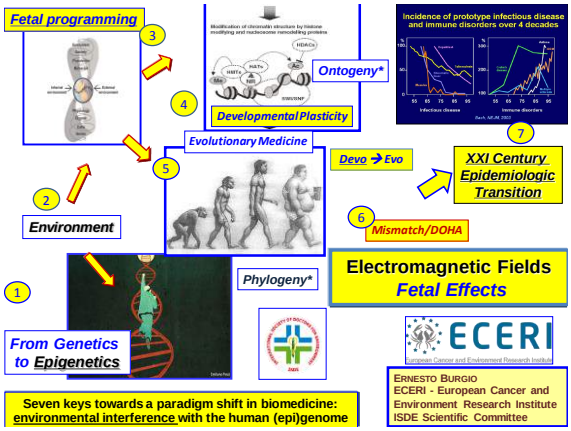


We are currently facing a ***paradigm shift*** in biomedicine

For the last 50 years it was agreed to consider **DNA as the code and the key project for the assembly of our phenotype**.

In the last ten years and especially since the appearance of **the first molecular epigenetic studies** we have begun to understand

that the construction of the phenotype is the **result of the interaction** between the **information** coming from the **environment**

and the **information** deeply inscribed inside the DNA

thanks to a very complex molecular network surrounding DNA: the epigenome

⇩

Therefore it can be argued that there is **no stable change in our phenotype (both physiological and pathological)** which is not

- ***environmentally*** induced
- ***modulated* by the *epigenome***
- ***conditioned*** by the DNA

Other **key concepts** (obviously interdependent) are:

- ***developmental plasticity***
- ***fetal programming***

allow ing us to understand how **the fetus epigenetically program (for life) all its cells in a *predictive* and *adaptive* way**

responding to **information** coming from the environment (through the ***mother bias***)

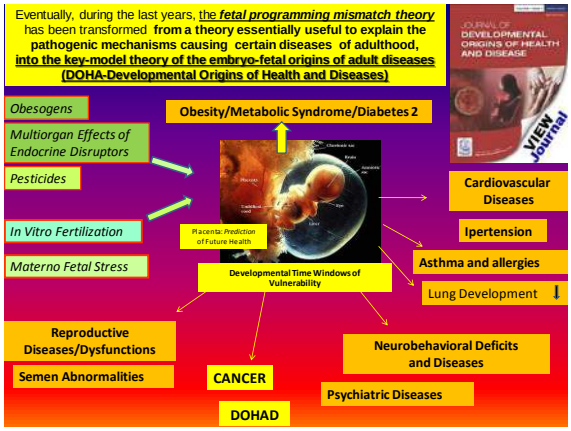
It is important to note that in this period

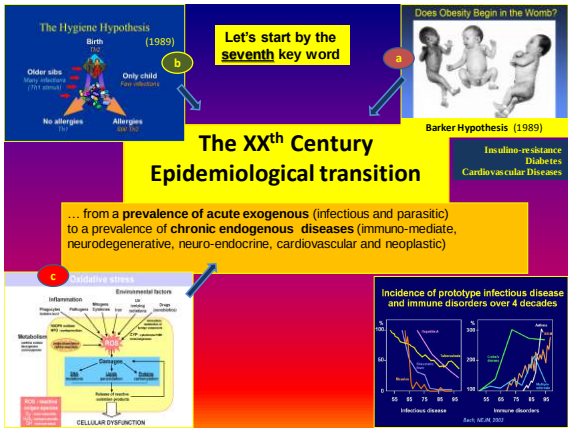
***incorrect information* (*pollutants, endocrine disruptors* ..)** and /or

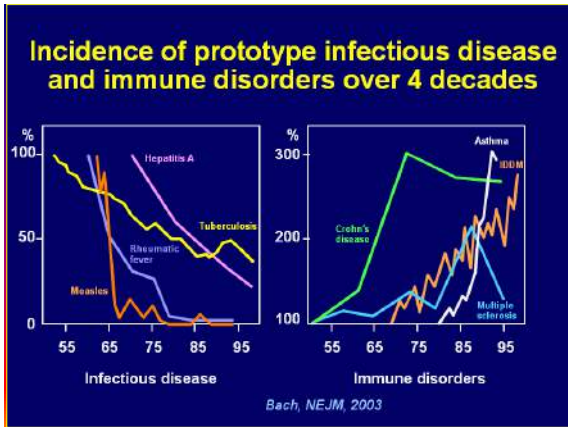
discrepancies between the **information** that the baby receives before and after birth **(*mismatch*)**

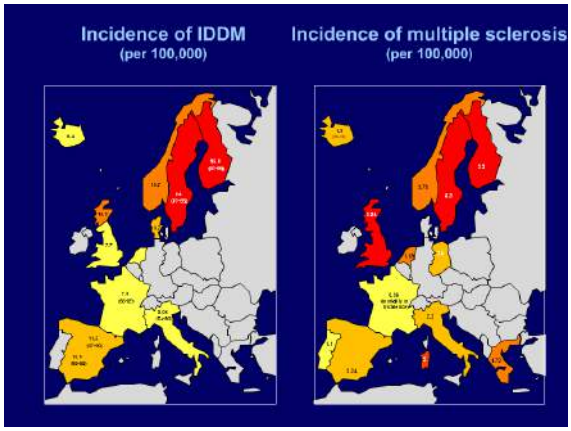
may create **epigenetically bad programmed cells** (including **gametes**), thus causing **chronic diseases in adulthood** or **even in subsequent generations**

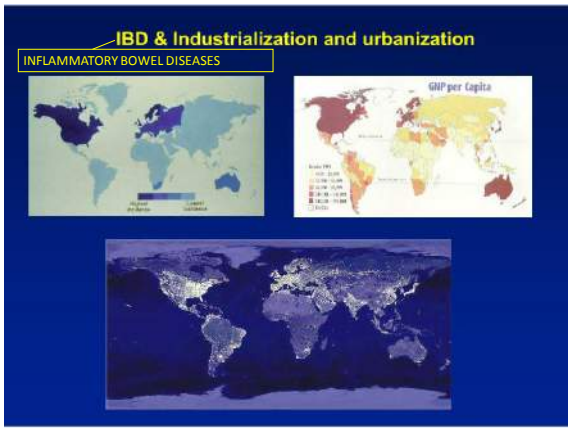
This theory (***DOHaD Developmental Origins of Health and Disease***) could help us to **explain the current epidemiological transition** ..

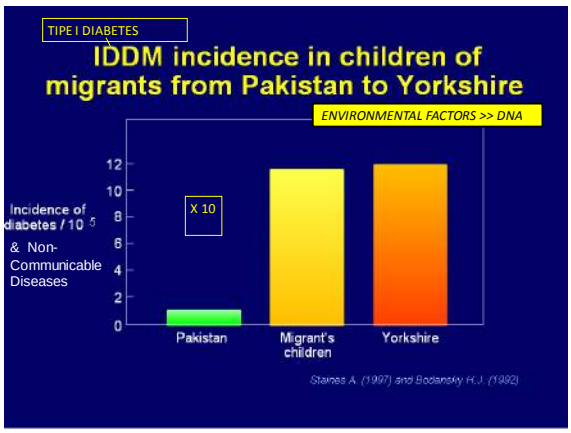

Eventually, during the last years, the fetal programming mismatch theory has been transformed from a theory essentially useful to explain the pathogenic mechanisms causing certain diseases of adulthood, into the key-model theory of the embryo-fetal origins of adult diseases (DOHA-Developmental Origins of Health and Diseases)
JOURNAL OF DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE
VIEW Journal
Obesogens
Multiorgan Effects of Endocrine Disruptors
Pesticides
In Vitro Fertilization
Materno Fetal Stress
Obesity/Metabolic Syndrome/Diabetes 2
Placenta: Prediction of Future Health
Developmental Time Windows of Vulnerability
Cardiovascular Diseases
Ipertension
Asthma and allergies
Lung Development
Reproductive Diseases/Dysfunctions
Semen Abnormalities
CANCER
DOHAD
Neurobehavioral Deficits and Diseases
Psychiatric Diseases


The Hygiene Hypothesis
(1989)
Birth
Older sibs
Only child
No allergies
Allergies
b
Let's start by the seventh key word
a
Does Obesity Begin in the Womb?
Barker Hypothesis (1989)
The XXth Century Epidemiological transition
Insulino-resistance
Diabetes
Cardiovascular Diseases
… from a prevalence of acute exogenous (infectious and parasitic) to a prevalence of chronic endogenous diseases (immuno-mediate, neurodegenerative, neuro-endocrine, cardiovascular and neoplastic)
c
Oxidative stress
Environmental factors
Inflammation
Metabolism
CELLULAR DYSFUNCTION
Incidence of prototype infectious disease and immune disorders over 4 decades
Infectious disease
Immune disorders
Bach, NEJM, 2003

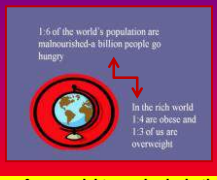

Incidence of prototype infectious disease and immune disorders over 4 decades
%
100
50
0
Hepatitis A
Tuberculosis
Rheumatic fever
Measles
55 65 75 85 95
Infectious disease
%
300
200
100
Asthma
IDDM
Crohn's disease
Multiple sclerosis
55 65 75 85 95
Immune disorders
Bach, NEJM, 2003


Incidence of IDDM
(per 100,000)
Incidence of multiple sclerosis
(per 100,000)


IBD & Industrialization and urbanization
INFLAMMATORY BOWEL DISEASES
GNP per Capita


TIPE I DIABETES
IDDM incidence in children of migrants from Pakistan to Yorkshire
ENVIRONMENTAL FACTORS >> DNA
Incidence of diabetes / 10 5
& Non-Communicable Diseases
X 10
12
10
8
6
4
2
0
Pakistan
Migrant's children
Yorkshire
Staines A. (1997) and Bodansky H.J. (1992)

The Obesity and Diabesity Pandemics



For the first time in human history, the number of overweight people rivals the number of underweight people.... While the world's **underfed population has slightly declined since 1980** to 1.1 billion, the number of **overweight people has surged** to 1.1 billion

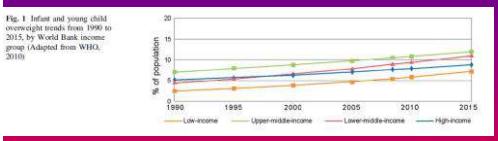
Mol Biol Rep
DOI 10.1007/s11033-014-3751-z

.. a ***pandemic*** of obesity / diabesity?

Obesity and diabetes: from genetics to epigenetics

Ernesto Burgio · Angela Lopomo · Lucia Migliore

Obesity is **not** a disease due to **accumulation of fat in adipose tissue**, but a ***progressive systemic endocrinopathy*** affecting hypothalamus, pituitary and adrenal gland, adipose tissue, muscles ..



Genetic factors in obesity and diabetes

The obesogen hypothesis

Epigenetic biomarkers

Beyond genetics

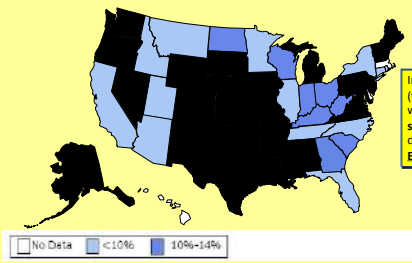
Diabetogens and diabetes epidemic

From genetics to epigenetics: fetal programming alterations

Is there a role for gut microbiota?

Obesity Trends* Among U.S. Adults 1985

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

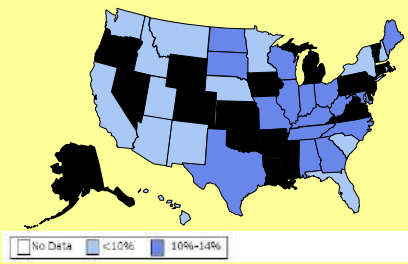


In the next **6 slides** (taken from **JAMA**) we'll follow, **in quick succession**, the dramatic, **TRULY EPIDEMIC SPREAD**

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

Obesity Trends* Among U.S. Adults 1987

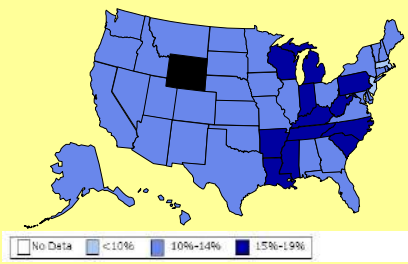
(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)



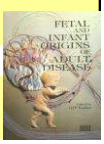
Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

Obesity Trends* Among U.S. Adults 1993

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

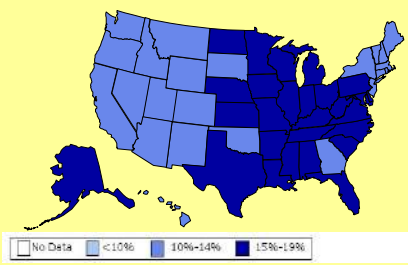


Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.



Obesity Trends* Among U.S. Adults 1995

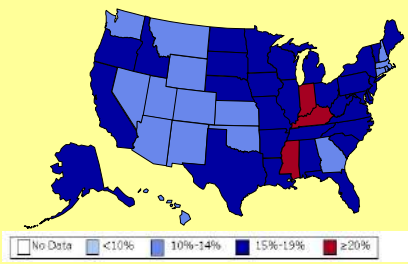
(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)



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

Obesity Trends* Among U.S. Adults 1997

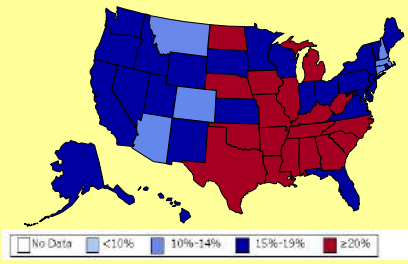
(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)



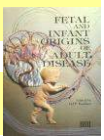
Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

Obesity Trends* Among U.S. Adults 1999

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

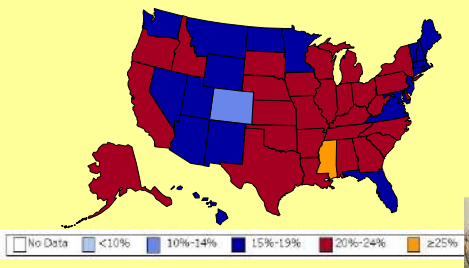


Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10



Obesity Trends* Among U.S. Adults 2001

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

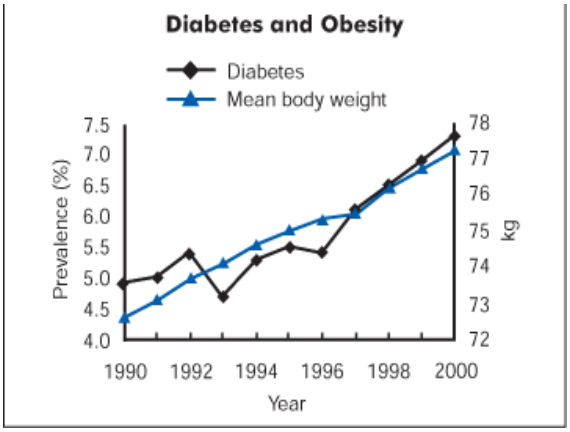


Today the situation has **further deteriorated:** **65%** of Americans are overweight, **35%** morbidly obese

The Childhood Obesity Epidemic

Matthew W. Gillman, MD, SM

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



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Health | Features | December 6, 2007 | 29 Comments | Email | Print

Is There Really an Autism Epidemic? [Preview]

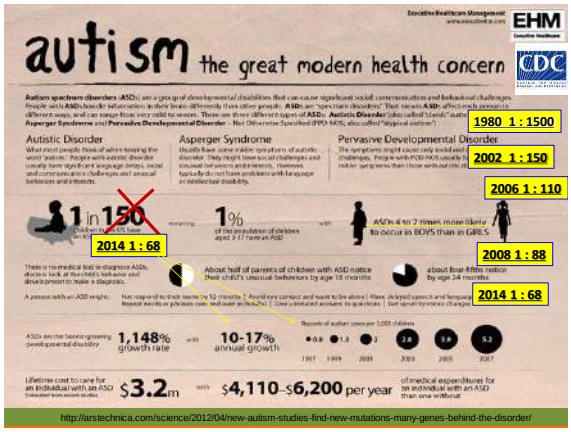
A closer look at the statistics suggests something more than a simple rise in incidence

See inside.

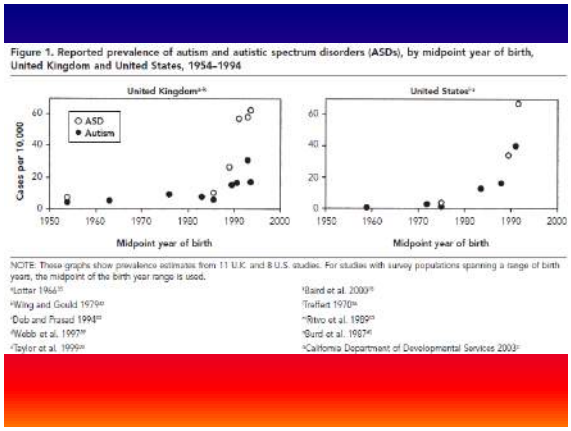
By Scott O. Lilienfeld and Hal Arkowitz

If the statistic "one in 166" has a familiar ring, perhaps that's because you recently heard it on a television commercial or read it in a magazine. According to widely publicized [illegible] the proportion [illegible] autism. This [illegible] high compared [illegible] oo that autism [illegible] decades. [illegible] od—1993 to [illegible].S. Department of Education revealed a 657 percent increase in the nationwide rate of autism.

Many scientists and researchers claim that Autism is **the fastest-growing developmental disorder in the world**, with the **prevalence of diagnosis having increased by 600 per cent over the last 20 years**.. And **from 1:1500 to 1:80 children in US in the last 30 years**



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



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Grandjean P.

A Silent Pandemic

Industrial Chemicals Are Impairing The Brain Development of Children Worldwide

For immediate release: Tuesday, November 7, 2006

Landrigan Ph

THE LANCET

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

Developmental neurotoxicity of industrial chemicals

P Grandjean, PJ Landrigan

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

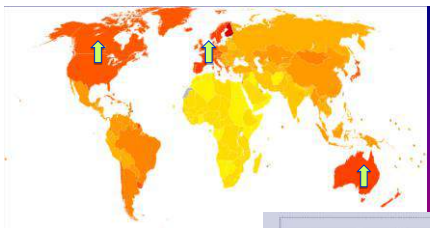
Neurobehavioural effects of developmental toxicity

Philippe Grandjean, Philip J Landrigan

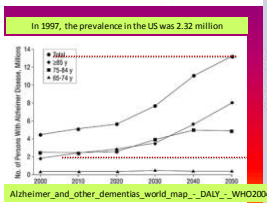
The Lancet Neurology, Volume 13, Issue 3 , Pages 330 - 338, March 2014

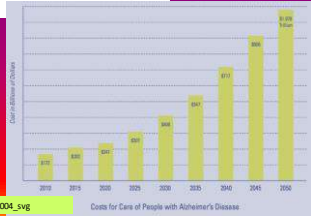
Neurodevelopmental disabilities, including autism, attention-deficit hyperactivity disorder, dyslexia, and other cognitive impairments, affect millions of children worldwide, and some diagnoses seem to be increasing in frequency. Industrial chemicals that injure the developing brain are among the known 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



In 1997, the prevalence in the US was 2.32 million





Alzheimer_and_other_dementias_world_map_-_DALY_-_WHO2004_svg

CANCER RESEARCH UK

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** ..

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.

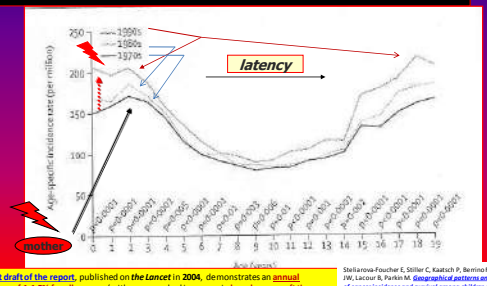
But crucially, this increasing lifetime risk of cancer is balanced by another powerful force – that of increasing survival rates. Against a backdrop of increasing cancer risk over the past 40 years, **survival rates have doubled in the UK.**

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

As we may easily argue from the recent project *ACCIS (Automated Childhood Cancer Information System)* - a comprehensive monitoring **conducted by a team of epidemiologists IARC on 63 cancer registries from 19 European countries**, for a total of over ***130 thousand tumors*** of all types (113 thousand children and 18 thou http://www.dep.iarc.fr/accis.htm

Cancer incidence in childhood and adolescence - EUROPE (1970-1999)



A first draft of the report, published on ***the Lancet*** in **2004**, demonstrates an **annual increase of 1-1,5% for all cancers** (with more marked increases in **lymphomas, soft tissue sarcomas, tumors of the nervous system...**).

Stellarova-Foucher E, Stiller C, Kaatsch P, Rennor 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

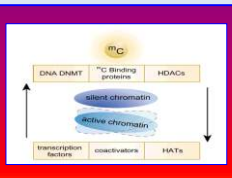
First European Cancer and Environment Research Institute Workshop

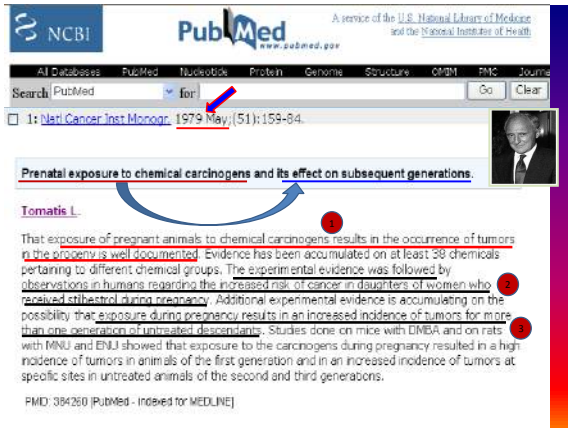
ECERI

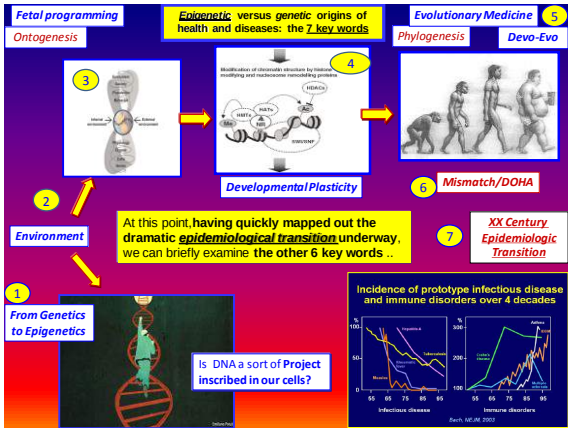
October the 26th 2012,
Académie Royale de Médecine de Belgique,
Belgium Royal Academy of Medicine,
Salle Albert I,
Brussels, Belgium

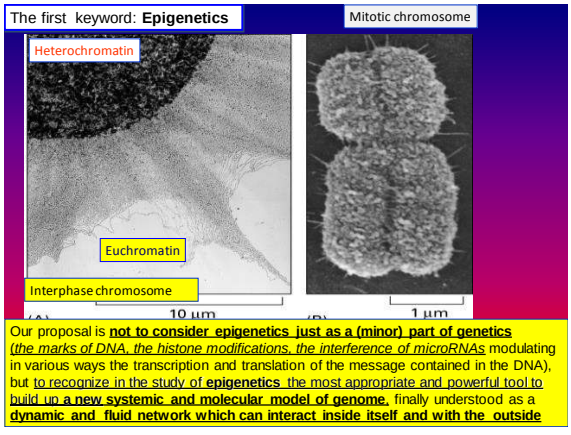
Notes on the epigenetic (transplacental and transgenerational) origins of childhood cancer

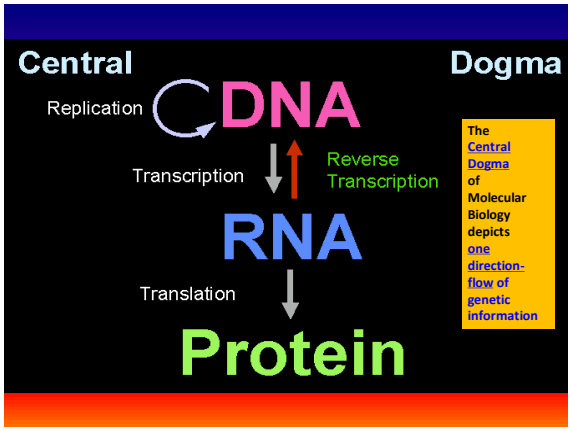
ERNESTO BURGIO
ECERI - European Cancer and Environment Research Institute
ISDE Scientific Committee

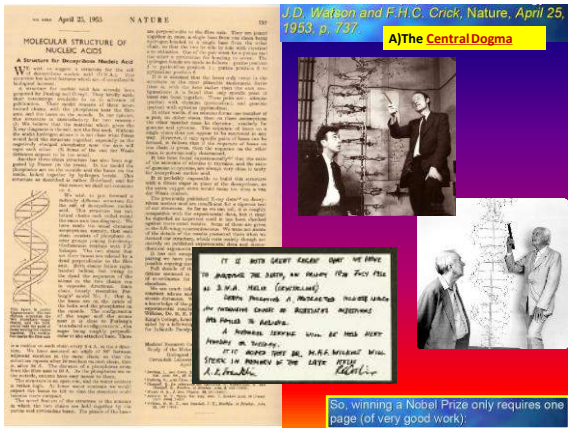


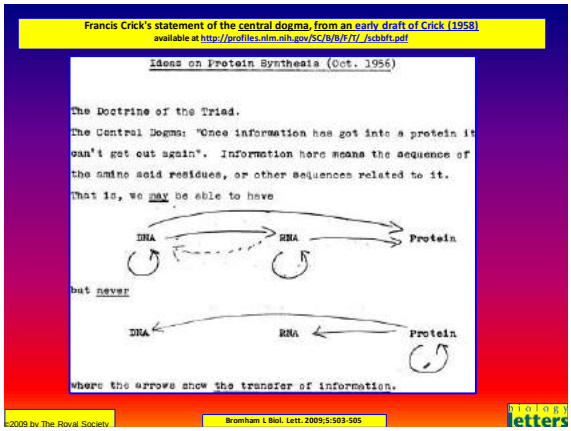

NCBI
PubMed
A service of the U.S. National Library of Medicine and the National Institutes of Health
www.pubmed.gov
All Databases PubMed Nucleotide Protein Genome Structure OMIM PMC Journa
Search PubMed for
Go Clear
1: Natl Cancer Inst Monogr. 1979 May;(51):159-64.
Prenatal exposure to chemical carcinogens 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]
1
2
3


Fetal programming
Ontogenesis
Epigenetic versus genetic origins of health and diseases: the 7 key words
Evolutionary Medicine
5
Phylogenesis
Devo-Evo
3
4
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
From Genetics to Epigenetics
Is DNA a sort of Project inscribed in our cells?
Incidence of prototype infectious disease and immune disorders over 4 decades
Infectious disease
Immune disorders


The first keyword: Epigenetics
Mitotic chromosome
Heterochromatin
Euchromatin
Interphase chromosome
10 µm
1 µm
Our proposal is not to consider epigenetics just as a (minor) part of genetics (the marks of DNA, the histone modifications, the interference of microRNAs modulating in various ways the transcription and translation of the message contained in the DNA), but to recognize in the study of epigenetics the most appropriate and powerful tool to build up a new systemic and molecular model of genome, finally understood as a dynamic and fluid network which can interact inside itself and with the outside


Central
Dogma
Replication
DNA
Transcription
Reverse
Transcription
RNA
Translation
Protein
The Central Dogma of Molecular Biology depicts one direction-flow of genetic information


J.D. Watson and F.H.C. Crick, Nature, April 25, 1953, p. 737.
A)The Central Dogma
So, winning a Nobel Prize only requires one page (of very good work).


Francis Crick's statement of the central dogma, from an early draft of Crick (1958)
available at http://profiles.nlm.nih.gov/SC/B/F/T/_/scbbft.pdf
Ideas on Protein Synthesis (Oct. 1956)
The Doctrine of the Tried.
The Central Dogma: "Once information has got into a protein it can't get out again". Information here means the sequence of the amino acid residues, or other sequences related to it.
That is, we may be able to have
DNA
RNA
Protein
but never
DNA
RNA
Protein
where the arrows show the transfer of information.
©2009 by The Royal Society
Bromham L Biol. Lett. 2009;5:503-505
biology letters

nature biotechnology

COMMENTARY

EPIGENESIS AND COMPLEXITY

The coming Kuhnian revolution in biology

Richard C. Strohman

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***)

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.

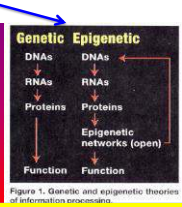


Figure 1. Genetic and epigenetic theories of information processing.

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**

In such a fluid and systemic model the ***epigenome*** (also defined by some scientists as **the controlling *software*** of the genome) behaves as a sort of *compensation chamber* - the specific place where the flow of **information** that comes from outside (*environment* and *microenvironment*) meets and interacts with the **information encoded in the genes** for millions years (the ***hardware***)

Epigenetic Regulation, a mechanism that

allows the genome to integrate

– ***intrinsic*** **with**

– ***environmental*** **signals**

Rudolf Jaenisch- Whitehead Institute and Dept. of Biology, MIT, Cambridge, MA

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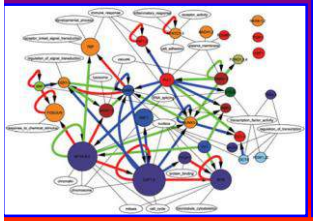
From directing **the fate of stem cells to determining how.. we grow**, **the genes in our body act in complex networks.**, the whole ***Genome*** is a Complex and **highly dynamic molecular Network** of ***interacting Genes*** and ***non-codifying sequences.*** and ***proteins***

….Genes Know How to Network…BUT…

Strohman R. , April 2001 ***Beyond genetic determinism***

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

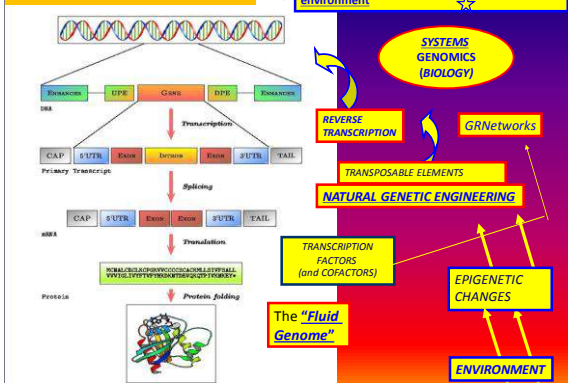


IN FACT Genes need to be told to switch "off" and "on":

- **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 dynamic-epigenetic networks have a life of their own —they follow network-rules not specified by DNA**

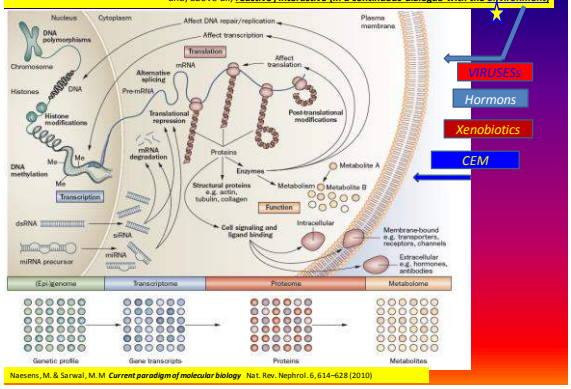
If the **Central Dogma** of Molecular Biology depicted **one direction-flow of genetic information**

we now know that things are quite different: **information flow is circular between genome and environment**



..configuring a new model of *genomic molecular network* composed by *DNA, epigenome, proteome sequences communicating in cis and trans*

and, above all, reactive /interactive (in a continuous dialogue with the environment)



Naesens, M. & Sarwal, M. M *Current paradigm of molecular biology* Nat. Rev. Nephrol. 6, 614–628 (2010)