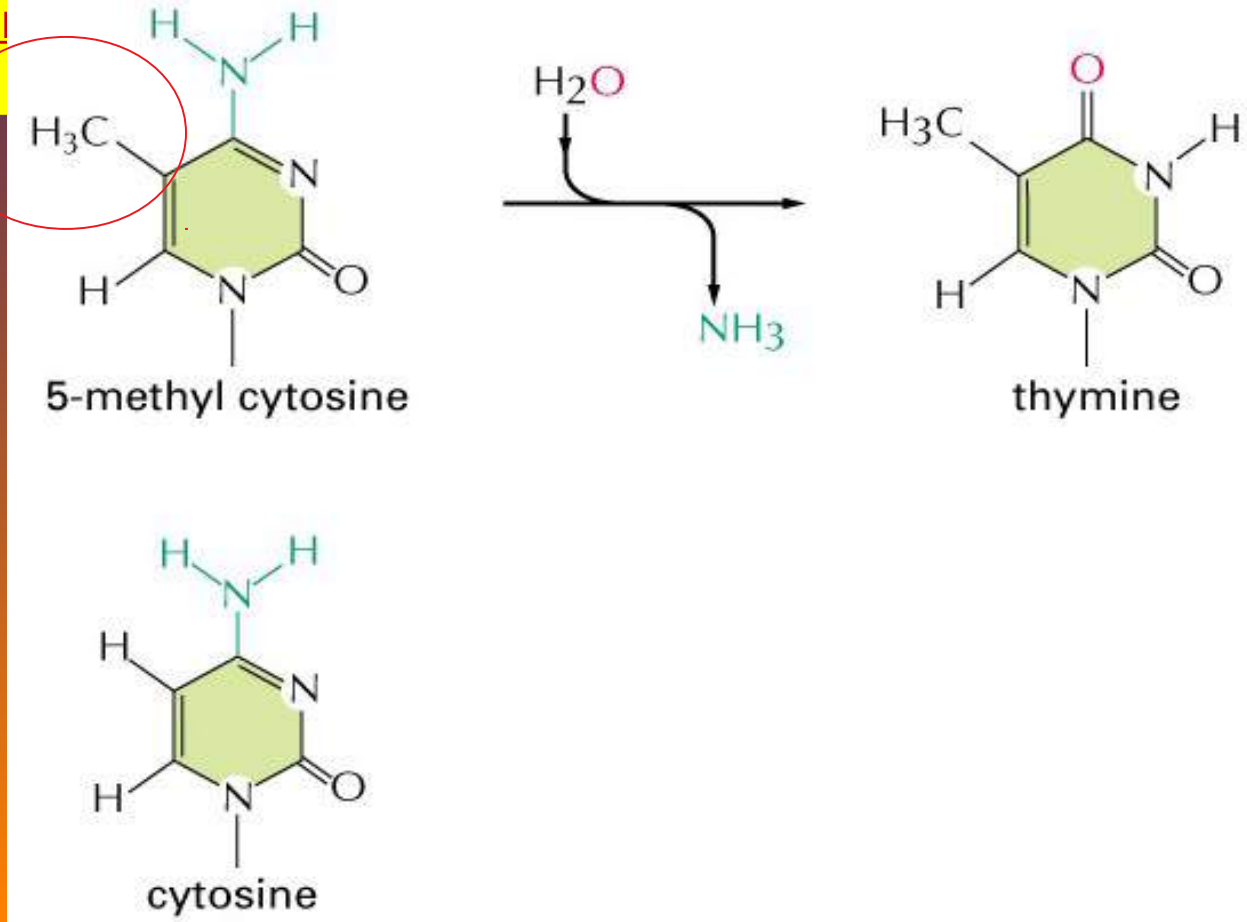
DNA methylation

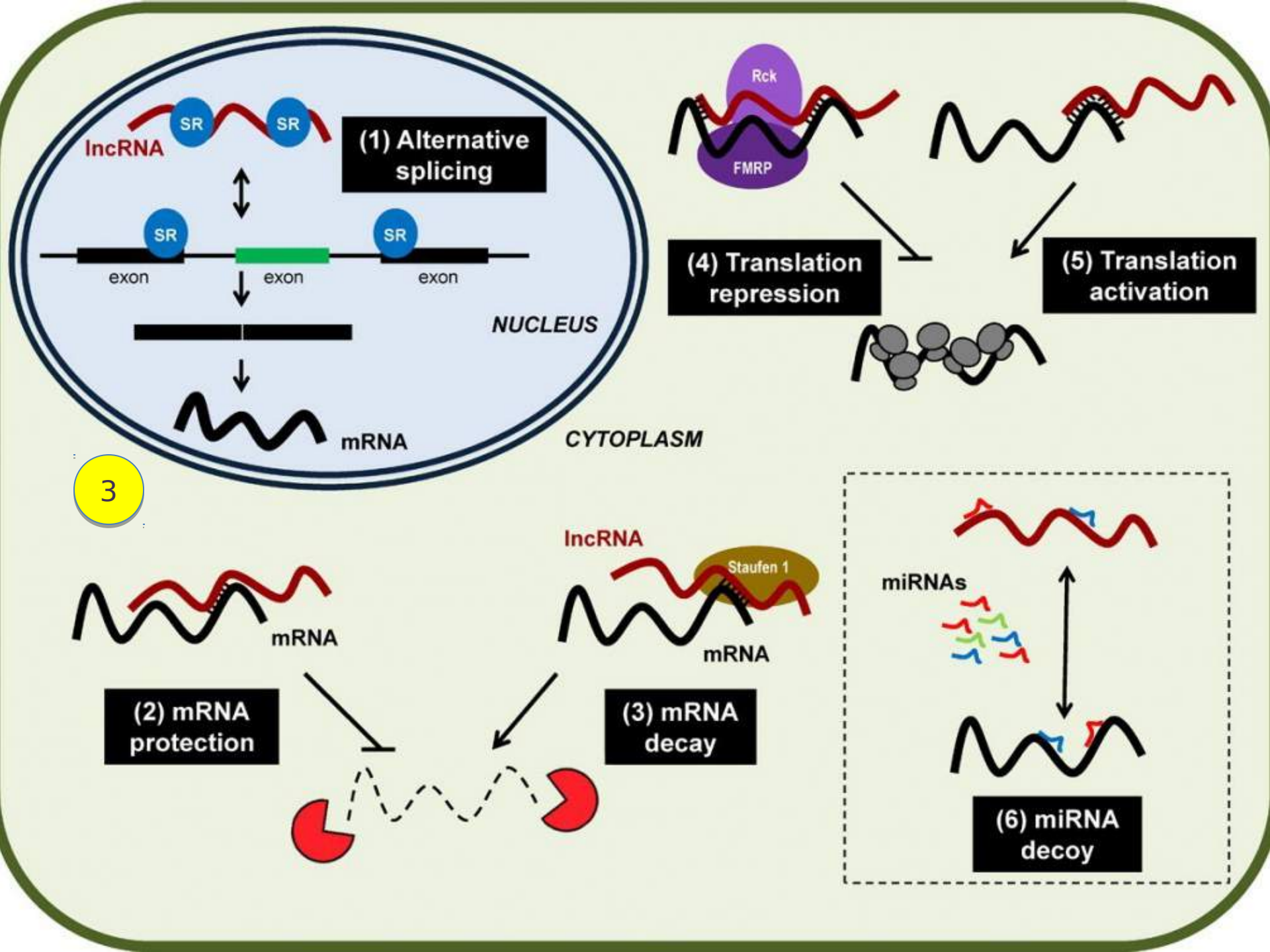
→ **Covalent modification of the DNA** is also important for gene silencing human cells.

→ **Most genes have GC rich areas of DNA in their promoter regions,** referred to as **CpG islands.**

→ **Methylation of the C … silenci…** 2

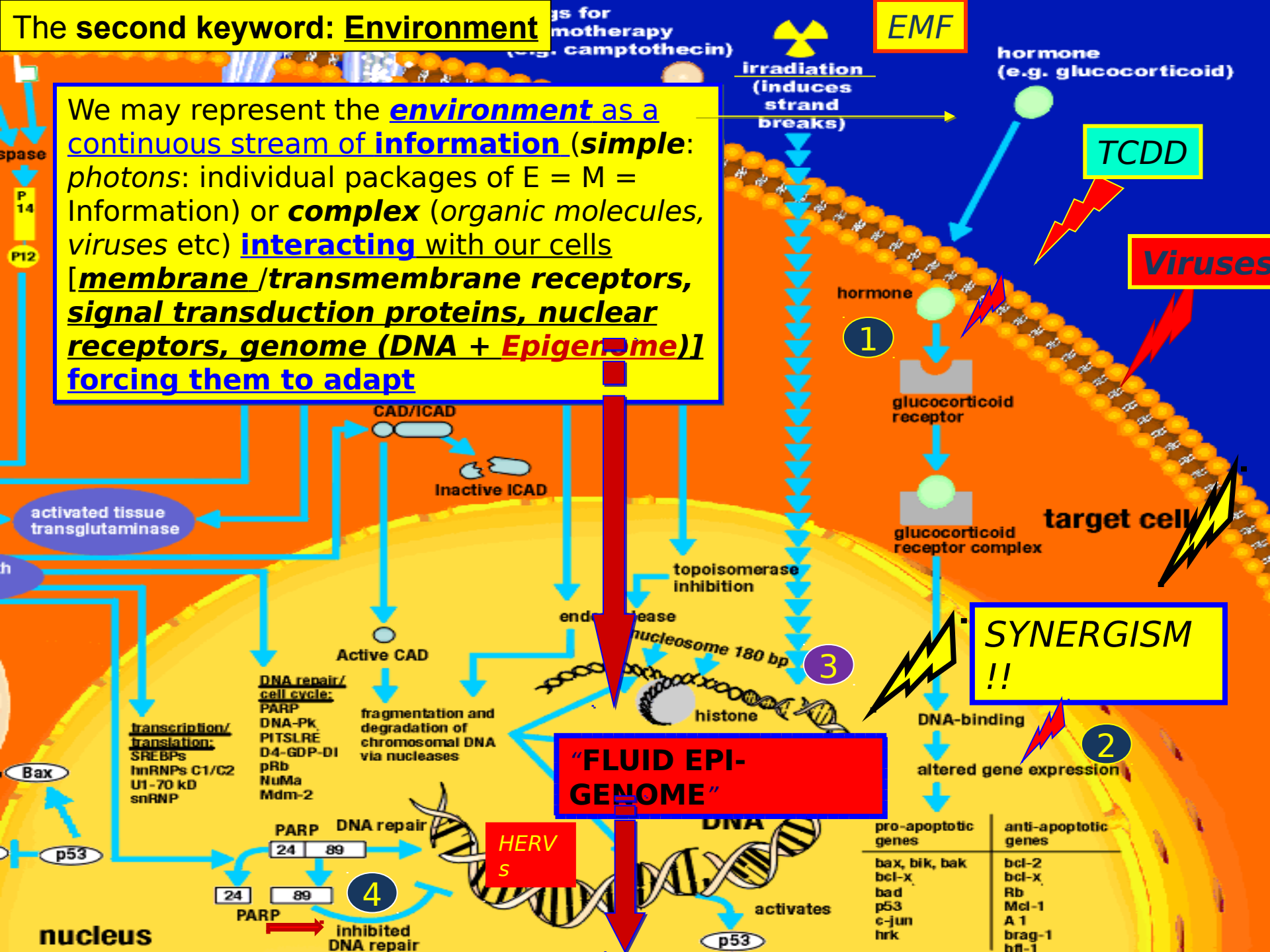
(highly *unstable* base)




lncRNA
SR
SR
(1) Alternative splicing
SR
SR
exon
exon
exon
NUCLEUS
mRNA
CYTOPLASM
Rck
FMRP
(4) Translation repression
(5) Translation activation
3
lncRNA
Staufen 1
mRNA
mRNA
(2) mRNA protection
(3) mRNA decay
miRNAs
(6) miRNA decoy

The **second keyword: Environment**

We may represent the ***environment*** as a continuous stream of **information** (***simple***: *photons*: individual packages of E = M = Information) or ***complex*** (*organic molecules, viruses* etc) **interacting** with our cells [***membrane /transmembrane receptors, signal transduction proteins, nuclear receptors, genome (DNA + Epigenome)***] **forcing them to adapt**

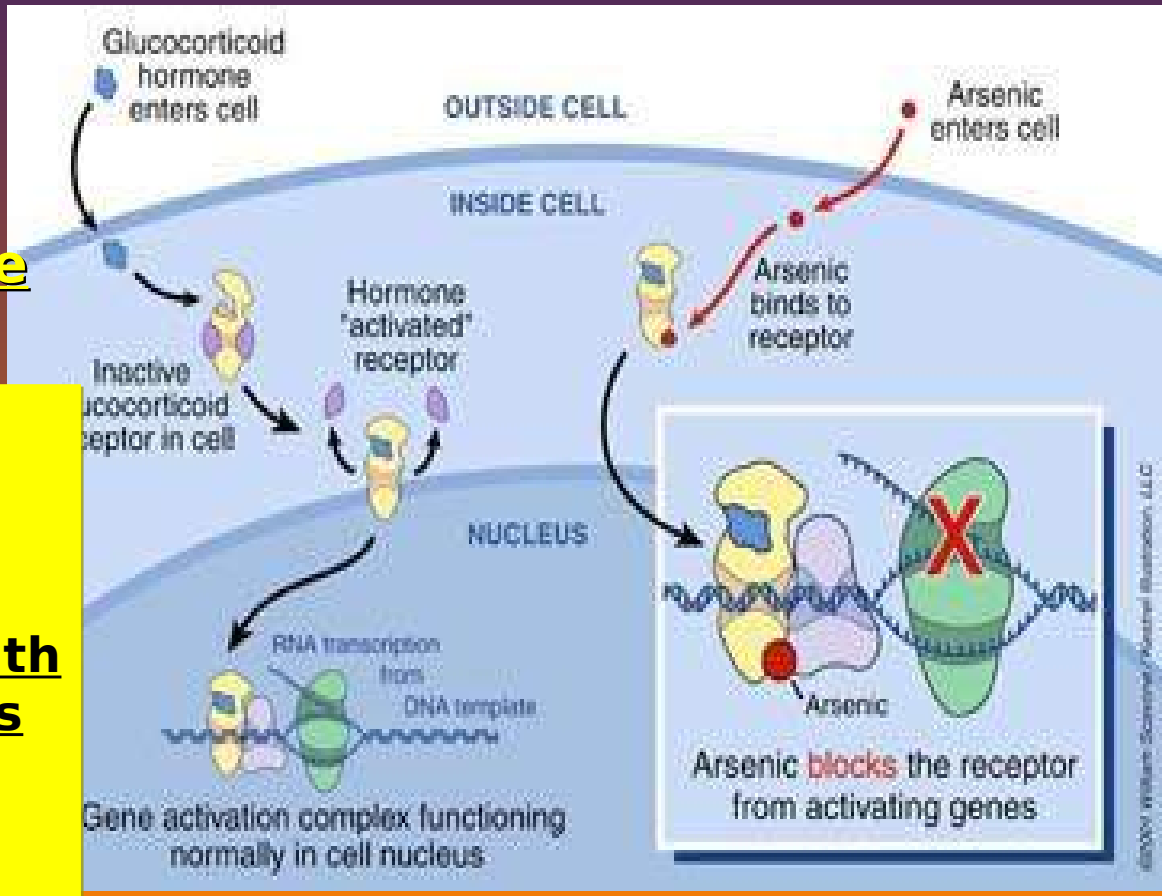


Everyday levels matter

At high levels… arsenic kills people

At moderately low levels… it causes a range of diseases

At truly low levels … it interferes with gene activation



Many of these substances (*Dioxins, Heavy Metals, Polycyclic aromatic Hydrocarbons)* are dangerous for humans health at very low-every day-doses (which are very difficult to be assessed by the **ordinary toxicological studies**)

Kaltreider *et al.* 2002

Epigenetics and environmental chemicals

Andrea Baccarelli and Valentina Bollati

Current Opinion in Pediatrics 2009, 21:243–251

Purpose of review

Epigenetics investigates heritable changes in gene expression occurring without changes in DNA sequence. Several methylation, histone modifications, a function under exogenous influence epigenetic alterations mediate toxic

Recent findings

In-vitro, animal, and human investiga environmental chemicals that modify arsenic, nickel, chromium, and meth (trichloroethylene, dichloroacetic aci carbon, and benzene), and endocrin (diethylstilbestrol, bisphenol A, persi conducted so far have been center investigations have studied environm and microRNA.

Summary

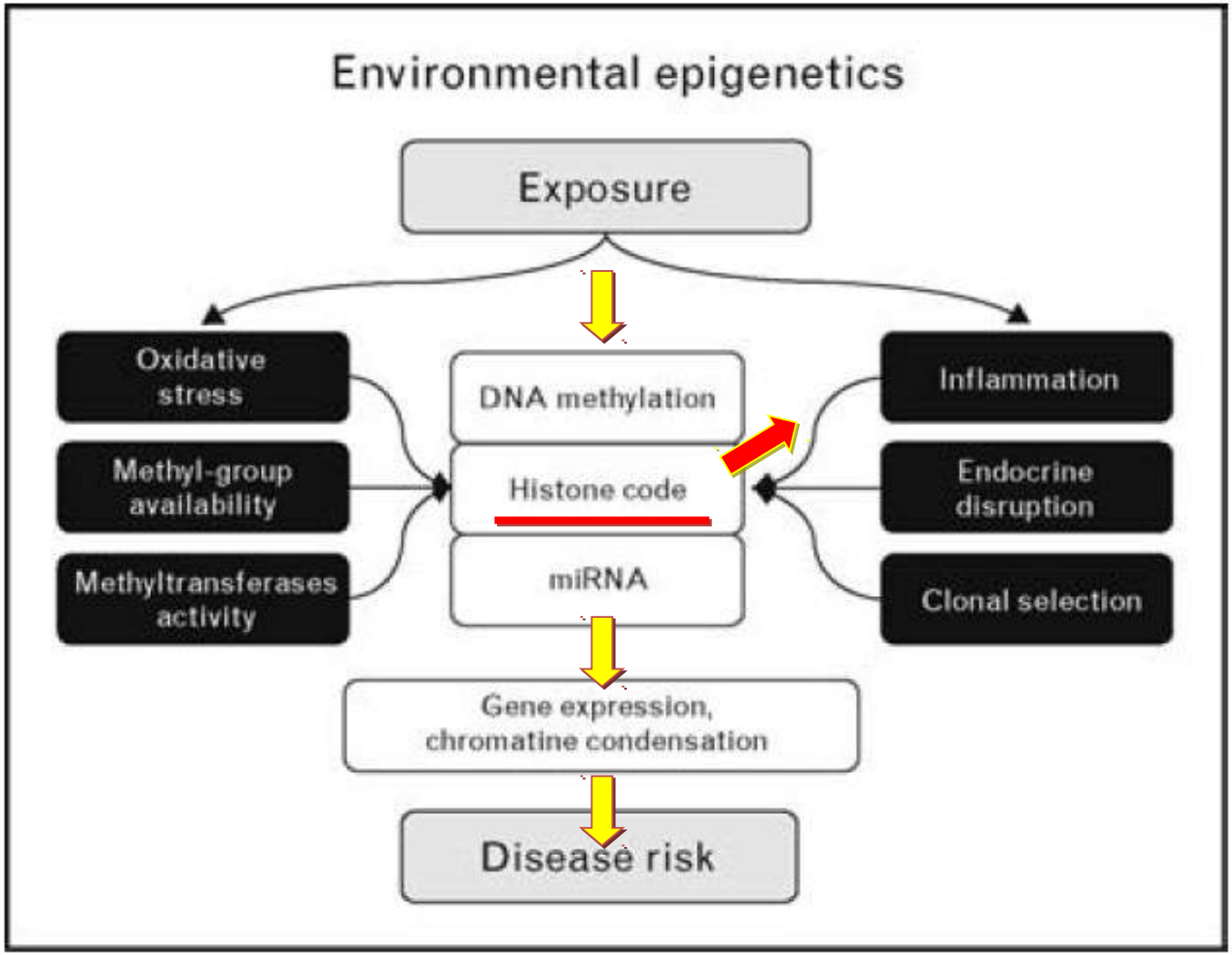
For several exposures, it has been proved that chem and that the same or similar epigenetic alterations c disease of concern or in diseased tissues. Future pros to determine whether exposed individuals develop epi in turn, which such alterations increase the risk of di needed to determine whether environmental epigene transgenerationally.

In-vitro, animal, and human investigations have identified several classes of **environmental chemicals that modify epigenetic marks..** including

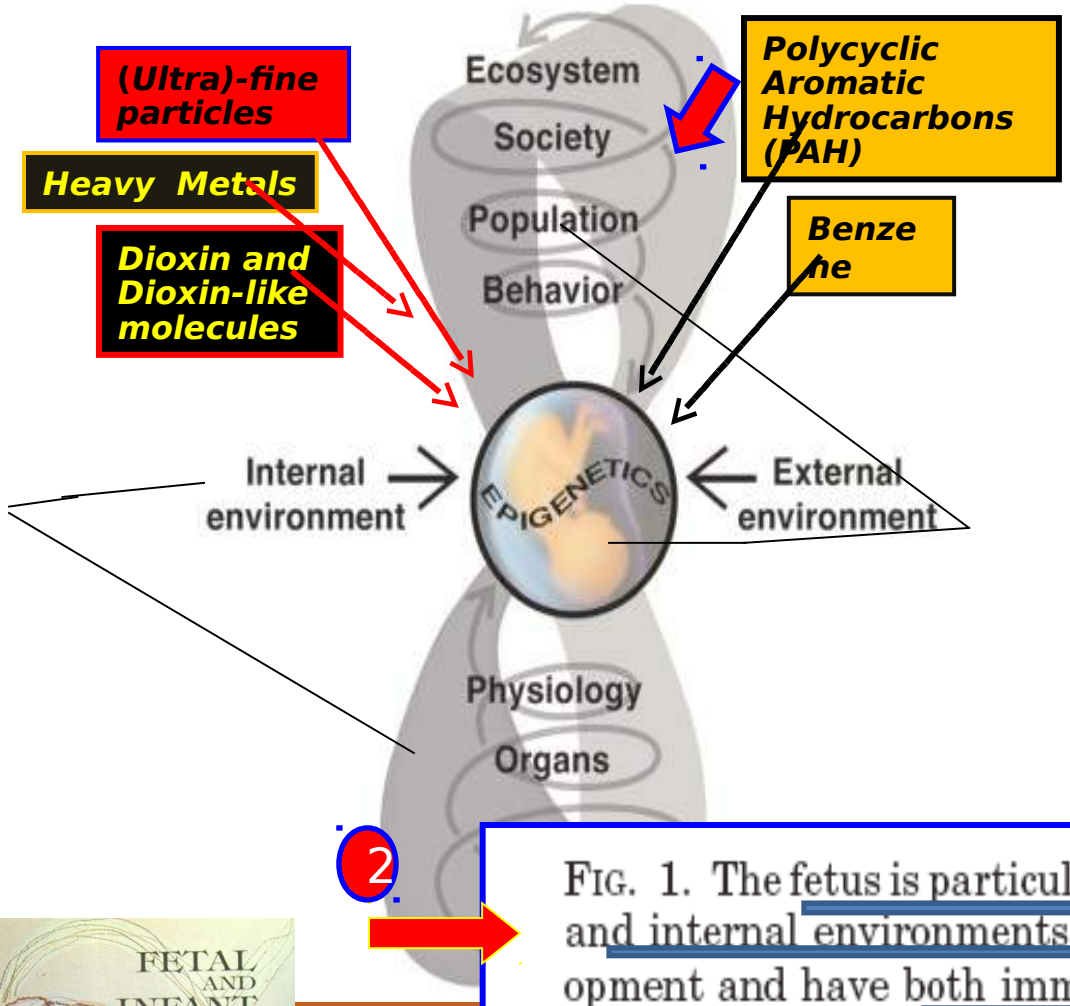
- ***metals*** (***cadmium, arsenic, nickel, chromium, CH3-mercury***),
- ***peroxisome proliferators*** (***trichloroethylene, dichloroacetic acid…***),
- ***Air Pollutants (PM 0,1/2,5/10, black carbon, benzene),***
- ***EDCs*** **- Endocrine-Disrupting/reproductive toxicants** (***DES, bisphenol A, persistent organic pollutants, dioxin***).

Because these **epigenetic changes are small, potentially cumulative**, **and they may develop over time**, it may be difficult to establish the cause-effect relationships among **environmental factors**, **epigenetic changes**, and **diseases**.

Figure 1 Potential mechanisms linking environmental exposures to epigenetic effects



The third key word is ***fetal programming***



this is **not a generic concept, concerning the way in which the "genetic program" contained in DNA is translated, during the nine months of the ontogenetic process, in a specific complex phenotype**.

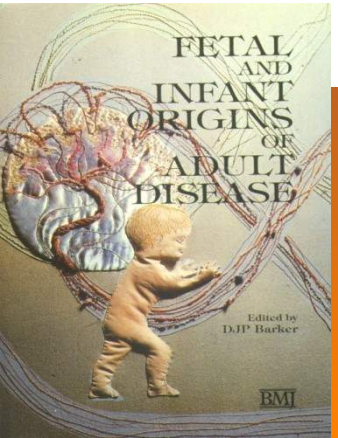
1

on the contrary,this is a **precise technical term that refers to the ability, and at the same time to the necessity, of embryo-fetal cells to define their epigenetic setting in adaptive (and predictive) response to the information** coming from the mother and, through her, from the outer world.

2

FIG. 1. The fetus is particularly vulnerable to changes in the external and internal environments, which interact to influence fetal development and have both immediate and life-long consequences. Such environmentally induced changes can occur at all levels of biological organization, from the molecular to the organism's behavior and place in society, and tend to be amplified in their consequences as they ascend through these levels. Ultimately, these influences may be epigenetic in nature, inducing mitotically heritable alterations in gene expression without changing the DNA.

3

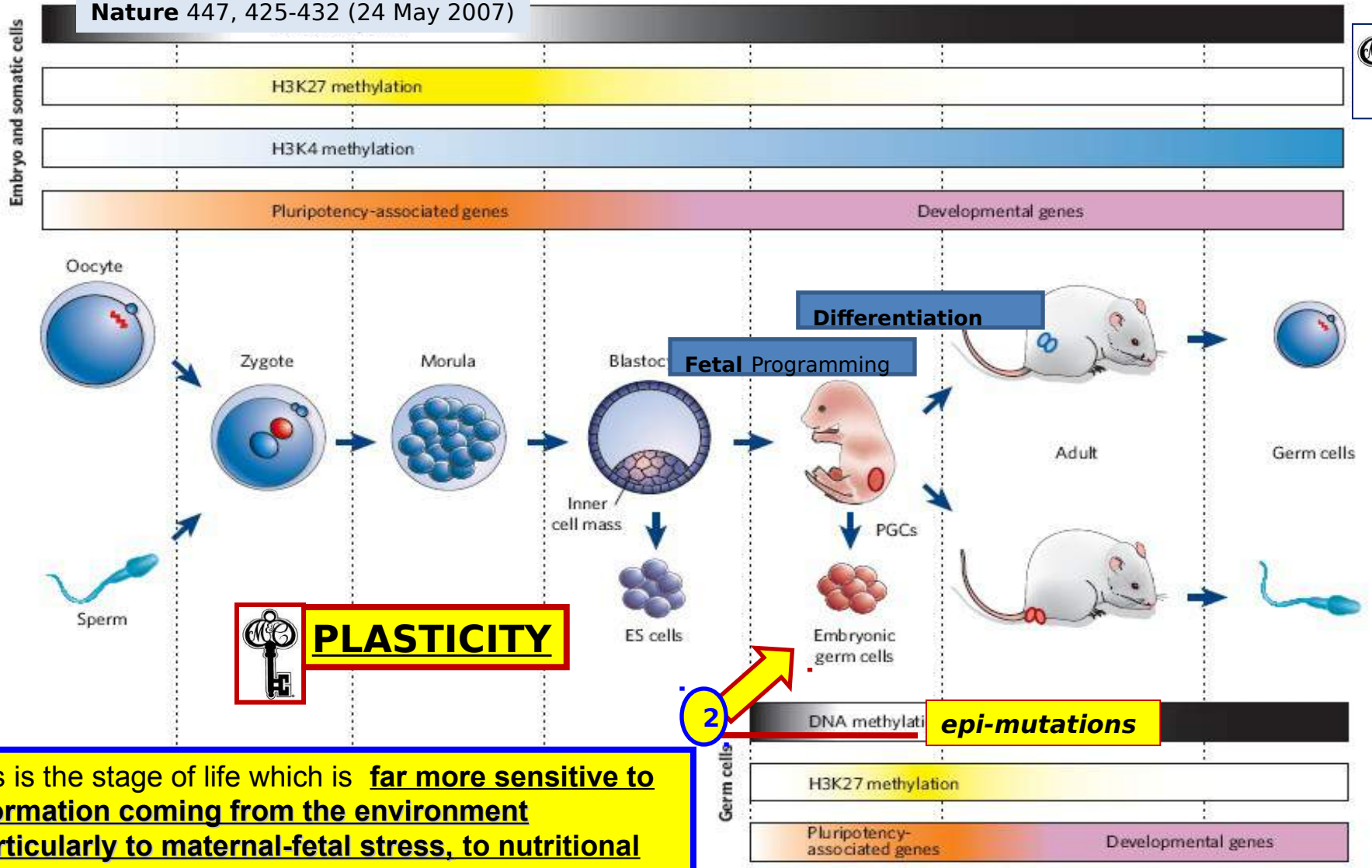


Cellular Differentiation: an Epigentic process

The actual genetic program of a particular individual is actually the product of nine months of epigenetic adaptive-predictive "formatting" of billions of cells).. 1

Stability and flexibility of epigenetic gene regulation in mammalian development

Nature 447, 425-432 (24 May 2007)



This is the stage of life which is **far more sensitive to information coming from the environment (particularly to maternal-fetal stress, to nutritional errors, to pollutants ..)**

Figure 1 | Epigenetic gene regulation during mammalian development.

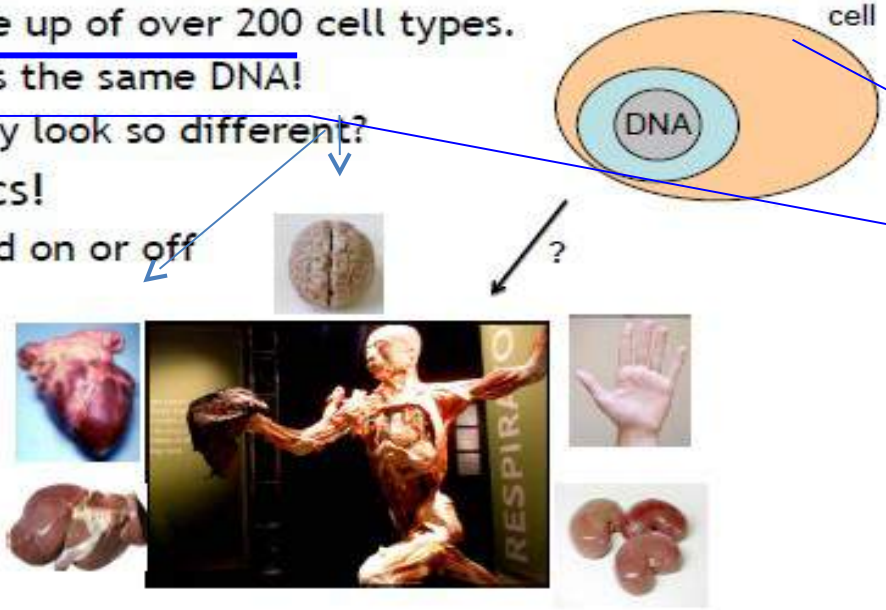
methylation. During the early development of PGCs, DNA methylation and

The **fourth** keyword is ***developmental plasticity***

Same DNA, Different Look

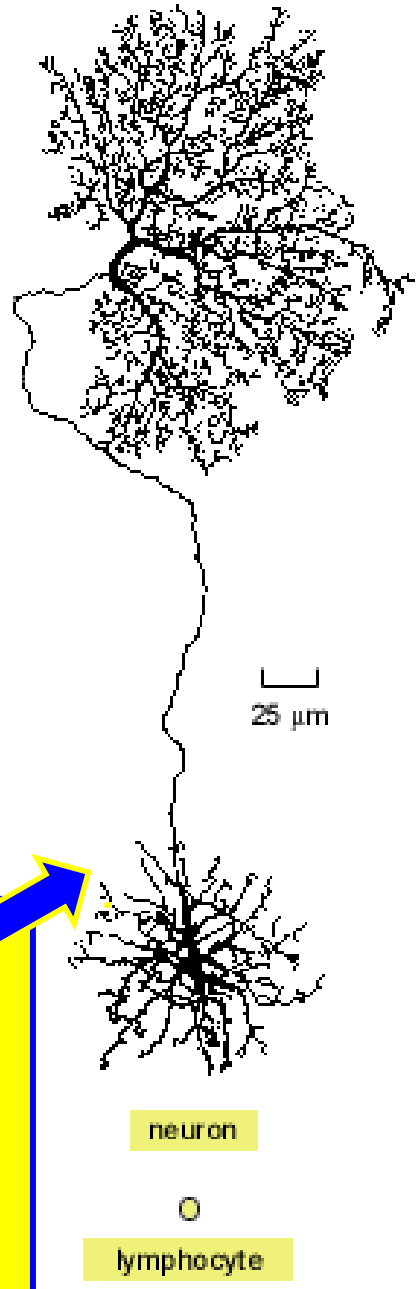
- We are made up of over 200 cell types.
- Each cell has the same DNA!
- How can they look so different?

  Epigenetics!
- Genes turned on or off



Wikimedia Commons, ORNL.gov, Flickr: richdelux

HARVARD MEDICAL SCHOOL



This image clearly shows the **"power" of the epigenome** and the **predominant role of environmental information in the phenotypic shaping of cells, tissues , organisms** .. the **huge phenotypic (morpho-functional) difference** between a *lymphocyte* and a *neuron* **is not due to DNA, which is virtually identical in the two cells** , but to the manner in which **the same genome has been utilized by the two cells**, on the basis of the **information (positional and environmental) received during the first months of life (for neuron in the first 2 years)** and **processed by the epigenetic networks**

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

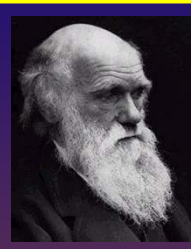
We are quite stable (for millions of years) both genetically and phenotypically

The chimpanzee DNA is for 98.77% identical to the hum

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

Species
phylogeny



From the Tree of the Life Website, University of Arizona

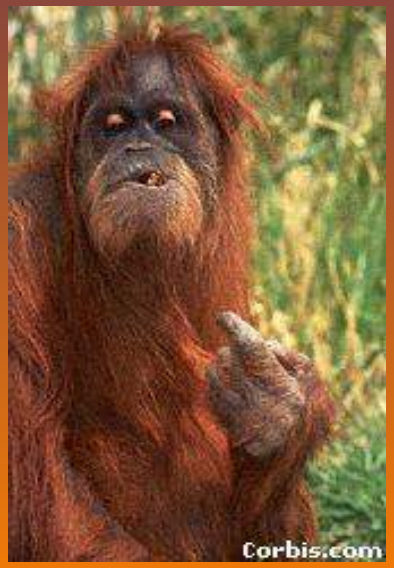
Evo

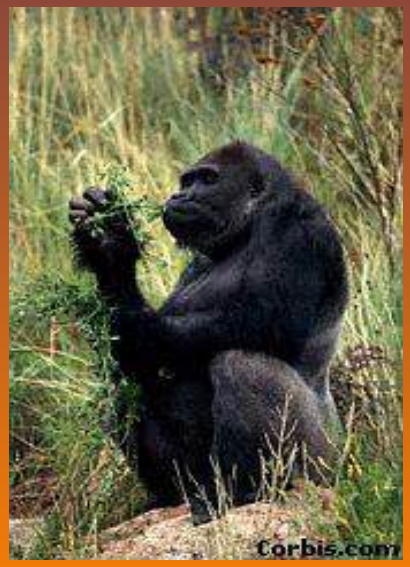
Orangutan

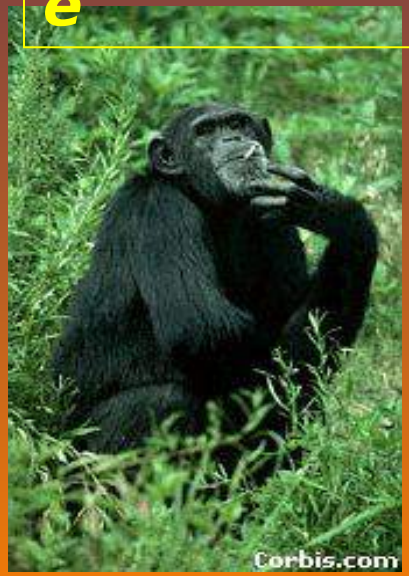
Gorilla

Chimpanzee

Human



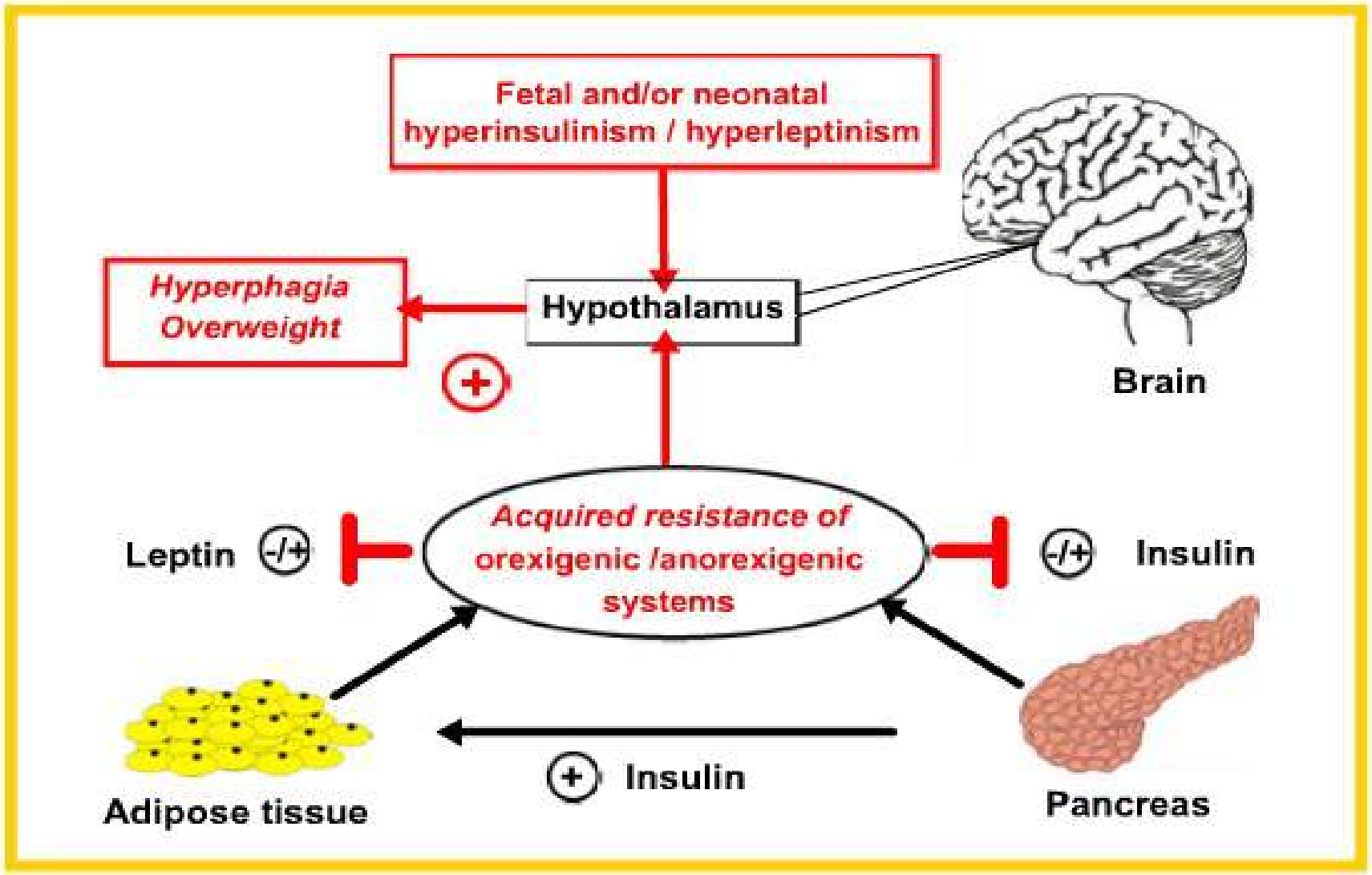




Sanger Institu

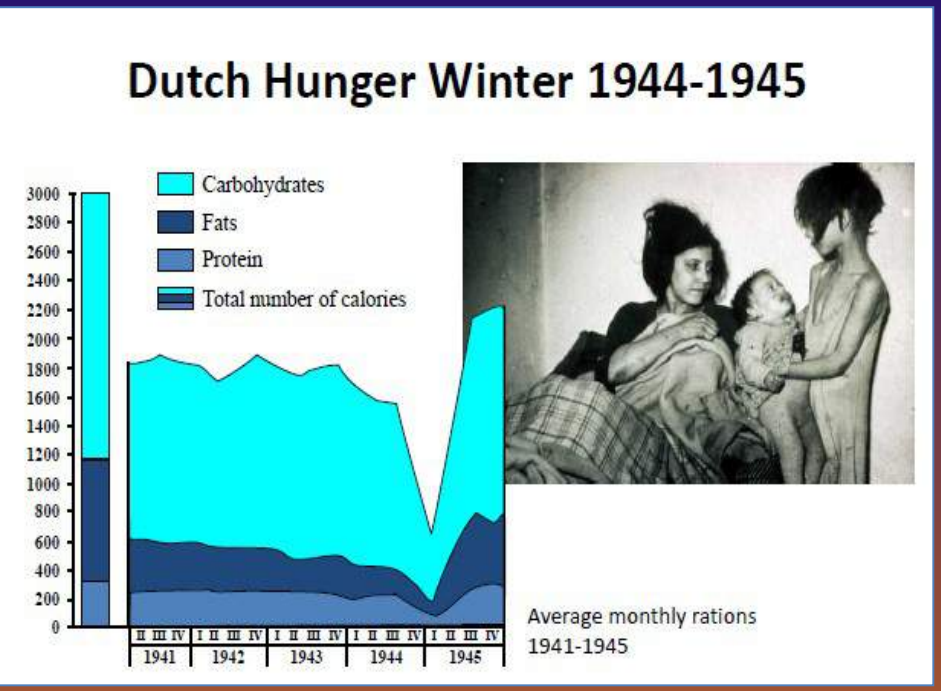
The **sixth key word** is (*epigenetic-phenotypical*) ***mismatch***
→ DOHA (Developmental Origins of Health and Diseases)

A mechanism of neuroendocrine 'malprogramming'



Plagemann, J. Perinat. Med. 32 (2004)

Dutch famine *versus* Leningrad Siege

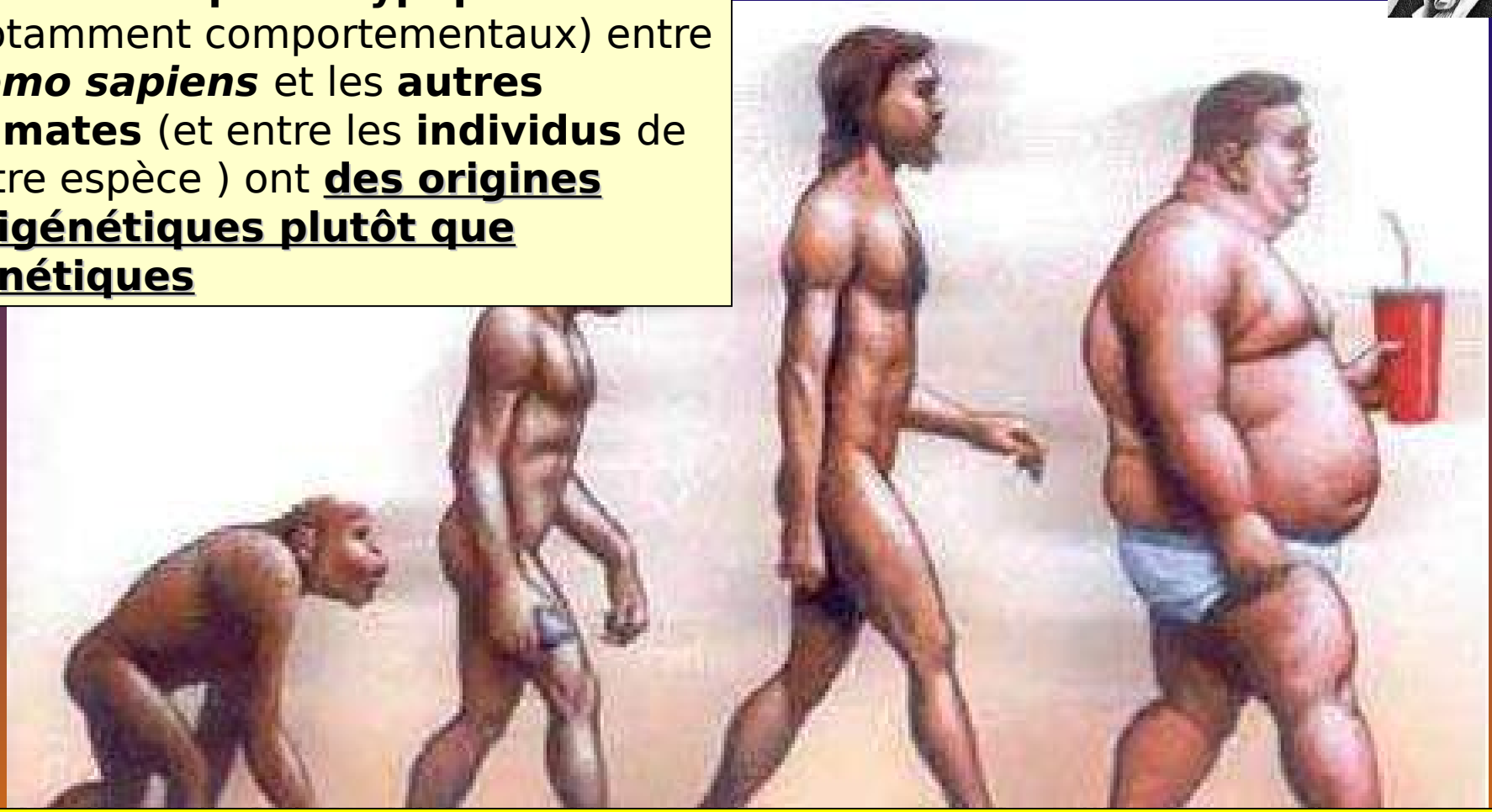


Roseboom TJ et al. ***Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview*** **Twin Res**. (2001);4(5):293-8

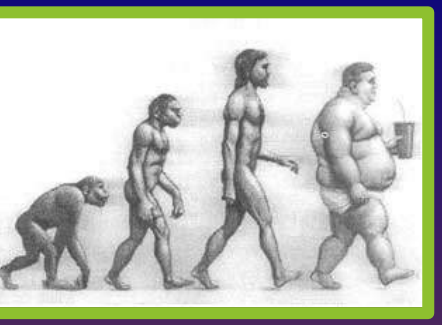
Stanner SA, Yudkin JS ***Fetal programming and the Leningrad Siege study*** ***Twin Res.***(2001); 4(5):287-92

La **programmation fœtale implique que pendant les périodes critiques de croissance prénatale, des changements permanents dans le métabolisme et / ou structures peuvent résulter des conditions intra-utérines défavorables** … Quoi qu'il en soit, **les changements épigénétiques étant potentiellement adaptatives**.. Ces sont plutôt les **discordances (*mismatch*)** entre l'information que l'enfant reçoive avant et après la naissance à produire une augmentation de ***maladies chroniques*** (obésité, diabètes 2, maladies cardio-vasculaires, ***maladies neuropsychiques*** …

Nous pouvons résumer tout cela en disant que les **principaux différences phénotypiques** (notamment comportementaux) entre ***Homo sapiens*** et les **autres primates** (et entre les **individus** de notre espèce) ont **des origines épigénétiques plutôt que génétiques**



Ce qui signifie également que les **variations** de **notre phénotype** (à la fois **physiologiques et pathologiques)** **ont leur première origine dans la *programmation fœtale*** et sont **induites par l'environnement** (constamment changeant) et **modulées**



Phylogenèse

de **4 milliards d'années de coévolution moléculaire*** (en particulier, notre **ADN** est le produit de ce long parcours) ..

Mismatch ?

Ontogenèse

et de **9 mois** de **développement individuel**

(..notre **epigénome** est le produit de 9 mois de **programmation cellulaire et tissulaire adaptative** à un **environnement** qui est en train de changer très vite..

Nous ne devrions jamais oublier que **nous sommes en *même temps*** le **produit**

Devo-Evo

l'ontogenèse *récapitule* ***la phylogenèse***

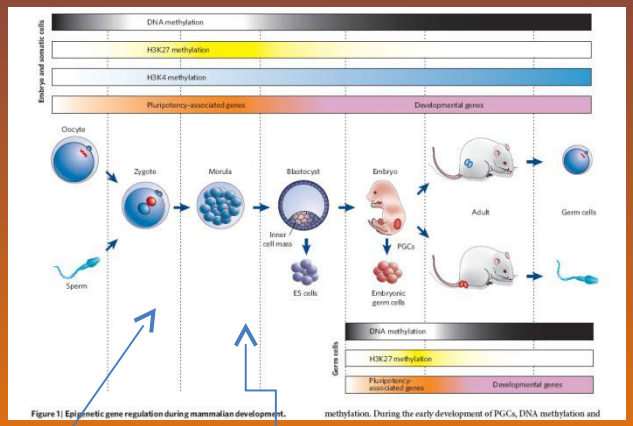
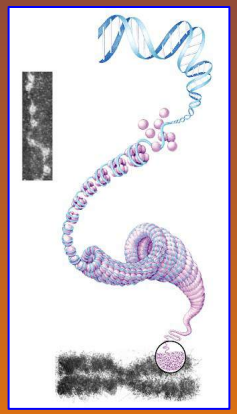


Figure 1| Epigenetic gene regulation during mammalian development. methylation. During the early development of PGCs, DNA methylation and



Un risque majeur: les ***EDCs*** et d'autres ***xénobiotiques*** (**n'étant pas** le produit de cette coévolution moléculaire*) peuvent **interférer** à ce niveau, en agissant comme des ***pseudo-morphogènes***..

..recently, the ***fetal programming mismatch theory*** has been transformed into the **key-moodel theory of DOHAD..**

Obesity/Metabolic Syndrome

Cardiovascular Diseases

Obesogens

Multiorgan Effects of Endocrine Disruptors

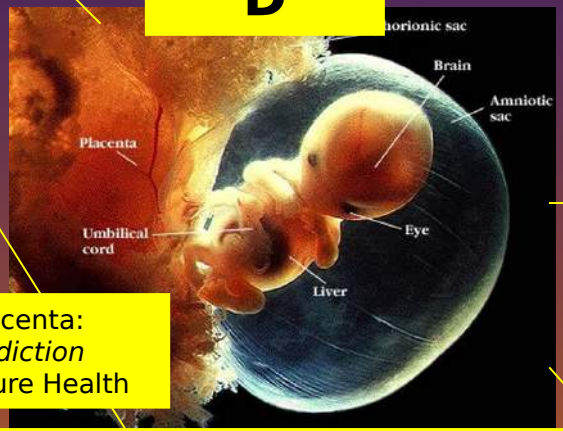
Pesticides

In Vitro Fertilization

Materno Fetal Stress

DOHAD

Ipertension



Placenta: *Prediction* of Future Health

OBESITY DIABESITY PANDEMICS

Asthma and allergi

Lung Development

Developmental Time Windows of Vulnerability

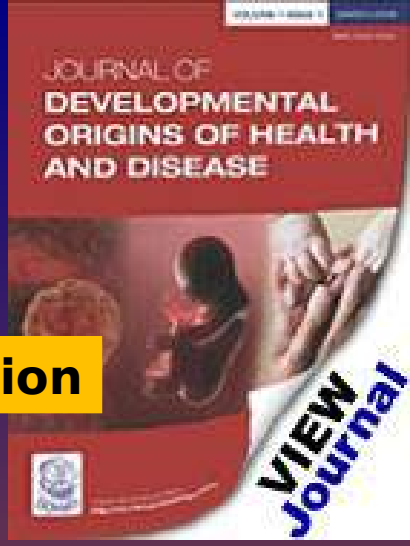
Reproductive Diseases/Dysfunctio

Semen Abnormalities

CANCER

Neurobehavioral Deficits and Diseases

Psychiatric Diseases



CHEMICAL FALL OUT

The gift our mothers never wanted to give us

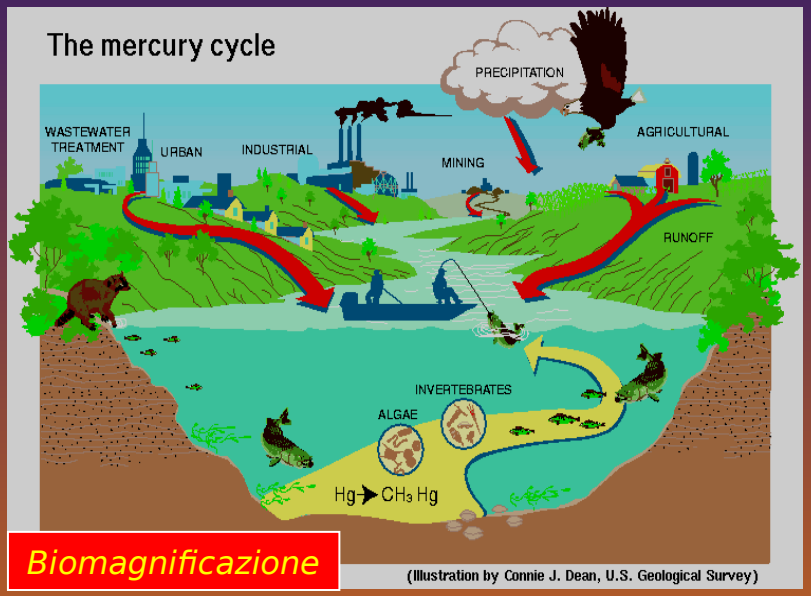
1. **ENDOCRINE DISRUPTORS**
   dioxin-like moleculles
2. **HEAVY METALS**
3. **ULTRAFINE PARTICLES**

That's why at present many studies in various parts of the world are evaluating the ***chemical body burden*** .. especially in women, children, embryos / fetuses, providing dramatic results.

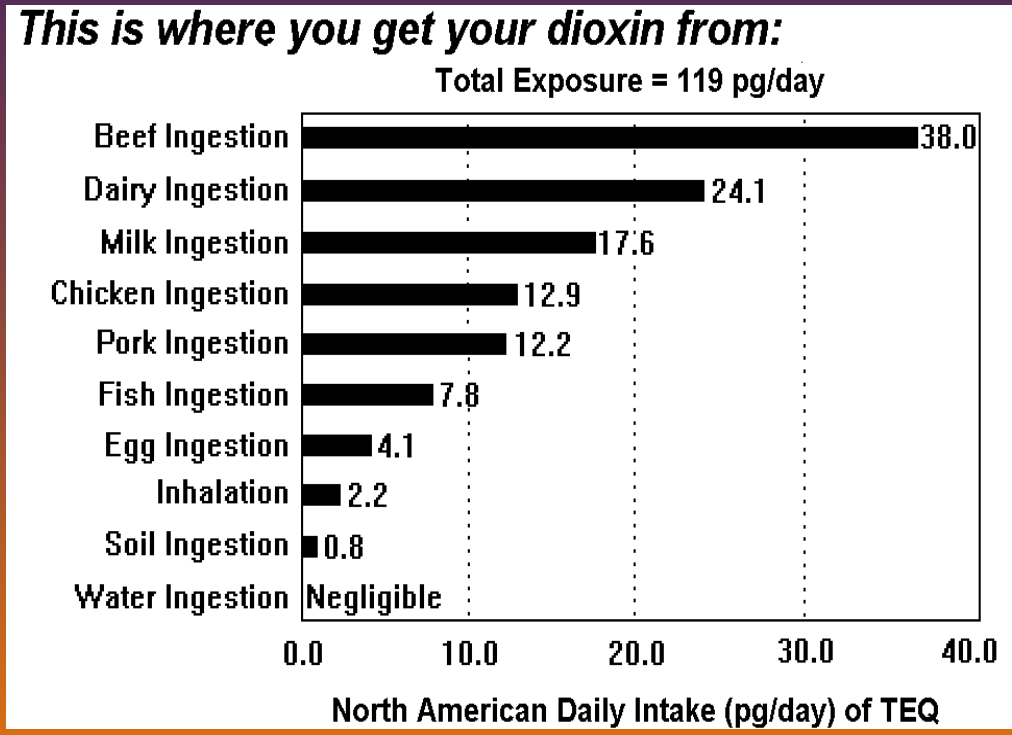
http://www.ewg.org/reports/generati

Heavy **metals, dioxins and other carcinogens** released into ecosphere, and conveyed in living organisms, may **bio-accumulate in *tissues*** (*bones* and *fat*) and **bio-magnify** in ***food chains***

And from **tissues where they accumulate (sometimes for decades), their release is generally slow and continuous**

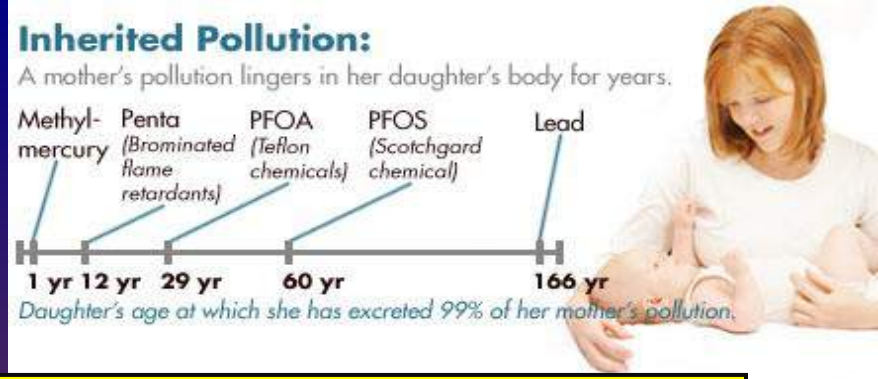


Biomagnificazione



What is the Global Chemical Burden..

Industrial chemicals in mothers and daughters:
the pollution we share and inherit



E' vero che **nel sangue e nei tessuti** di **tutti** gli uomini e le donne che vivono in ambienti urbani e/o industriali e persino nel **sangue cordonale e placentare** e nei **tessuti fetali** sono presenti questi stessi inquinanti in quantità di anno in anno, di decennio in decennio maggiori ?

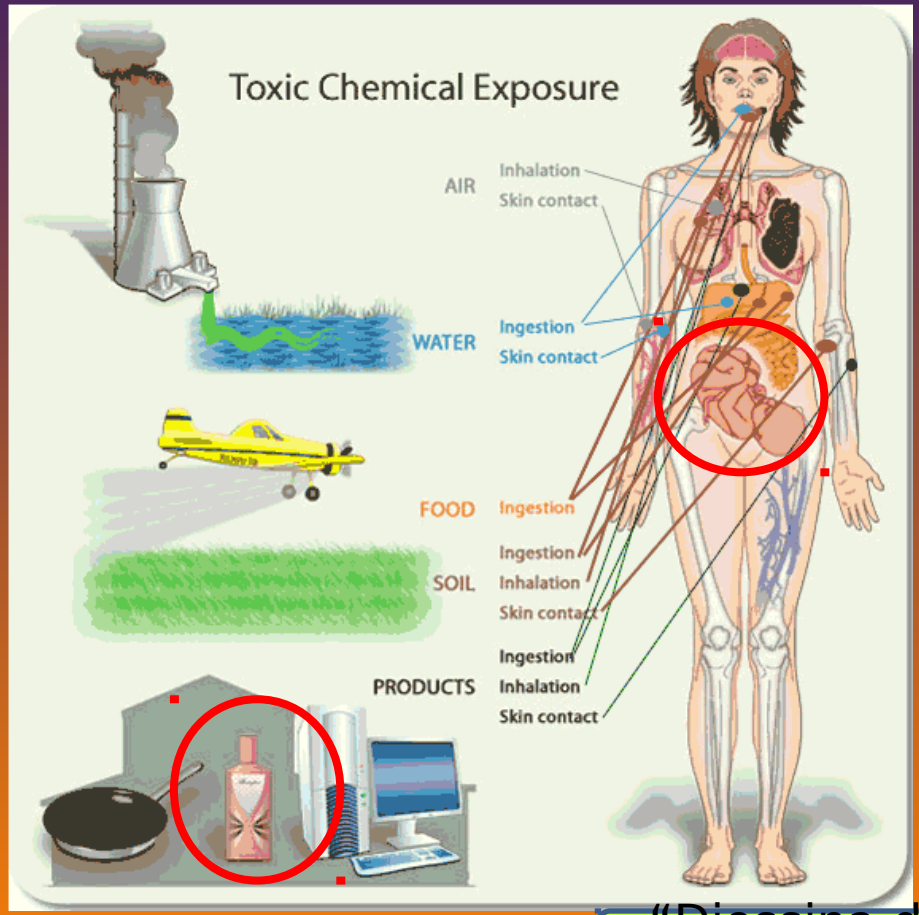
Table 1. Chronology of human exposure.

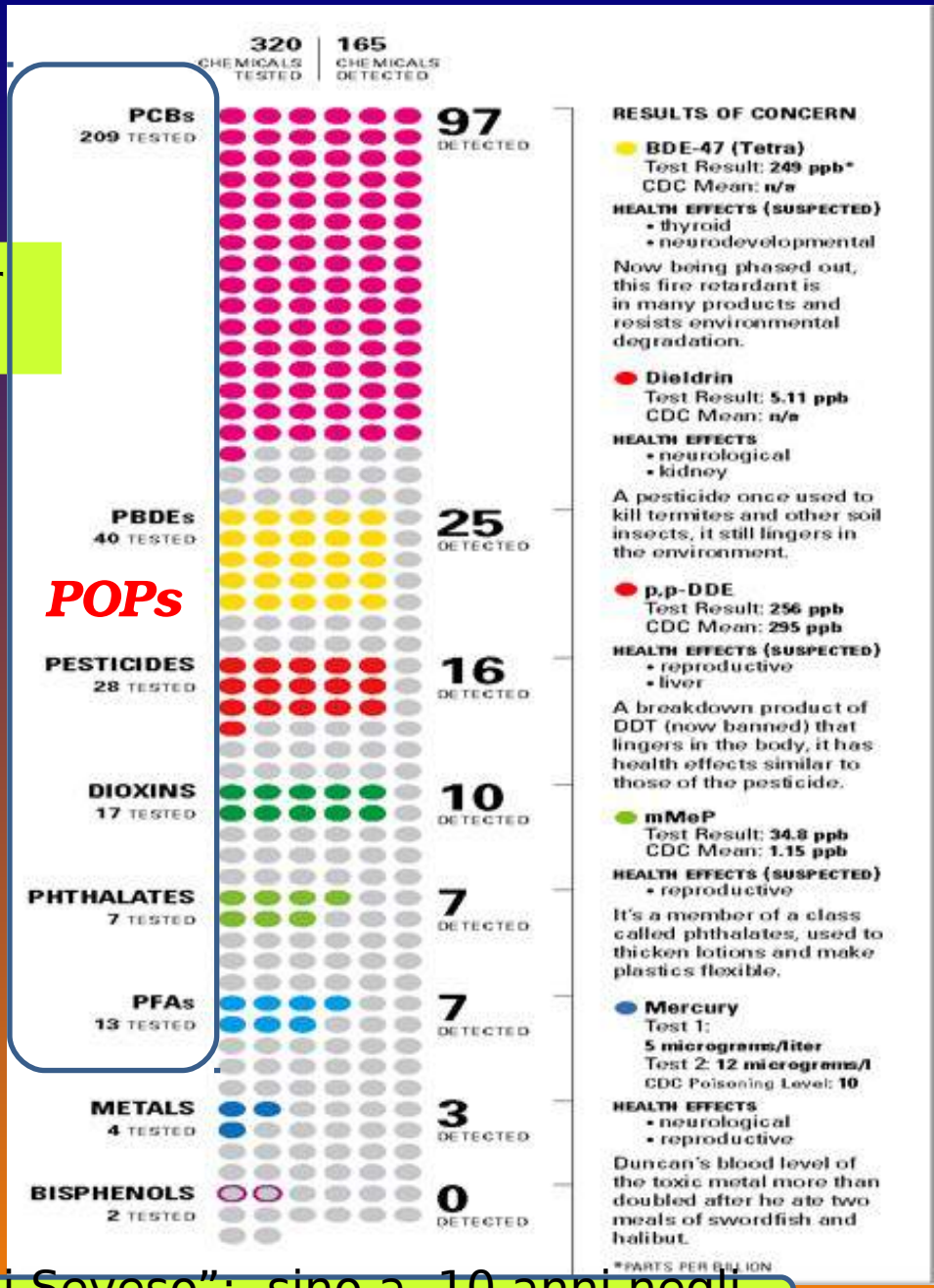
Years	Exposure scenario
1920s–1930s	BPA, PCBs, and DDT commercially introduced. Chlorine industry expanding. Discrete postnatal and prenatal exposure.
1940s–WWII	First wide-scale production and exposure to the above and other chemicals including plastics and chlorinated compounds as technology advanced.
1940s–1950s	First generation widely exposed postnatally and some who may have been exposed prenatally.
1950s–1970s	First generation born that was widely exposed prenatally.
1970s–1990s	First generation that was widely exposed prenatally reached reproductive age.
1980s–present	Second generation born that was exposed in the womb and beginning to produce the third generation. Production volume and exposure still increasing.

Is it true that these ***pollutants*** are present **in blood and tissues** of all men and women living in **urban** and **industrial environments** and even in the **cord blood and placental and fetal tissues** in more and more significant amounts year after year ?

Monitoring Body-Burdens

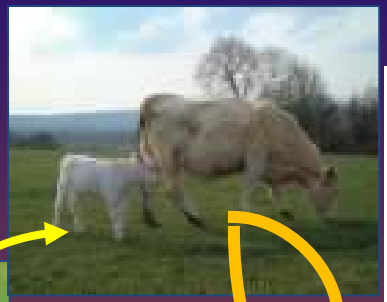
700 different synthetic chemicals or heavy metals found in human blood,

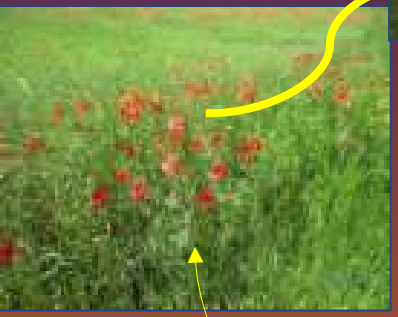


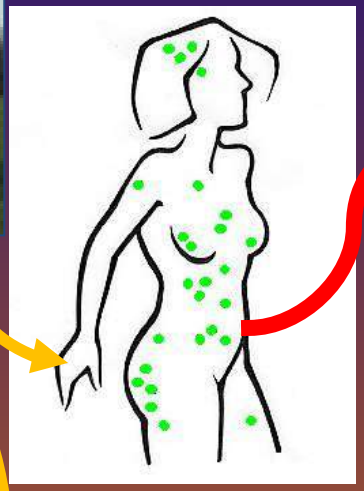


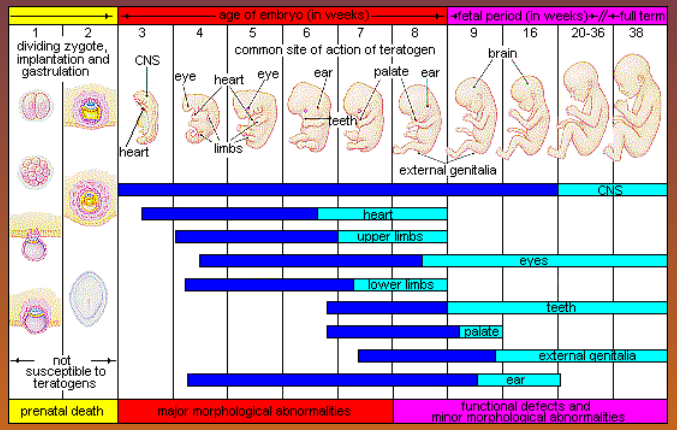
"Diossina di Seveso": sino a 10 anni negli adipociti !

E’ vero, in particolare, che **metalli, diossine e altri inquinati lipofili** <u>**accumulati nei tessuti materni**</u> possono passare, <u>anche **a distanza di anni dal loro assorbimento**</u>, **nel sangue** e raggiungere il **feto** ?





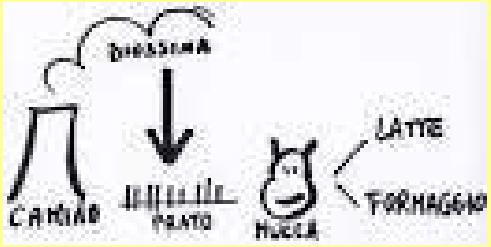




Is it true that **metals, dioxins** and other **lipophilic pollutants,** accumulated in maternal tissue, may pass,

pre or postnatal exposure ?

Diossine e Furani



Discariche storiche, inceneritori, primitive waste recycle, etc.

Higher PCDD/F levels were found in placenta (10.3 TEq-pg/g lipid) and venous serum (9.1 TEq-pg/g lipid), compared to those in breast milk (7.6 TEq-pg/g lipid).

Chemosphere. 2004 Mar;54(10):1459-73. ***Infant exposure to polychlorinated dibenzo-p-dioxins, dibenzofurans and biphenyls (PCDD/Fs, PCBs)--correlation between prenatal and postnatal exposure***. Wang SL, Lin CY, Guo YL, Lin LY, Chou WL, Chang LW.

pre or postnatal exposure ?

POLICLO-
BIFENILI

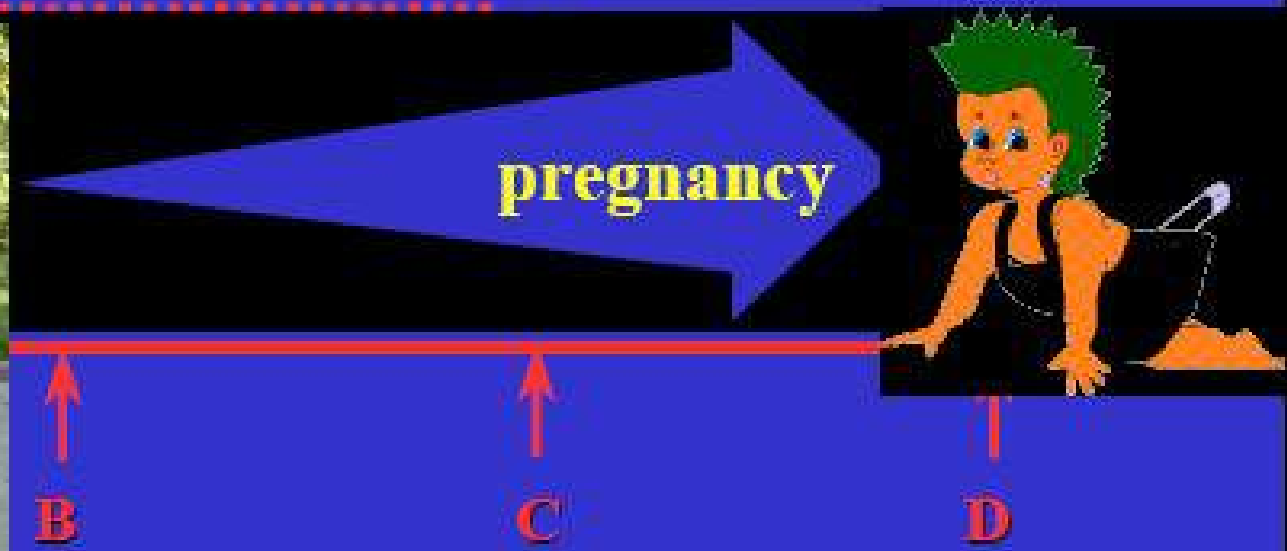
Vernici, lubrificanti, pesticidi
Vietati in Francia dal 1987

on a lipid basis, the highest concentration of **PCB** in placenta (5027 ng/g fat) was **2.8 times higher** than the highest concentration of PCB in breast milk (1770 ng/g fat)

J Expo Anal Environ Epidemiol. 2000 May-Jun;10(3):285-93. PCB exposure in utero and via breast milk. A review. DeKoning EP, Karmaus W. Et al.

Exposure → Health outcome

Prental Exposure to FP



Interviews on prental nutrition

B Weiss, P J Landrigan
The developing brain and the environment: an introduction. Environ

B Weiss
Vulnerability of children and the developi ng brain to neurotoxic hazards. Environ Health

J W Olney, N B Farber, D F Wozniak, V Jevtovic-Todorovic, C Ikonomidou **Environmental agents that have the potential to trigger massive apoptotic neurodegeneration in the developing brain.** Environ Health

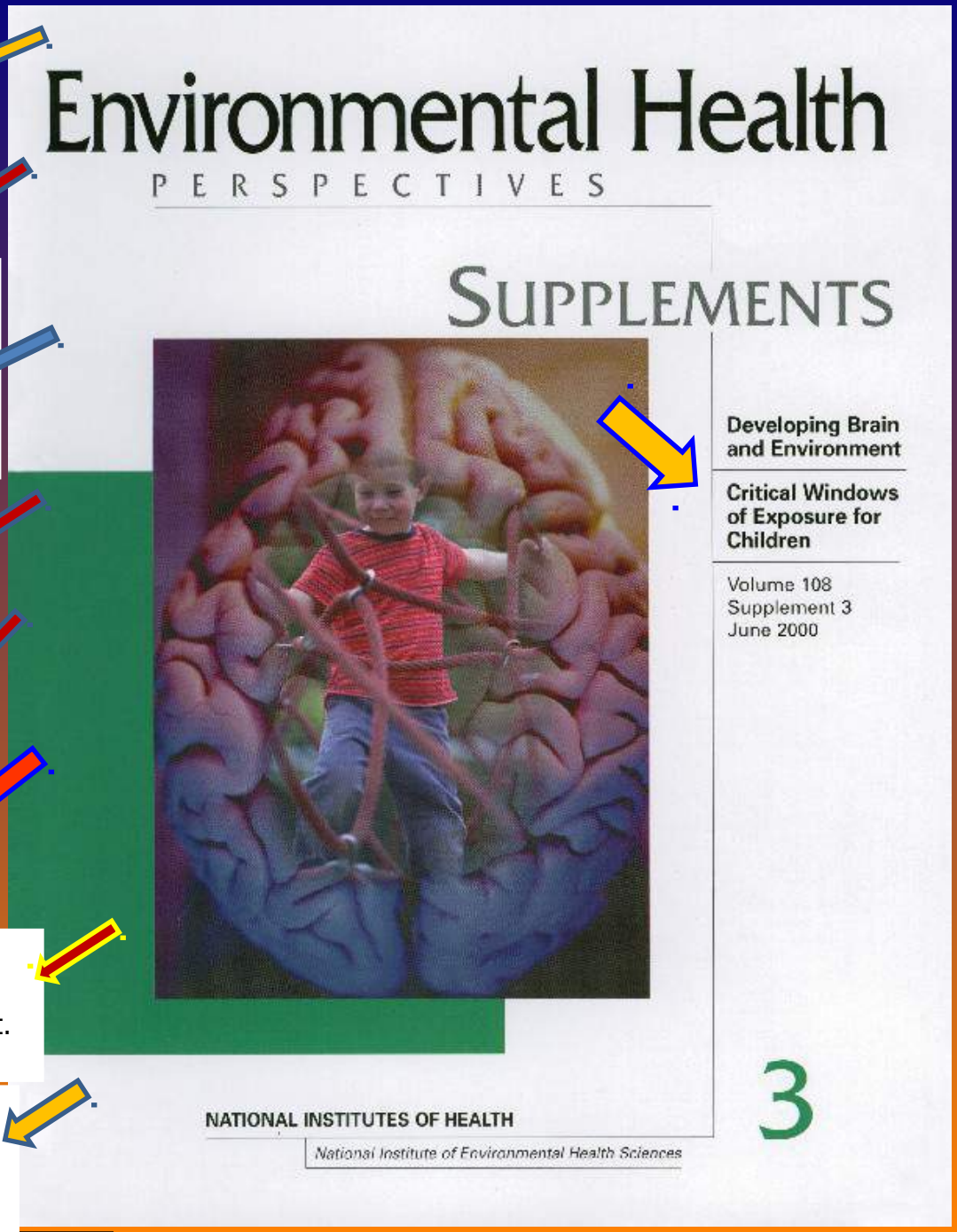
E A London
The environment as an etiologic factor in autism: a new direction for research. Environ Health Perspect. 2000 June; 108(Suppl 3): 401–404.

D C Rice **Parallels between attention deficit hyperactivity disorder and behavioral deficits produced by neurotoxic exposure in monkeys.**Environ Health Perspect. 2000 June; 108(Suppl 3): 405–408.

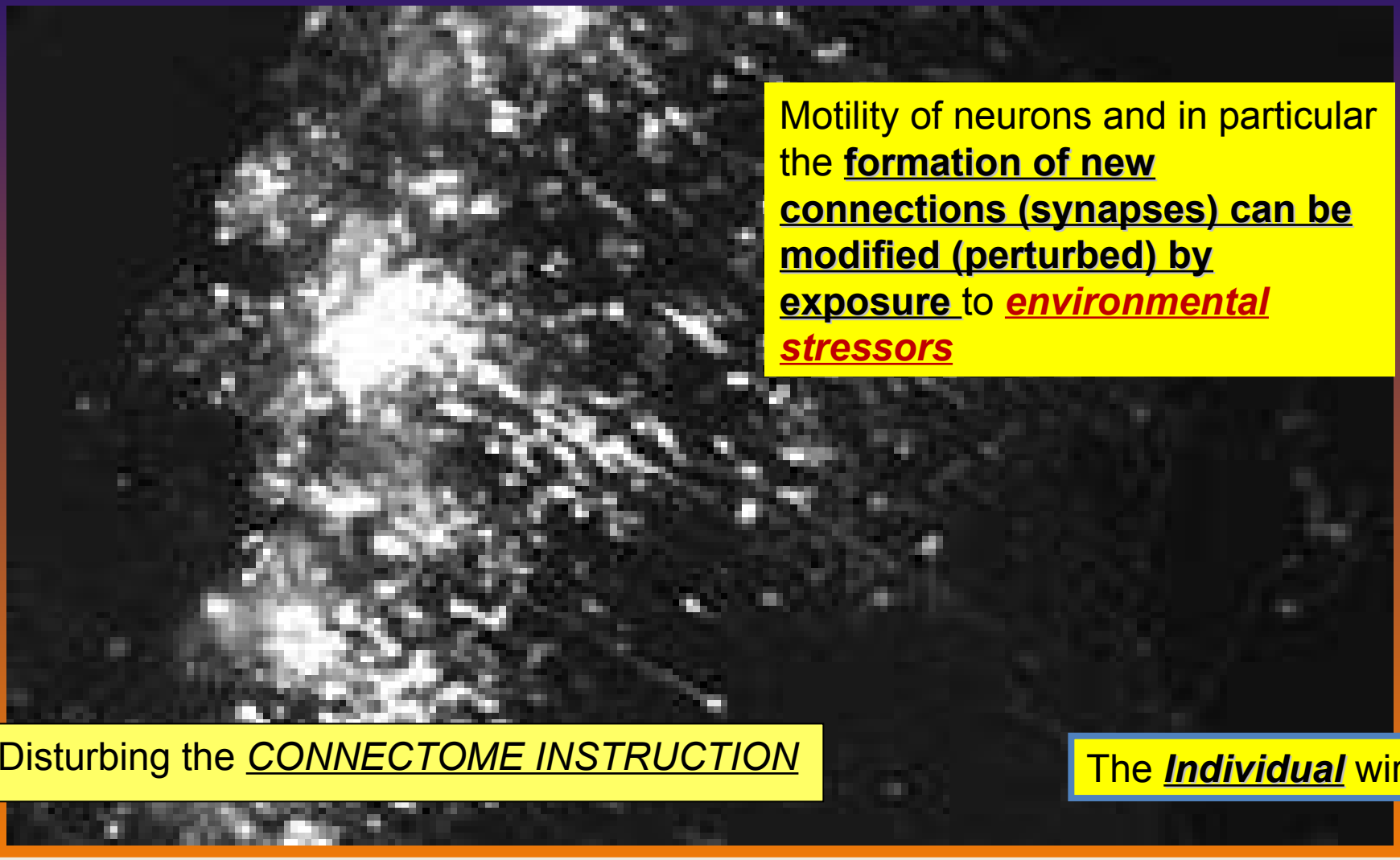
G J Myers, P W Davidson **Does methylmercury have a role in causing developmental disabilities in children?** Environ Health Perspect. 2000 June; 108(Suppl

S P Porterfield **Thyroidal dysfunction and environmental chemicals--potential impact on brain development.** Environ Health Perspect. 2000 June; 108(Suppl 3): 433–438.

SG Selevan, CA Kimmel, P Mendola
Identifying critical windows of exposure for children's health. Environ Health Perspect. 2000 June; 108(Suppl 3): 451–455.



Brain plasticity and modulation of its structure and its functions



Motility of neurons and in particular the **formation of new connections (synapses) can be modified (perturbed) by exposure** to ***environmental stressors***

Disturbing the *CONNECTOME INSTRUCTION*

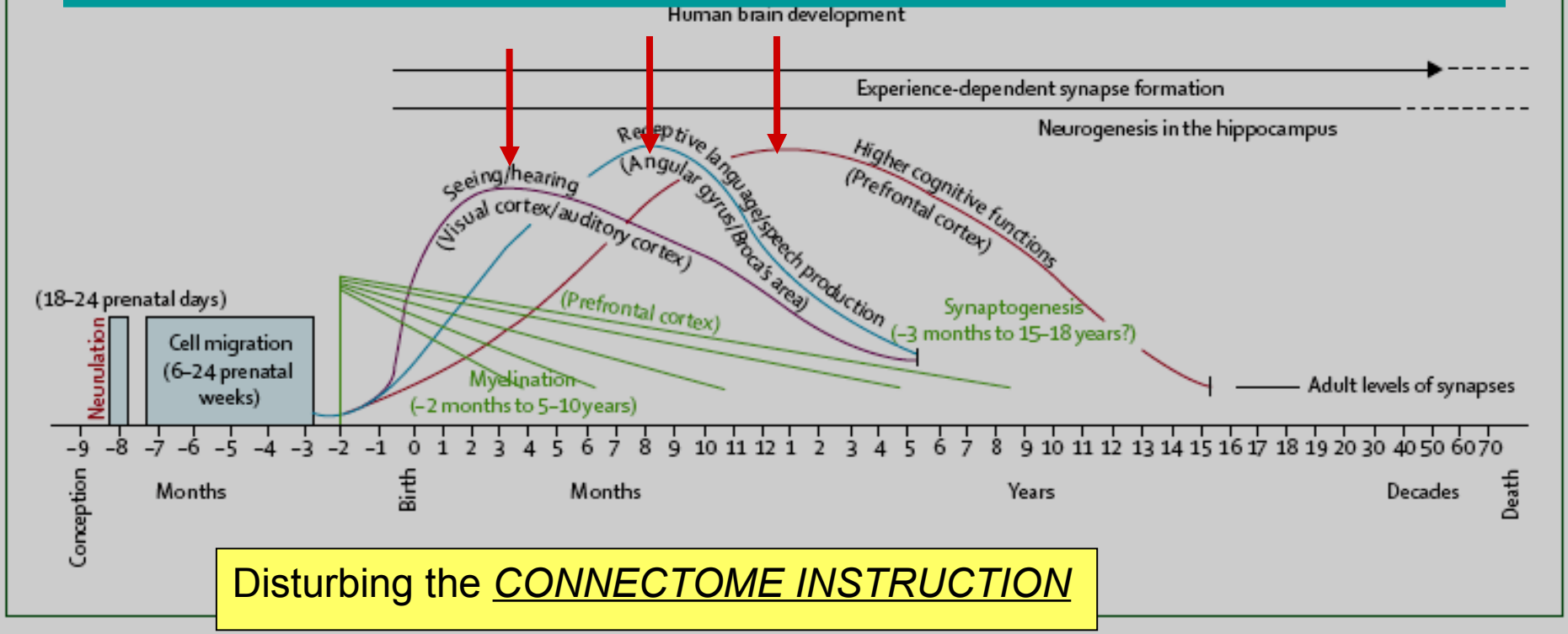
The ***Individual*** wiring

Wingate ***Imagining the brain cell: the neuron in visual culture***. Nature Rev Neuroscience 2006; 7: 745-752

development of SYNAPTOGENESIS and brain functions

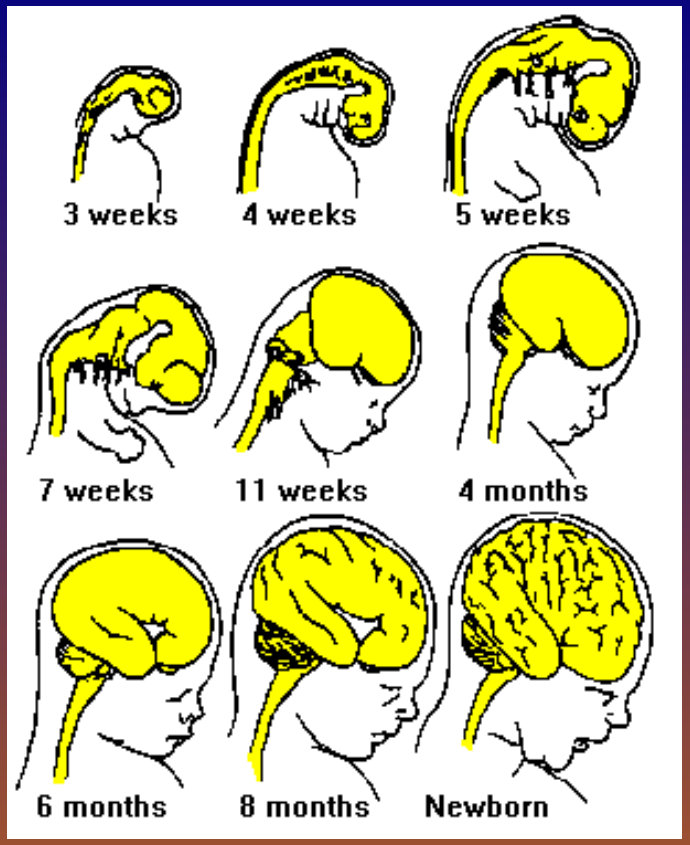
The ***Individual*** wiring

Formation of new synapses following stimulation..



Disturbing the *CONNECTOME INSTRUCTION*

Figure 1: **Human brain development**
Reproduced with permission of authors and American Psychological Association[17] (Thompson RA, Nelson CA. Developmental science and the media: early brain development. *Am Psychol* 2001; **56**: 5–15).



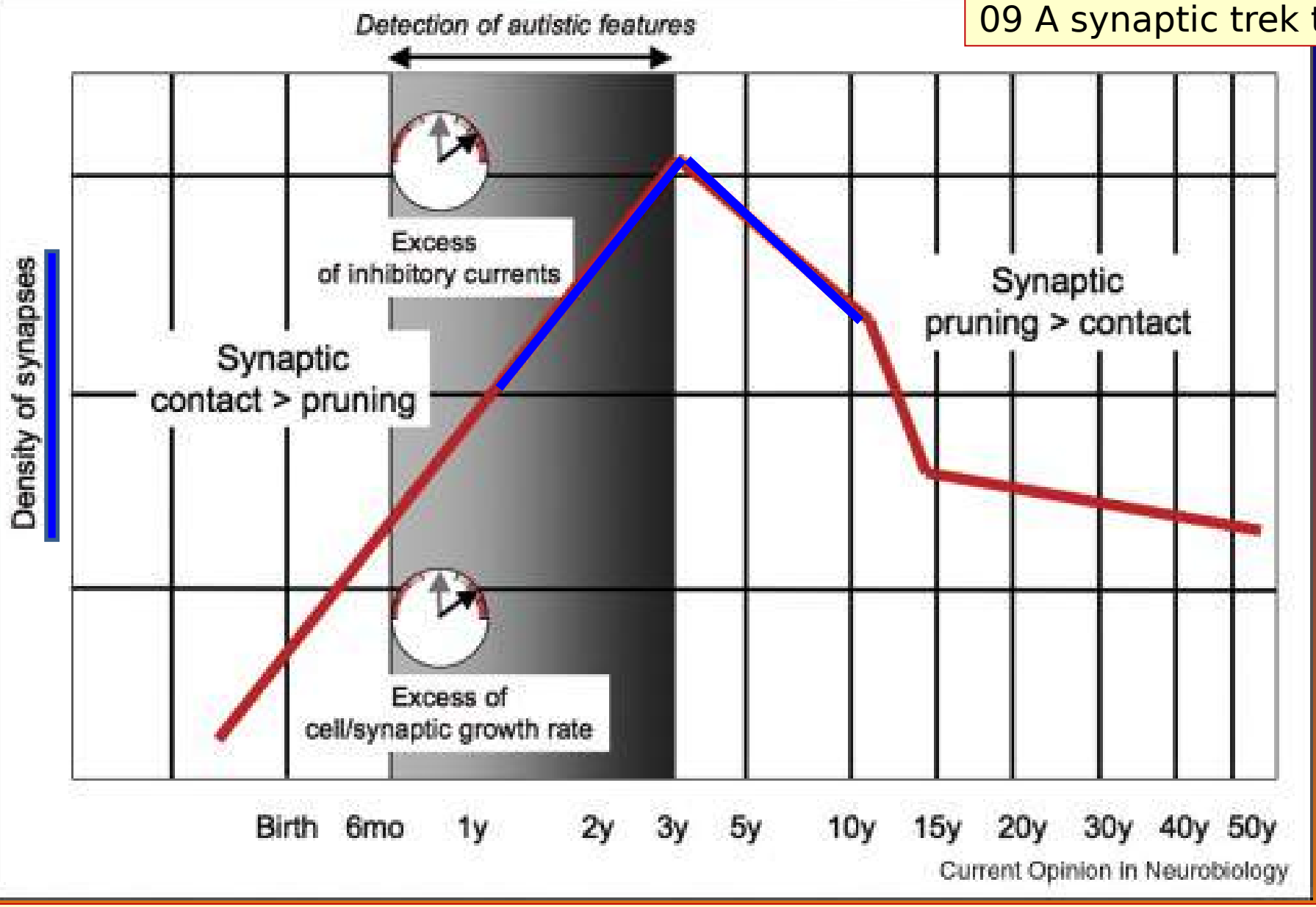
Disturbing the *CONNECTOME INSTRUCTION*

The brain grows at an amazing rate during development. At times during brain development, **250,000 neurons are added every minute!**
At birth,
almost all the neurons that the brain will ever have are present.

However, the brain continues to grow for many years after birth.

By the age of 2 years old, the brain is about **80% of the adult size**

A **stegosaurus dinosaur weighed approximately 1,600 kg but had a brain that weighed only approximately 70 grams (0.07 kg).** Therefore, **the brain was only 0.004% of its total body** weight. In contrast, an adult human weighs approximately 70 kg and has a brain that weighs approximately 1.4 kg. Therefore, **the human brain is about 2%**



Schematic representation of the **different phases of synaptogenesis** in the human brain. **During the first three years of life, an excess of cell/synaptic growth rate and inhibitory currents could increase**

Research | Children's Health

A Section 508–conformant HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1408133.

VOLUME 123 | NUMBER 3 | March 2015 • Environmental Health Perspectives

Autism Spectrum Disorder and Particulate Matter Air Pollution before, during, and after Pregnancy: A Nested Case–Control Analysis within the Nurses' Health Study II Cohort

Raanan Raz,[1] Andrea L. Roberts,[2] Kristen Lyall,[3,4] Jaime E. Hart,[1,5] Allan C. Just,[1] Francine Laden,[1,5,6] and Marc G. Weisskopf[1,6]

BACKGROUND: Autism spectrum disorder (ASD) is a developmental disorder with increasing prevalence worldwide, yet has unclear etiology.

OBJECTIVE: We explored the association between maternal exposure to particulate matter (PM) air pollution and odds of ASD in her child.

METHODS: We conducted a nested case–control study of participants in the Nurses' Health Study II (NHS II), a prospective cohort of 116,430 U.S. female nurses recruited in 1989, followed by biennial mailed questionnaires. Subjects were NHS II participants' children born 1990–2002 with ASD (n = 245), and children without ASD (n = 1,522) randomly selected using frequency matching for birth years. Diagnosis of ASD was based on maternal report, which was validated against the Autism Diagnostic Interview-Revised in a subset. Monthly averages of PM with diameters ≤ 2.5 μm ($PM_{2.5}$) and 2.5–10 μm ($PM_{10-2.5}$) were predicted from a spatiotemporal model for the continental United States and linked to residential addresses.

RESULTS: $PM_{2.5}$ exposure during pregnancy was associated with increased odds of ASD, with an adjusted odds ratio (OR) for ASD per interquartile range (IQR) higher $PM_{2.5}$ (4.42 μg/m^3) of 1.57 (95% CI: 1.22, 2.03) among women with the same address before and after pregnancy (160 cases, 986 controls). Associations with $PM_{2.5}$ exposure 9 months before or after the pregnancy were weaker in independent models and null when all three time periods were included, whereas the association with the 9 months of pregnancy remained (OR = 1.63; 95% CI: 1.08, 2.47). The association between ASD and $PM_{2.5}$ was stronger for exposure during the third trimester (OR = 1.42 per IQR increase in $PM_{2.5}$; 95% CI: 1.09, 1.86) than during the first two trimesters (ORs = 1.06 and 1.00) when mutually adjusted. There was little association between $PM_{10-2.5}$ and ASD.

CONCLUSIONS: Higher maternal exposure to $PM_{2.5}$ during pregnancy, particularly the third trimester, was associated with greater odds of a child having ASD.

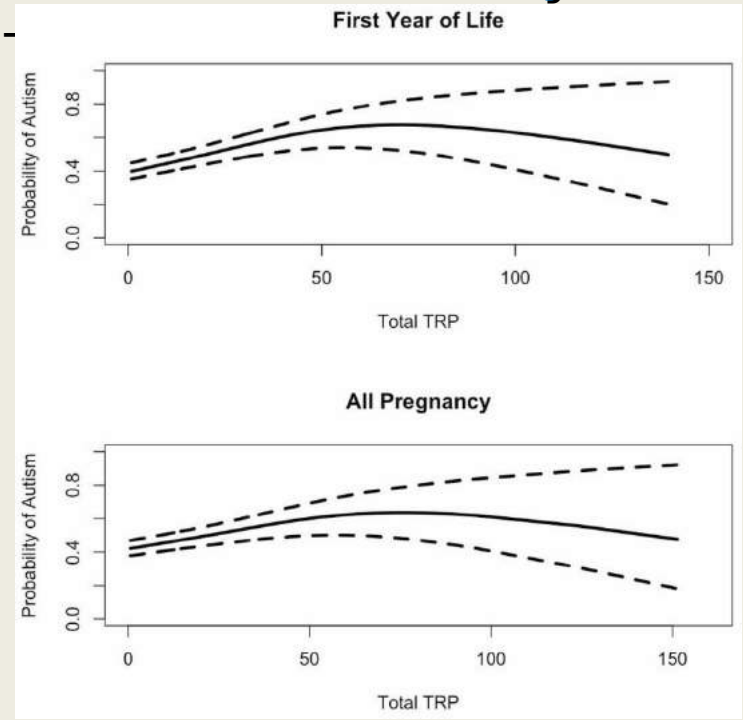
Rischio ASDs molto aumentato (OR > 50%) ed in modo **statisticamente significativo** tra le mamme esposte ad inquinamento atmosferico da **polveri (PM 2.5) e non da PM 2,5-10** durante il **terzo trimestre di gravidanza (sinaptogenesi!) ..**

altri due studi caso-controllo 2013 avevano mostrato la correlazione **JAMA Psy** 2013;70(1):71-7; **EHP** 2013;121(3):380-6

Living near a freeway, based on the location of the birth, and third trimester address, and **autism**

PM2.5, PM10, and NO2 at residences were higher in children with autism.

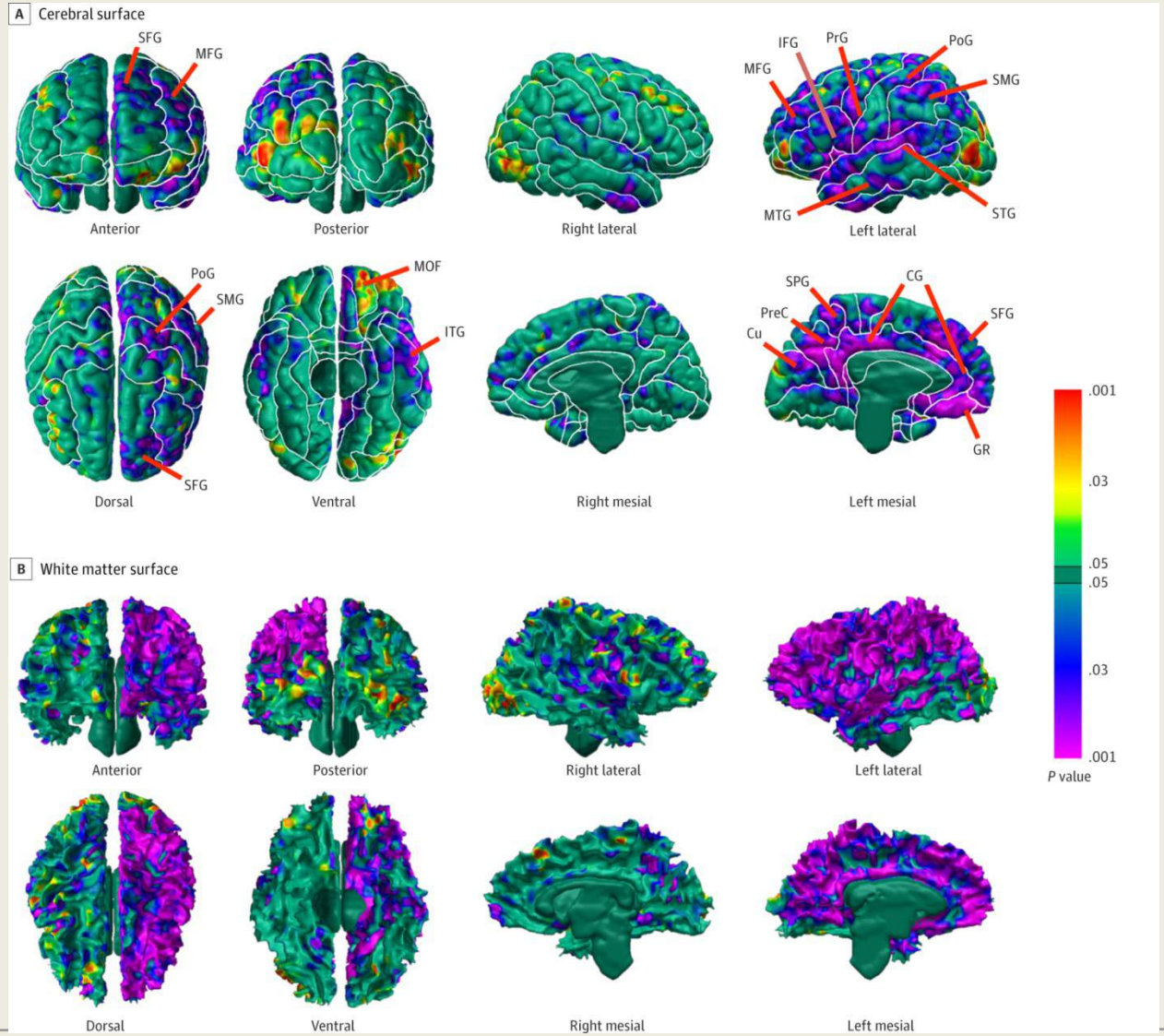
The magnitude of these **associations** appear to be **most pronounced during late gestation** (OR=1.98, 95%CI 1.20–3.31) **and early life / first year of life** (OR=1.98, 95%CI 1.20-



JAMA Psychiatry. 2013 January ; 70(1): 71–77. doi:10.1001/jamapsychiatry.2013.266

From: **Effects of Prenatal Exposure to Air Pollutants (Polycyclic Aromatic Hydrocarbons) on the Development of Brain White Matter, Cognition, and Behavior in Later Childhood**

JAMA Psychiatry. **Published online March 25, 2015**. doi:10.1001/jamapsychiatry.2015.57



Abbiamo rilevato una **correlazione dose-risposta** tra **-esposizione prenatale a IPA** e **-- riduzione della sostanza bianca nella tarda infanzia nell'emisfero cerebrale sinistro** (coinvolgente l'intera corteccia)

Toxicologic Pathology

http://tpx.sagepub.com

Pediatric Respiratory and Systemic Effects of Chronic Air Pollution Exposure: Nose, Lung, Heart, and Brain Pathology

Lilian Calderón-Garcidueñas, Maricela Franco-Lira, Ricardo Torres-Jardón, Carlos Henriquez-Roldán, Gerardo Barragán-Mejía, Gildardo Valencia-Salazar, Angelica González-Maciel, Rafael Reynoso-Robles, Rafael Villarreal-Calderón and William Reed

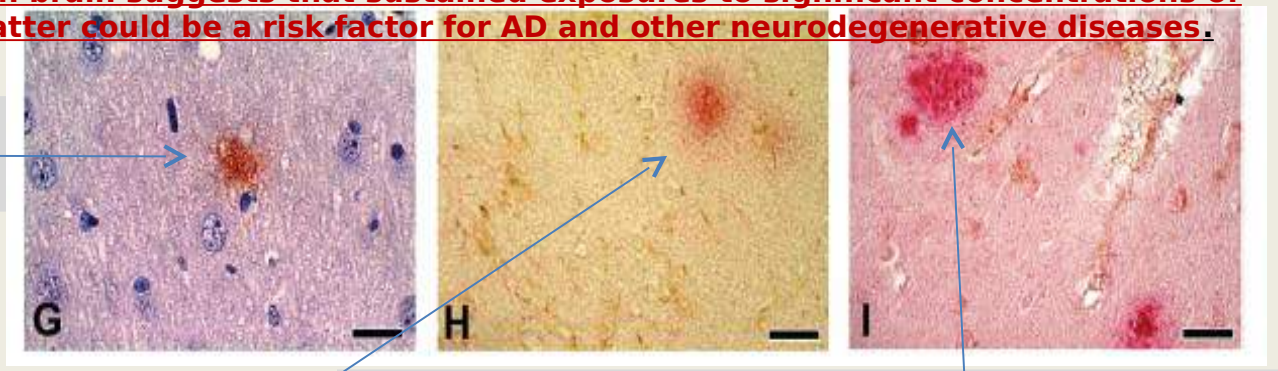
Toxicol Pathol 2007; 35; 154

DOI: 10.1080/01926230601059985

Exposures to **particulate matter and gaseous air pollutants** have been associated with **respiratory tract inflammation**, disruption of the nasal respiratory and olfactory barriers, **systemic inflammation**, production of mediators of inflammation capable of **reaching the brain and systemic circulation of particulate matter**. **Mexico City (MC) residents** are exposed to significant amounts of **ozone, particulate matter** and associated **lipopolysaccharides**. **MC dogs exhibit brain inflammation** and an **acceleration of Alzheimer's-like pathology, suggesting that the brain is adversely affected by air pollutants**. **MC children, adolescents and adults have a significant upregulation of cyclooxygenase-2 (COX2) and interleukin-1β (IL-1β) in olfactory bulb and frontal cortex, as well as neuronal and astrocytic accumulation of the 42 amino acid form of β-amyloid peptide (Aβ42), including diffuse amyloid plaques in frontal cortex**.

The pathogenesis of Alzheimer's disease (AD) is characterized by brain inflammation and the accumulation of Aβ42, which precede the appearance of neuritic plaques and neurofibrillary tangles, the pathological hallmarks of AD. **Our findings of nasal barrier disruption, systemic inflammation, and the upregulation of COX2 and IL-1β expression and Aβ42 accumulation in brain suggests that sustained exposures to significant concentrations of air pollutants such as particulate matter could be a risk factor for AD and other neurodegenerative diseases.**

The frontal cortex of an **11-month-old healthy MC dog e**xhibits **A*β42*** *staining of a* ***diffuse plaque****, surrounded by a microglia-like nucleus*

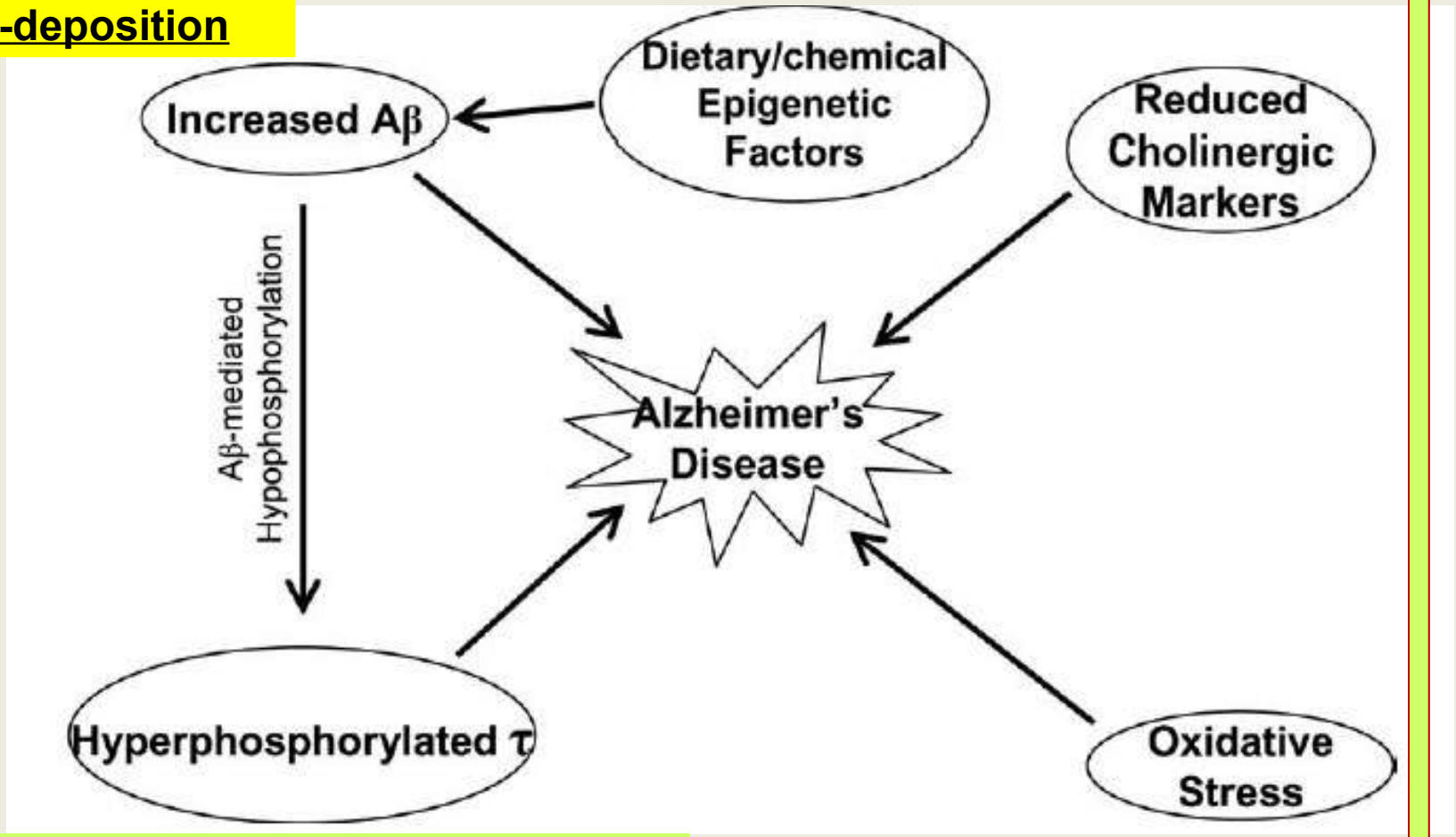


The frontal cortex of a **17-year-old MC boy**… shows **a diffuse**

The **frontal cortex of a 36-year-old MC male** with an E3/E4 ApoE genotype .. shows **abundant mature and diffuse A*β42 plaques*** *(red stain) along*

And even in this case we have many evidences of an **early origin of the disease** and of a **progressive anticipation in the age of onset** (LEARn) model

Increased amyloid Aβ-deposition



Accumulation of hyperphosphorylated microtubule associated protein τ **"tangles"**

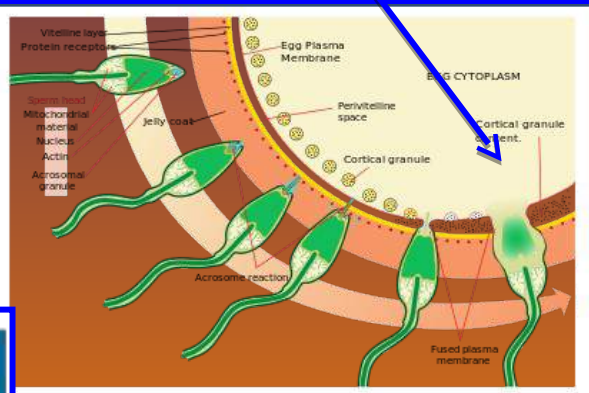
5° Journée annuelle de l'Impact de l'environnement sur la santé de la femme, mère & de l'enfant

30 avril 2015

Focus sur la périconception

et la grossesse

The overlooked heritage: the genetic transmission by the father

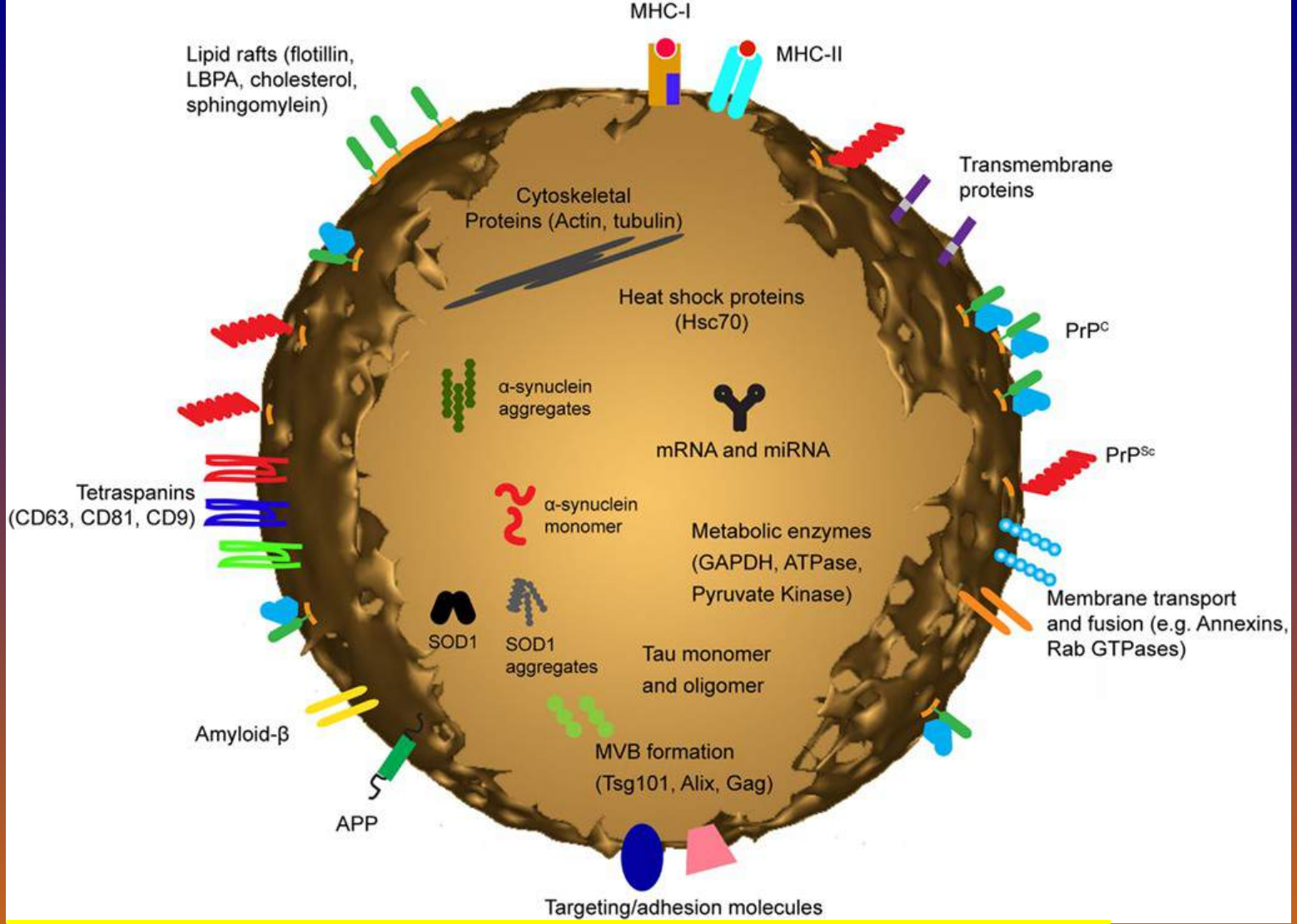


Everything You Always Wanted to Know About Sex (But Were Afraid to Ask)
Woody Allen dressed as a sperm (1972)

Tout ce que vous avez toujours voulu savoir sur le sexe (sans jamais oser le demander)

ECERI
European Cancer and Environment Research Institute

ERNESTO BURGIO
ECERI - European Cancer and Environment Research Institute



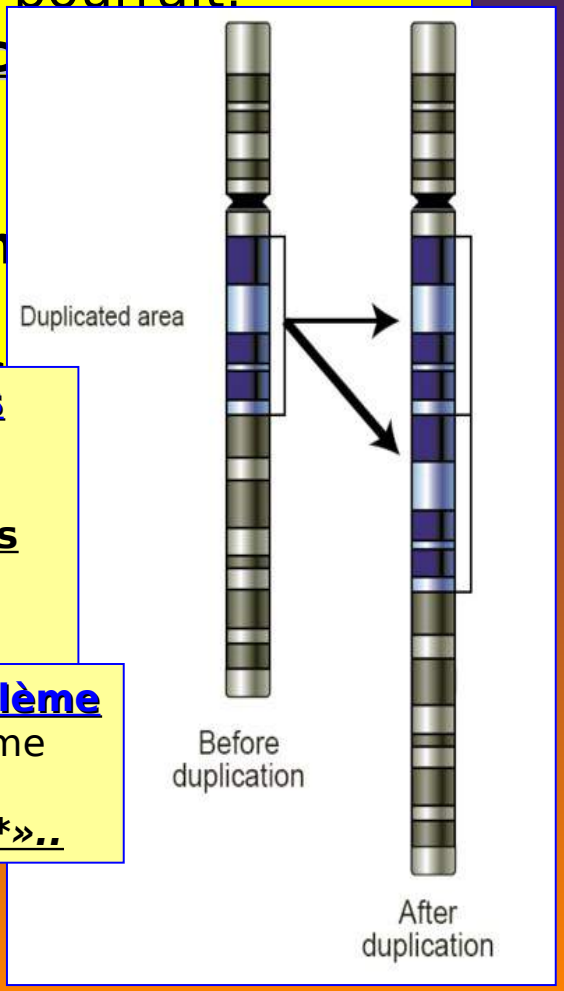
http://www.frontiersin.org/files/Articles/25554/fphys-03-00124-HTML/image_m/fphys-03-00124-g002.jpg

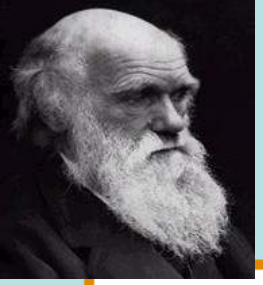
Exosomes are small membrane bound **vesicles containing mRNA and miRNA**, and a vast array of different proteins depending on their host cell...Scientists that are actively researching **the role that exosomes may play in cell-to-cell signaling, hypothesize that**

..que des ***CNVs de novo*** (i. e. des **mutations réactives-défensives**)**
dans les gamètes soient les **plus fréquentes** et **les plus importantes**
mutations génétiques pour ce qui concerne **les troubles du spectre autistique**.. est une découverte jusqu'ici **extrêmement sous-estimée**.. d'autant que ça pourrait:
- **expliquer toute seule l'augmentation spec**
cas
de ces dernières années
- **se connecter à toutes les théories concern**
l'origine «toxique» de l'autisme
-con uire à une nouvelle augmentation des c
(par **:rans**

La plupart de ces mutations sont des variations *de novo* du nombre de copies des gènes ou des segments de gènes (CNVs): c'est dire des ***mutations réactives et défensives localisés*** **dans des zones chromosomiques caractérisés par la présence des *clusters* de gènes soumis à**

Tout cela dit.. il est absolument nécessaire de **reconsidérer le problème des plusieurs expositions environnementales précoces** ou même **gamètiques,** et leur **synergie possible..** qui peut induire *soit* une ***instabilité épigénétique,*** *soit* des telles ***mutations « réactives ****»..



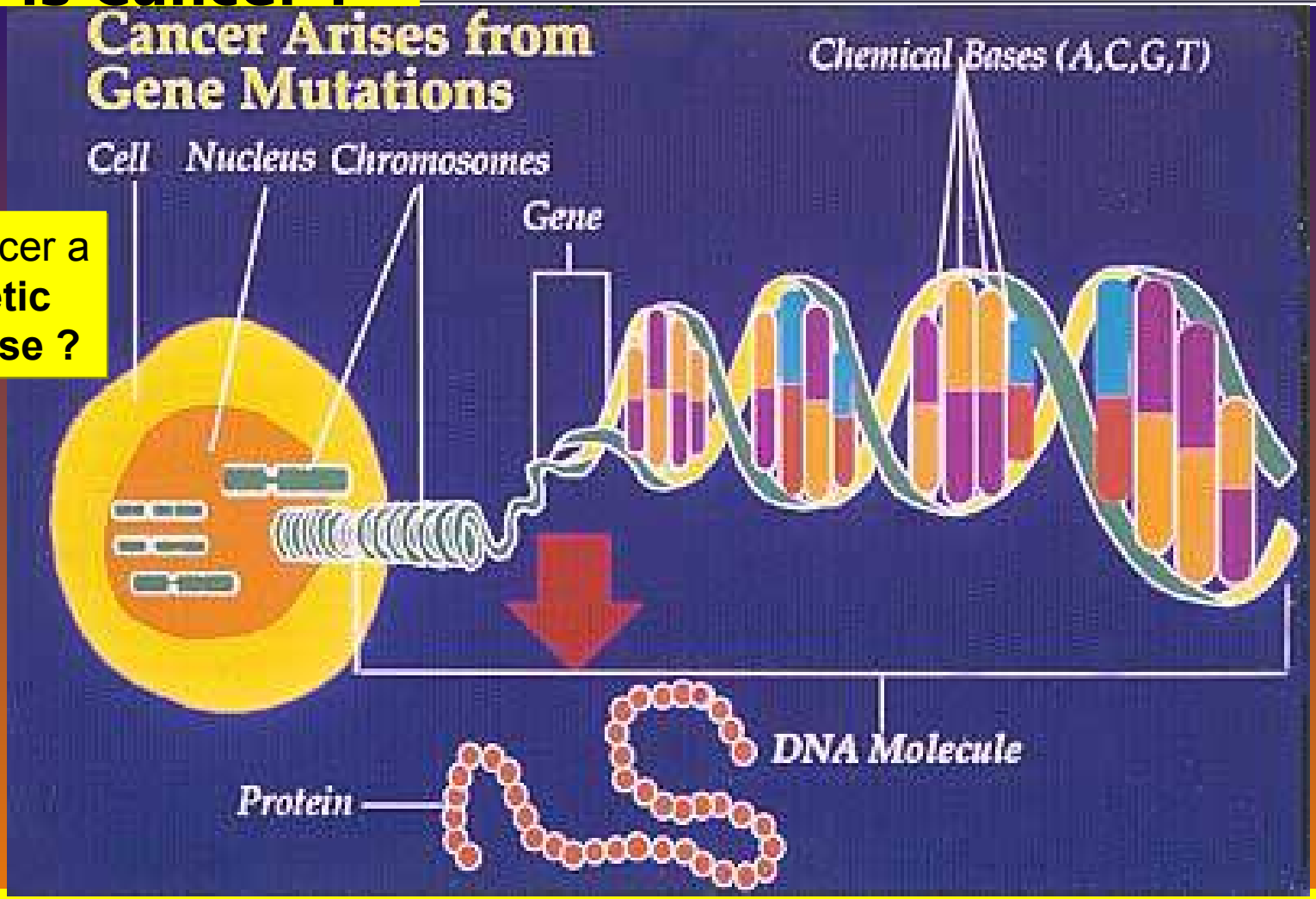


Is Cancer Risk Determined by Developmental Programming Induced by Environmental Exposures?

Ce sont des **quantités minimales de molécules (epi)génotoxiques**, induisant
des **transformations continuelles de la chromatine**, qui constituent le véritable problème. C'est un processus très lent pouvant démarrer lors des **premières**
étapes du développement fœtal. Et, même dans les ***gamètes***.
Si les tissus du fœtus sont mal programmés au début et s'il y a un stress épigénétique progressif, les mutations génétiques et

What is Cancer ?

Is cancer a **Genetic Disease ?**



Do the **somatic cells of a single tissue** undergo regression for intrinsic, **accidental reasons (*mutations* or *epi-mutations*) and de-differentiate**

The Inside Matters: Random Gene Changes

The **Somatic Mutation Theory** of Carcinogenesis

Over your lifetime, **random gene changes** are passed along as your body cells grow and divide, so they **accumulate**

Nature

Cell
Volume 100, Issue 1, 7 January 2000, Pages 57-70

What's *Cancer* ?

Review

The Hallmarks of Cancer

Douglas Hanahan [1], and Robert A. Weinberg [2]

[1] versity of California at San Francisco, San Francisco, California 94143, USA

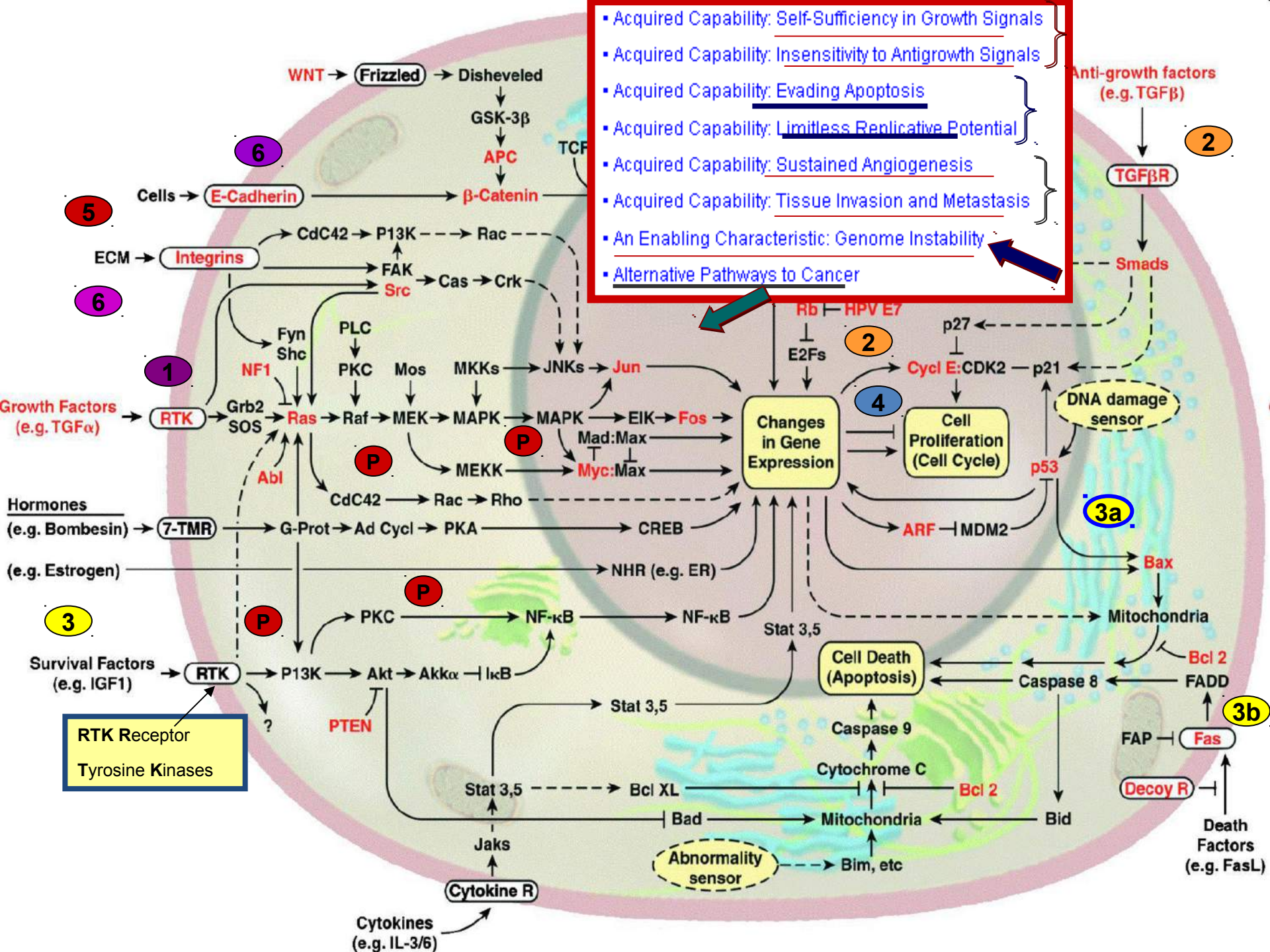
[2] usetts Institute of Technology, Cambridge, Massachusetts 02142, USA

We suggest that **the vast catalogues of cancer cell genotypes is a manifestation of six essential alterations in cell physiology that collectively dictate malignant growth**

Tumor development proceeds via a process formally analogous to Darwinian evolution, in which a succession of stochastic mutations, each conferring one or another type of **growth advantage**, leads to the progressive conversion of normal human cells into CA-cells...

CA-cells have defects in regulatory circuits that govern normal cell proliferation and homeostasis... the vast catalog of CA-cell genotypes is a manifestation of **six essential alterations in cell physiology that collectively**

- Acquired Capability: Self-Sufficiency in Growth Signals 1
- Acquired Capability: Insensitivity to Antigrowth Signals 2
- Acquired Capability: Evading Apoptosis 3
- Acquired Capability: Limitless Replicative Potential 4
- Acquired Capability: Sustained Angiogenesis 5
- Acquired Capability: Tissue Invasion and Metastasis 6
- An Enabling Characteristic: Genome Instability
- Alternative Pathways to Cancer


Acquired Capability: Self-Sufficiency in Growth Signals
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Acquired Capability: Limitless Replicative Potential
Acquired Capability: Sustained Angiogenesis
Acquired Capability: Tissue Invasion and Metastasis
An Enabling Characteristic: Genome Instability
Alternative Pathways to Cancer
WNT
Frizzled
Disheveled
GSK-3β
APC
β-Catenin
TCF
Cells
E-Cadherin
ECM
Integrins
CdC42
P13K
Rac
FAK
Src
Cas
Crk
Fyn
Shc
PLC
PKC
Mos
MKKs
JNKs
Jun
NF1
Growth Factors
(e.g. TGFα)
RTK
Grb2
SOS
Ras
Raf
MEK
MAPK
MAPK
EIK
Fos
Mad:Max
Myc:Max
MEKK
Abl
CdC42
Rac
Rho
Hormones
(e.g. Bombesin)
7-TMR
G-Prot
Ad Cycl
PKA
CREB
(e.g. Estrogen)
NHR (e.g. ER)
PKC
NF-κB
NF-κB
Survival Factors
(e.g. IGF1)
RTK
P13K
Akt
Akkα
IκB
?
PTEN
Stat 3,5
Stat 3,5
Jaks
Cytokine R
Cytokines
(e.g. IL-3/6)
Rb
HPV E7
E2Fs
Changes
in Gene
Expression
Cell
Proliferation
(Cell Cycle)
Cycl E:CDK2
p27
p21
DNA damage
sensor
p53
ARF
MDM2
Bax
Mitochondria
Cell Death
(Apoptosis)
Caspase 8
Bcl 2
FADD
Caspase 9
Cytochrome C
Bcl XL
Bcl 2
Bad
Mitochondria
Bid
Abnormality
sensor
Bim, etc
FAP
Fas
Decoy R
Death
Factors
(e.g. FasL)
Anti-growth factors
(e.g. TGFβ)
TGFβR
Smads
RTK Receptor
Tyrosine Kinases
1
2
3
3a
3b
4
5
6
6
P
P
P

2 JANUARY 2015 • VOL 347 ISSUE 6217

BIOMEDICINE

The bad luck of cancer

Analysis suggests most cases can't be prevented

By Jennifer Couzin-Frankel

Random mutations in healthy cells may explain two-thirds of cancers, like this one in the colon.

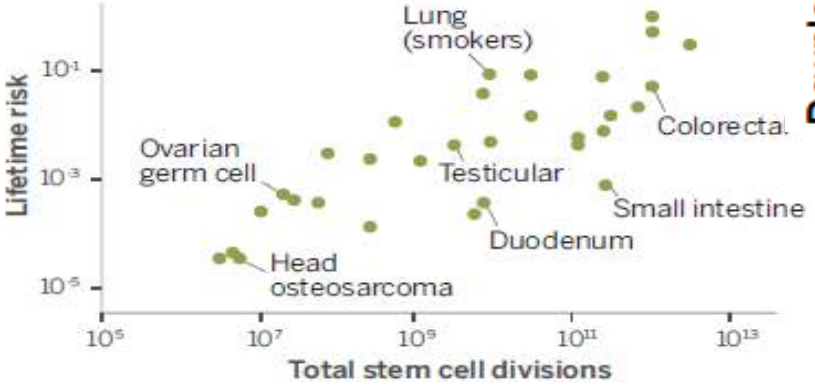
CANCER ETIOLOGY

Variation in cancer risk among tissues can be explained by the number of stem cell divisions

Cristian Tomasetti[1]* and Bert Vogelstein[2]*

Charting cancer risk

As the number of stem cell divisions in a tissue rises, so does the chance of cancer striking that site.



International Agency for Research on Cancer

World Health Organization

PRESS RELEASE
N° 231

13 January 2015

Most types of cancer not due to "bad luck"
IARC responds to scientific article claiming that environmental and lifestyle factors account for less than one third of cancers

Lyon, France, 13 January 2015 - The International Agency for Research on Cancer (IARC), the World Health Organization's specialized cancer agency, strongly disagrees with the conclusion of a scientific report[1] on the causes of human cancer published in the journal *Science* on 2 January 2015 by Dr Cristian Tomasetti and Dr Bert Vogelstein.

The study, which has received widespread media coverage, compares the number of lifetime stem cell divisions across a wide range of tissues with lifetime cancer risk and suggests that random mutations (or "bad luck") are "the major contributors to cancer overall, often more important than either hereditary or external environmental factors."

The past five decades of international epidemiological research have shown that most cancers that are frequent in one population are relatively rare in another and that these patterns vary over time[2]. For example, oesophageal cancer is common among men in East Africa but rare in West Africa. Colorectal cancer, once rare in Japan, increased 4-fold in incidence in just two decades. These observations are characteristic of many common cancers and are consistent with a major contribution of environmental and lifestyle exposures, as opposed to genetic variation or chance ("bad luck").

Furthermore, IARC experts identify several limitations in the report itself. These include the emphasis on very rare cancers (e.g. osteosarcoma, medulloblastoma) that together make only a small contribution to the total cancer burden. The report also excludes, because of the lack of data, common cancers for which incidence differs substantially between populations and over time. The latter category includes some of the most frequent cancers worldwide, for example those of the stomach, cervix, and breast, each known to be associated with infections or lifestyle and environmental factors. Moreover, the study focuses exclusively on the United States population as a measure of lifetime risk. The comparison of different populations would have yielded different results.

What are the hallmarks of cancer?

The seminal article by Douglas Hanahan and Robert Weinberg on the hallmarks of cancer is 10 years old this year and its contribution to how we see cancer has been substantial. But, in embracing this view, have we lost sight of what makes cancer cancer?

Yuri Lazebnik is at Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, New York, USA.
e-mail: lazebnik@cshl.edu

NATURE REVIEWS | CANCER
APRIL 2010 | VOLUME 10

some ***benign tumours*** *can weigh many* ***kilograms*** at the time of diagnosis

sustained angiogenesis is a feature of both benign and malignant tumours

RB protein is deficient both in retinoblastoma, a malignant tumour of the eye, and in ***retinoma***, a benign tumour of this organ.

evasion of apoptosis has been implicated in the pathogenesis of **malignant and benign** tumours

insensitivity to antigrowth signals and **evasion of cell death** also seem to be **characteristic of both benign and malignant tumours**

five of the proposed hallmarks of cancer **are also characteristic of** ***benign tumours***

La **seule caractéristique distinctive du cancer** est la **capacité à métastaser** (qui n'est pas, comme nous le verrons, le résultat des mutations, mais la **réactivation d'un programme génétique embryonnaire** !!)

NEWS FEATURE

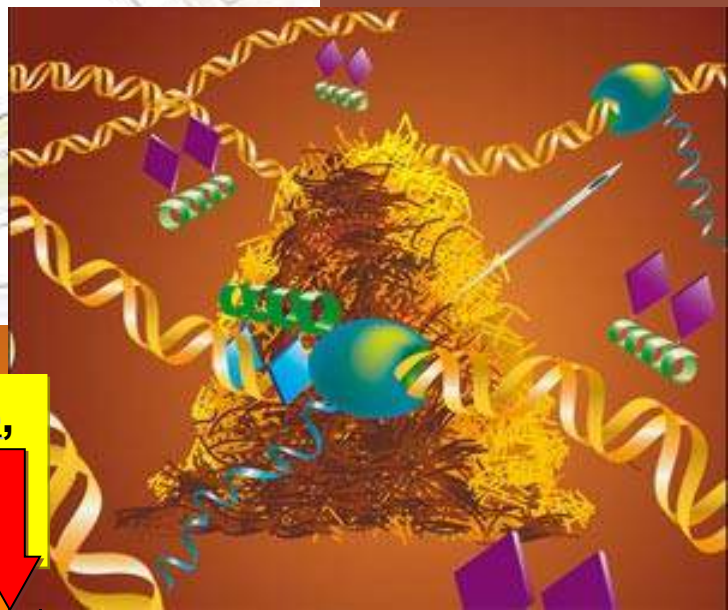
NATURE Vol 464 15 April 2010

The GWAS efforts are certainly creating **bigger haystacks** …

The CANCER GENOME challenge

Databases could soon be flooded with genome sequences from 25,000 tumours. **Heidi Ledford** looks at the obstacles researchers face as they search for meaning in the data.

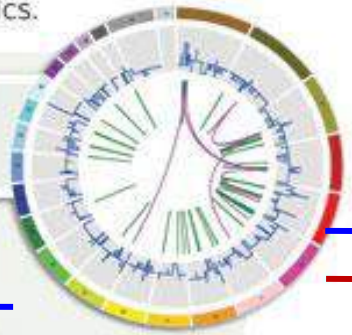
In a recent **editorial** on *Nature* Heidi Ledford stated that **the millions of genetic sequences and SNPs accumulated** in an attempt to **decipher the genetics of cancer** have built **giant haystacks in which researchers have gone lost …**



The full genome sequence of a lung cancer cell line, for example, yielded 22,910 point mutations, only 134 of which were in protein-coding regions

CANCER GENOMES COMING FAST

A few examples of fully and partially sequenced cancer genomes and their defining characteristics.



LUNG CANCER

Cancer: small-cell lung carcinoma

- Sequenced: full genome
- Source: NCI-H209 cell line
- Point mutations: 22,910
- Point mutations in gene regions: 134
- Genomic rearrangements: 58
- Copy-number changes: 334

Highlights:
Duplication of the *CHD7* gene confirmed in two other small-cell lung carcinoma cell lines.

Source: E. D. Pleasance *et al. Nature* **463,** 184–190 (2010).

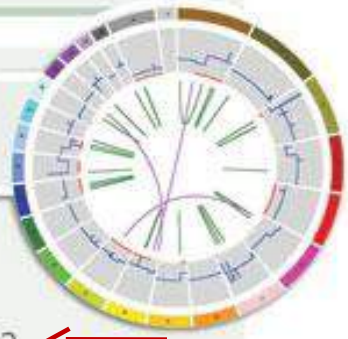
BREAST CANCER

Cancer: basal-like breast cancer

- Sequenced: full genome
- Source: primary tumour, brain metastasis, and tumours transplanted into mice
- Point mutations: 27,173 in primary, 51,710 in metastasis and 109,078 in transplant
- Point mutations in gene regions: 200 in primary, 225 in metastasis, 328 in transplant
- Genomic rearrangements: 34
- Copy-number changes: 155 in primary, 101 in metastasis, 97 in transplant

Highlights:
The *CTNNA1* gene encodes a putative suppressor of metastasis that is deleted in all tumour samples.

Source: L. Ding *et al. Nature* **464,** 999–1005 (2010).



SKIN CANCER

Cancer: metastatic melanoma

- Sequenced: full genome
- Source: COLO-829 cell line
- Point mutations: 33,345
- Point mutations in gene regions: 292
- Genomic rearrangements: 51
- Copy-number changes: 41

Highlights:
Patterns of mutation reflect damage by ultraviolet light.

Source: E. D. Pleasance *et al. Nature* **463,** 191–196 (2010).

BRAIN CANCER

Cancer: glioblastoma multiforme

- Sequenced: exome (no complete Circos plot)
- Source: 7 patient tumours, 15 tumours transplanted into mice (follow-up sequencing on 21 genes for 83 additional samples)
- Genes containing at least one protein-altering mutation: 685
- Genes containing at least one protein-altering point mutation: 644
- Copy-number changes: 281

Highlights:
Mutations in the active site of *IDH1* have been found in 12% of patients.

Source: E. R. Mardis *et al. N. Engl. J. Med.* **361,** 1058–1066 (2009).

First European Cancer and Environment Research Institute Workshop

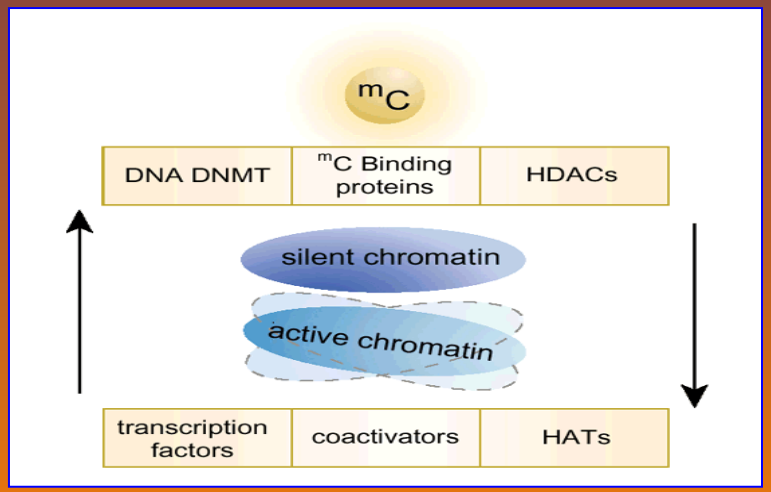
ECERI
European Cancer and Environment Research Institute

October the 26th 2012,
Académie Royale de Médecine de Belgique,
Belgium Royal Academy of Medicine,
Salle Albert I,
Brussels, Belgium

Notes on the epigenetic (transplacental and transgenerational) origins of childhood cancer

ERNESTO BURGIO
ECERI - European Cancer and Environment Research Institute
ISDE Scientific Committee

doctors for the environment ISDE



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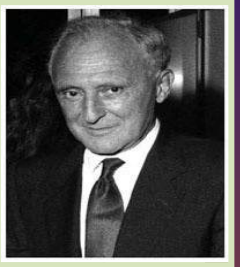
Search PubMed for [ ] Go Clear

1: Natl Cancer Inst Monogr. 1979 May;(51):159-84.



Prenatal exposure to chemical carcinogens and its effect on subsequent generations.

Tomatis L.

That exposure of pregnant animals to chemical carcinogens results in the occurrence of tumors in the progeny is well documented. Evidence has been accumulated on at least 38 chemicals pertaining to different chemical groups. The experimental evidence was followed by observations in humans regarding the increased risk of cancer in daughters of women who received stilbestrol during pregnancy. Additional experimental evidence is accumulating on the possibility that exposure during pregnancy results in an increased incidence of tumors for more than one generation of untreated descendants. Studies done on mice with DMBA and on rats with MNU and ENU showed that exposure to the carcinogens during pregnancy resulted in a high incidence of tumors in animals of the first generation and in an increased incidence of tumors at specific sites in untreated animals of the second and third generations.

PMID: 384260 [PubMed - indexed for MEDLINE]

Carcinogenesis vol.13 no.2 pp.145–151, 1992

COMMENTARY

Transgeneration transmission of carcinogenic risk

L.Tomatis, S.Narod[1] and H.Yamasaki

International Agency for Research on Cancer, Lyon, France and [1]McGill University, The Montreal General Hospital Research Institute, Montreal, Canada

Transmission of carcinogenic risk is best demonstrated by cancer-prone families. The best-known cancer syndrome is hereditary retinoblastoma, for which germ cell alterations of the Rb gene have been identified. A recent study suggests that germ-line mutations of the p53 gene are responsible for the Li–Fraumeni syndrome, an association of tumors including breast cancer and soft tissue sarcomas.

Genetic alterations of germ cells predisposing to cancer may result from intrinsic genetic instability or from exposure to mutagens. It is our principal aim to consider the possible effect of mutagenic carcinogens on germ cells as the origin of genetic predisposition to cancer.

What happened?

Que s'est-il passé? **Chez les filles l'exposition au DES à l'âge de fœtus** augmenta considérablement le **risque du cancer du sein et du vagin (++),** chez les garçons cela conduit à un **développement anormal des testicules** et un **risque accru de 20 fois** pour ***hypospadias***

- *Parental generation:* DES exposure moderately elevated the risk of breast cancer later in life in mothers that took the drug
- 1st generation offspring: DES exposure caused a suite of reproductive abnormalities
  - In girls, DES exposure as a fetus led to 2.5 fold increase in breast cancer risk, greatly elevated risk of uterine cancer (during ages 20-40) and abnormal urogenital development
  - In males, DES exposure has an elevated risk of epididymal cysts and sometimes led to abnormal testicular development and 20-fold increased chance of hypospadia

Aujourd'hui, nous savons que .. l'exposition précoce au **DES induit des changements dans l'expression de plusieurs gènes** impliqués dans la structuration des tissus, tels que **Wnt7a, HOXA9, HOXA10** et **HOXA11** qui contribuent à la **programmation de l'architecture des tissus** et de leur morphologie ...

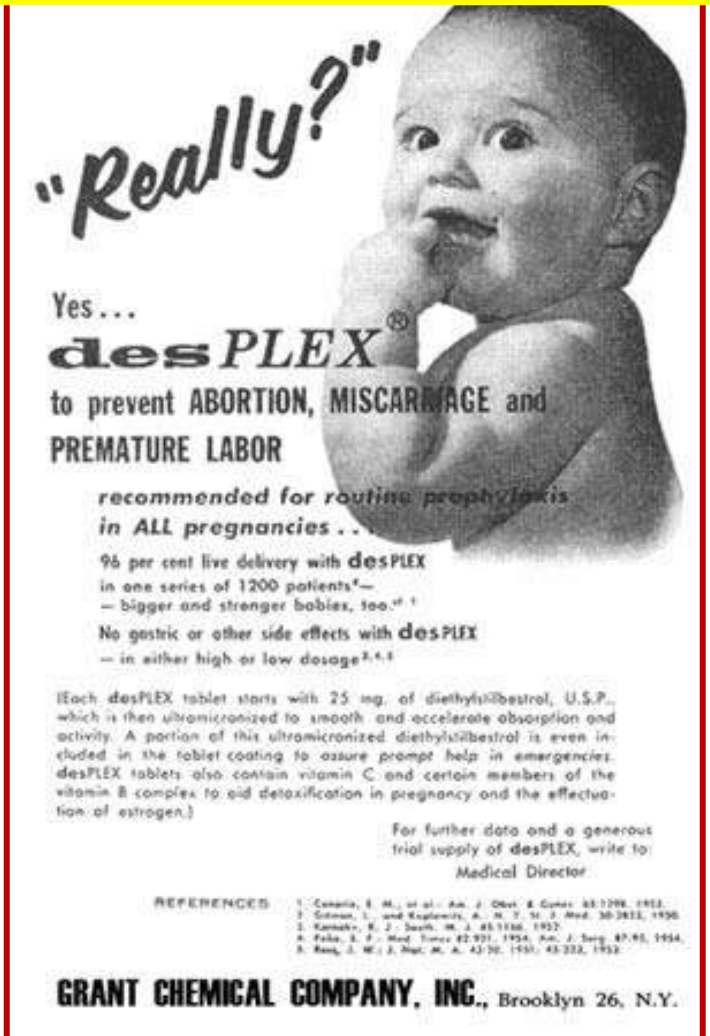
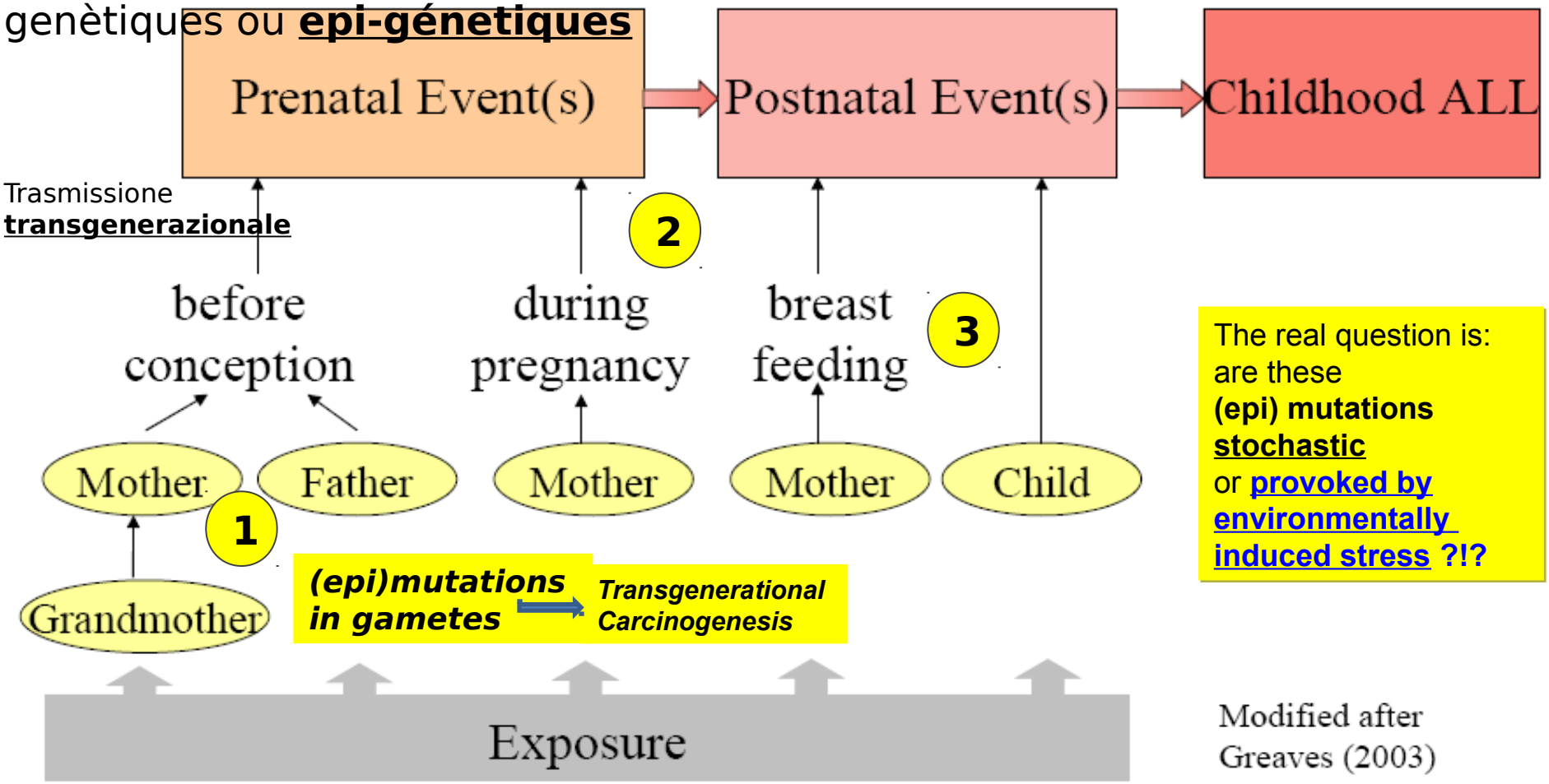


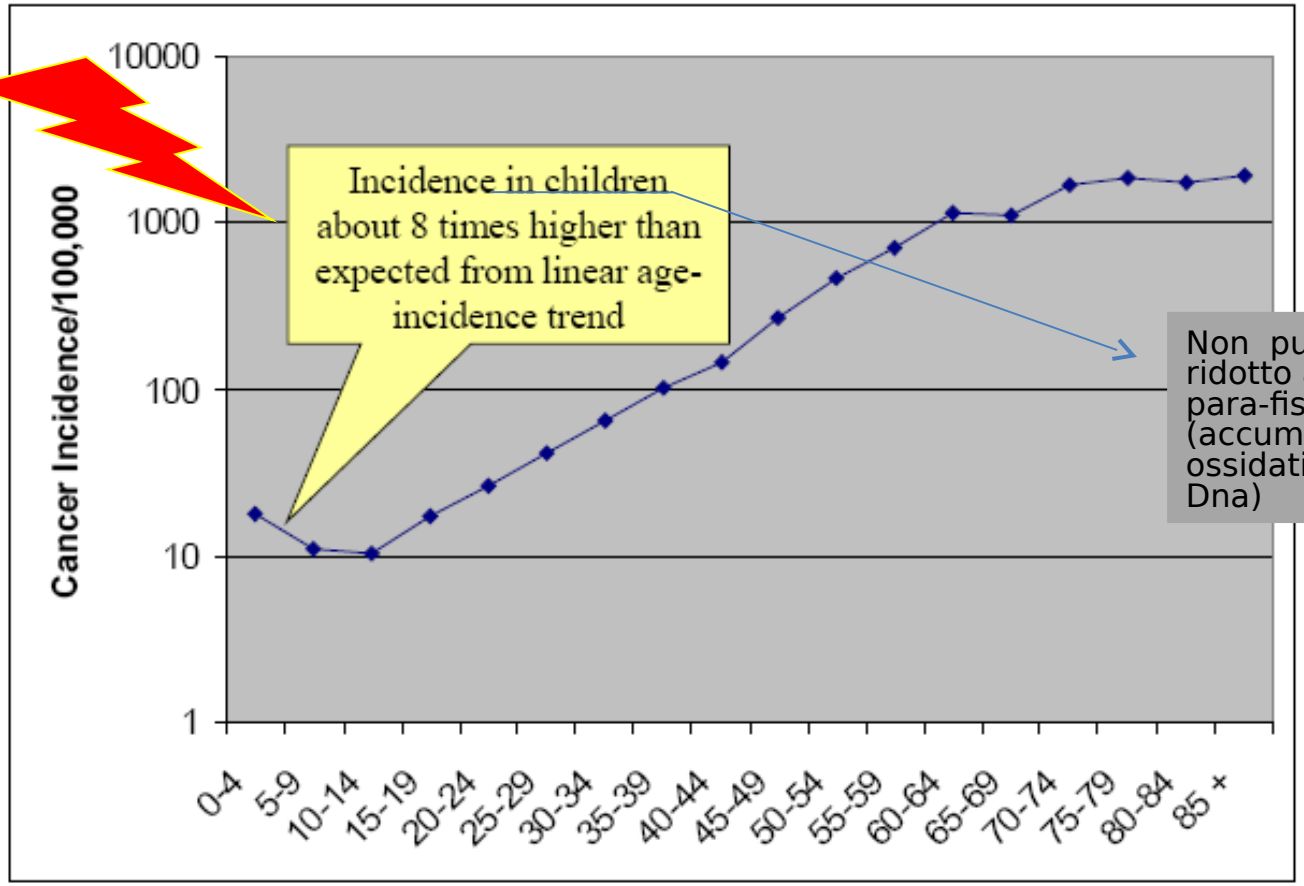
Figure 2
Medical journal advertisement for prenatal tablets with vitamins and diethylstilbestrol

Il n'y a que **deux** possibilités:
1) l'exposition du fœtus à des agents ***physiques*** (***X-rays***), ***chimiques*** ou ***biologiques (****virus****)*** (transmis par transmission **trans-placentaire**) qui puissent endamager directement le foetus
2) la transmission ***trans-generationelle*** d'une ou plusieurs lesions genètiques ou **epi-génetiques**



The real question is: are these **(epi) mutations stochastic** or **provoked by environmentally induced stress ?!?**

Cancer Incidence by Age



Non può essere ridotto a fenomeno para-fisologico (accumulo di lesioni ossidative a carico del Dna)

Austria, 2003

Early Human Development (2005) 81, 123–129

ELSEVIER

Early Human Development

www.elsevier.com/locate/earlhumdev

In utero origins of childhood leukaemia

Mel Greaves*

Abstract Chimaeric fusion genes derived by chromosome translocation are common molecular abnormalities in paediatric leukaemia and provide unique markers for the malignant clone. They have been especially informative in studies with twins concordant for leukaemia and in retrospective scrutiny of archived neonatal blood spots. These data have indicated that, in paediatric leukaemia, the majority of chromosome translocations arise in utero during foetal haemopoiesis. Chromosomal translocations and preleukaemic clones arise at a substantially higher frequency (~100×) before birth than the cumulative incidence or risk of disease, reflecting the requirement for complementary and secondary genetic events that occur postnatally. A consequence of the latter is a very variable and occasionally protracted postnatal latency of disease (1–15 years). These natural histories provide an important framework for consideration of key aetiological events in paediatric leukaemia.

1

.. the first unambiguous evidence for a **prenatal origin of leukaemia** was derived **from studies in identical twins with leukaemia**. A case of **identical (monozygotic) infant twins with leukaemia was recorded in 1882,** and, since that time, more than 70 pairs have been published albeit in variable detail ...

2

The **concordance** rate of leukaemia varies according to subtype and age.

For infants with ALL, the ra is exceedingly high (> 50%), for "COMMON" child-ALL, is ~10%.

3

Chromosomal translocations and preleukaemic clones arise at a substantially higher frequency (~100 X) before birth than the cumulative incidence or risk of disease, reflecting the requirement for complementary and **secondary genetic events** that occur postnatally. A consequence of the latter is a very variable and occasionally protracted **postn**

~1% of newborns had TEL-AML1 positive B lineage clones... which represents **100 times** the incidence of **TEL-AML1 positive ALL (~1**

TEL-AML1 in cord blood: 1% or 0.01%?

Competing models of TEL-AML1^{+} leukemogenesis.

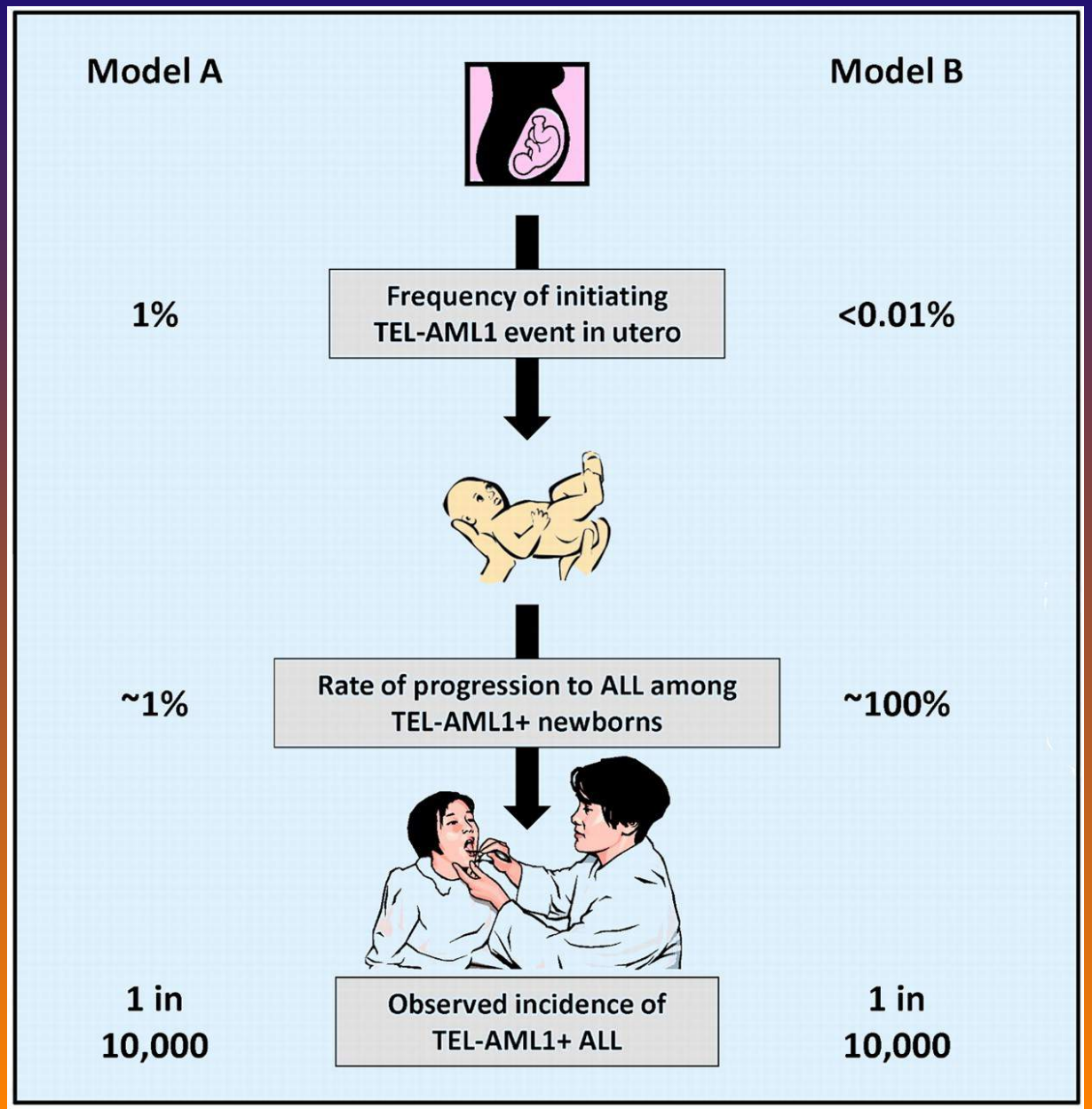
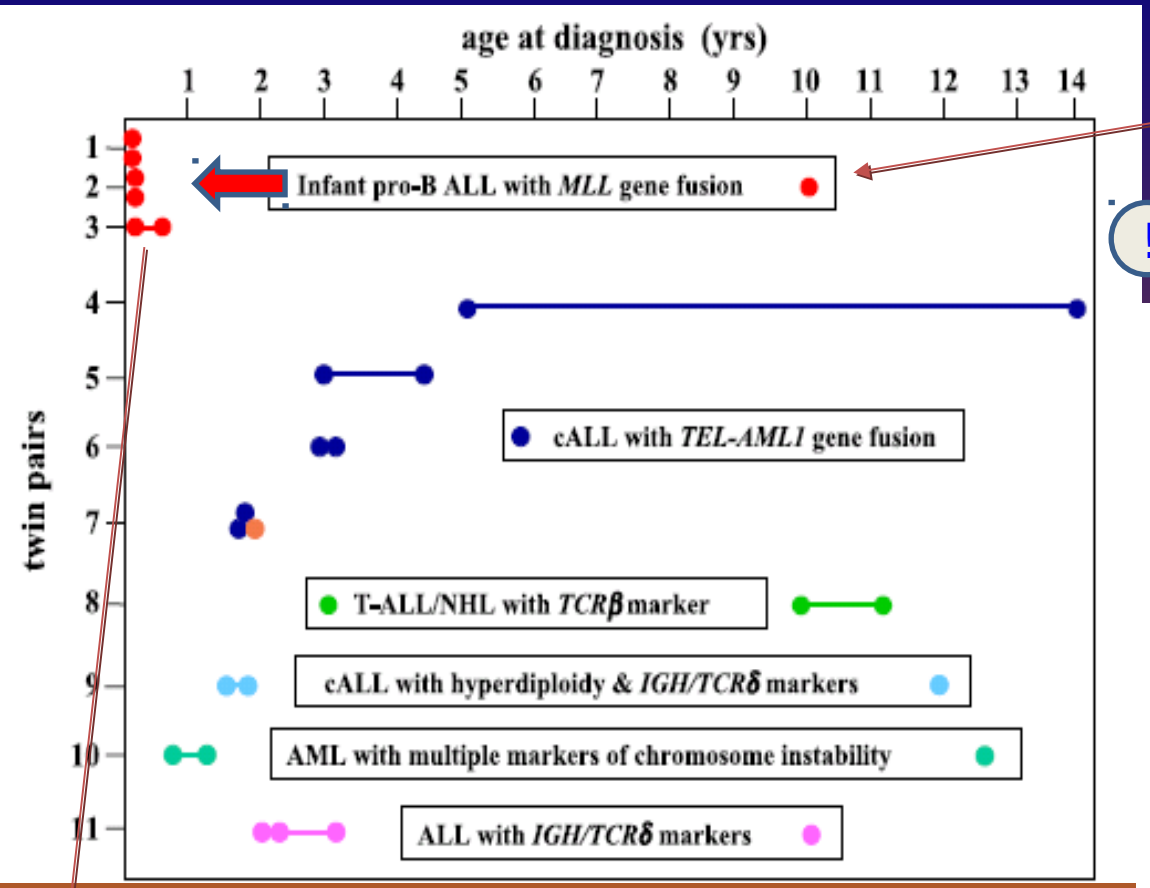


Figure 1 Concordant leukaemia in identical twins: the LRF Series (1993–2003). Figure illustrates age at diagnosis for each twin in the 11 pairs studied, the biological subtype of leukaemia and the molecular markers of clonality used.



MLL rearranged leukemias are associated with **poor prognosis** and **very brief latency** for MLL-AF4+ infant B ALL. This raises the question of how this disease can evolve so quickly,

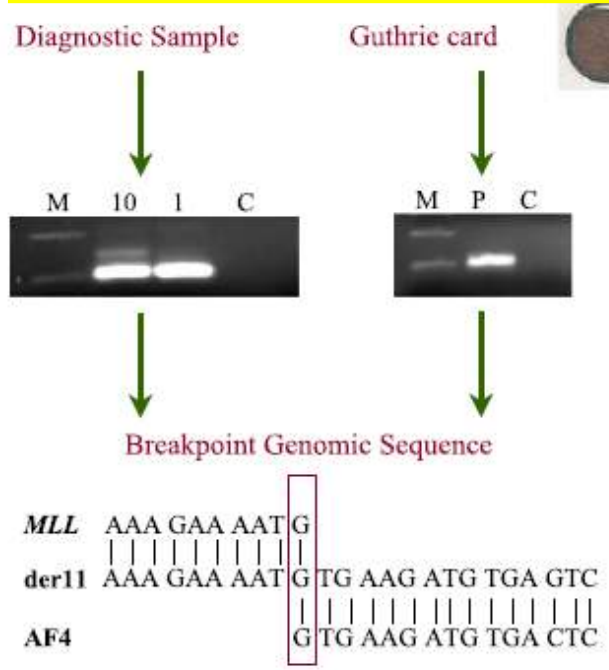
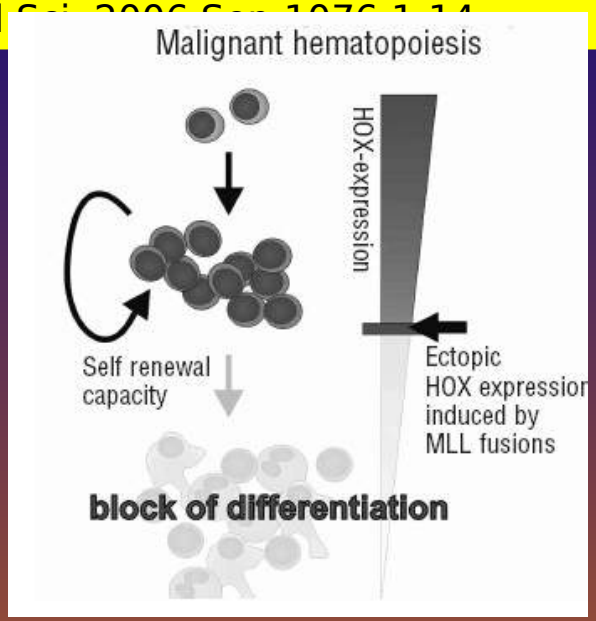


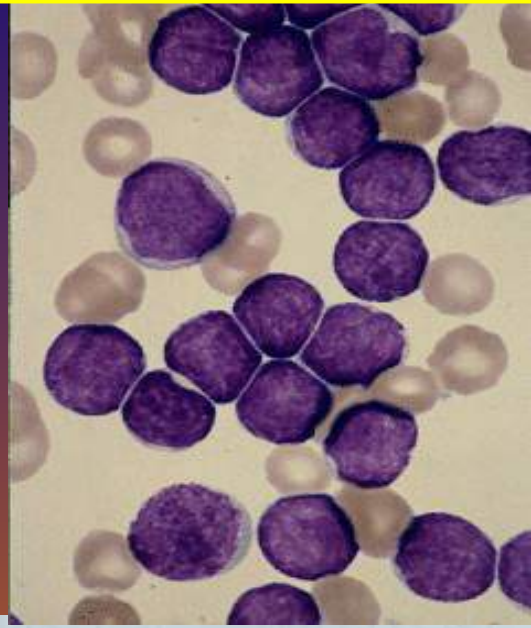
Figure 3 Detection of clonotypic fusion gene sequences (*MLL-AF4*) in neonatal blood spots (Guthrie card). 10, 1 μg DNA; C, control DNA; M, marker. Diagnostic DNA amplified by long-range PCR or long-distance inverse PCR [21]. Guthrie card DNA amplified by short-range (conventional) PCR using primers based on diagnostic DNA-derived genomic *MLL-AF4* sequence. Note diagnostic (leukaemic) DNA and Guthrie card contain the same unique *MLL-AF4* sequence as shown here for one case.

Even if **leukaemia fusion gene** formation is spontaneous, the risk of this occurring may be **modified by other factors, including folate availability**. There is dietary and genetic evidence that **folate has an impact on the risk of infant and childhood**

Translocations typical of myeloid leukaemia, probably due to maternal exposure to some toxic compound, were shown to be **present at birth in children who developed the disease years later** (while not sufficient per se to cause the disease, they might increase the risk for leukaemia by inducing genomic instability) Tomatis L. ***Identification of carcinogenic agents and primary prevention of cancer.*** Ann N Y Acad

Translocation **involving band 11q23 in AML** may occur as a result of a **deletion or trans-locations** with a number of other chromosomes and is usually associatedwith **M4** or **M5** and a poor prognosis





MLL (myeloid/lymphoid or mixed lineage leukemia)

IN ALL AND AML, THE ***ALL1*** (ALSO NAMED ***MLL***) GENE CAN **FUSE WITH 1 OF MORE THAN 50 GENES**. **ALL1 IS PART OF A MULTIPROTEIN COMPLEX**. MOST OF THE PROTEINS IN THE COMPLEX ARE COMPONENTS OF **TRANSCRIPTION COMPLEXES**; OTHERS ARE INVOLVED IN **HISTONE METHYLATION AND RNA PROCESSING.** THE ENTIRE **COMPLEX REMODELS, ACETYLATES, DEACETYLATES, AND METHYLATES NUCLEOSOMES** AND **HISTONES**. THE **FUSION OF ALL1 WITH 1 OF these 50 PROTEINS** RESULTS IN THE **FORMATION OF THE CHIMERIC PROTEINS** THAT UNDERLIE ALL AND AML.

ALL1 (MLL) FUSION PROTEINS DEREGULATE HOMEOBOX GENES

The first and most striking property of MLL fusion proteins is their inc
diversity. MLL has been found in **73 different translocations** and **5
partner genes** have been cloned
(*http://atlasgeneticsoncology.org/Genes/MLL.html).*

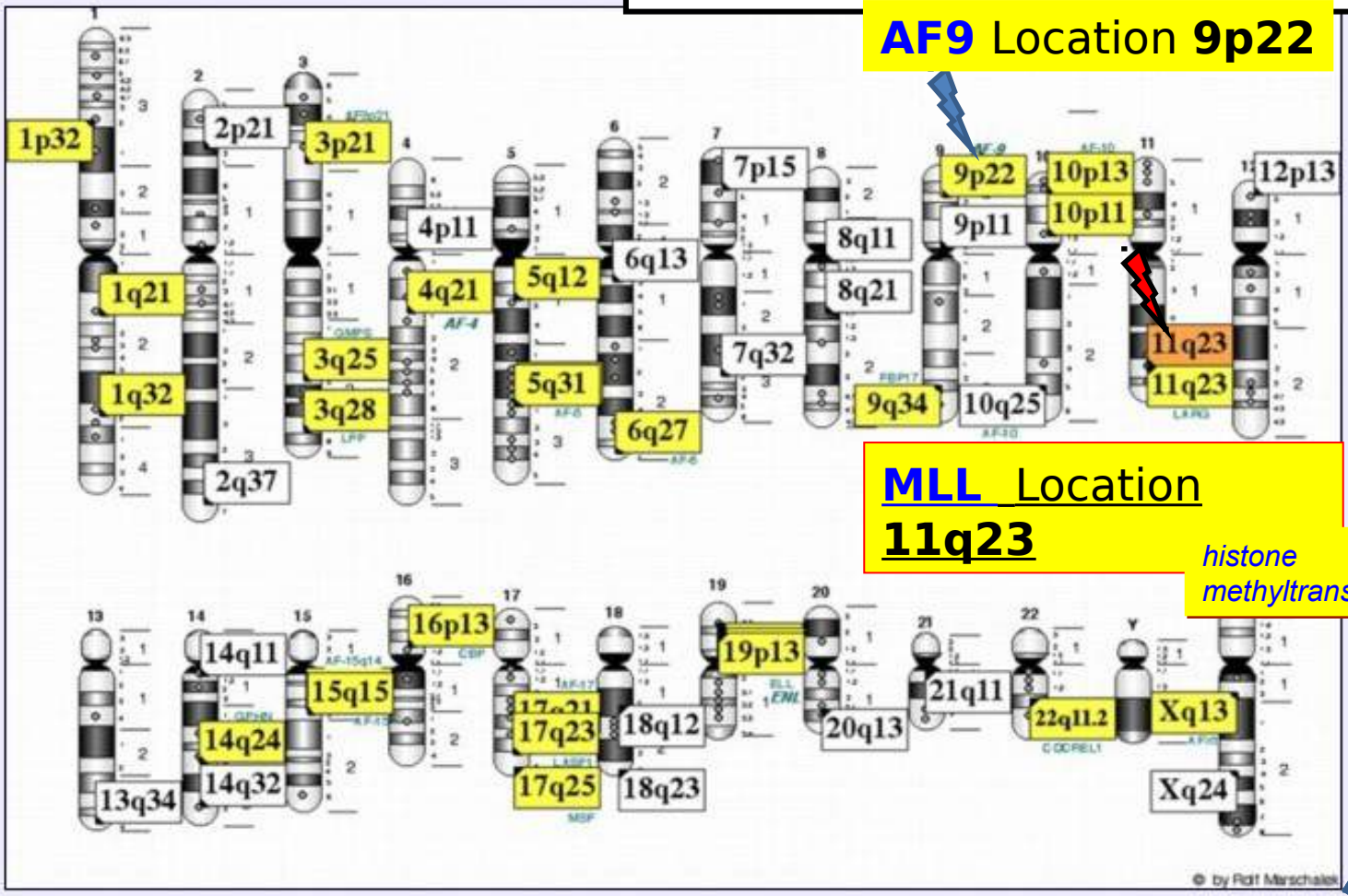
ALL1, HRX, Htrx (human trithorax), TRX1

MLL

11q23

telomeric to PLZF, centromeric from RCK

Nakamura T, Mori T, Tada S, et al. ***ALL-1 is a histone methyltransferase that assembles a supercomplex of proteins involved in transcriptional regulation.*** Mol Ce
2002;10:1119-1128.



Several lines of evidence point to a mishap in non-homologous end joining of double strand breaks as the most likely reason fo

[CANCER RESEARCH 61, 2542–2546, March 15, 2001]

Transplacental Chemical Exposure and Risk of Infant Leukemia with *MLL* Gene Fusion[1]

Freda E. Alexander,[2] Sherry L. Patheal, Andrea Biondi, Silvia Brandalise, Maria-Elena Cabrera, Li C. Chan, Zhu Chen, Giuseppe Cimino, Jose-Carlos Cordoba, Long-Jun Gu, Hany Hussein, Eiichi Ishii, Azza M. Kamel, Silvia Labra, Isis Q. Magalhães, Shuki Mizutani, Eleni Petridou, Maria Pombo de Oliveira, Patrick Yuen, Joseph L. Wiemels, and Mel F. Greaves

Infant acute leukemia (IAL) frequently involves breakage and recombination of the *MLL* gene with one of several potential partner genes. These gene fusions arise *in utero* and are similar to those found in leukemias secondary to chemotherapy with inhibitors of topoisomerase II (topo-II). This has led to the hypothesis that *in utero* exposures to chemicals may cause IAL via an effect on topo-II. We report a pilot case-control study of IAL across different countries and ethnic groups. Cases ($n = 136$) were population-based in most centers. Controls ($n = 266$) were selected from inpatients and outpatients at hospitals serving the same populations.

ing Baygon). Elevated odds ratios were observed for MLL [illegible] not MLL^{-ve}) leukemias (2.31 for DNA-damaging drugs, $P = 0.03$; [illegible] dipyrone, $P = 0.001$; and 9.68 for mosquitocidals, $P = 0.003$). Although it is unclear at present whether these particular exposures operate via an effect on topo-II, the data suggest that specific chemical exposures of the fetus during pregnancy may cause *MLL* gene fusions. Given the widespread use of dipyrone, Baygon, and other carbamate-based insecticides in certain settings, confirmation of these apparent associations is urgently required.

Our study has supported the hypothesis that ***in utero* exposure to chemicals causes MLL*** infant leukemia and has generated specific hypotheses that require further testing. Exposure to ***dipyrone*** is widespread, particularly in Central and South America where it is available as an inexpensive, nonprescription drug. *Mosquitocidals* are similarly in general use in these same settings. ***Propoxur*** (***Baygon***°) is also widely used against cockroaches, fleas, and similar pests. Therefore, it is important that the associations observed in this study are reevaluated in an extended case-control study

N Engl J Med 2008;359:722-34.

REVIEW ARTICLE

MOLECULAR ORIGINS OF CANCER

Chromosomal Abnormalities in Cancer

Stefan Fröhling, M.D., and Hartmut Döhner, M.D.

CYTOGENETIC ABNORMALITIES ARE A CHARACTERISTIC ATTRIBUTE OF cancer cells. To date, clonal chromosome aberrations have been found in all major tumor types from more than 54,000 patients (http://cgap.nci.nih.gov/Chromosomes/Mitelman), and their identification continues as a result of technical improvements in conventional and molecular cytogenetics. The World Health Organization Classification of Tumours recognizes a growing number of such genetic changes and uses them to define specific disease entities. Many of these aberrations have emerged as prognostic and predictive markers in hematologic cancers and certain types of solid tumors. Furthermore, the molecular characterization of cytogenetic abnormalities has provided insights into the mechanisms of tumorigenesis and has, in a few instances, led to treatment that targets a specific genetic abnormality. This article discusses examples of two main classes of chromosomal abnormalities — balanced chromosomal rearrangements and chromosomal imbalances (Fig. 1 an

plications

Dans un tel contexte: les ***translocations*** devraient être considérés des ***aberrations chromosomiques*** ou des ***réarrangements*** actifs?

Carcinogenesis Advance Access first published online on March 16, 2006
This version published online on April 25, 2006
Carcinogenesis, doi:10.1093/carcin/bgl011

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Revised February 11, 2006
Accepted March 7, 2006

MOLECULAR EPIDEMIOLOGY AND CANCER PREVENTION

t(14;18) translocations in lymphocytes of healthy dioxin-exposed individuals from Seveso, Italy

Andrea Baccarelli [1], Carsten Hirt [2], Angela C. Pesatori [1], Dario Consonni [1], Donald G. Patterson Jr. [3], Pier Alberto Bertazzi [1], Gottfried Dölken [4], and Maria Teresa Landi [5] *

Exposure to **NHL-associated carcinogens**,
such as **dioxin or pesticides**, may cause
expansion of t(14;18)-positive clones.

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Carcinogenesis vol.27 no.10 pp.2001–2007, 2006
doi:10.1093/carcin/bgl011
Advance Access publication March 16, 2006

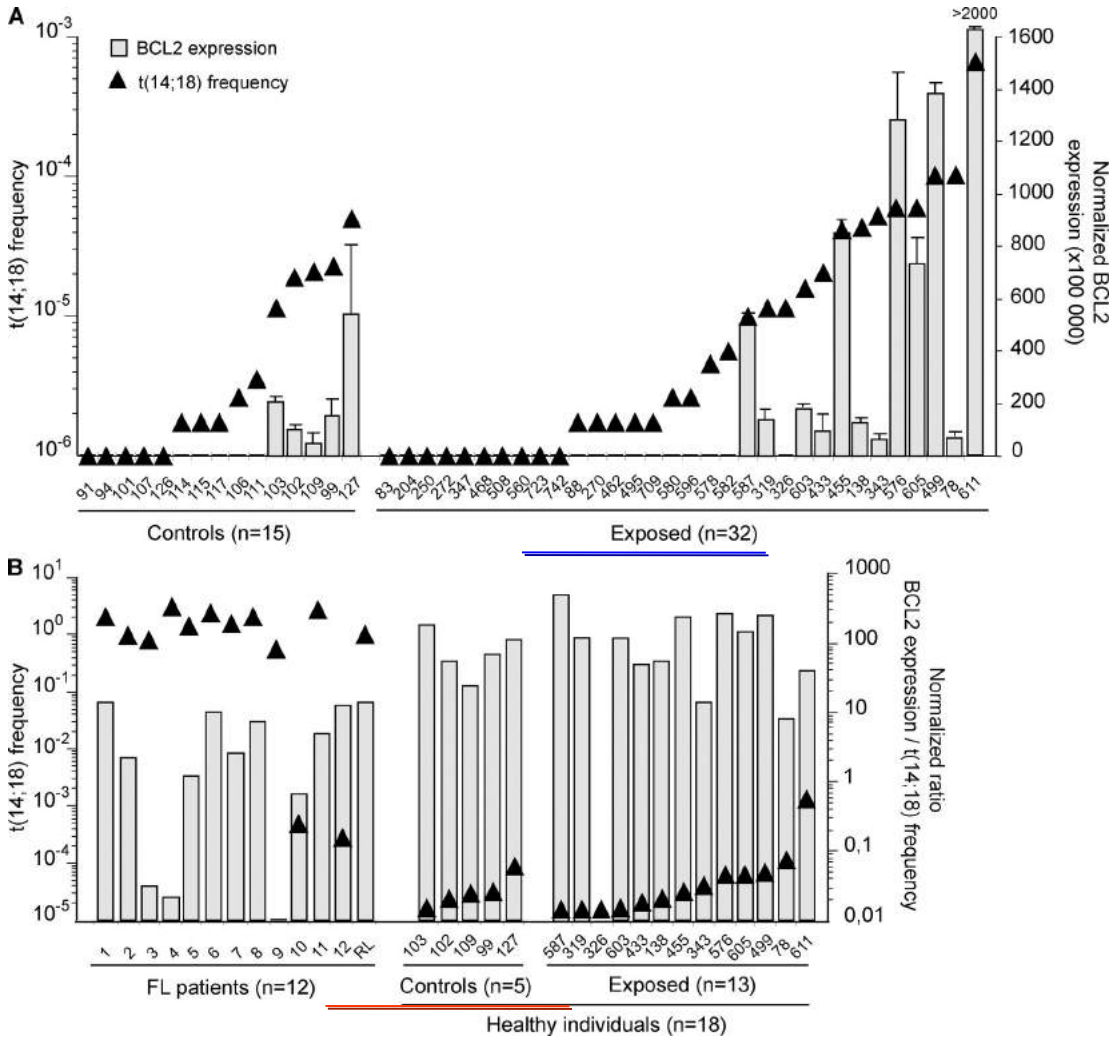
t(14;18) translocations in lymphocytes of healthy dioxin-exposed individuals from Seveso, Italy

Table III. Prevalence and frequency of t(14;18) translocations by plasma TCDD levels, zone of residence and diagnosis of chloracne

	t(14;18)-positive subjects		t(14;18) frequency[a]	
	%	(Positive/total)	Mean	(95% CI)
Plasma TCDD				
<10 p.p.t.	34.7	(25/72)	4.2[b]	(2.9–6.2)
10.0–475.0 p.p.t.	34.7	(25/72)	9.9[b]	(6.8–14.5)
Zone of residence at the time of the accident				
Reference	42.4	(14/33)	4.3[c]	(2.3–8.0)
R	26.9	(7/26)	4.9[c]	(2.2–10.7)
B	29.4	(10/34)	7.2[c]	(3.8–13.6)
A	37.3	(19/51)	9.3[c]	(5.8–14.8)
Chloracne after the accident				
No	35.2	(32/91)	6.2	(3.7–10.6)
Yes	34.0	(18/53)	6.7	(4.7–9.6)

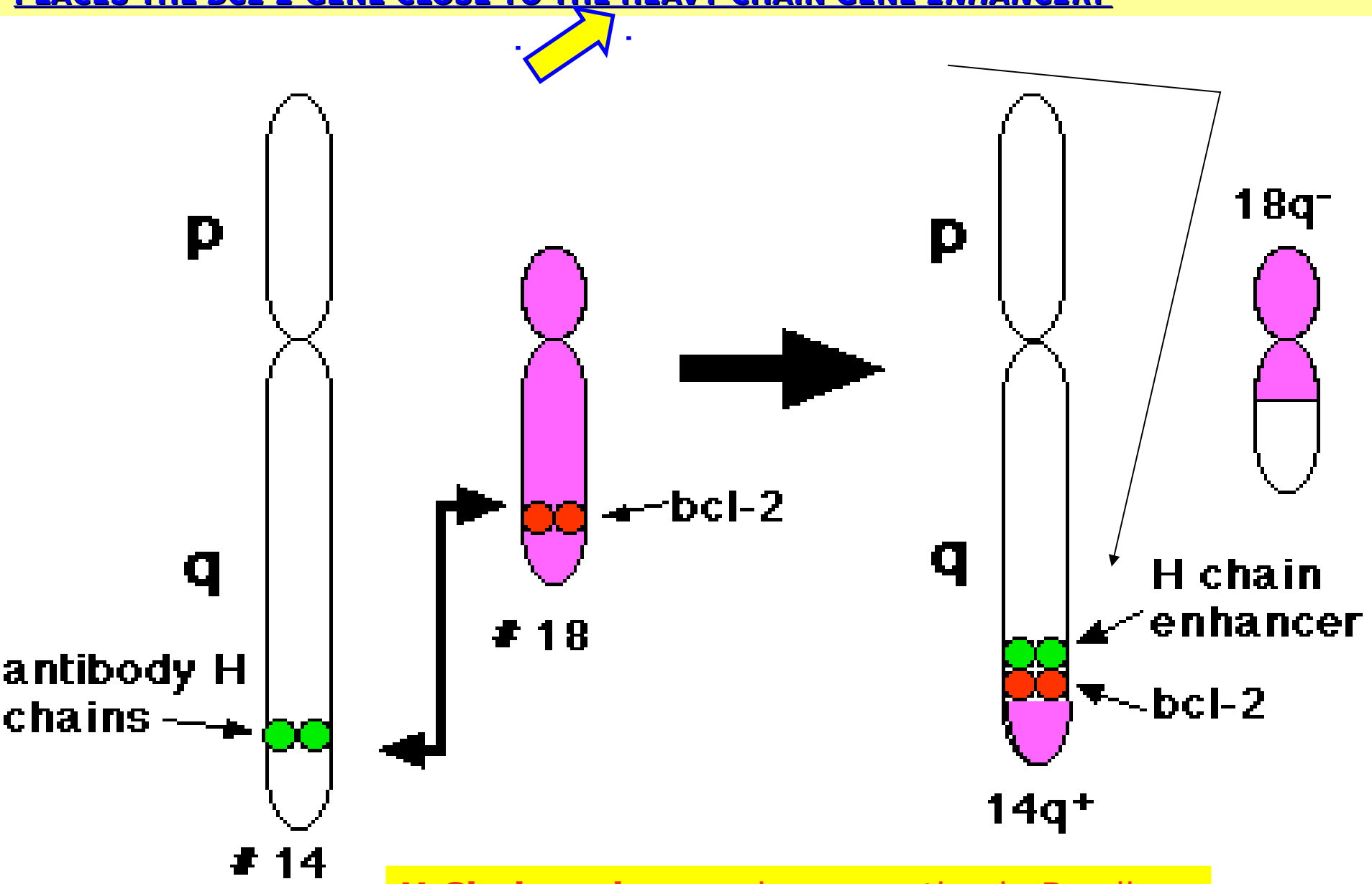
[a]Geometric means and 95% CIs of the number of t(14;18) translocations/10^6 lymphocytes among t(14;18)-positive subjects, adjusted for age, smoking status (never, ex or current smoker) and smoking duration in multivariable analysis.
[b]$P = 0.006$, test for difference in mean t(14;18) frequency between plasma TCDD categories.
[c]$P = 0.04$, test for trend in mean t(14;18) frequency across residence zones.

Figure 2. t(14;18)+ cells in HI are actively transcribing BCL2 from the translocated allele



We can find exactly the **same (reactive) translocation** (++ expression of the **anti-apoptotic gene BCL-2**) in many **subjects chronically exposed to pesticides ..**

IN THE CANCEROUS B CELLS, THE PORTION OF CHROMOSOME 18 CONTAINING THE *BCL-2* LOCUS HAS UNDERGONE A **RECIPROCAL TRANSLOCATION WITH THE PORTION OF CHROMOSOME 14 CONTAINING THE ANTIBODY HEAVY CHAIN LOCUS**. **THIS T(14;18) TRANSLOCATION PLACES THE *BCL-2* GENE CLOSE TO THE HEAVY CHAIN GENE *ENHANCER*.**



H Chain-enhancer is very active in B cells...

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2004;351:250-9.

ORIGINAL ARTICLE

Lymphoma-Specific Genetic Aberrations in Microvascular Endothelial Cells in B-Cell Lymphomas

Berthold Streubel, M.D., Andreas Chott, M.D., Daniela Huber, Markus Exner, M.D., Ulrich Jäger, M.D., Oswald Wagner, M.D., and Ilse Schwarzinger, M.D.

BACKGROUND

The growth of most tumors depends on the formation of new blood vessels. In contrast to genetically unstable tumor cells, the endothelial cells of tumor vessels are considered to be normal diploid cells that do not acquire mutations.

RESULTS

We found that 15 to 85 percent (median, 37 percent) of the microvascular endothelial cells in the B-cell lymphomas harbored lymphoma-specific chromosomal translocations. In addition, numerical chromosomal aberrations were shared by the lymphoma cells and the endothelial cells.

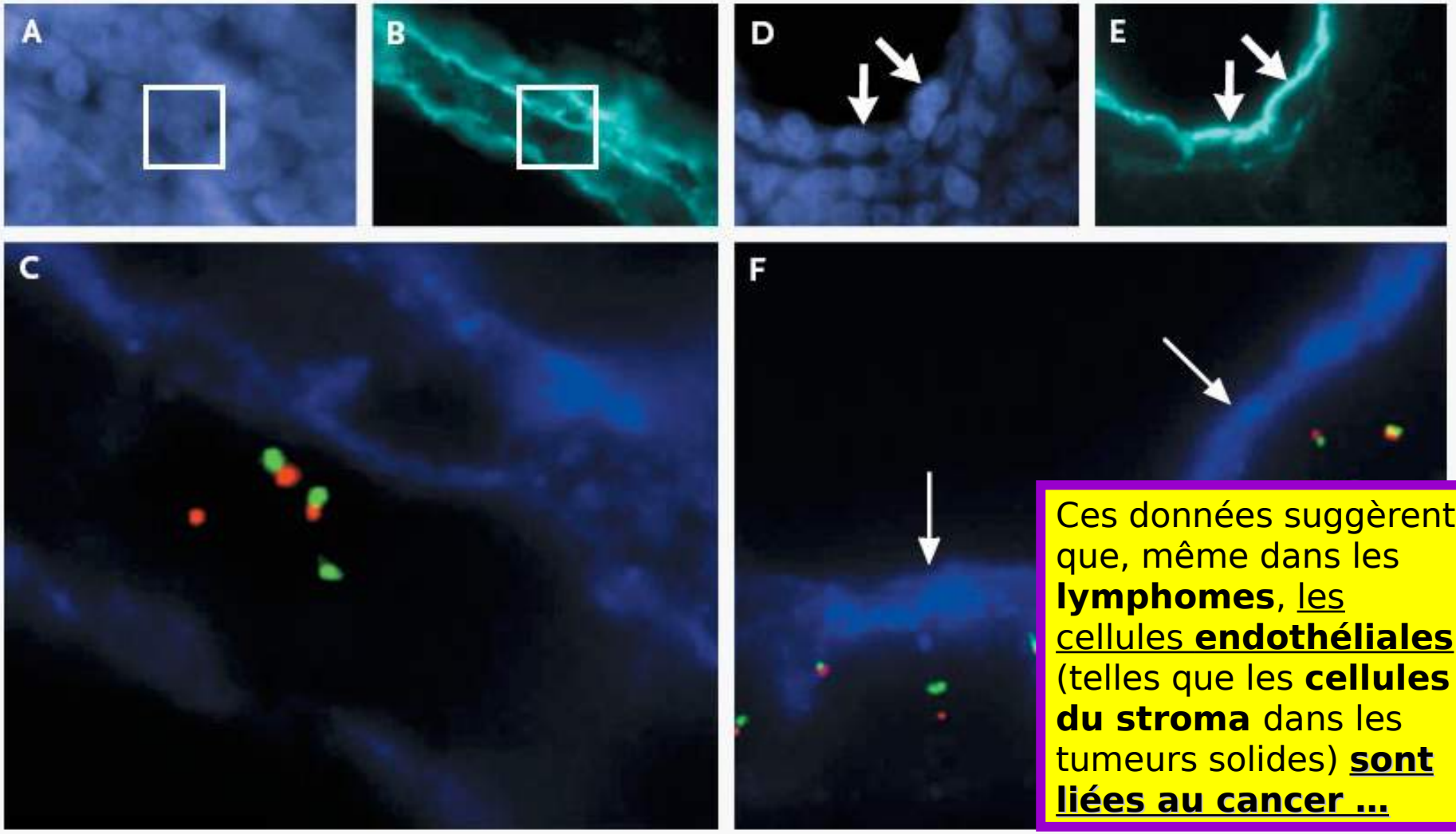
CONCLUSIONS

Our findings suggest that microvascular endothelial cells in B-cell lymphomas are in part tumor-related and therefore reflect a novel aspect of tumor angiogenesis.

…. les **mêmes mutations génétiques et chromosomiques**, d'ailleurs **toujours assez complexes (*aneuploïdie*, *translocations*, *mutations* des oncogènes et des gènes suppresseurs)** se trouvent non seulement dans les cellules du **clone néoplasique primaire** (dans ce cas, les **lymphocytes**), mais **dans plusieurs tissus intéressés …**

Table 1. Cytogenetic Findings in 27 B-Cell Non-Hodgkin's Lymphomas and the Corresponding Tumor Endothelial Cells.*

Case No.	Diagnosis	Site	Patient's Age and Sex	Cytogenetic Aberrations		Endothelial-Cell Markers	Endothelial Cells with Genetic Aberrations
				In Lymphoma Cells (Stem-Cell Line)	In Endothelial Cells		
							%
1	FL 1†	Lymph node	55 yr, M	49,XY,+X,+11,t(14;18)(q32;q21),+21	t(14;18)(q32;q21), +X,+11,+21	CD31, WF	21
2	FL 3†	Lymph node	43 yr, M	53,XY,+2,+3,+7,+7,+8,+11,+12, t(14;18)(q32;q21)	t(14;18)(q32;q21), +2,+3,+7,+7,+8,+11,+12	CD31, UEL	32
3	FL 2†	Lymph node	61 yr, F	49,XX,+X,+5,der(5)t(1;5)(q11;q31), +i(6)(p10),t(14;18)(q32;q21)	t(14;18)(q32;q21),+X,+5	CD31, WF	28
4	FL 2†	Lymph node	83 yr, F	47,XX,+7,t(14;18)(q32;q21)	t(14;18)(q32;q21),+7	CD31, CD34	29
5	FL 1†‡	Lymph node	32 yr, M	46,XY,t(14;18)(q32;q21)	t(14;18)(q32;q21)	CD31, WF, UEL, CD34	80
6	FL 3	Lymph node	60 yr, F	t(14;18)(q32;q21)(IGH con BCL2×2)	t(14;18)(q32;q21)	CD31, WF, UEL, CD34	53
7	FL 1†	Lymph node	48 yr, M	46,XY,t(14;18)(q32;q21)	t(14;18)(q32;q21)	CD31, UEL	48
8	FL 1†	Lymph node	54 yr, F	49,XX,t(1;X)(q43;q24), +2,der(4)t(4;12)(p15;q13),del(6)(q21),+7, dup(9)(q21q32),+13,t(14;18)(q32;q21)	t(14;18)(q32; q21),+2,+7,+13	CD31, WF	50
9	FL 1†	Lymph node	39 yr, F	46,XX,t(14;18)(q32;q21)	t(14;18)(q32;q21)	CD31, WF	63
10	FL 1†	Lymph node	40 yr, M	46,XY,t(14;18)(q32;q21)	t(14;18)(q32;q21)	CD31, CD34	27
11	FL 1†	Lymph node	46 yr, M	46,XY,t(14;18)(q32;q21),del(13)(q12q31)	t(14;18)(q32;q21), del(13)(q14)(RB1×1)	CD31, WF, UEL, CD34	18
12	FL 1†	Lymph node	60 yr, F	48,XX,+5,+5,t(14;18)(q32;q21)	t(14;18)(q32;q21),+5,+5	CD31, WF, UEL, CD34	21



Ces données suggèrent que, même dans les **lymphomes**, les cellules **endothéliales** (telles que les **cellules du stroma** dans les tumeurs solides) **sont liées au cancer …**

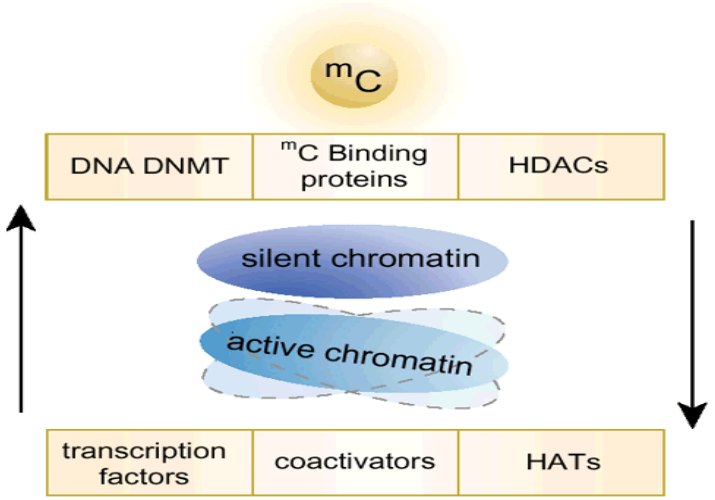
Figure 2. ***IGH*** **Translocations in Endothelial Cells in Follicular Lymphoma and Mantle-Cell Lymphoma.**

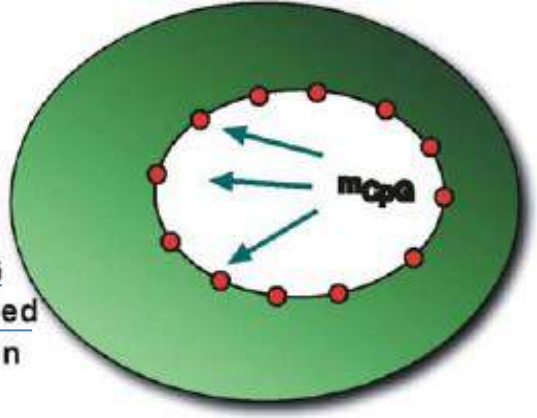
In a follicular lymphoma (Case 11), the nucleus of an endothelial cell (Panel A, box) that is labeled with the use of anti–von Willebrand factor antibody (Panel B, box) reveals two fusion signals for the green *IGH* probe and the red *BCL2* probe (Panel C), indicating t(14;18)(q32;q21). In a mantle-cell lymphoma (Case 20), arrows indicate nuclei that belong to the endothelial cells of a cross-sectioned vessel (Panel D) with staining for CD34 (Panel E). Two CD34+ endothelial cells (Panel F, arrows) show two and three fusion signals for t(11;14)(q13;q32), respectively.

Towards an epigenetic model in carcinogenesis

- .. there is ***now ample evidence*** that some **specific epigenetic alterations**, (primarily the ***hypomethylation* of DNA**, with **activation of oncogenes** and **increased mobility of mobile sequences**) ** **are the result of protracted genomic *stress* (eg chronic inflammation and persistent oxidative stress)**
- and generally **anticipate**, to some extent **preparing** it, **genetic modification** and **an overall genomic instability**
- **Should these data change our way of representing cancer ?**

** + an **hypermethylation of tumor suppressor genes promoters**



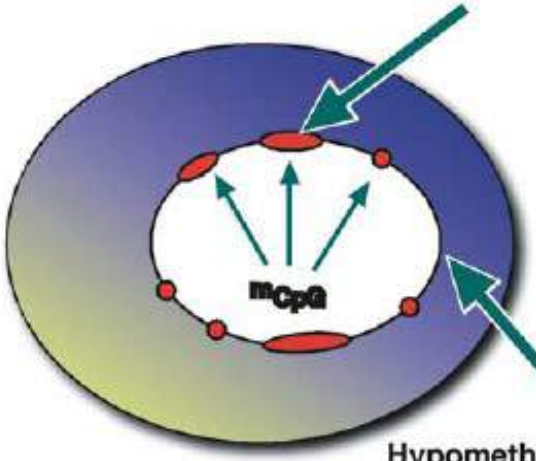


The **"methylation paradox" of cancer cells**.

In fact **cancer cells present a gain of methylated streches at regions that are usually unmethylated (*hypermethylation*)** concomitantly with **loss of methylation at genomic loci that are normally methylated *(global hypomethylation)*.**

Trigger (?)

Hypermethylation:
- Silencing of tumor suppressor genes
- Gene mutation



Hypomethylation:
- Potential activation of oncogenes
- Genome instability

Retrosequences activation

R Villa, F De Santis, A Gutierrez, S Minucci, PG Pelicci, L Di Croce ***Epigenetic gene silencing in acute promyelocytic leukemia*** Biochem Pharmacol (2004)

Mol Biol Rep
DOI 10.1007/s11033-014-3804-3

Published online: 12 November 2014

Springer

Towards a systemic paradigm in carcinogenesis: linking epigenetics and genetics

Ernesto Burgio · Lucia Migliore

Abstract For at least 30 years cancer has been defined as a genetic disease and explained by the so-called somatic mutation theory (SMT), which has dominated the carcinogenesis field. Criticism of the SMT has recently greatly increased, although still not enough to force all SMT supporters to recognize its limits. Various researchers point out that cancer appears to be a complex process concerning a whole tissue; and that genomic mutations, although variably deleterious and unpredictably
mining the establishment
not the primary origin
attempt to describe the
demonstrate that epigen
carcinogenesis.

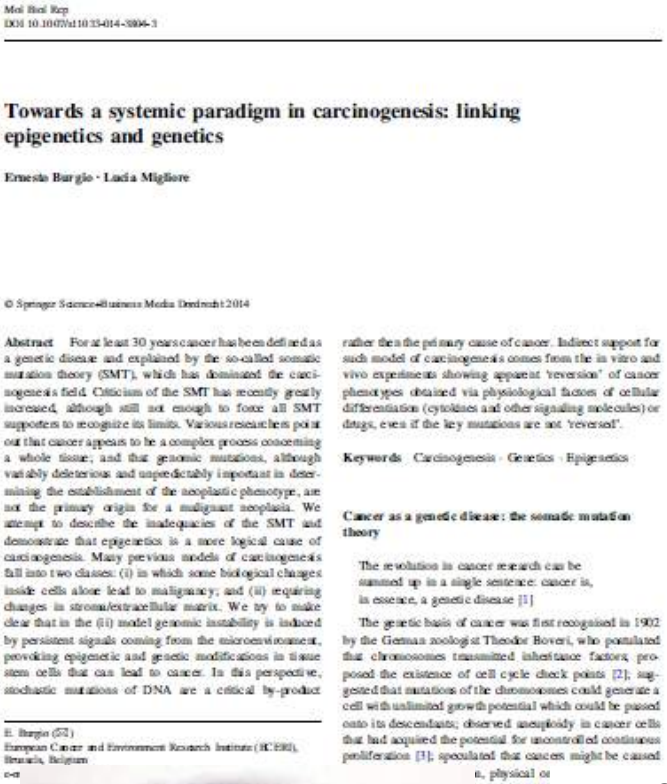
Is the carcinogenic process the **ontogenic development gone awry** ?

Is the main cause of cancer a **block in cell differentiation programs** (just the "**hallmark",** inexplicably **neglected by major theorists of SMT**) ?

The Embryonic Rest Theory and the field theories of cancer

Some **Virckow**'s followers (1870 ca) formulated the theory that adult tissues contain ***dormant embryonic remnants*** that could be activated to become **cancer** Perhaps the most intriguing aspect of the theory concerned the hypothesized trigger of the process: ..**a change in the environment, a "disequilibrium" in the surrounding tissue,** that would induce these embryonic remnants to resume cell proliferation and to produce masses of cells resembling fetal tissues (***field theory***)

The Embryonic Rest Theory and the field theories of cancer



Mol Biol Rep
DOI 10.1007/s11033-014-3304-3

Towards a systemic paradigm in carcinogenesis: linking epigenetics and genetics

Ernesto Burgio · Lucia Migliore

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Abstract For at least 30 years cancer has been defined as a genetic disease and explained by the so-called somatic mutation theory (SMT), which has dominated the carcinogenesis field. Criticism of the SMT has recently greatly increased, although still not enough to force all SMT supporters to recognize its limits. Various researchers point out that cancer appears to be a complex process concerning a whole tissue, and that genomic mutations, although variably deleterious and unpredictably important in determining the establishment of the neoplastic phenotype, are not the primary origin for a malignant neoplasia. We attempt to describe the inadequacies of the SMT and demonstrate that epigenetics is a more logical cause of carcinogenesis. Many previous models of carcinogenesis fall into two classes: (i) in which some biological changes inside cells alone lead to malignancy; and (ii) requiring changes in stroma/extracellular matrix. We try to make clear that in the (ii) model genomic instability is induced by persistent signals coming from the microenvironment, provoking epigenetic and genetic modifications in tissue stem cells that can lead to cancer. In this perspective, stochastic mutations of DNA are a critical by-product rather than the primary cause of cancer. Indirect support for such model of carcinogenesis comes from the in vitro and vivo experiments showing apparent 'reversion' of cancer phenotypes obtained via physiological factors of cellular differentiation (cytokines and other signaling molecules) or drugs, even if the key mutations are not 'reversed'.

Keywords Carcinogenesis · Genetics · Epigenetics

Cancer as a genetic disease: the somatic mutation theory

The revolution in cancer research can be summed up in a single sentence: cancer is, in essence, a genetic disease [1]

The genetic basis of cancer was first recognised in 1902 by the German zoologist Theodor Boveri, who postulated that chromosomes transmitted inheritance factors; proposed the existence of cell cycle check points [2]; suggested that mutations of the chromosomes could generate a cell with unlimited growth potential which could be passed onto its descendants; observed aneuploidy in cancer cells that had acquired the potential for uncontrolled continuous proliferation [3]; speculated that cancers might be caused

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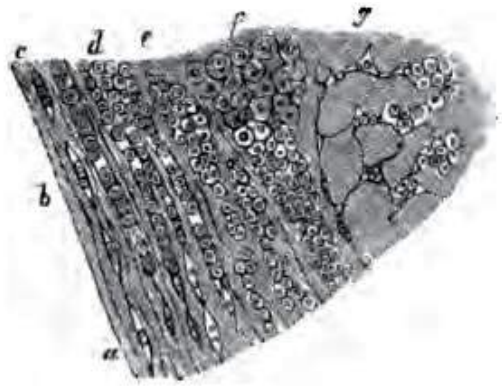
From **Cellular Pathology**: *Development of cancer from connective tissue in the carcinoma of the breast*



Virchow and other well known pathologists, on observing cancer tissue under the microscope, noted the **similarity between embryonic tissue and cancer,** and suggested that **tumors arise from embryo-like cells** [105]. On this basis, some Virckow's followers [106-107] formulated the **theory that adult tissues contain *dormant embryonic remnants* that could be activated to become cancer**.

Perhaps the most intriguing aspect of the theory concerned the **hypothesized trigger** of the process: it would be **a change in the environment, a "disequilibrium" in the surrounding tissue,** that **would induce these embryonic remnants to resume cell proliferation and to produce masses of cells that resembled fetal tissues (*field theory*).**

Virchow, Rudolf. ***Cellular Pathology as Based Upon Physiological and Pathological Histology***. London, 1860

Figure
Click here to download Figure: Fig2 Burgio&MiglioreCarcinogenesis 14.pptx

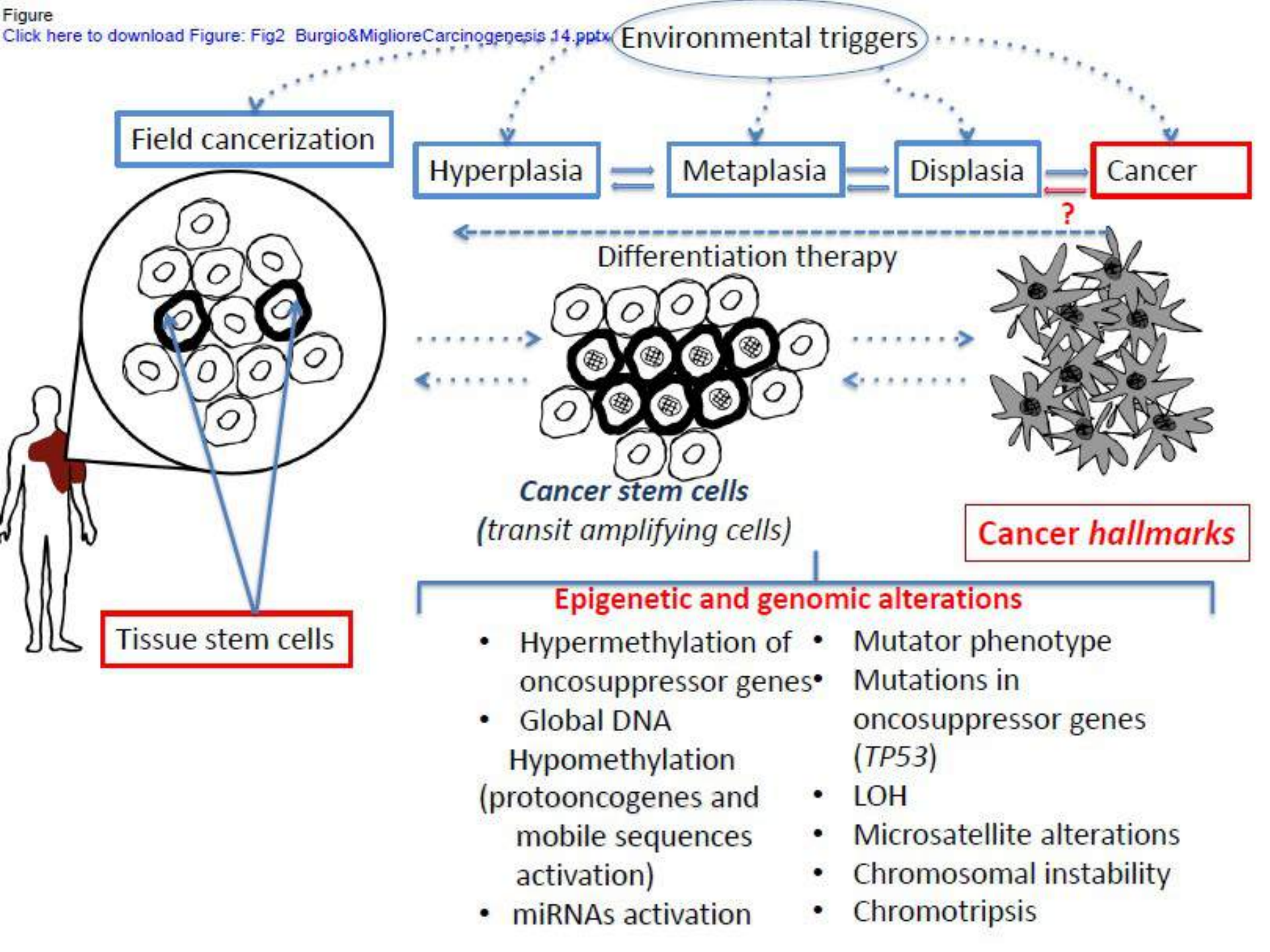


Figure 1 Hh and Wnt signalling pathways. Simplified views of the Hh and Wnt signalling pathways, with emphasis on components implicated in cancer or tissue regeneration. Green and red colours denote pathway components with primarily positive or negative roles, respectively, in pathway activation. Shaded components

Tissue repair and stem cell renewal in carcinogenesis

Nature. 2004 Nov 18;432(7015):324-31.

Philip A. Beachy[1,4], Sunil S. Karhadkar[1,2] & David M. Berman[2,3,4]

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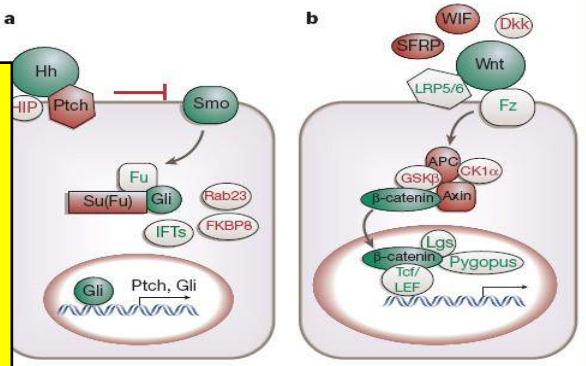
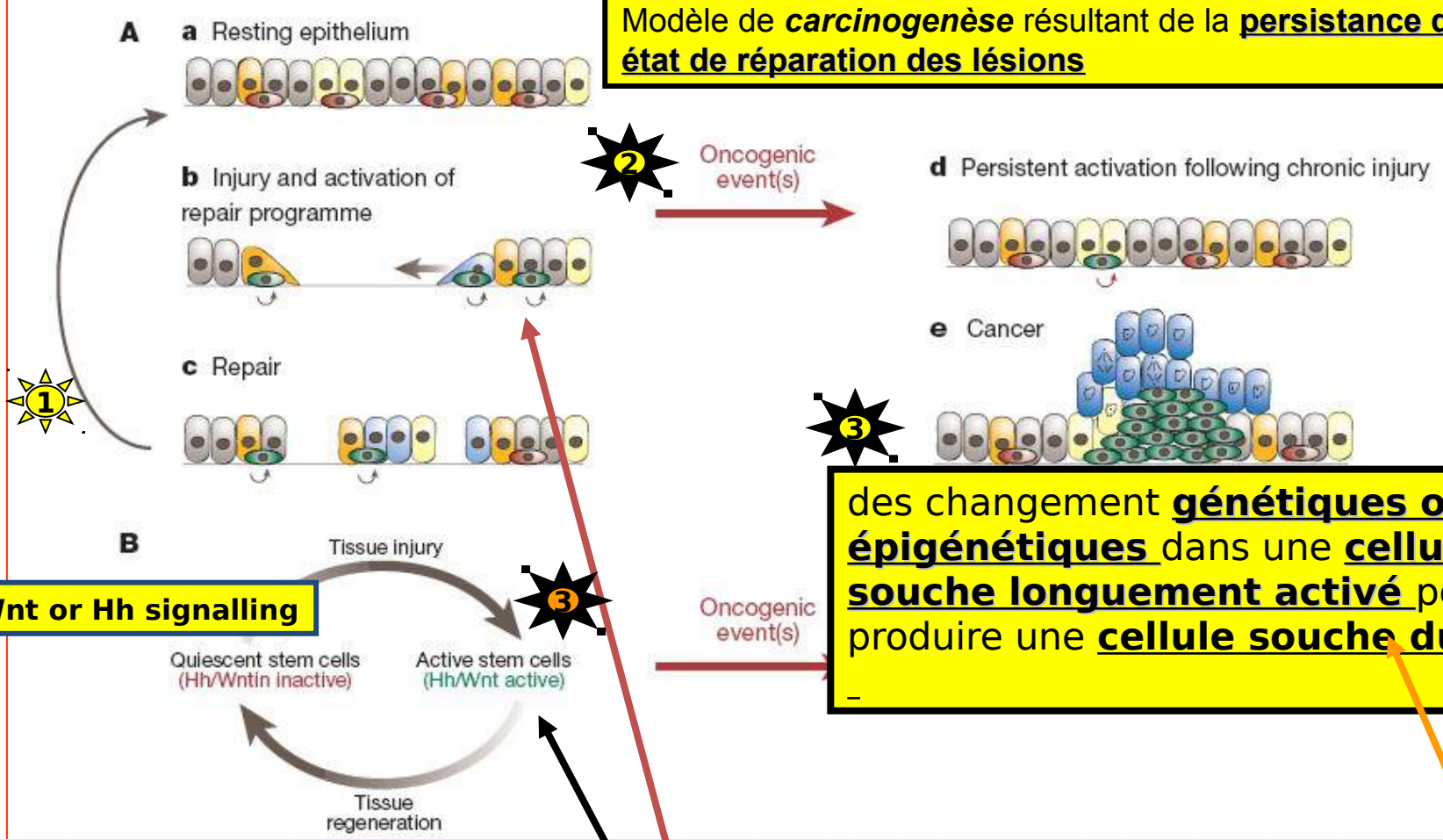
Cancer is increasingly being viewed as a stem cell disease, both in its propagation by a minority of cells with stem-cell-like properties and in its possible derivation from normal tissue stem cells. But stem cell activity is tightly controlled, raising the question of how normal regulation might be subverted in carcinogenesis. The long-known association between cancer and chronic tissue injury, and the more recently appreciated roles of Hedgehog and Wnt signalling pathways in tissue regeneration, stem cell renewal and cancer growth together suggest that carcinogenesis proceeds by misappropriating homeostatic mechanisms that govern tissue repair and stem cell self-renewal.



Le **cancer** est de plus en plus considérée comme **une maladie des cellules souches** .. L'association connue depuis longtemps entre le **cancer et les lésions tissulaires chroniques**, et les rôles compris, plus récemment, des **voies de signalisation Wnt et Hedgehog** dans la **régénération des tissus**, le **renouvellement des cellules souches** et le **développement du cancer** suggèrent que la ***carcinogenèse*** se produit **en détournant les mécanismes homéostatiques qui régissent la réparation des tissus et de l'auto de cellules souches –renouvellement.**

Modèle de ***carcinogenèse*** résultant de la **persistance d'un état de réparation des lésions**



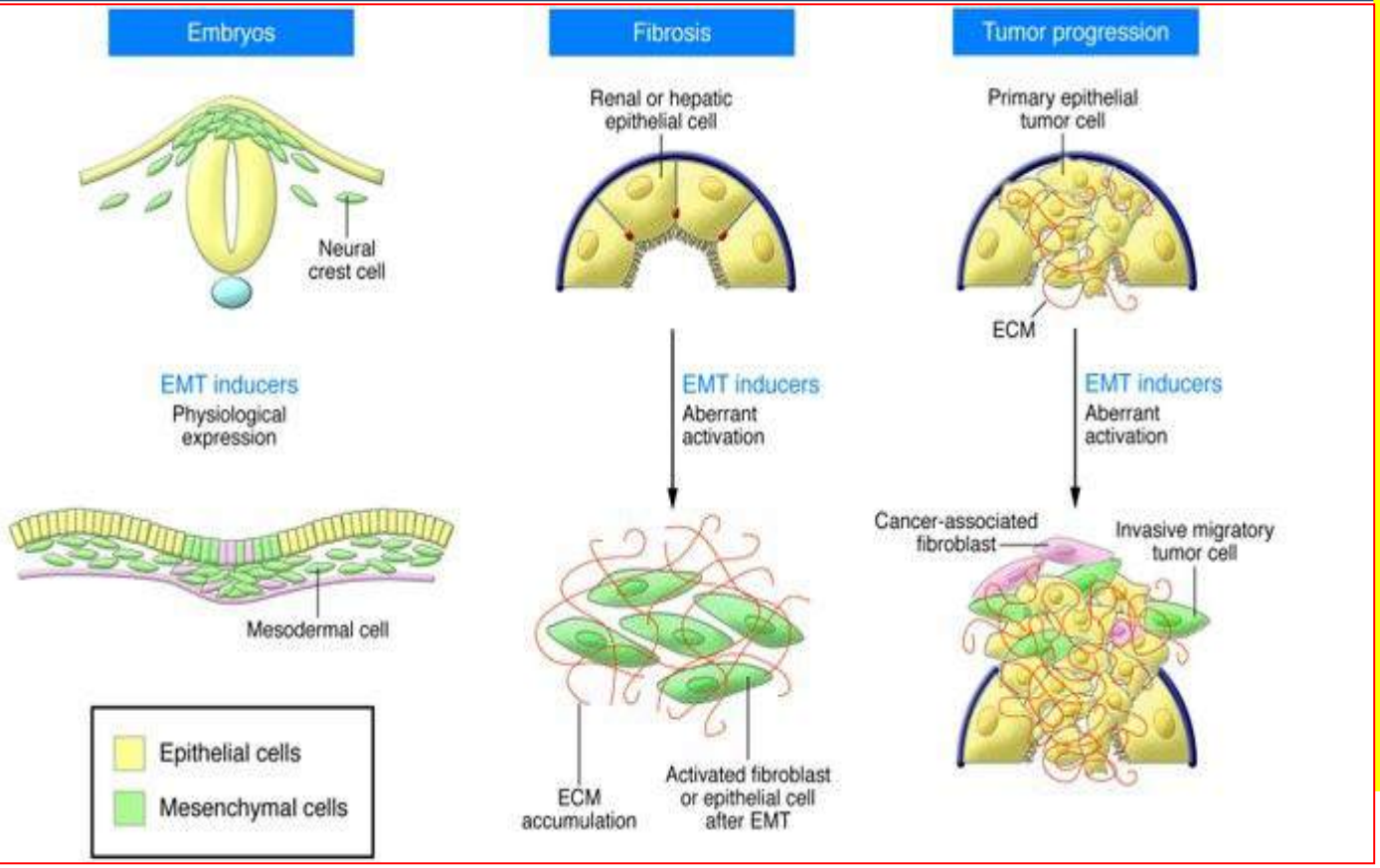
des changement **génétiques ou épigénétiques** dans une **cellule souche longuement activé** peuvent produire une **cellule souche du cancer**

Figure 2 Model for carcinogenesis resulting from persistence of a state of injury repair. **A**, Cellular events of epithelial repair. **a**, Resting epithelium with several differentiated cell phenotypes (brown, orange, and yellow) derived from tissue stem cells, now quiescent (red). Pathways such as Hh and Wnt signalling pathways that have a role in the renewal of stem cells are not active. **b**, Epithelial defect resulting from acute injury. Loss of epithelial continuity activates a repair program which is driven by Hh or Wnt signalling. This program results in the acquisition by epithelial cells of a more mesenchymal phenotype, including flattening and movement of cells (straight arrow) to cover the wound, activation (green), and expansion of stem cells through renewal divisions (curved arrows). **c**, The wound is repaired, first by rapid cell movement, and then by restoration of cell numbers resulting from the amplification of stem cells and the differentiation of their progeny. Subsequently, either epithelial continuity and patterning is restored, Hh and Wnt signalling ceases, and the stem cell compartment returns to quiescence (**a**); or oncogenic event(s) may trap a stem cell in an activated state of continuous renewal, which is driven by autonomous Wnt or Hh signalling (**d**). Further genetic or epigenetic change in such a persistently activated stem cell (curved red arrows) might produce a cancer stem cell (green) which is capable of aggressively propagating a cancer (**e**). This may result from enhanced proliferation and production of more cancer stem cells as well as from differentiated cancer cells (blue). **B**, Stem cells cycle between quiescence and activity as a consequence of Hh/Wnt driven responses to injury. Oncogenic event(s) may trap activated stem cells in a permanent state of Hh/Wnt driven activity, resulting in cancer stem cells.

J Clin Invest. 2009;119(6):1438–1449.

Epithelial-mesenchymal transitions: the importance of changing cell state in development and disease

Hervé Acloque,[1] Meghan S. Adams,[2] Katherine Fishwick,[2] Marianne Bronner-Fraser,[2] and M. Angela Nieto[1]



La seule caractéristique fondamentale (***hallmark***) du cancer est sa tendance à la ***métastase*** qui **n'est pas due à des mutations**, mais à la **réactivation d'un programme embryonnaire, la transition épithéliale-mésenchymateuse (EMT) qui permet aux cellules foetales de l'embryon de migrer** vers leur **destination finale dans les divers tissus**

Les inducteurs de EMT sont bloqués chez l'adulte.. Mais ils sont **activées dans la fibrose d'organes et dans les fases invasives des cancers**

seminars in **CANCER BIOLOGY**, Vol. 12, 2002: pp. 339–346
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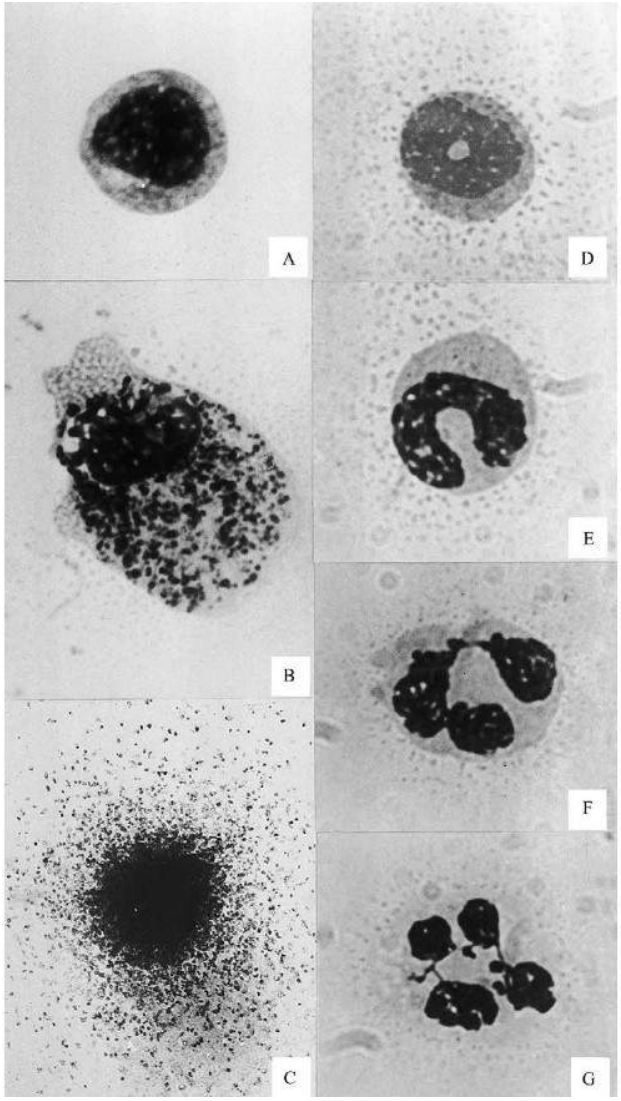
Epigenetics wins over genetics: induction of differentiation in tumor cells

*Joseph Lotem and Leo Sachs**

Malignant cells are genetically abnormal, but can the malignant phenotype revert to a non-malignant phenotype without correcting these genetic abnormalities? It has been found that this reversion can be achieved by reprogramming tumor cells by epigenetic changes induced by differentiation. The epigenetic suppression of malignancy by inducing differentiation bypasses the genetic abnormalities in tumor cells. Studies with myeloid leukemic cells have shown that some leukemic cells can be induced to differentiate by cytokines that control normal hematopoiesis, and that myeloid leukemic cells resistant to normal cytokines can be induced to differentiate by compounds that use alternative differentiation pathways. The epigenetic reprogramming of tumor cells by inducing differentiation has also been found with other types of tumors and can be used for tumor therapy. By this reversion of the malignant to non-malignant phenotype, epigenetics wins over genetics.



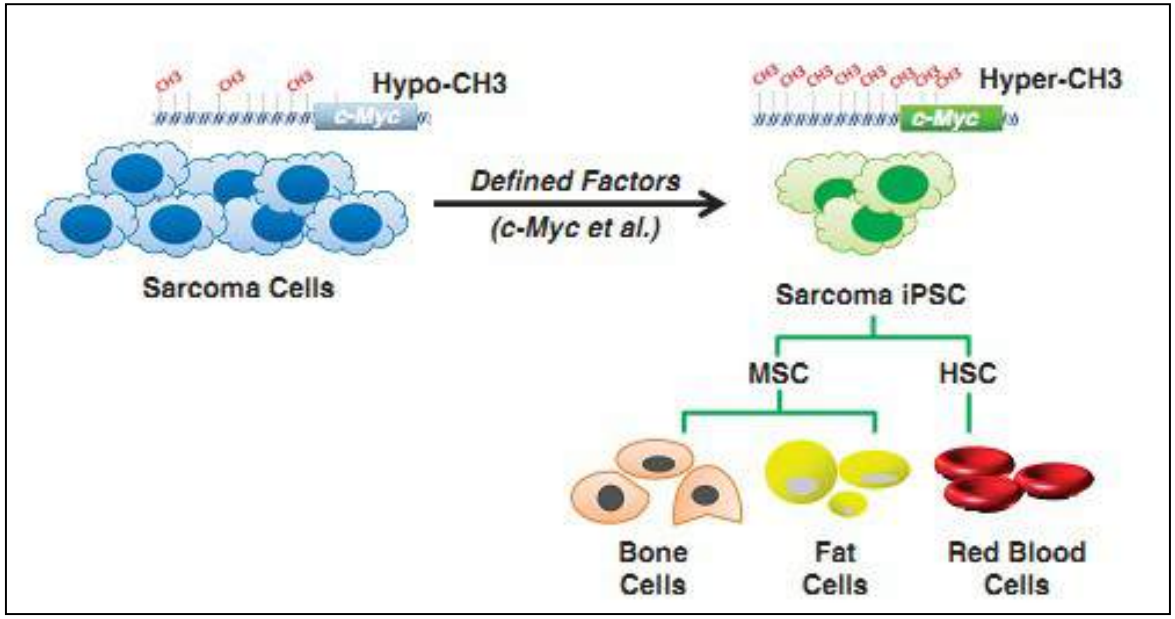
COMMENTARY

Reprogramming cancer cells: back to the future

J-Y Lang, Y Shi and YE Chin

Reprogramming healthy somatic cells into induced pluripotent stem cells (iPSCs) with four defined factors (*Oct4*, *Sox2*, *c-Myc* and *Klf4*) has been intensively investigated. However, reprogramming diseased cells such as cancer cells has fallen much behind. In this issue of *Oncogene*, Zhang *et al.* demonstrated that reprogrammed sarcoma cells with defined factors, as well as *Nanog* and *Lin28*, lost their tumorigenicity and dedifferentiated to mesenchymal stem cells (MSC) and hematopoietic stem cell (HSC)-like cells that can be terminally differentiated into mature connective tissues and red blood cells, suggesting sarcoma cells may be reversed back to a stage of common ancestor iPSC bifurcating for HSC and MSC ontogeny. It may, therefore, provide a novel strategy for cancer treatment via ancestor pluripotency induction

Oncogene (2013) **32,** 2247–2248; doi:10.1038/onc.2012.349; published online 6 August 2012



Childhood cancers and atmospheric carcinogens

E G Knox

J Epidemiol Community Health 2005;**59**:101–105. doi: 10.1136/jech.2004.021675

Main results: Significant birth proximity relative risks were found within 1.0 km of hotspots for carbon monoxide, PM10 particles, VOCs, nitrogen oxides, benzene, dioxins, 1,3-butadiene, and benz(a)pyrene. Calculated attributable risks showed that most child cancers and leukaemias are probably initiated by such exposures.

Conclusions: Reported associations of cancer birth places with sites of industrial combustion, VOCs uses, and associated engine exhausts, are confirmed. Newly identified specific hazards include the known carcinogens 1,3-butadiene, dioxins, and benz(a)pyrene. The mother probably inhales these or related materials and passes them to the fetus across the placenta.

Key points

Childhood cancer/leukaemia births are closely associated with high atmospheric emissions from combustion processes, mainly oil based, and from organic evaporation. Demonstrated associations with 1–3,butadiene, dioxins, and benz(a)pyrene, but possibly others as well, are probably causal. Such toxic emissions may account for a majority of all cases.

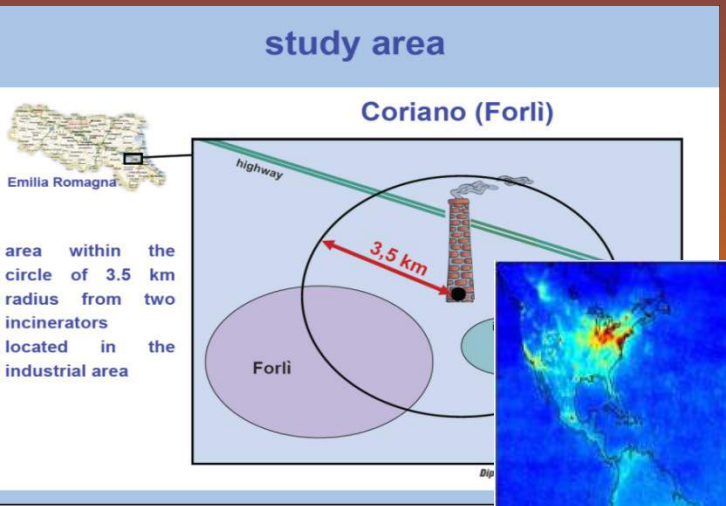
Our **common ways of evaluating the risks for our health and the risks for the new generations' health**, **directly** connected to environmental pollution, are **absolutely insufficient**. As a matter of fact **"classic" epidemiological and toxicological studies** are not the right way to evaluate the threat posed by **"global" environmental pollution** to our health, to **new**

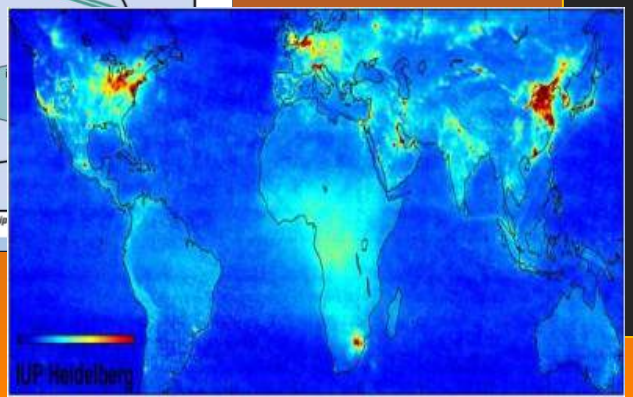
ms. ..

Epidemiologists generally evaluate the diseases' burden directly connected with environmental pollution by comparing **two populations** - the **one more directly exposed** to a known **source of pollution**
(a factory/industrial implant or incinerator or a highway with high traffic rate)

the **other supposed** to be **much less exposed..** *Systematically forgetting* that nowadays **we are all exposed** (through the **nutritional chains** and through direct transgenerational **transmission of pollutants from our mothers**)

to a **constantly growing burden of xenobiotics** (more than 100.000 synthetic molecules) that cannot be recognized by our cellular and nuclear receptors and that may **interact in a wrong way with our biochemical pathways** and sometimes even with the **genetic expression** of our cells and tissues.





Endocrine disruptors have also been cited with producing
one effect at ***high dose*** and a different effect at ***low doses***

Limits and problems with *traditional toxicology*:
dose-response or **exposure-response relationship**
→ *acute/direct toxicity*
Collective and ubiquitous exposure to minimal doses; synergism..
Daily *bioaccumulation* and ***biomagnification***
EDCs /Barker Hypothesis /Transgenerational transmission

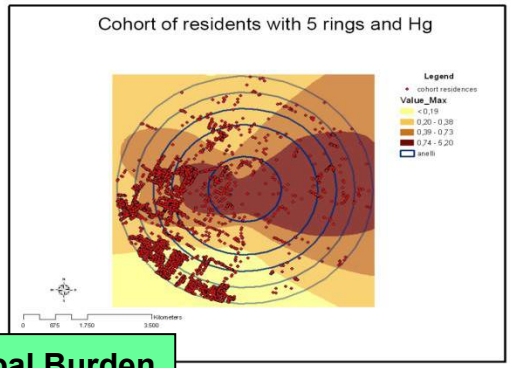
A scientific challenge

Toxicology as it has been practiced for decades is highly likely to have underestimated hazards.

Human epidemiology as it is been traditionally practiced is highly biased toward false negatives.

Limits and problems with (*classic) epidemiology*
(Difficult) comparison among **populations directly exposed**
Collective and ubiquitous exposure to minimal doses
Daily *bioaccumulation* and ***biomagnification***
(*Barker Hypothesis/Transgenerational transmission/long latency*)

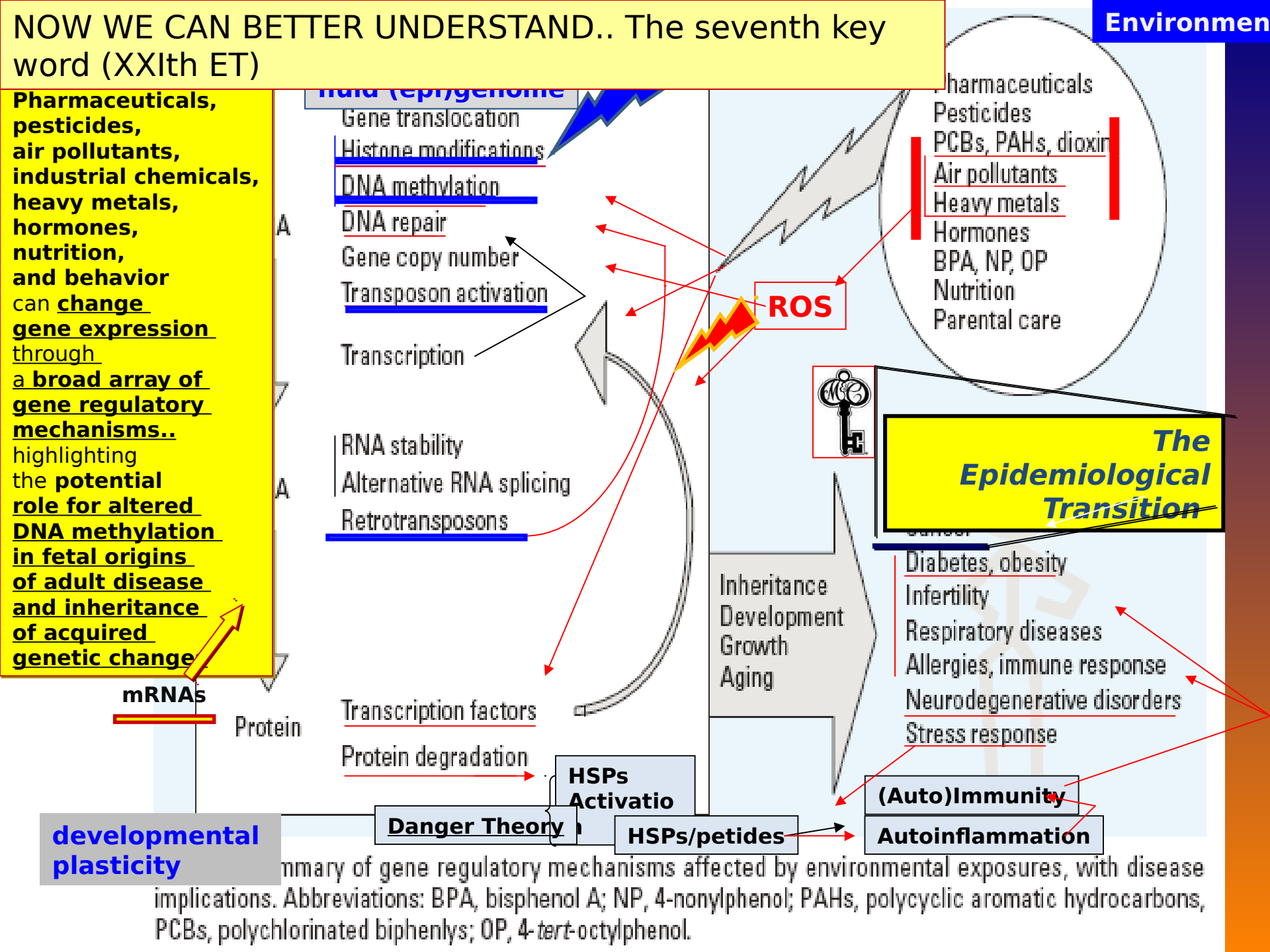
Environmental Health Sciences



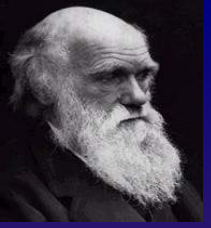
SOLUTIONS: **Calculating Emissions** and **Chemical Global Burden**

NOW WE CAN BETTER UNDERSTAND.. The seventh key word (XXIth ET)

Pharmaceuticals, pesticides, air pollutants, industrial chemicals, heavy metals, hormones, nutrition, and behavior can **change gene expression** through a **broad array of gene regulatory mechanisms..** highlighting the **potential role for altered DNA methylation in fetal origins of adult disease and inheritance of acquired genetic change**



mmary of gene regulatory mechanisms affected by environmental exposures, with disease implications. Abbreviations: BPA, bisphenol A; NP, 4-nonylphenol; PAHs, polycyclic aromatic hydrocarbons, PCBs, polychlorinated biphenlys; OP, 4-*tert*-octylphenol.



Macroevolution

A

Symbiogenesis

Horizontal gene transfer

Neodarwinistic Paradigm

EMERGENT PROPERTIES

Master Genes

GRNs

Environmental crisis

(microevolution)

NEW DEVELOPMENTAL PATTERNS

Genes

Natural Genetic Engineering

(Fluid) Genome

(ecosystems)

Random Mutations

Mobile Sequences

(Fluid) Epigenome

Phenotype

Reverese Transcriptase

Ribotype

Environment

Natural Selection
(Environment)

B

HATs

HDACs

DMTs

NRs

TFs

Proteome

Phenotype

Organisms

Rs

Cells

Rs

Molecules

microevolution

Neo-Lamarckian-Constructive Paradigm

Natural Selection

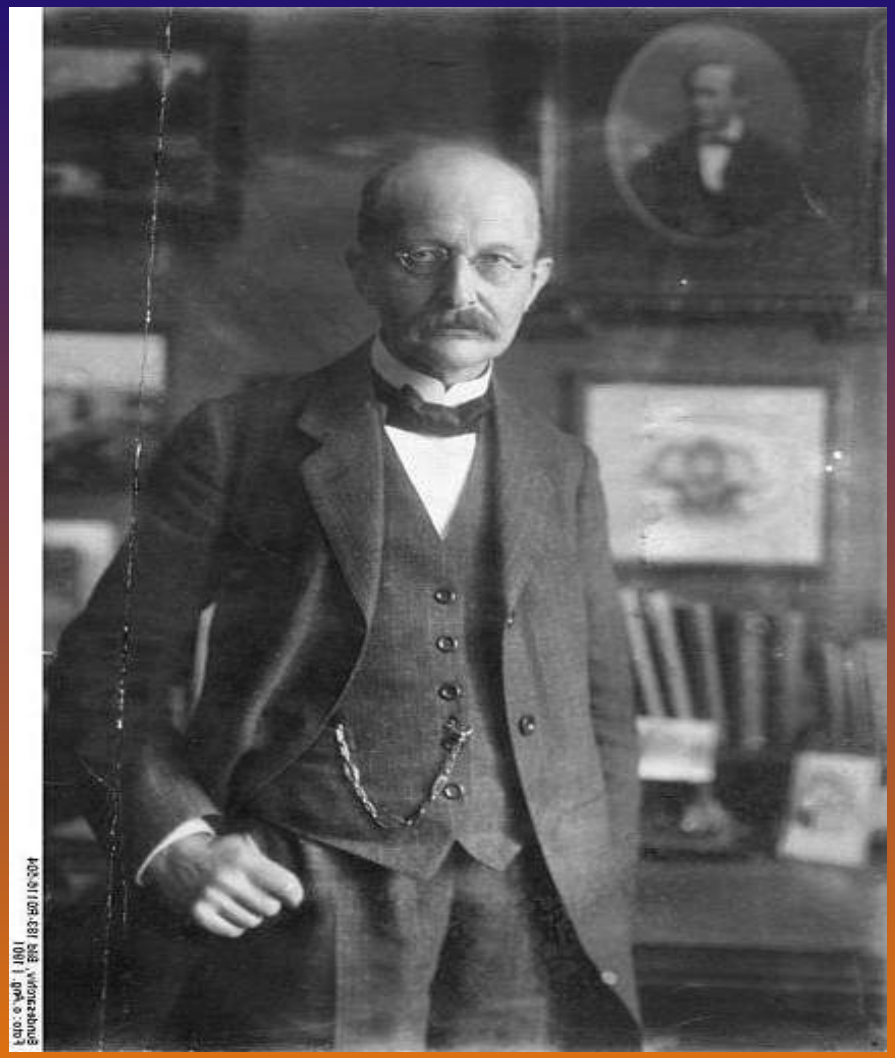
Rs: Receptors

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)



1: Ann N Y Acad Sci. 2002 Dec;982:190-7.

Primary prevention protects public health.

Tomatis L.

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It is widely accepted that epidemiological data provide the only reliable evidence of a carcinogenic effect in humans, but epidemiology is unable to provide early warning of a cancer risk. The experimental approach to carcinogenicity can ascertain and predict potential cancer risks to humans in time for primary prevention to be successful. Unfortunately, only in rare instances were experimental data considered sufficiently convincing per se to stimulate the adoption of preventive measures. The experimental testing of environmental agents is the second line of defense against potential human carcinogens. The first line is the testing of synthesized agents, be these pesticides, medical drugs, or industrial chemical/physical agents, at the time of their development. We do not know, however, how many substances have been prevented from entering the environment because most tests are carried out by commercial or private laboratories and results are rarely released. A better understanding of the mechanisms underlying the sequence of events of the carcinogenesis process will eventually lead to a m accurate characterization and quantification of risks. However, the ways that mechanistic d have been used lately for evaluating evidence of carcinogenicity have not necessarily meant the evaluations were more closely oriented toward public health. A tendency has surfaced to dismiss the relevance of long-term carcinogenicity studies. In the absence of absolute certainty, rarely if ever reached in biology, it is essential to adopt an attitude of responsible caution, in line with the principles of primary prevention, the only one that may prevent unlimited experimentation on the entire human species.