Università degli Studi di Padova

Dipartimento di Psicologia Generale

**16 Aprile 2018**
Aula I. Nievo Palazzo del Bo
Università di Padova

# Science of Consciousness

**con la partecipazione di FEDERICO FAGGIN**

INGRESSO LIBERO
(fino a esaurimento posti)

Questo evento, promosso dal Science of Consciousness Research Group del Dipartimento di Psicologia Generale, ha lo scopo di presentare per la prima volta a studenti, colleghi e al pubblico, **lo stato dell'arte della ricerca sulla natura della coscienza**, dell'esperienza soggettiva e della sua relazione con il mondo fisico.
La scienza della coscienza è una disciplina nuova e intimamente interdisciplinare comprendente le neuroscienze, la filosofia, la psicologia, la fisica e l'antropologia, che indaga **la relazione ancora incompresa tra la mente, il cervello e la realtà fisica**.
Si affronteranno quindi temi che spaziano dalle implicazioni epistemologiche alla base della scienza della coscienza, agli aspetti psicologici e neurobiologici (Facco e Burgio) per estendersi fino alla fisica dell'infinitamente piccolo (Fracas), dell'infinitamente grande (Tormen) e all'intelligenza artificiale (Faggin).

## PROGRAMMA

*9.15: Presentazione a cura di **Daniela Lucangeli***

*Relazioni*

9.30: **Enrico Facco**
L'enigma della Coscienza

10.30: **Ernesto Burgio**
Evoluzione e sviluppo del cervello ed emergere della coscienza

*Pausa*

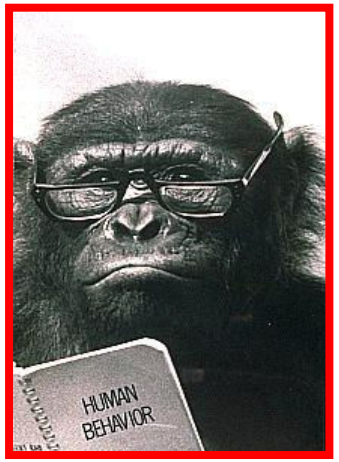
11.45: **Fabio Fracas**
Il mondo secondo la Fisica Quantistica

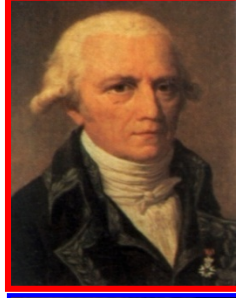
12.45: **Giuseppe Tormen**
Noi e l'infinitamente grande

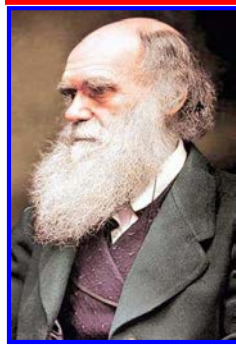
*Pausa*

14.45: **Federico Faggin**
Robot coscienti: realtà o fantascienza?

*16.00: Tavola rotonda con tutti i relatori e dibattito generale*





# Evoluzione e Sviluppo del Cervello
e(d emergere) della **Coscienza**

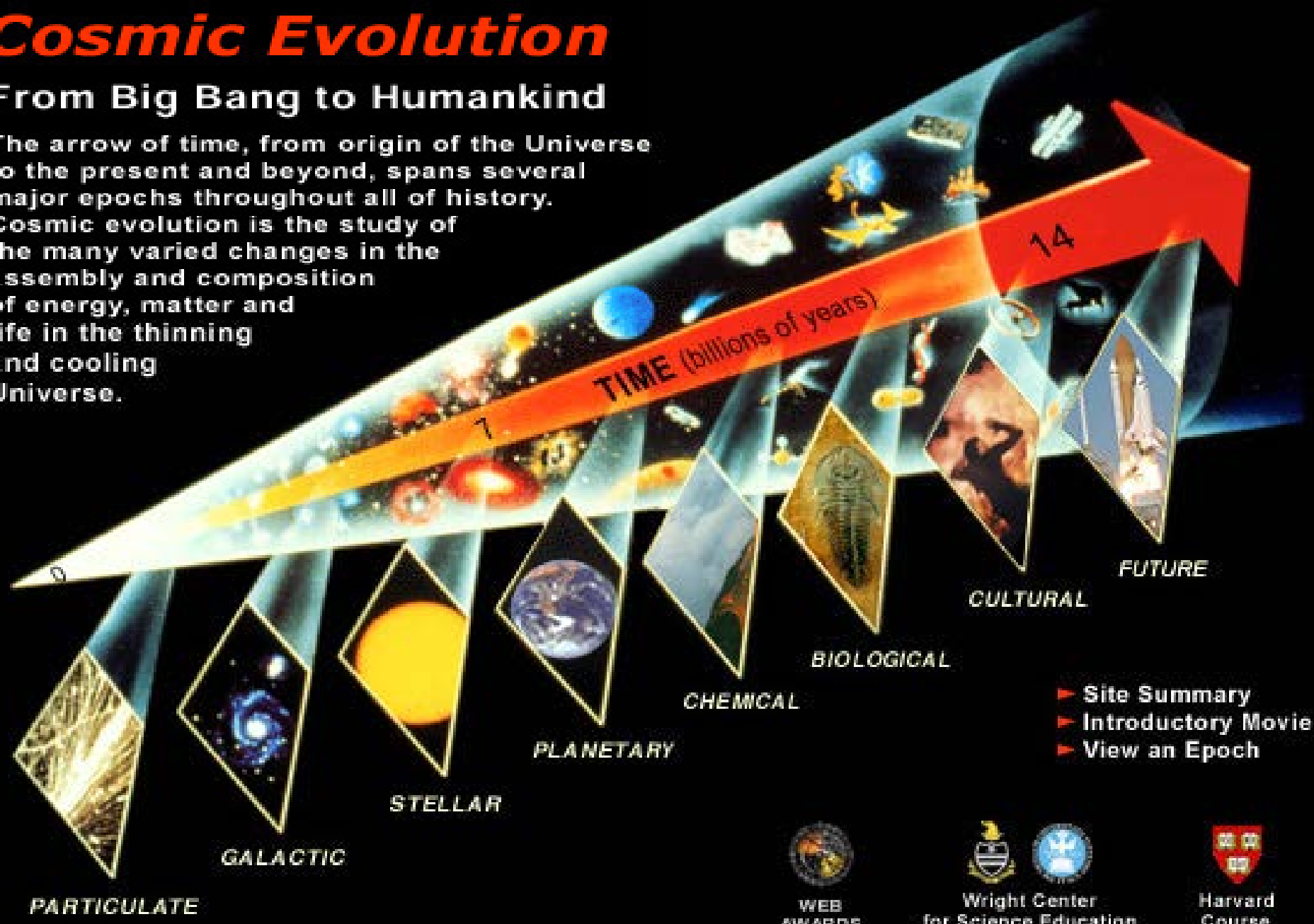
Ernesto Burgio (ECERI, Brussels, Belgium

ECERI
European Cancer and Environment Research Institute

# Cosmic Evolution

## From Big Bang to Humankind

The arrow of time, from origin of the Universe to the present and beyond, spans several major epochs throughout all of history. Cosmic evolution is the study of the many varied changes in the assembly and composition of energy, matter and life in the thinning and cooling Universe.




- Site Summary
- Introductory Movie
- View an Epoch

WEB AWARDS

Wright Center for Science Education Tufts University

Harvard Course Syllabus

http://www.mukto-mona.com/Special_Event_/Darwin_day/


Jurassic period
Triassic period
Permian period
Pennsylvanian period
Mississippian period
Devonian period
Silurian period
Ordovician period
Cambrian period
Precambrian era
Paleozoic era
Mesozoic era
Cretaceous period
Cenozoic era
Tertiary period
Eocene epoch
Oligocene epoch
Miocen epoch
Pliocen epoch
Pleistocene epoch
Holocene epoch
ERA
PERIOD
EPOCH
144 m.y.
206 m.y.
251 m.y.
300 m.y.
320 m.y.
354 m.y.
409 m.y.
439 m.y.
510 m.y.
543 m.y.
1 b.y.
2 b.y.
3 b.y.
4 b.y.
4.6 billion years ago
65 m.y.
57 m.y.
35 m.y.
23 m.y.
5 m.y.
1.8 m.y.
0.01 million years ago
Evolution of cells with nucleus
Oldest fossil cells
Oldest rocks dated on Earth

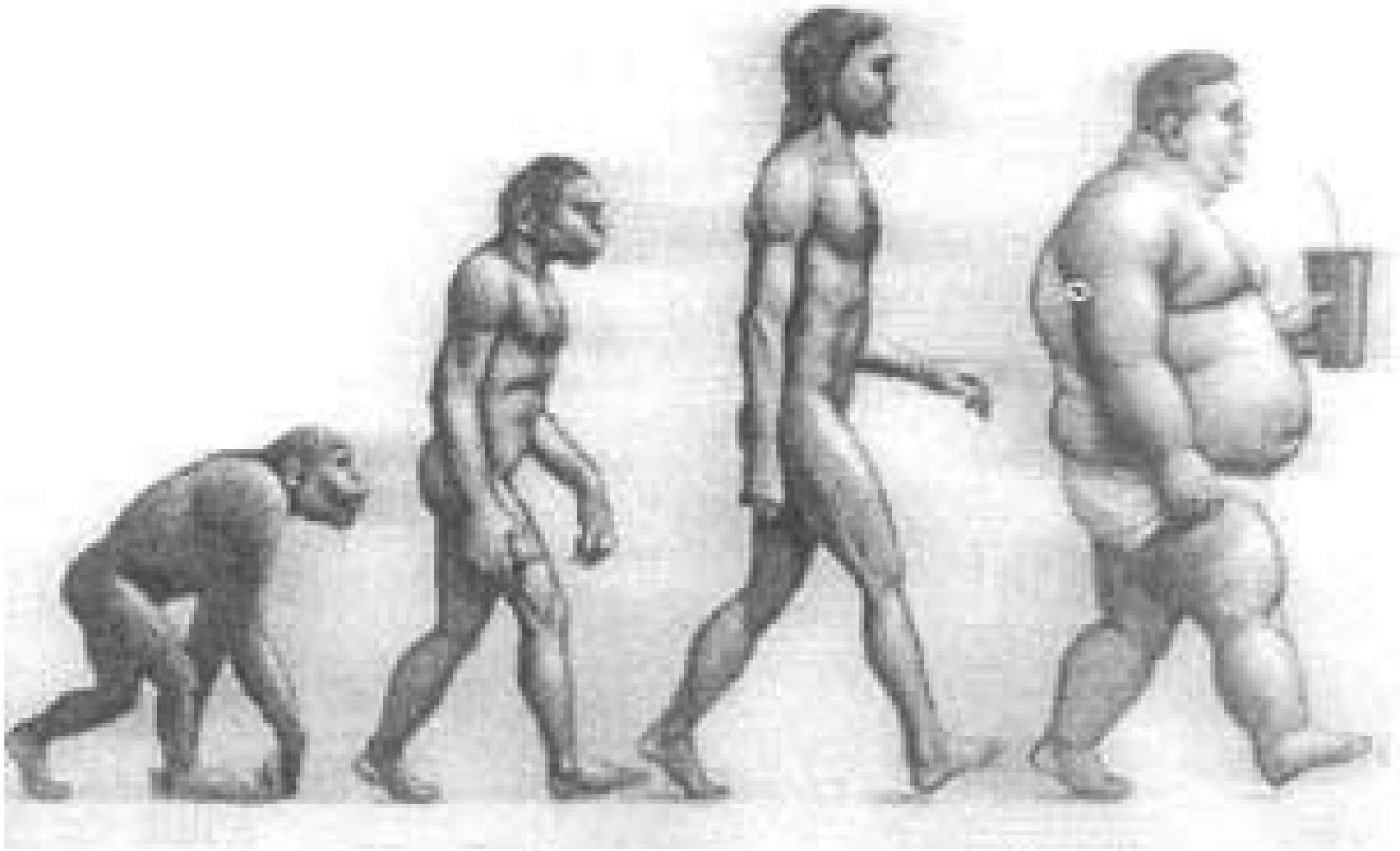
## (***OLOCENE***)

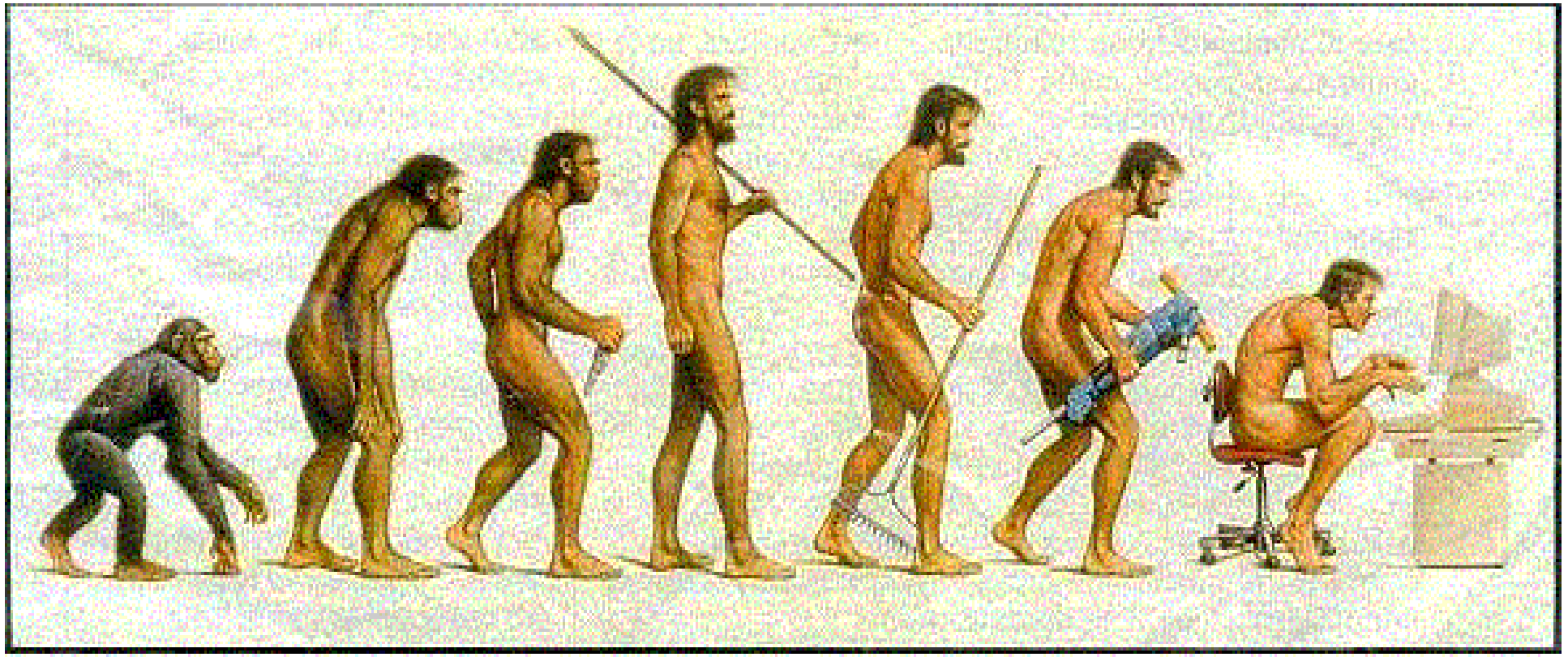
## 31 DICEMBRE - ULTIMO MINUTO

- ore 23,59'15" --> i **Sumeri** in Mesopotamia
- ore 23,59'43" -->Alessandro Magno - Primo "**Impero**"
- ore 23,59'46" --> **Gesù Cristo**
- ore 23,59'49" -->**Caduta Impero** Romano d'Occidente
- ore 23,59'57" --> Scoperta dell'**America**
- ore 23,59'59" --> **Rivoluz. Industriale** * e Francese - Colonialismo- Guerre Mondiali- **Globalizzazione**

***"*Antropocene*": con la **I (Carbone/Macchine)** e soprattutto con la **II (Chimica/Petrolio) Rivoluz. Industriale** l'***Homo S. Sapiens*** si è trasformato in ***potenza tellurica*** (*Stoppani1873-Crutzen 1995*)


HOMINIDAE
The Human Story



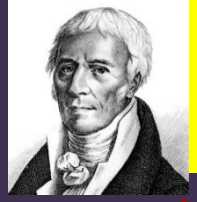



**Irgendwo lief irgendetwas falsch...**


HOMINIDAE
The Human Story
PINO ANTORO
98

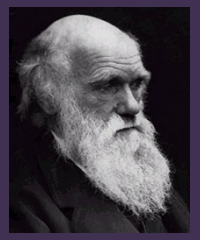
# The **fifth** key word is **phylogeny**

**The chimpanzee DNA is for 98.77% identical to the human .**
**On average, a gene encoding a protein in a man differs from its chimpanzee ortholog by only two aa substitutions**
**.. almost one third of human genes**
has exactly the **same protein translation** as their orthologs
in chimpanzee



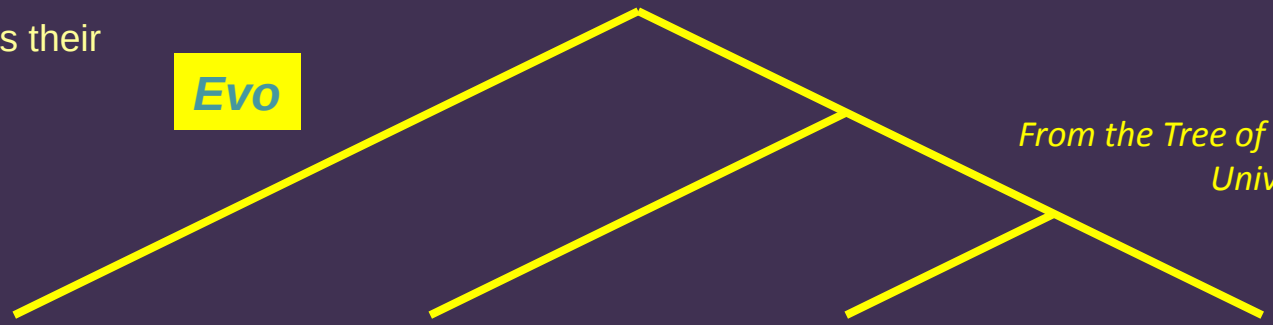
**We are quite stable (for millions of years) both genetically and phenotypically**

Species ***phylogeny***

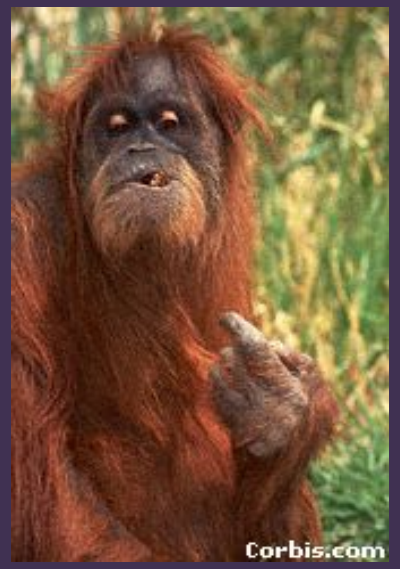


*From the Tree of the Life Website, University of Arizona*

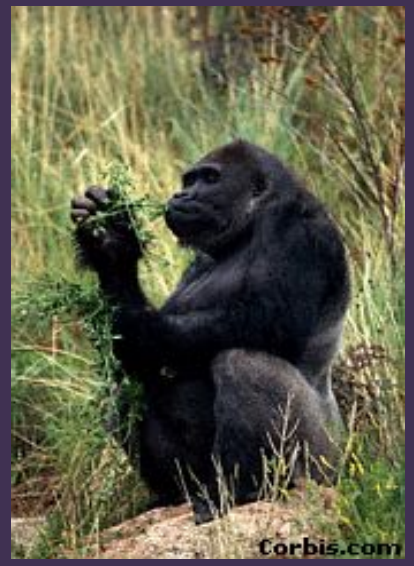
***Evo***



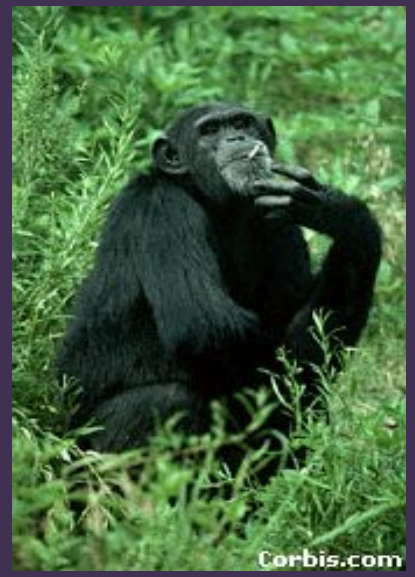
*Orangutan*




*Gorilla*

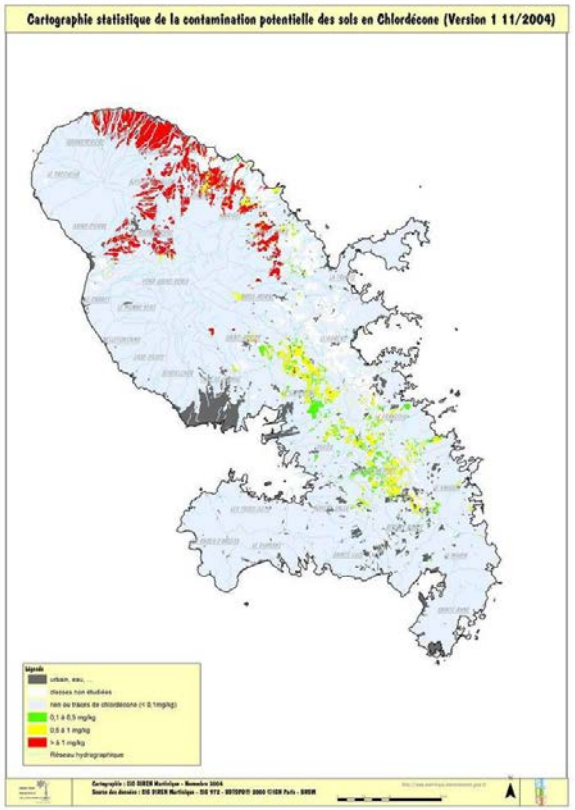



***Chimpanzee***




***Human***

***Sanger Institute***





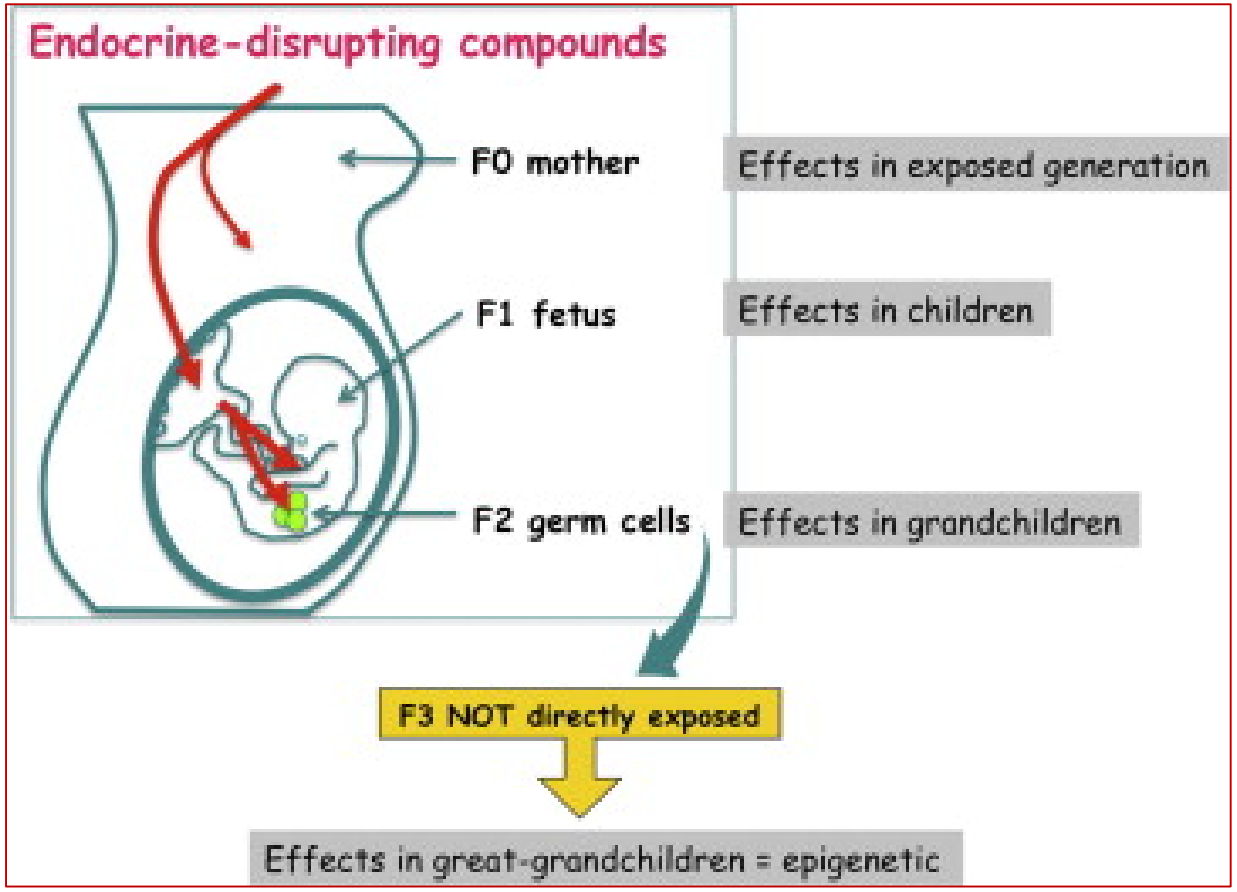
ERNESTO BURGIO
ECERI - European Cancer and Environment Research Institute

ECERI
European Cancer and Environment Research Institute

# Trois Questions

Question 1

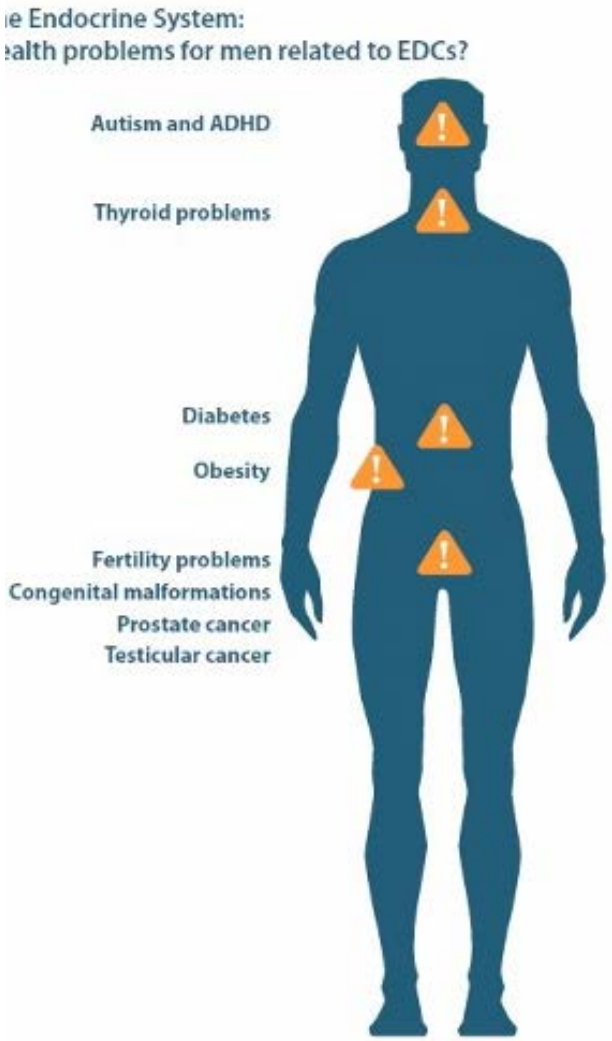
- Dans quelle mesure **l'exposition des mamans et des fœtus aux perturbateurs endocriniens**
- et à d'autres **molécules epi-génotoxiques qui interfèrent avec la programmation fœtale fœtale**
- représente une **grave menace pour la santé des enfants et des générations futures?**

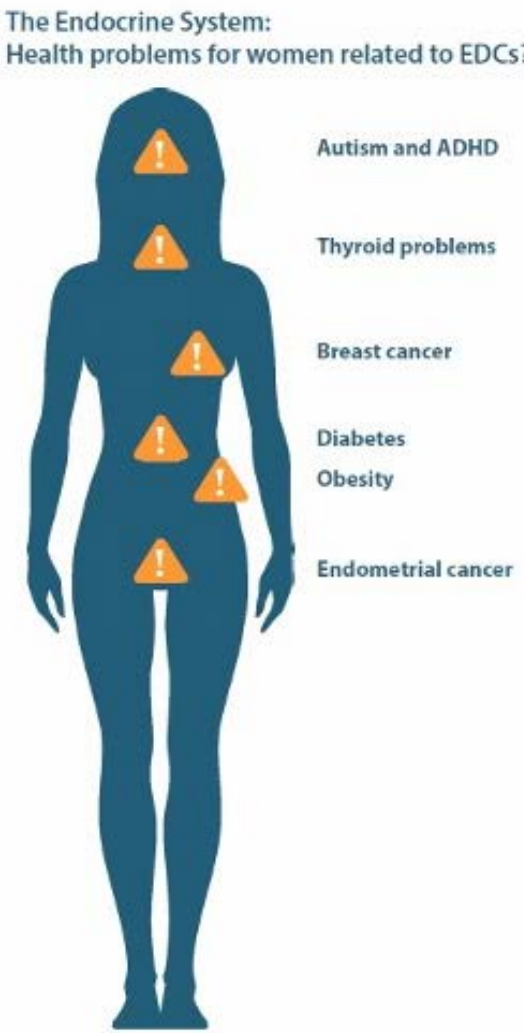



https://www.sciencedirect.com/science/article/pii/S0303720711006356

Question 2

Quel est le rôle de **cette exposition de mamans et des foetus** aux molécules epi-génotoxique dans la genèse de la ***Transition Epidémiologique*** actuelle: ***Pandémies* d'obésité et de diabète juvenile**, augmentation continuelle des pathologies **allergiques et auto-immunes**, des **troubles** du neuro-**développement**, des **maladies neurodégénératives**, et du **cancer** (surtout chez les nourrissons et les jeunes) ?



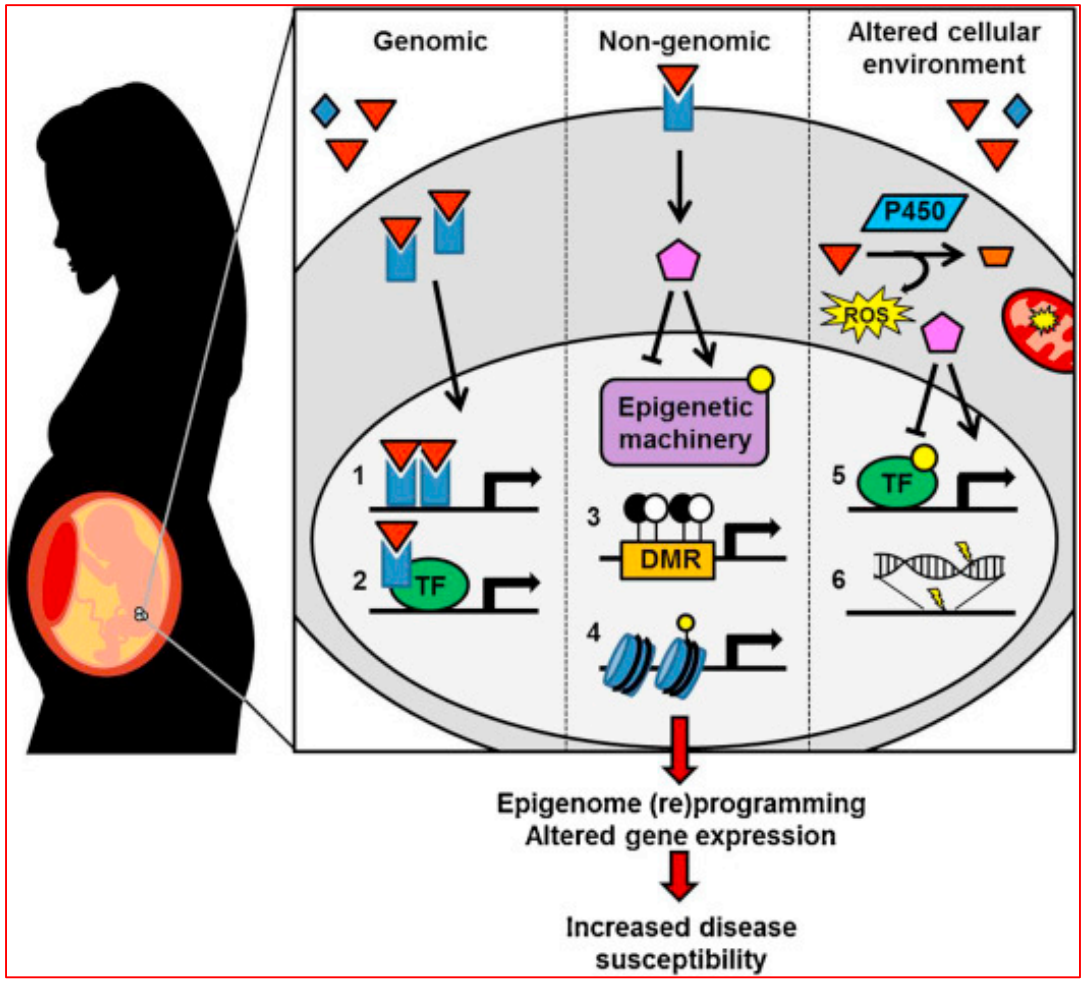




http://www.env-health.org/news/latest-news/article/health-costs-in-the-eu-how-much-is

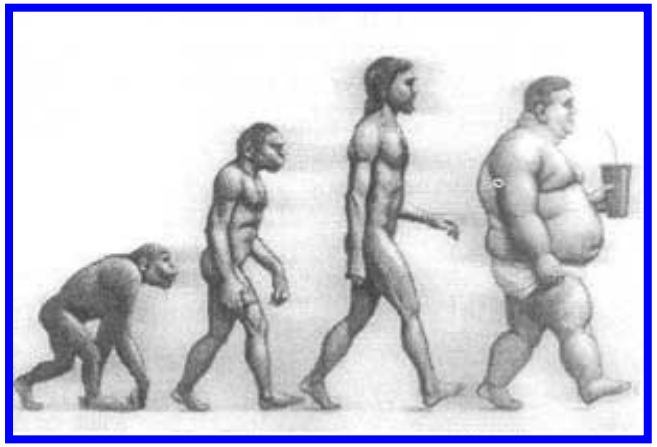
Question 3

Peut-on encore avoir des doutes

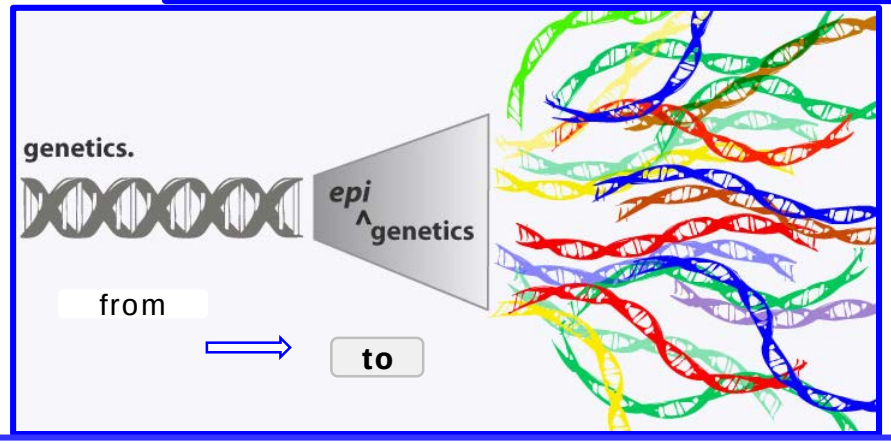
que **la présence dans les chaînes alimentaires et les aquifères d'un pays** et donc **dans les organismes de jeunes à l'âge de procréer** et dans leurs **gamètes** de molécules epi-génotoxiques telles que la ***dioxine*** à Seveso ou à Taranto et la ***chlordécone*** en Martinique et en Guadeloupe est-elle **une cause primaire de la mauvaise programmation fœtale des tissus et organes** et donc de **l'augmentation des tumeurs** (en particulier du ***cancer de la prostate***) et **des autres maladies chroniques dégénératives et inflammatoires**?




https://www.sciencedirect.com/science/article/pii/S1084952115001056

# Evolution of DOHaD: the impact of environmental hazards on the origins of current “pandemics”

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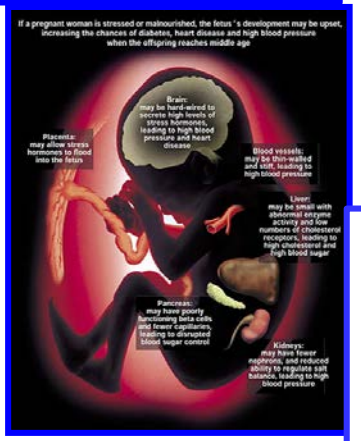
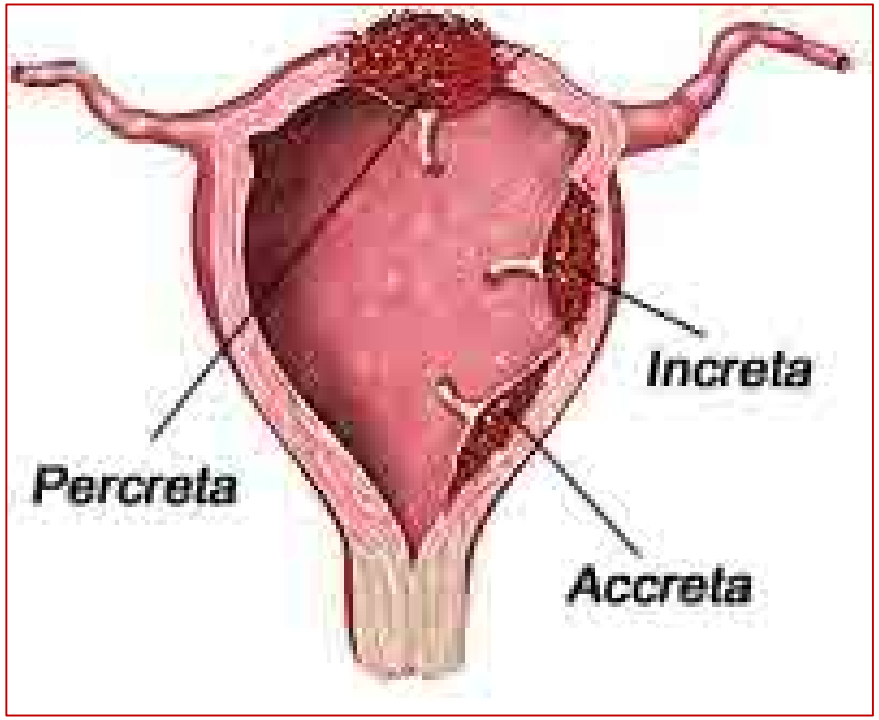



On sait depuis de nombreuses années que **le fetus n'est pas entièrement protégé dans le microenvironnement utérin**. **Mais seulement au cours de la dernière décennie** nous nous sommes concentrés sur **les mécanismes et les modalités de l'exposition maternelle et fœtale** à une gamme impressionnante de **produits chimiques (ex: perturbateurs endocriniens), physiques (ex: CEM) et biologiques** (ex: virus) capable **d'induire des changements épigénétiques potentiellement adaptatifs et prédictifs dans le génome embryo-fœtal, interférant ainsi avec la programmation des tissus et des organes de l'enfant de manière souvent irréversible.**

1

**Les altérations placentaires** sont de plus en plus fréquentes

Le ***placenta accreta*** est une insertion du placenta (fait de villosités) **dans le myomètre**.
On en distingue trois types **selon la profondeur d'insertion des villosités** dans le myomètre
- le ***placenta accreta*** proprement dit : les villosités sont en contact du myomètre et pénètrent plus ou moins profondément dans le myomètre ;
- le ***placenta increta*** : les **villosités envahissent le myomètre** ;
le ***placenta percreta*** : les villosités dépassent le myomètre, **envahissant parfois les organes voisins (vessie)…**




…c'est comme si **les mécanismes (immunologiques) de la tolérance materno-fœtale s'affaiblissaient**.
… il ne faut pas oublier que le placenta est en grande partie un **organe embryo-fœtal (que l'embryon produit pour se connecter à la mère…** certainement **pas pour l'envahir**)

**Choriocarcinoma**

***Le placenta est une "éponge" qui absorbe et accumule des traces de pesticides* présents dans la chaîne alimentaire.**

Malheureusement, ***100% des femmes enceintes logent dans leur placenta au moins un type de ces substances toxiques et cancérigènes*** maintenant **omniprésentes**

CORRIERE DELLA SERA.it

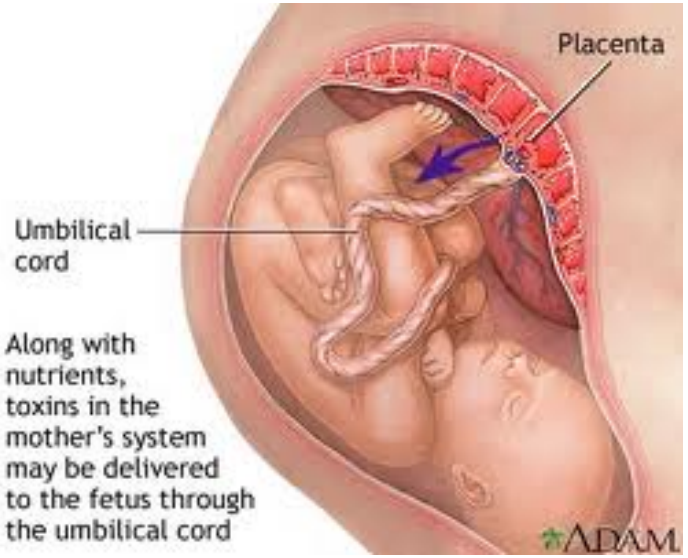
*16 maggio 2007*

Una ricerca dell'università di Granada su un campione di 308 partorienti

## I pesticidi preferiscono la placenta

***Fra le sostanze trovate più frequentemente nelle donne incinte un parente del Ddt e un composto di shampo antipidocchi***

La placenta delle donne incinte è una spugna che assorbe e accumula le tracce di pesticidi presenti nella catena alimentare. Purtroppo il 100% delle donne gravide ospita almeno un tipo di queste ormai onnipresenti sostanze tossiche e cancerogene.



https://cordis.europa.eu/result/rcn/84240_fr.html

Commissione europea

CORDIS

Servizio Comunitario di Informazione in materia di Ricerca e Sviluppo







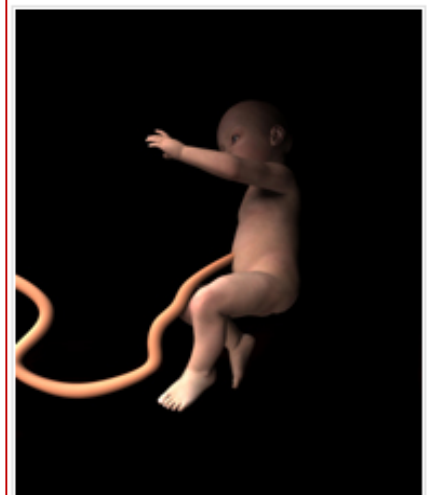
# PLUTOCRACY — Résultat en bref

Project ID: QLK4-CT-2000-00279
Financé au titre de: FP5-LIFE QUALITY

## Le placenta transmet les pesticides au fœtus

***L'incidence des allergies comme l'asthme a augmenté au cours des dernières décennies. Dans le cadre des efforts menés pour en trouver la raison, les scientifiques ont étudié le transport des composés chimiques à travers le placenta, du milieu environnant vers le fœtus.***

**Les scientifiques ont constaté que tous les xénobiotiques traversaient la barrière placentaire** par diffusion passive et atteignaient le fœtus, le DCB (dichlorobenzène) étant celui se diffusant le plus rapidement.
**Dans les principaux organes de fœtus, la concentration de certains de ces pesticides était plus élevée que dans les organes maternels** correspondants.
Notamment dans **le sang, la rate, la moelle osseuse, le cerveau et le foie.**
Les implications de cette recherche sont d'une grande portée car **l'accumulation de composés organochlorés dans les tissus fœtaux pourrait avoir une incidence sur le développement des systèmes immunitaire et nerveux** de l'enfant à naître.



LA GAZZETTA DEL MEZZOGIORNO.it

MARTEDÌ 20 FEBBRAIO 2018 | 16:16

# Il più grande siderurgico d'Europa.

Taranto è diventata la capitale dell'acciaio grazie al più grande stabilimento siderurgico d'Europa, ma ha pagato anche un prezzo altissimo sotto il profilo dell'inquinamento. Nei mesi scorsi una perizia medico-epidemiologica, compiuta nell'ambito di un procedimento giudiziario, per la prima volta ha certificato una correlazione tra emissioni nocive, malattie e morte. L'odierna Ilva era sino al 1995 l'Italsider di Stato, che arrivò ad

Taranto, partorisce mamma con «placenta accreta»

**Taranto est devenue la capitale de l'acier grâce à la plus grande aciérie d'Europe**, mais a également payé **un prix très élevé en termes de pollution. L'usine d'Ilva est presque deux fois plus grande que la ville de Tarente**. Ses dimensions énormes ont conditionné la relation entre l'usine et la ville. Pour le construire, des milliers d'oliviers ont été explantés et la mémoire historique de la zone proche du quartier Tamburi a été presque effacée ... Ces derniers mois, **un examen médico-épidémiologique réalisé dans le cadre d'une procédure judiciaire a permis d'établir une corrélation entre émissions nocives, maladies et mort ....**

Germana Carillo **INFORMARSI** **AMBIENTE** 19-09-2016

# A Taranto i bimbi continuano a morire di tumori. Il 30% in più si ammala di cancro

A Taranto, 30% d'enfants de plus que dans les autres villes tombent malades et meurent du cancer

Dominella Trunfio **INFORMARSI** **AMBIENTE** 09-12-2016

# Ilva di Taranto, nuovo allarme del ministero: "Rischi neurologici per i bambini"

A Taranto, la **nouvelle alarme du ministère: l'autisme augmente chez les enfants**

*Il dossier dell'Istituto superiore per la sanità pone l'accento su un altro rischio, dopo quello dei tumori. Il*

CHEMICAL FALL OUT

ENDOCRINE DISRUPTORS 1

2 HEAVY METALS

3 ULTRAFINE PARTICLES

The gift our mothers never wanted to give us

# BodyBurden

## The Pollution in Newborns

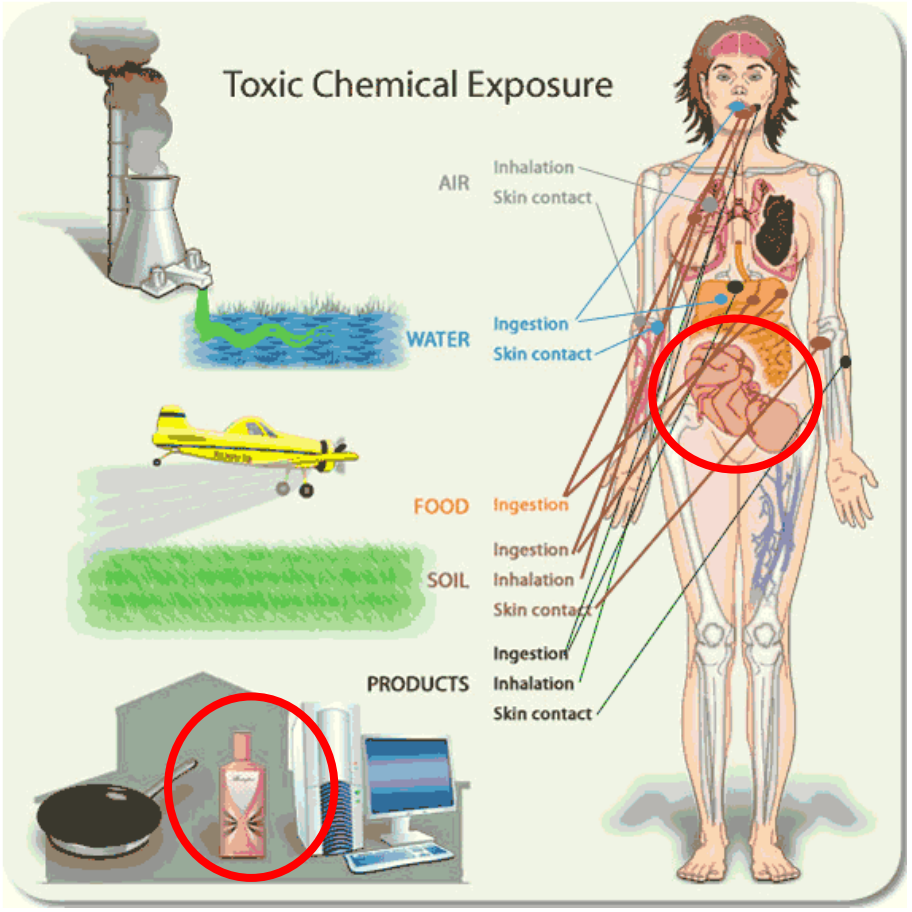
A benchmark investigation of industrial chemicals, pollutants, and pesticides in human umbilical cord blood

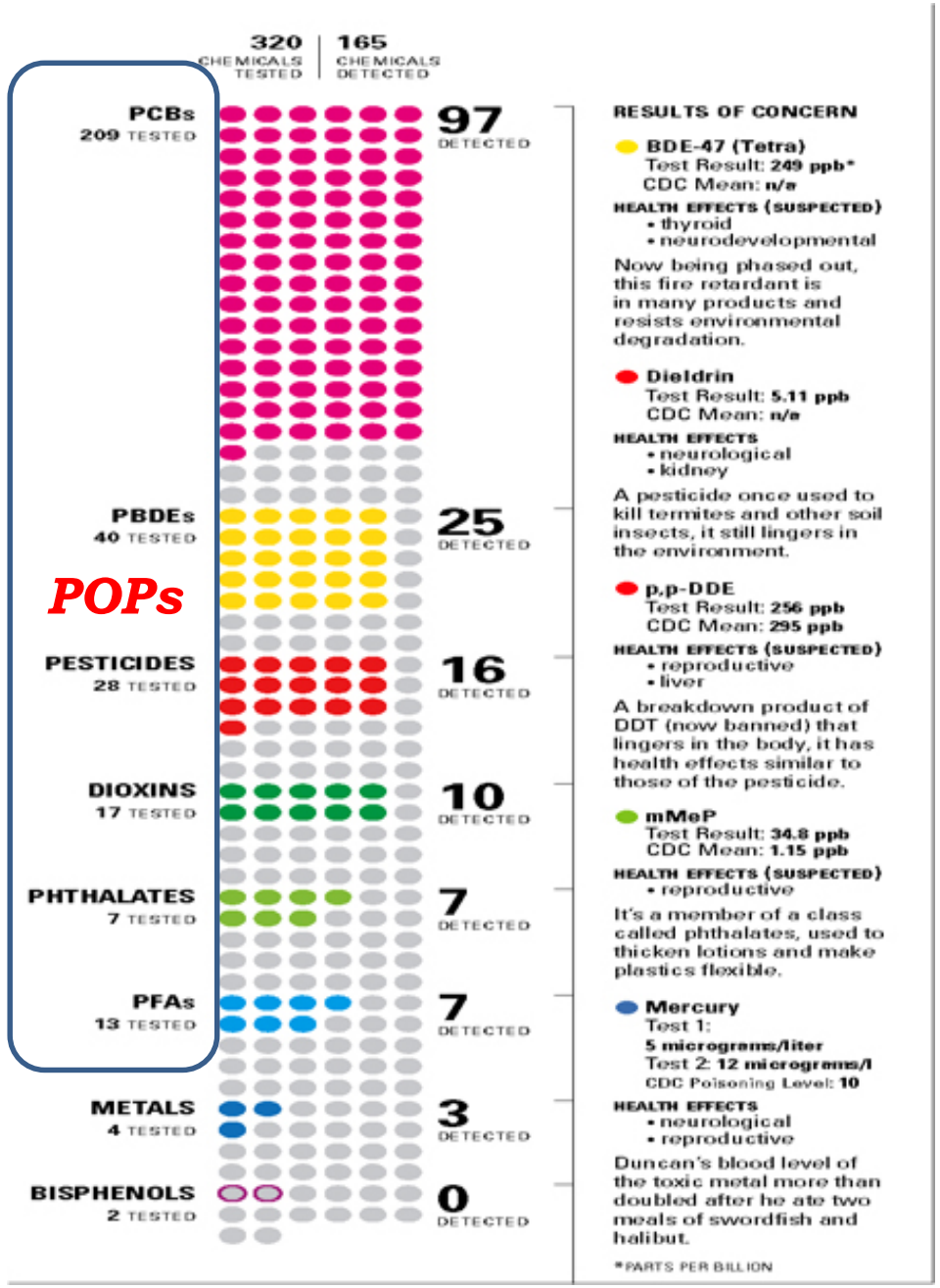
http://www.ewg.org/reports/generations/

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

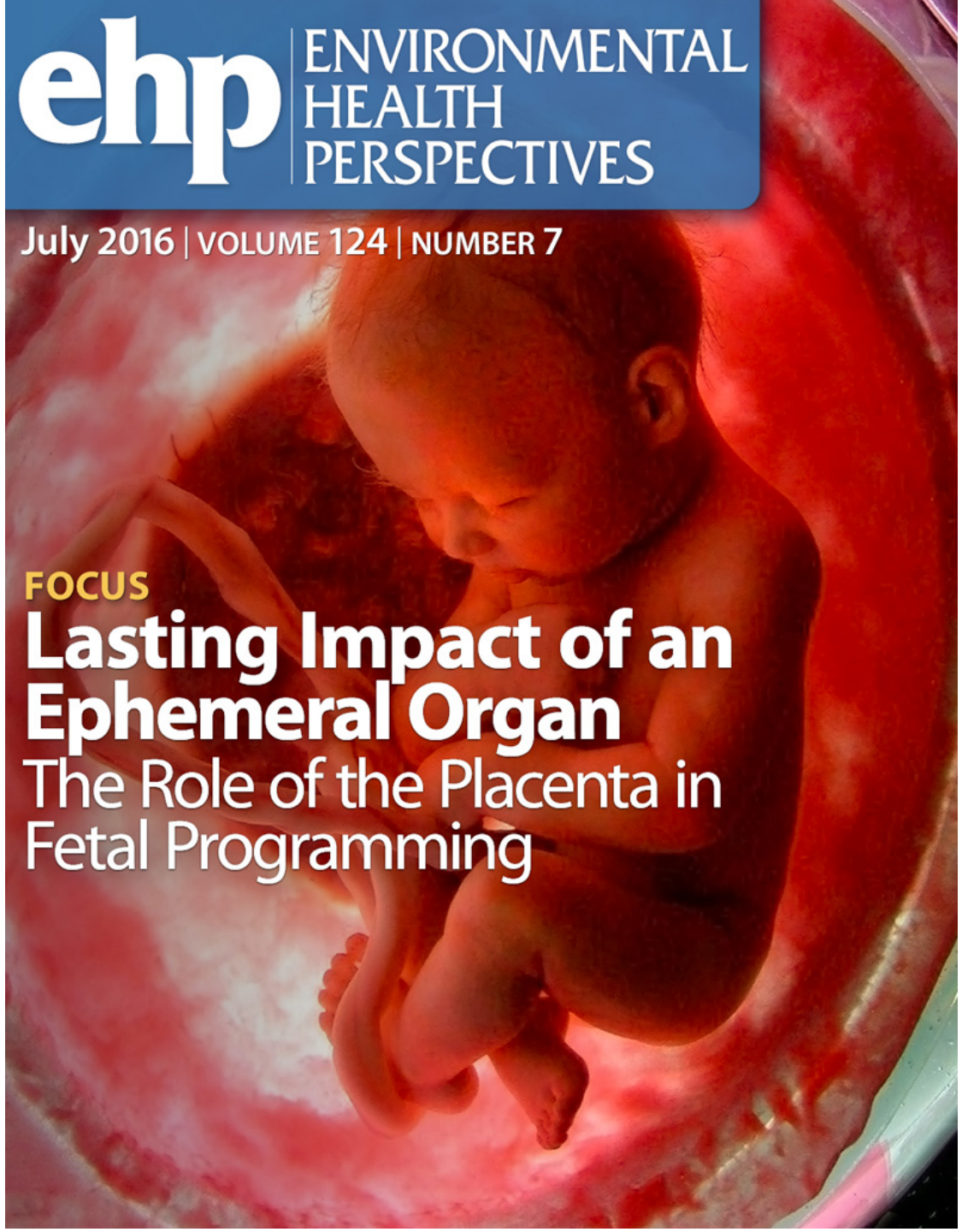
# Monitoring Body-Burdens

**> 700 different synthetic chemicals or heavy metals found in cord blood..**



Dans ce contexte, **l'organe qui acquiert une importance vraiment extraordinaire** est le **PLACENTA**: un organe qui a été **très peu étudié jusqu'à il y a quelques années** et qui émerge comme une sorte de "**salle de contrôle" pour la programmation (épigénétique) de différents tissus et organes foetaux**





Published in final edited form as:

*Am J Obstet Gynecol*. 2015 October ; 213(4 0): S14–S20. doi:10.1016/j.ajog.2015.08.030.

# THE PLACENTA IS THE CENTER OF THE CHRONIC DISEASE UNIVERSE

**Kent L. Thornburg**[1,2,3] and **Nicole Marshall**[2,3]

[1]Department of Medicine, School of Medicine, Oregon Health & Science University Portland, Oregon 97239

[2]Knight Cardiovascular Institute, Center for Developmental Health, School of Medicine, Oregon Health & Science University Portland, Oregon 97239

[3]Department of Obstetrics & Gynecology, Oregon Health & Science University Portland, Oregon 97239

## Abstract

Over the past quarter century it has become clear that adult onset chronic diseases like heart

| PROGRAMMA CCM 2017– PROGETTI ESECUTIVI IN ORDINE DECRESCENTE DI PUNTEGGIO DI VALUTAZIONE | | | | |
|---|---|---|---|---|
| **N.** | **TITOLO** | **ENTE PARTNER** | **ID** | **IMPORTO** |
| **1** | URBAN HEALTH: BUONE PRATICHE PER LA VALUTAZIONE DI IMPATTO SULLA SALUTE DEGLI INTERVENTI DI RIQUALIFICAZIONE E RIGENERAZIONE URBANA E AMBIENTALE | LOMBARDIA | 4 | € 450.000,00 |
| **2** | SCEGLIERE LE PRIORITÀ DI SALUTE E SELEZIONARE GLI INTERVENTI EFFICACI PER PREVENIRE IL CARICO DELLE MALATTIE CRONICHE NON TRASMISSIBILI | PIEMONTE | 6 | € 449.250,00 |
| **3** | SVILUPPO E VALIDAZIONE DI UN SISTEMA DI MONITORAGGIO EPIDEMIOLOGICO DELLE DEMENZE BASATO SUI DATI DEI SISTEMI INFORMATIVI SANITARI | CAMPANIA | 5 | € 450.000,00 |
| **4** | AMBIENTE, PROGRAMMAZIONE EPIGENETICA FETALE E PREVENZIONE DELLE PATOLOGIE CRONICHE | SARDEGNA | 9 | € 448.000,00 |

**Étude du placenta** (**Taranto**, Cagliari, Milano, Pisa):
- **Spectrométrie de masse** (IZS - Bologna)
- **immunohistochimie** (Université de Cagliari)
- **épigénétique** (Université de Pise)
- **mitochondries** (Université de Milan)
- **métabolomique** (Université de Cagliari)

**Follow-up des enfants à risque** (FIMP):
- **diagnostic précoce !!**
- **traitement personnalisé !!**

L'INSERM définit aujourd'hui **différents stades de prématurité** :

faiblement prématurés (de 35 à 37 SA),

modérément prématurés (de 32 à 34 SA),

**grands prématurés (de 27 à 31 SA),**

**extrêmes prématurés (de 22 à 26 SA)**

2

**… encore plus fréquente c'est la prématurité** (aujourd'hui **un enfant sur 10** naît prématurément ... ce qui représente une **augmentation de 30%** au cours des 35 dernières années….) qui est **un autre symptôme d'intolérance materno-fœtale** (qui ne devrait pas être sous-estimé)

## Épidémiologie [ modifier | modifier le code ]

En 2012, plus d'un bébé sur dix naît prématurément dans le monde[5] sans évidence de décroissance avec le temps[6].

Les naissances prématurées concernent 11 à 13 % des naissances aux États-Unis, soit près du double du taux des autres pays industrialisés et une augmentation de 30 % par rapport à 1981[7]. Plus du quart des décès néonataux seraient la conséquence de la prématurité[8].

Les données sont probablement assez solides et permettent d'avoir aujourd'hui un aperçu évolutif concernant les trois dernières décennies en France.

**Évolution des taux d'incidence de la prématurité en France**

| | 1972 | 1981 | 1988 | 1995 | 2003 |
|---|---|---|---|---|---|
| **Très grande prématurité (de 22 à 27 SA)** | - | - | - | 0,4 % | 0,5 % |
| **Grande prématurité (de 28 à 32 SA)** | 1,3 % | - | 1 % | 1,2 % | 1,3 % |
| **Prématurité (de 33 à 37 SA)** | 8,2 % | 5,7 % | 4,8 % | 5,9 % | 7,2 % |

L'incidence est donc en augmentation, ce que confirme les chiffres d'autres pays, en particulier américains[7].

OXFORD ACADEMIC

American Journal of Epidemiology


Volume 179, Issue 5

1 March 2014

# Chlordecone Exposure, Length of Gestation, and Risk of Preterm Birth FREE

Philippe Kadhel ✉, Christine Monfort, Nathalie Costet, Florence Rouget, Jean-Pierre Thomé, Luc Multigner, Sylvaine Cordier

*American Journal of Epidemiology*, Volume 179, Issue 5, 1 March 2014, Pages 536–544, https://doi.org/10.1093/aje/kwt313

**Le chlordécone est un pesticide organochloré qui a été largement utilisé …dans les Antilles françaises. Les données de l'étude de cohorte mère-enfant Timoun réalisée en Guadeloupe entre 2004 et 2007** ont permis d'examiner les **associations de concentrations de chlordécone dans le plasma maternel avec la durée de gestation et le taux de prématurité chez 818 femmes enceintes…Une augmentation de 1-log10 de la concentration de chlordécone a été associée à une diminution de la durée de gestation (-0,27 semaines, intervalle de confiance à 95%: -0,50, -0,03) et à un risque accru d'accouchement prématuré (60%; 130).** …Ces résultats sont pertinents pour la santé publique en raison de la persistance prolongée du chlordécone dans l'environnement et du **taux élevé de naissances prématurées dans cette population.**

Mais surtout, il est de plus en plus évident que **les conséquences les plus graves de la souffrance embryofoetale d'un enfant s'observent après des décennies (et parfois seulement dans les générations suivantes)**

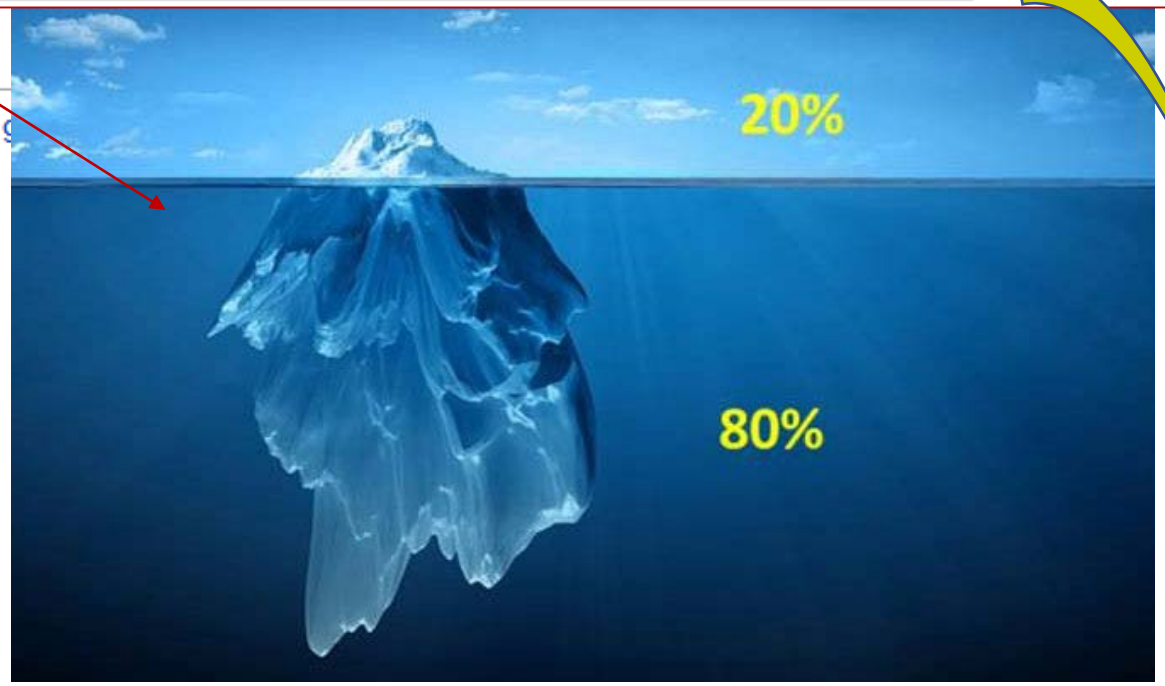
## Conséquences à long terme

(reconnaissables dans les premières années de la vie)

Le tableau ci-dessous offre une vision gl

**Données générales chez les nourrissons de moins de 32 SA et/ou moins de 1 500 g (en %)**

| | Séquelles majeures | Séquelles mineures | Total |
|---|---|---|---|
| **Psychomotrices** | 17 | 28 | 45 |
| **Visuelles** | 2 | 26 | 28 |
| **Respiratoires** | 1 | 26 | 27 |
| **Langage** | 20 | 20 | 40 |
| **Auditive** | 2 | 4 | 6 |




Les données de l'étude épidémiologique française ÉPIPAGE sur les petits âges gestationnels permettent de déceler un lien évident entre la survenue d'un handicap et l'importanc de la prématurité. Près de 40 % des grands prématurés présentent des séquelles - troubles moteurs, sensoriels ou cognitifs - à l'âge de 5 ans, sévères dans 5 % des cas, modérées pour 9 % des enfants, légères pour les autres[22]. Ces données sont cohérentes avec celles issues d'autres études d'autres pays[23].

**The Barker Hypothesis**

**Fetal Origins of Adult Disease**

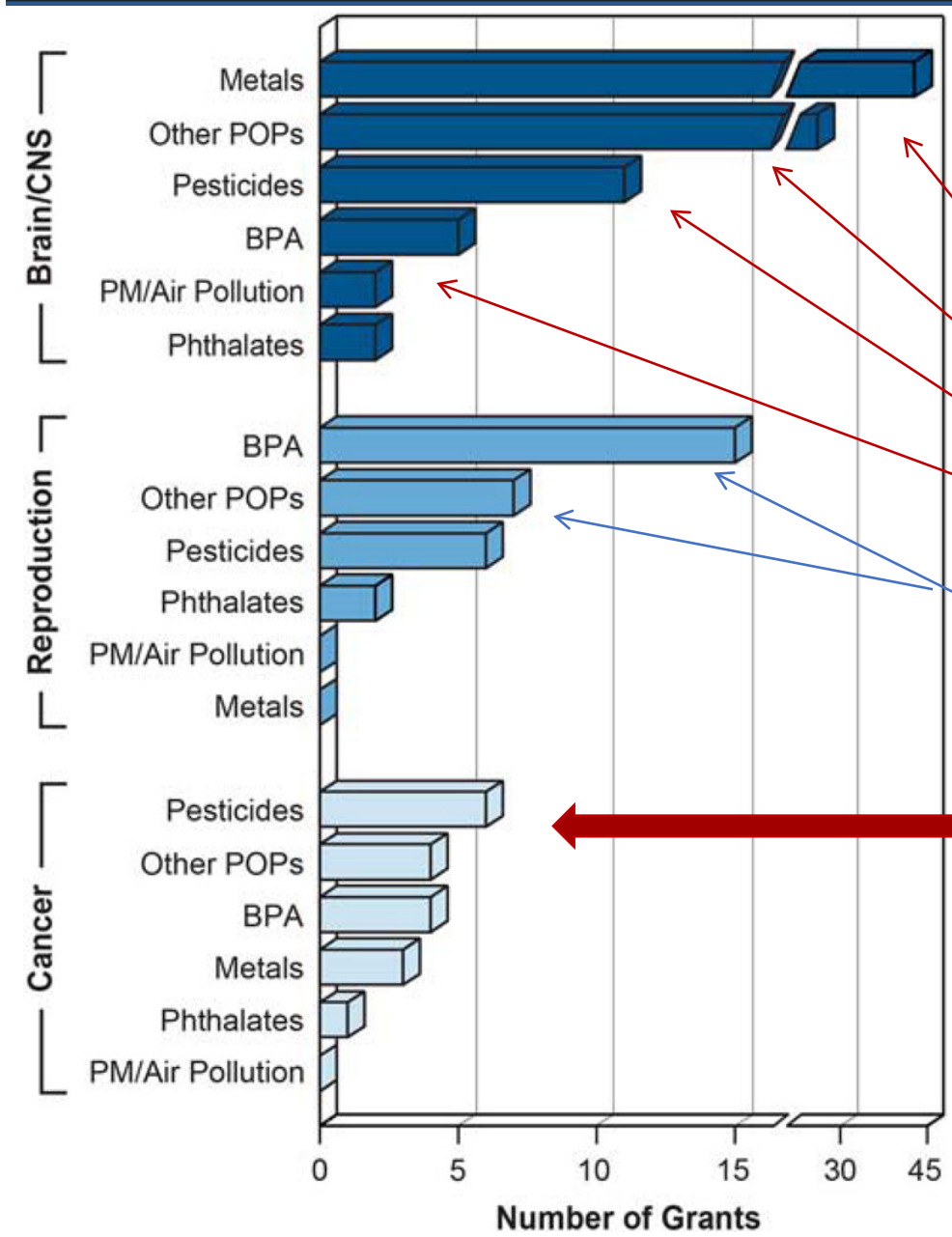
Adverse intrauterine events permanently "program" postnatal structure/function/homeostasis

⬇

"Adapted Birth Phenotype"

* Better chance of fetal survival
* Increased risk of adult disease

(Les **événements indésirables intra-utérins programment en permanence la structure, les fonctions et l'homéostasie des organes et des tissus** → **DOHaD theory**)





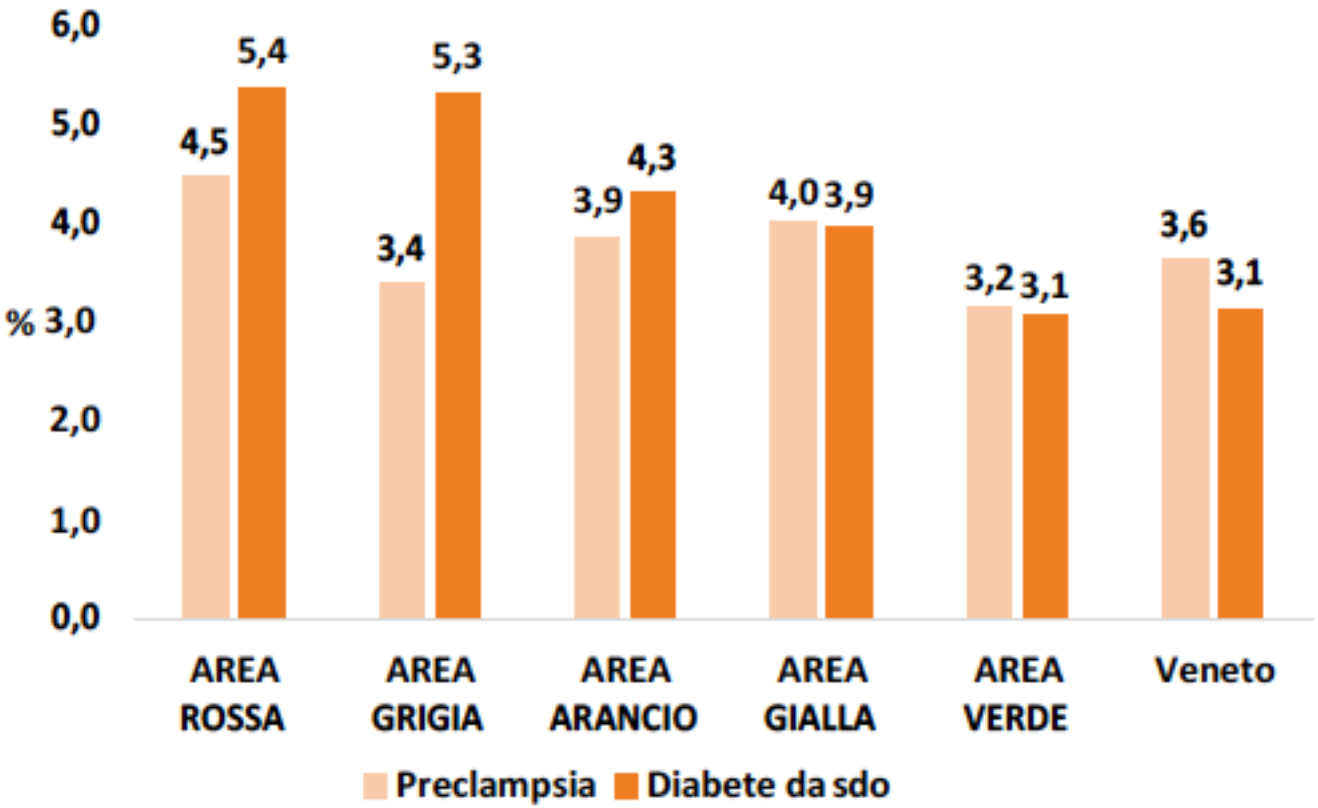
Most studied **disease/organ endpoints** and associated **toxicity endpoints**.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4393755/figure/F3/

# Studio sugli esiti materni e neonatali in relazione alla contaminazione da sostanze perfluoroalchiliche (Pfas)

*A cura del Registro Nascita – Coordinamento Malattie Rare Regione Veneto*

Indagando, attraverso le SDO, la presenza di specifiche patologie emerge invece che le madri dell'area rossa hanno un rischio più elevato di preclampsia (4,46% vs 3,6%) e di diabete gestazionale (5,35% vs 3,13%), maggiore del Veneto nell'insieme, ma anche di tutte le altre aree se considerate separatamente (tabella 11



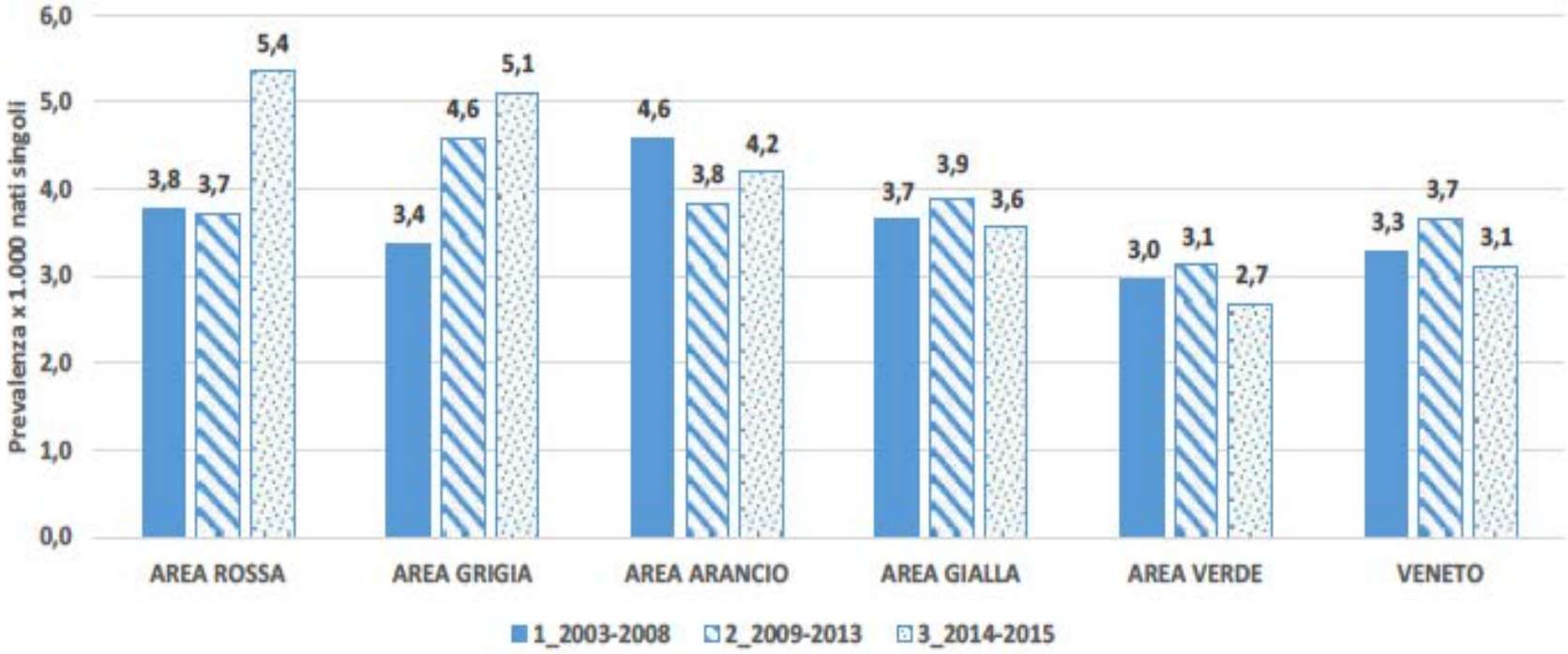

Vincenzo Cordiano
Vincenzo Cordiano

## Studio sugli esiti materni e neonatali in relazione alla contaminazione da sostanze perfluoroalchiliche (Pfas)

*A cura del Registro Nascita – Coordinamento Malattie Rare Regione Veneto*

Analizzando i bassissimi pesi (<1000 grammi), spicca la crescita in area rossa registrata nel periodo 2014-2015 (5,4% vs 3,1%), come illustrato nella figura sottostante (Figura 8 allegato).

**Prevalenza di nati singoli con peso <1.000 grammi per periodo e area.**



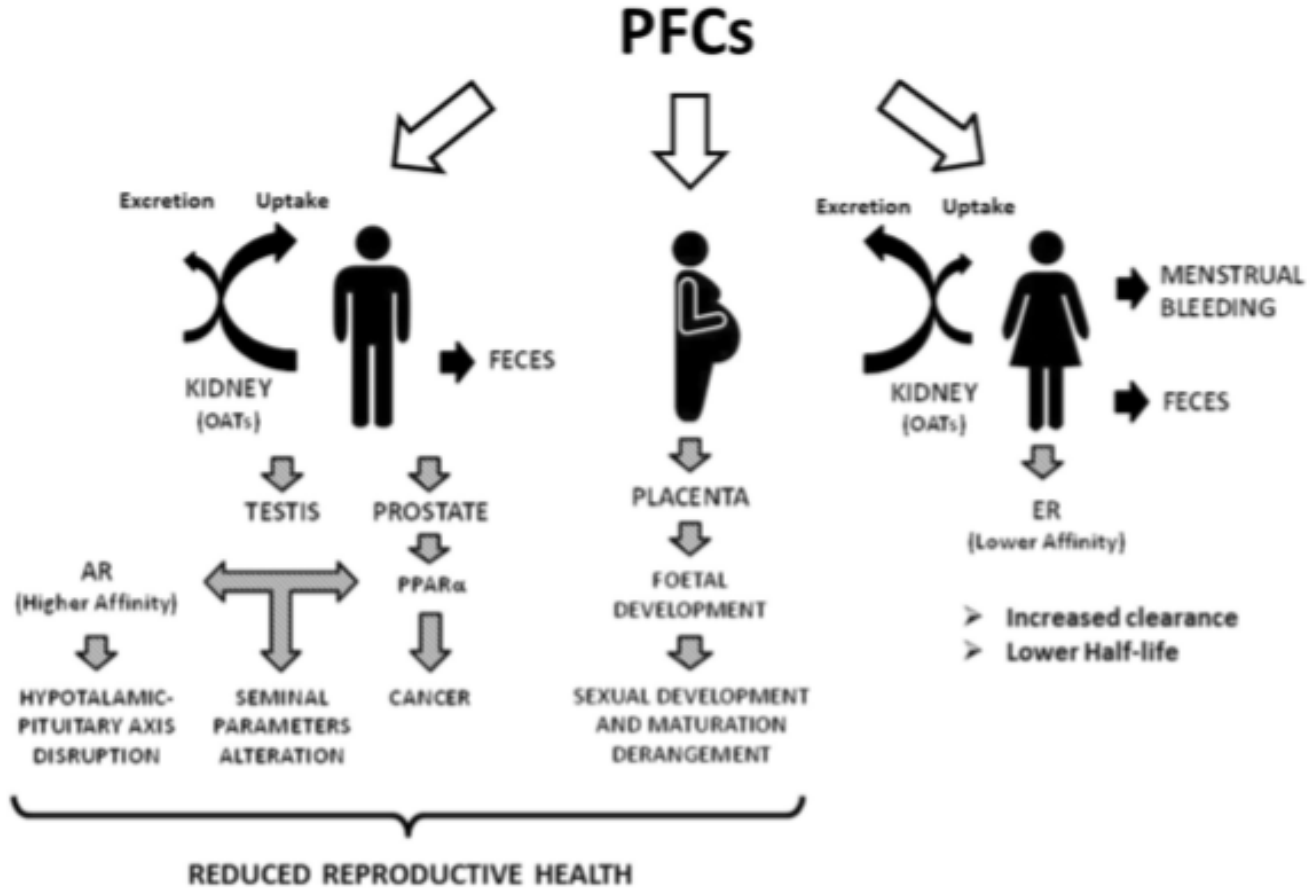

Vincenzo Cordiano

Analizzando per singoli apparati, spicca, nell'area rossa (Tabelle 17, 19 allegato), una prevalenza più elevata per le anomalie del sistema nervoso (5,1‰ vs 3,6‰), attuale campo di indagine tra i ricercatori, del sistema circolatorio (1,0‰ vs 0,6‰) e per le anomalie cromosomiche (2,2‰ vs 1,6‰).

# Impact of perfluorochemicals on human health and reproduction: a male's perspective

C. Foresta[1] · S. Tescari[1] · A. Di Nisio[1]

Journal of Endocrinological Investigation
https://doi.org/10.1007/s40618-017-0790-z



www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2015;4(2):e040237
doi: 10.7363/040237
Received: 2015 Sept 21; accepted: 2015 Oct 10; published online: 2015 Oct 26

Editorial

# Environment and fetal programming: the origins of some current "pandemics"

**Ernesto Burgio**

ECERI – European Cancer and Environment Institute, Bruxelles, Belgium

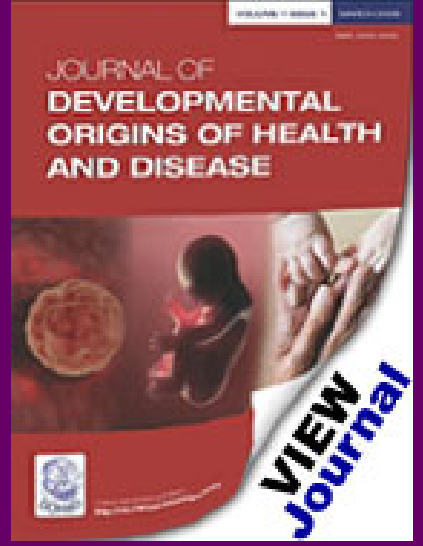
ISDE – International Society of Doctors for Environment (Scientific Office), Arezzo, Italy

*"The womb may be more important than the home"*
David Barker

This new paradigm is important not only to explain in a more exhaustive way the embryo-foetal origins of all the above mentioned disorders and their dramatic increase over the last decades, but also to try to effectively face this epidemiological transition. The key-term in this context is certainly primary prevention: only by reducing the maternal-foetal factors of distress and the exposure of the foetus (and of its gametes) to pollutants, it would be possible to protect the correct programming of cells, tissues and organs.

The key-term in this context is certainly ***primary prevention***

Finalement, **au cours des dernières années la Barker Hypothesis a été transformée**
a partir d'une théorie utile pour expliquer l'origine de certaines maladies de l'âge adulte,
**dans la théorie-clé des origines embryo-fœtales des maladies chroniques (DOHA-Developmental Origins of Health and Maladies)**




*Obesogens*

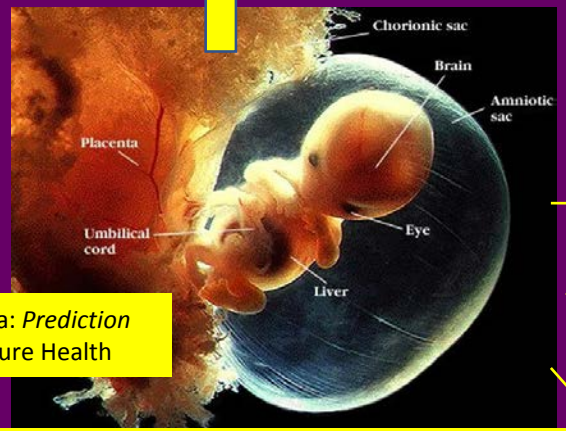
*Multiorgan Effects of Endocrine Disruptors*

*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**

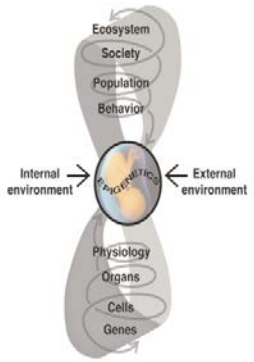
**DOHAD**

**Neurobehavioral Deficits and Diseases**

**Psychiatric Diseases**

# The 7 keywords: from genetics to *epigenetics*

3




## *Fetal programming*

the capability and, at the same time, the necessity for embryo-foetal cells **to define their epigenetic setting in a *predictive* and *adaptive* way …**

2

## *Environment*

The ***environment*** should be considered as a **continuous flow of information** coming from outside and reaching the epigenome, **causing it to activate and to continuously change** its molecular **three-dimensional structure (Chromatin)**


1

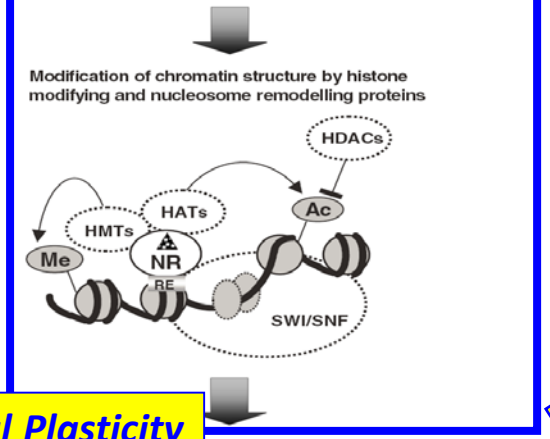
## *From Genetics to Epigenetics*

**the controlling *software*** of the genome

## *Ontogeny**

4

## *Developmental Plasticity*

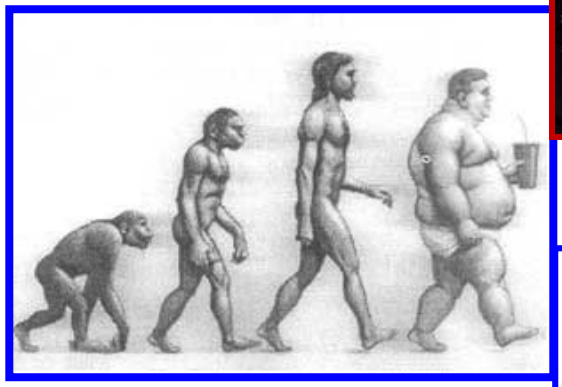


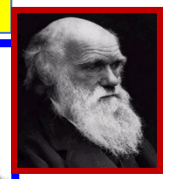

## *Phylogeny**

## *Evolutionary Medicine*

5

## *Devo → Evo*

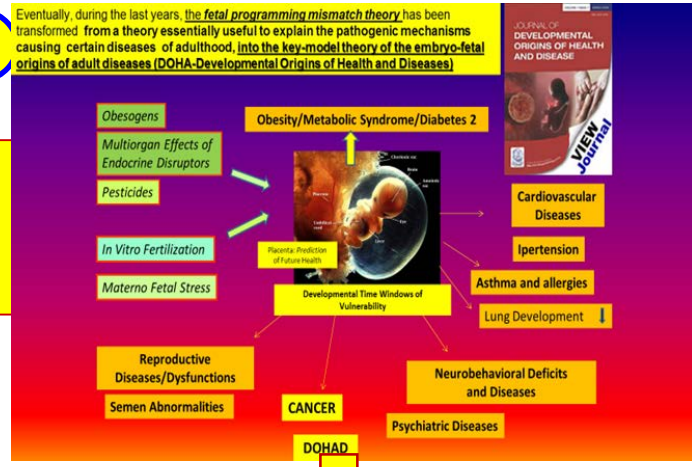




According to a **Neo-*Lamarckian paradigm***, the **environment not only selects, but also actively induces the main changes that shape the evolution of living beings** ..

## *Epi-genetic Mismatch DOHA*

6

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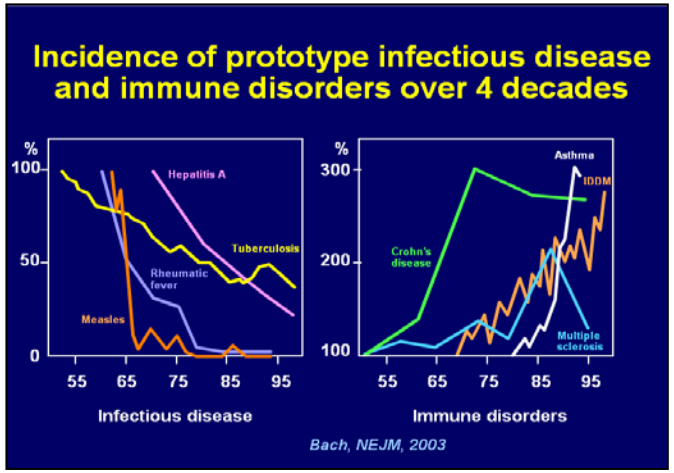



## *XXI Century Epidemiological Transition*

**Towards a paradigm shift in biomedicine.**
**Environmental interference with the human (epi)genome**

# Towards a *paradigm shift* in biomedicine…

BioEssays Vol. 18 no. 9
© ICSU Press 1996 pp. 695–696 BIO1029

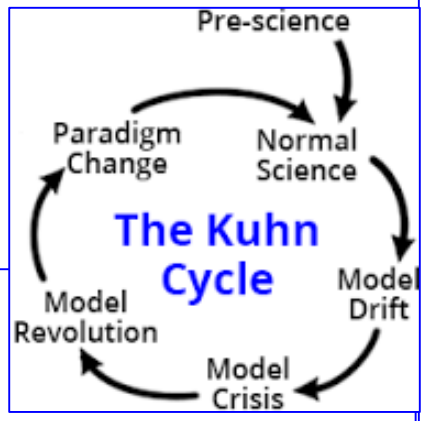
## Are there 'Kuhnian' revolutions in biology?

**Adam S. Wilkins**

The recent death, on 17 June 1996, of the noted philosopher of science, Thomas Kuhn, at age 73, provides a suitable occasion to remember and commemorate his contributions to the philosophy of science. It also provides an appropriate moment to ask how well the Kuhnian idea of scientific revolutions, which was developed principally from study of the physical sciences, applies to biology.

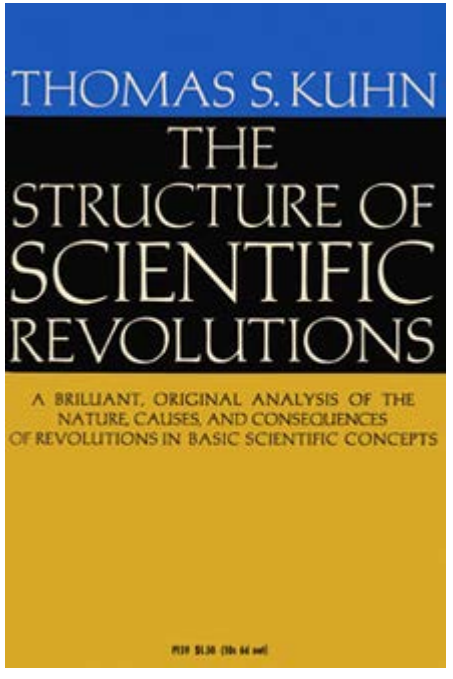
Kuhn, a professor emeritus at MIT in recent years, had written or coauthored five books and numerous scholarly articles, but he is undoubtedly best known, and will be best remembered, for *The Structure of Scientific Revolutions*[1], first published in 1962. In this seminal work, Kuhn argued persuasively against the traditional idea of 'scientific progress', the notion that scientific knowledge involves the steady growth of understanding through the application of something called 'The Scientific Method'. He argued that, in reality, science involves two distinctly different processes. For the most part, scientists work within certain conceptual frameworks or models, 'paradigms'. This work serves to embellish and strengthen the central paradigm at the heart of each field and is essentially conservative in nature. Kuhn termed such activities 'normal science'. Yet, the continued practice of normal science within a field often shows up weaknesses in the central paradigm. When these weakdigms' and the like. The notion that what scientists believe at any one time is determined in part by group consensus – in some corridors, there were mutterings that the idea involved little more than 'mob rule' in deciding scientific truth, a notion vehemently denied by Kuhn himself[3] – was unsettling. Furthermore, the neurological implications – that young brains are much more likely to generate and be receptive to major conceptual breakthroughs – though not new, could not have been comforting to those past their first youth. Nevertheless, the impact of Kuhn's idea was immediate and pervasive. It would not be inappropriate to refer to the 'Kuhnian revolution' in the philosophy of science.

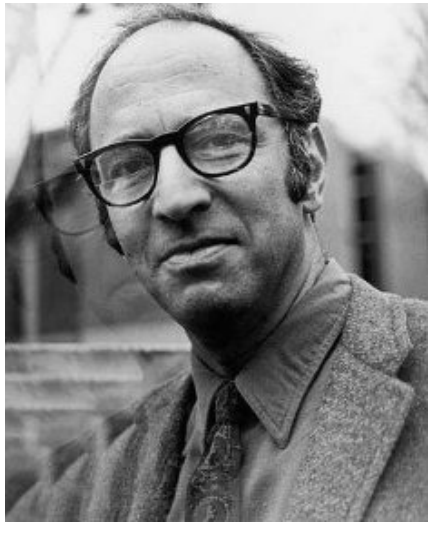
The question of generality, however, still nags. In contrast to many earlier, *a priori*, philosophical theories of knowledge, Kuhn built his case from examples, in effect inductively. (Kuhn's ideas co-exist uneasily today with those of Karl Popper, an arch-foe of argument from induction; it is, in fact, impossible to be both a Kuhnian and a Popperian, at least at the same instant.) Kuhn's primary examples were all drawn from physics and chemistry – Kuhn had taken his bachelor's degree in physics – and involved some of the classic discoveries in those sciences: the Copernican, Newtonian and Einsteinian revolutions and Lavoisier's disproof of the phlogiston theory.




In a **seminal article** published on *Bioessays* in 1996, **Adam WIlkins** wondered why in the twentieth century ***theoretical physics*** had faced its ***Kuhnian Revolution*** (from the *Newtonian model* to *quantum mechanics* and the *theory of relativity*) whereas **biology** (by definition the science of *complexity*) had **not yet experienced its *paradigm shift*** …

.. I will try to show that **the twenty-first will be the century of the *Kuhnian Revolution* in biology, evolutionary biology and biomedicine** and that the keywords are: ***epigenome / epigenetics, microbiome / metagenomics / hologenomics, DOHaD / fetal programming, stress-induced/epigenetically modulated evolution …***



**Towards a Kuhnian Revolution in Biology**

nature biotechnology

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COMMENTARY

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.

2

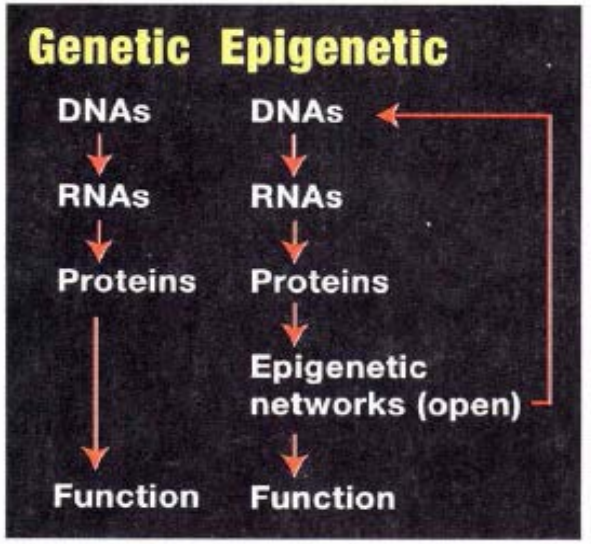



Figure 1. Genetic and epigenetic theories of information processing.

1

In 1997 the well known molecular biologist **R. Strohman** attempted an oblique **attack against the *central dogma* of molecular biology**; the **deterministic, linear, uni-directional pathway from DNA to RNA to proteins to phenotype..**

3

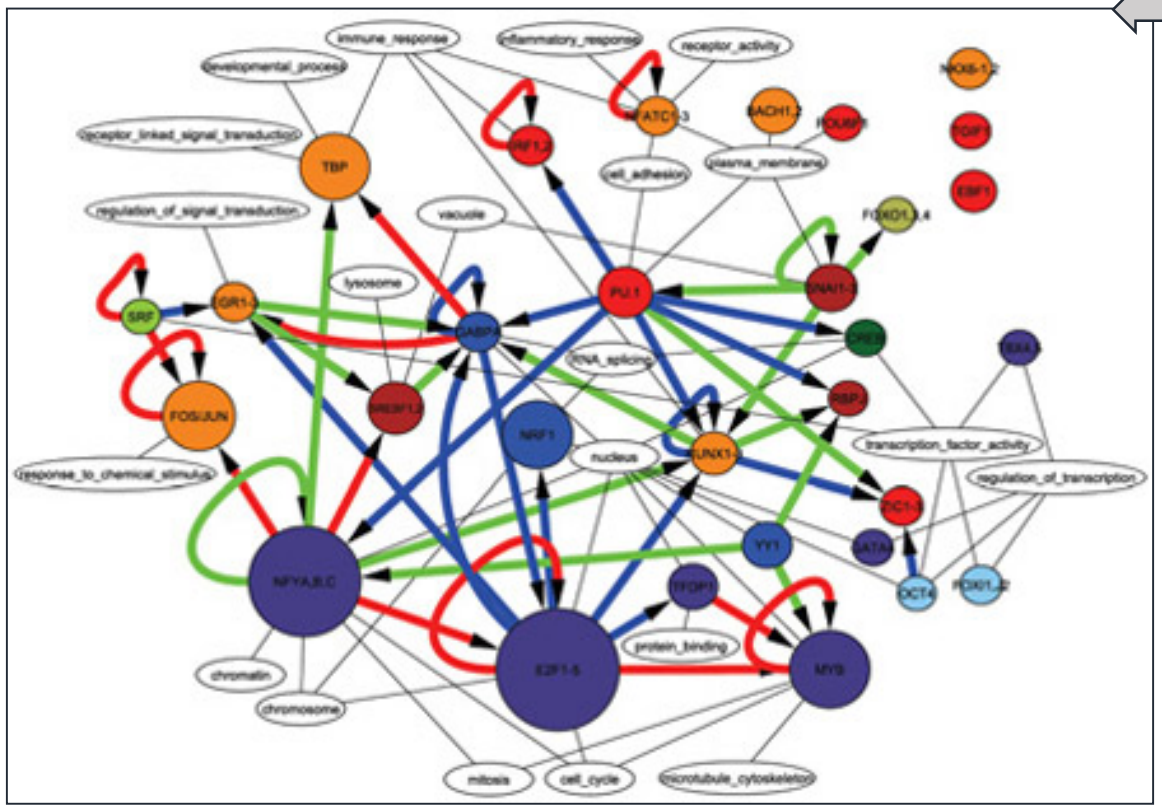
We have **wrongly extended the linear theory of the gene** to the "realm" of the gene management... but the **gene management is an entirely different process,** involving **interactive cellular processes that display an interactive complexity... which is epigenetic in nature**

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 dynamic molecular Network** of ***interacting Genes*** and ***non-codifying sequences.***. and ***proteins***

***….Genes Know How to Network…BUT…***



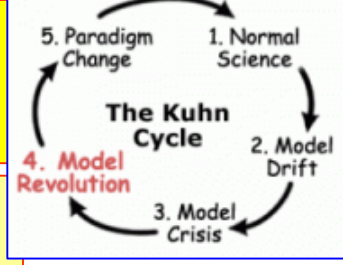

http://news.sciencemag.org/sciencenow/2009/04/21-03.html

**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**

Strohman R. , April 2001 Beyond genetic determinism

Nous nous trouvons actuellement face
à une véritable **révolution conceptuelle** en biomédecine




Depuis 50 ans il est convenu de considérer l'**ADN comme le code/projet fondamental** de la **construction de notre phénotype.**

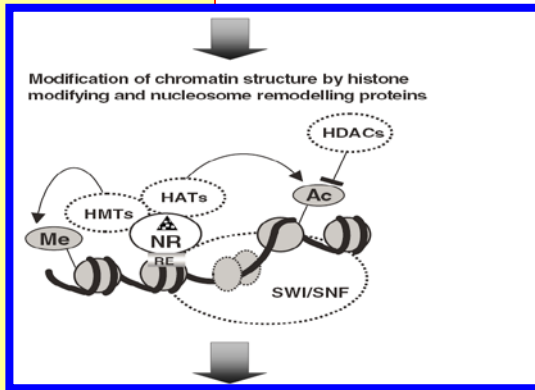
Depuis une dizaine d'années et surtout dès l'apparition des **premières études d'épigénétique moléculaire,** on a commencé à comprendre

que la construction du phénotype est le **résultat de l'interaction** des **informations provenant de l'environnement**

sur les informations contenues dans l'**ADN**

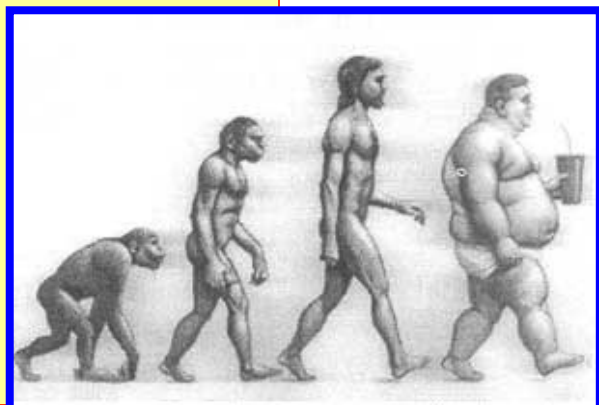
grâce a un véritable ***réseau moléculaire*** qui entoure

l'ADN et qui constitue l'***épigénome***




En conséquence on pourrait affirmer qu'il n y a **aucun changement stable de notre phénotype** (aussi bien physiologique que pathologique) qui ne soit à la fois

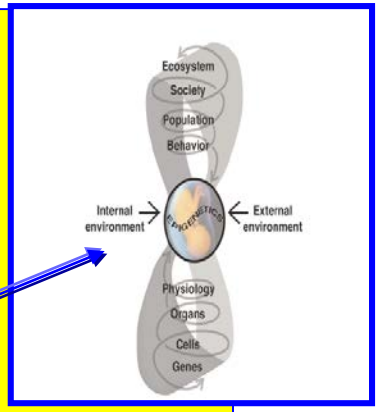
- **induit** par l'***environnement***
- **modulé** par l'***épigénome***
- **conditionné** par l'***ADN***



Les **autres concepts-clés** (par ailleurs **interdépendants**) sont :

- celui de plasticité développementale (***developmental plasticity***)
- celui de programmation fœtale (***fetal programming***)

qui nous permettent de comprendre comment dans cette période **le fœtus programme épigénétiquement (pour la vie) toutes ses cellules d'une façon prédictive et adaptative en réponse aux informations** qui lui arrivent de l'environnement (par le **biais maternel**)




Il est important de souligner que dans cette période **des informations incorrectes (*polluants, perturbateurs endocriniens*..)** et/ou des **discordances (*mismatch*)** entre l'information que l'enfant reçoit avant et après la naissance

peuvent **induire une mauvaise programmation des cellules (y compris les gamètes)** et, par là,

**provoquer des maladies chroniques à l'âge adulte ou même chez les générations suivantes**

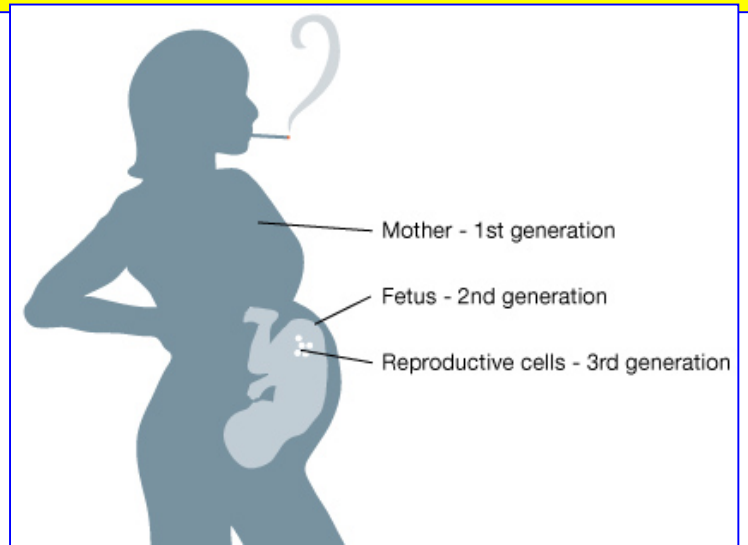
Cette théorie des ***origines développementales*** de la santé et des maladies chroniques (***DOHaD pour Developmental Origins of Health and Diseases***) peut nous aider à expliquer la ***transition épidémiologique actuelle*** ..

Mais les **découvertes  les plus importantes** et capables d'imposer une **révision radicale du modèle** dominant

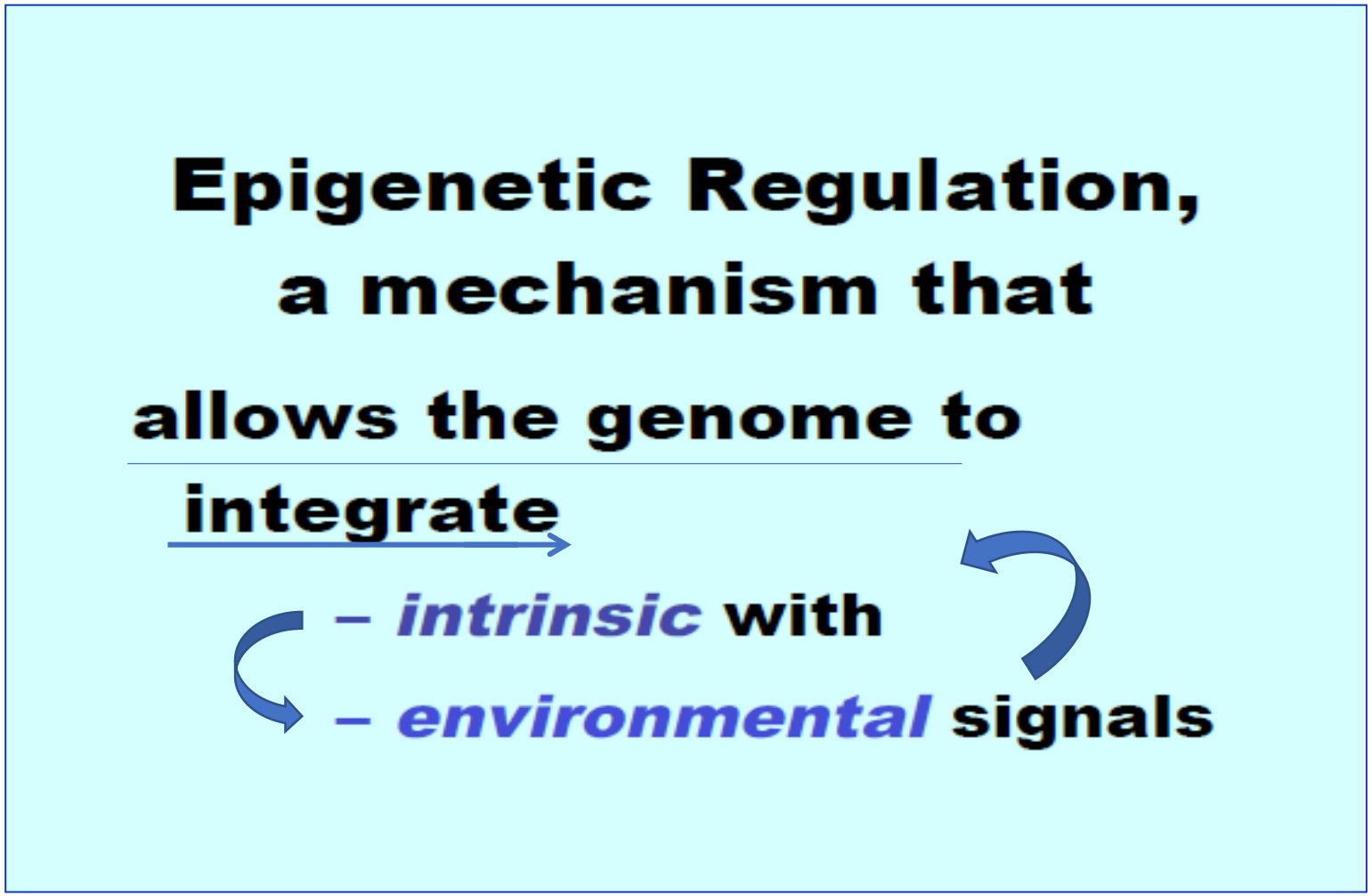
- à la fois dans le domaine ***bio-médical***
- et ***biologique*** (***modèle néodarwinien***)

concernent les **mécanismes *épigénétiques* de transmission transgénérationnelle des caractères acquis** sous forme de

modifications **d'adaptation ciblée du génome des gamètes** sur la base des **informations** provenant des parents (et probablement transmises aux gamètes par des ***microRNAs*** ou des ***exosomes***)



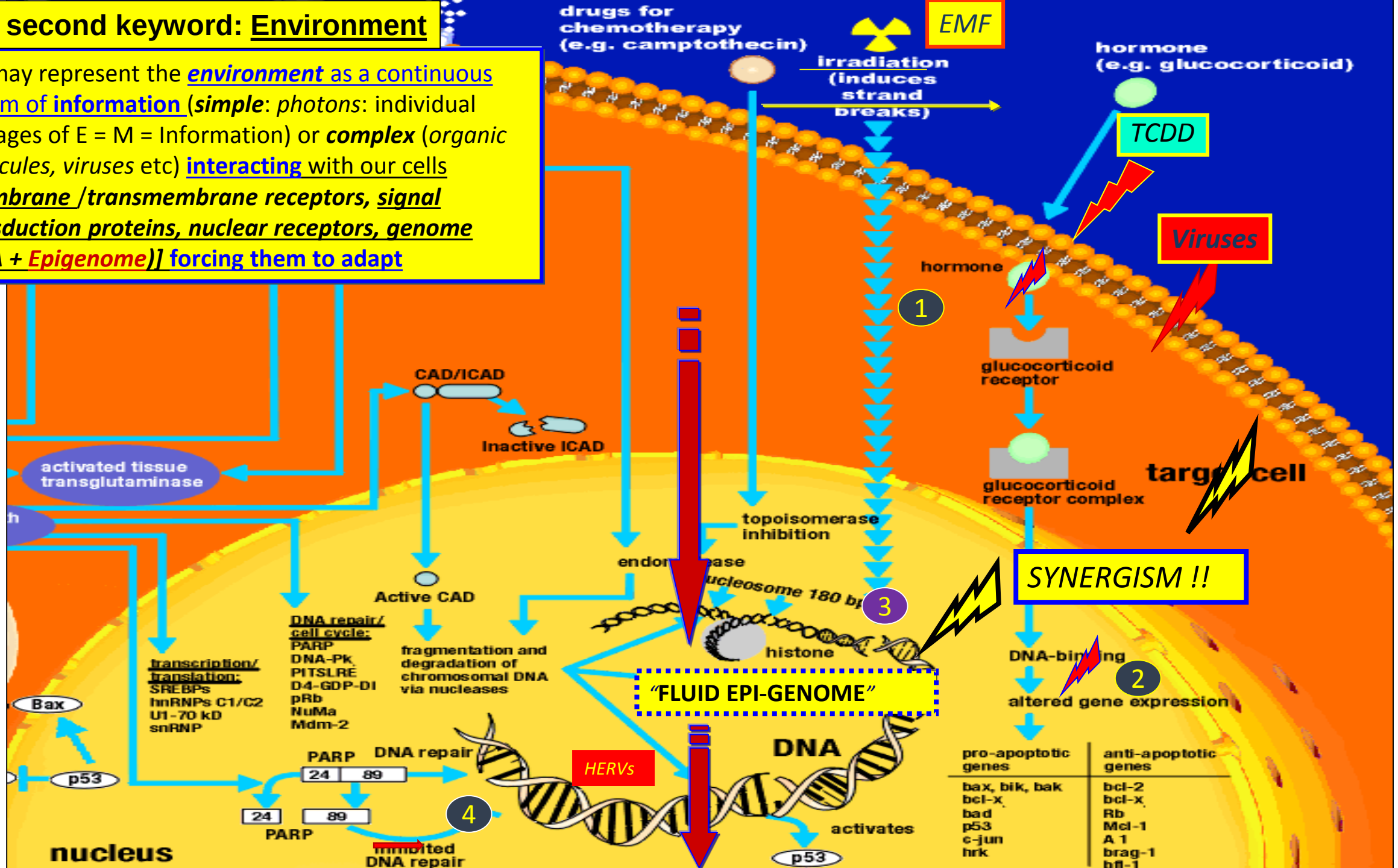

In such a **fluid and systemic model** the ***epigenome*** (also defined by some scientists as **the controlling *software*** of the genome) behaves as a sort of *compensation chamber* - the specific place where the flow of **information** that comes from outside (*environment* and *microenvironment*)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




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

# 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

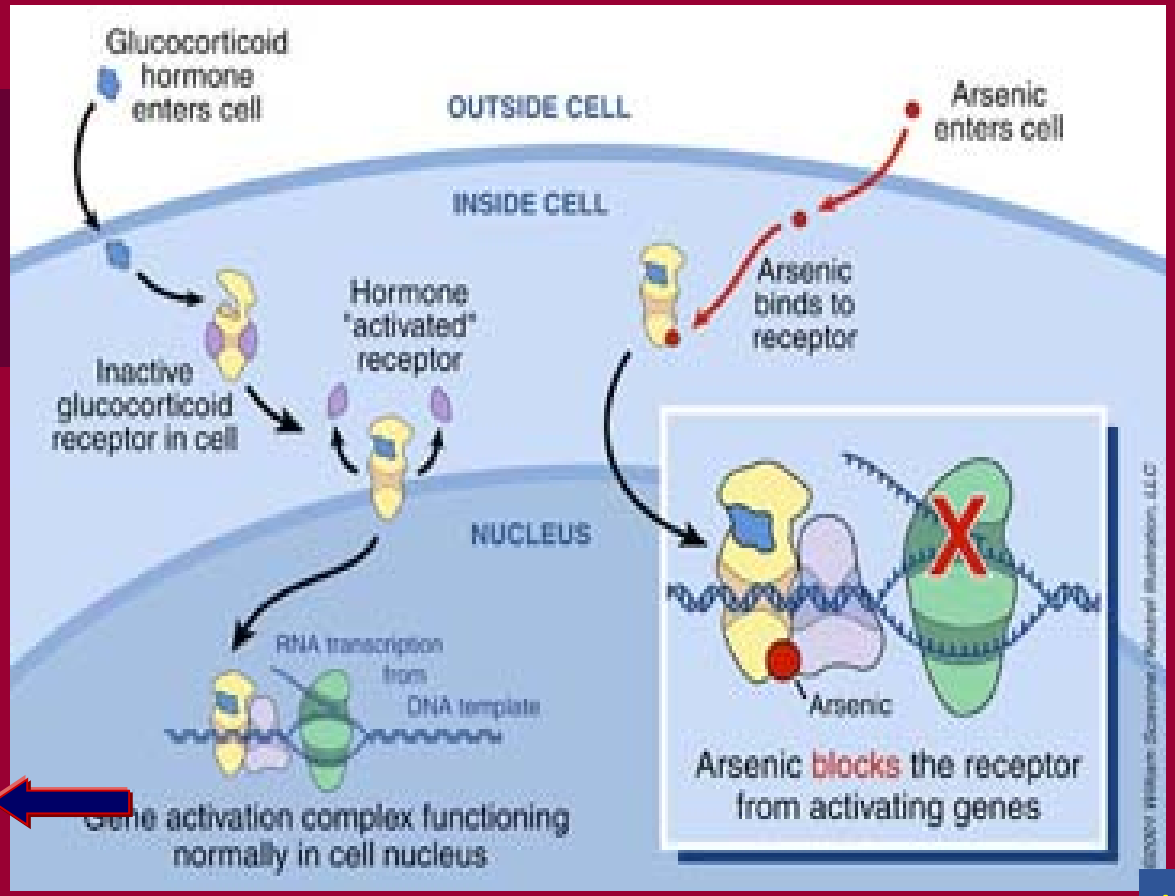
At high levels… arsenic kills people

**At moderately low levels… it causes a range of diseases**

**At truly low levels …**
**it interferes with gene activation, changing the epigenetic program**

**Many of these pollutants** (***EDCs, Heavy Metals, Polycyclic aromatic hydrocarbons (PAHs)***) are **mutagens or epi-mutagens, carcinogens or co-carcinogens** at **infinitesimal doses**,

It is universally known that their **dangerousness** is linked to **daily exposure to very-small doses** rather than to **massive exposure**

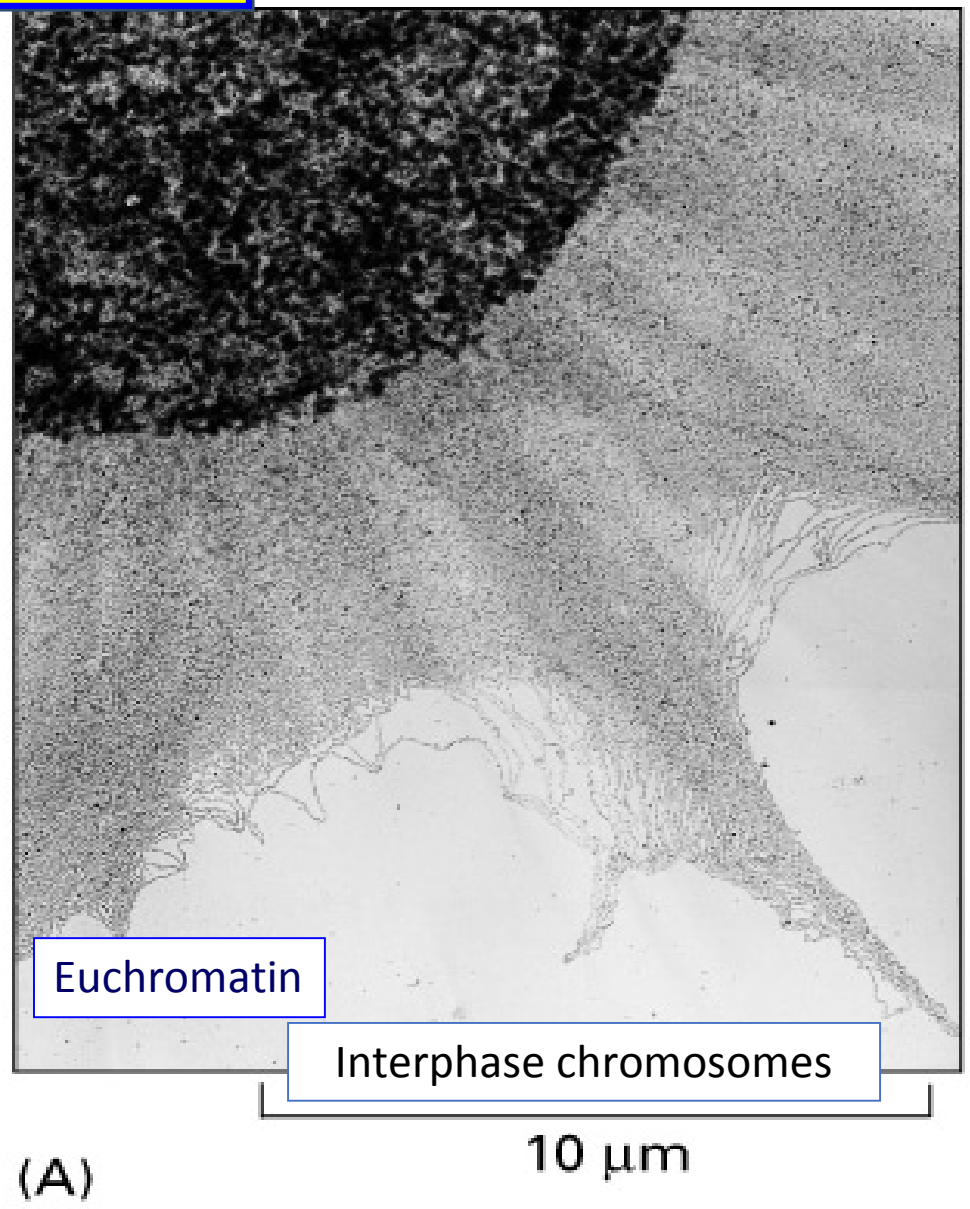



Kaltreider *et al*. 2002

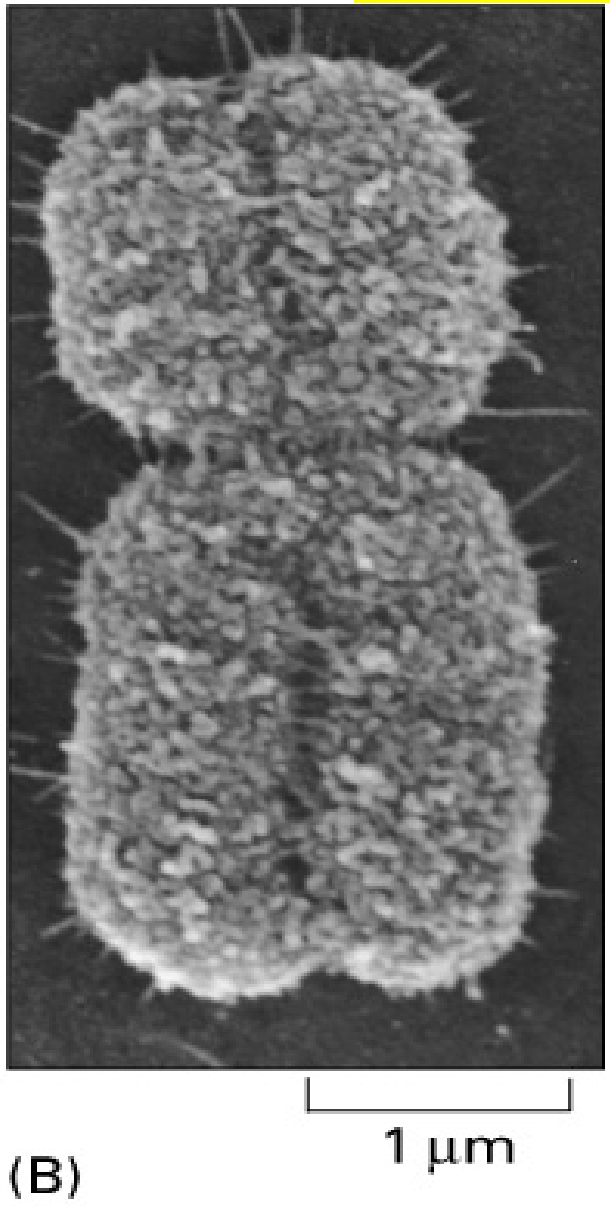
The first keyword: **Epigenetics**

Heterochromatin

***Epigenetics*** appears to be the most appropriate and **powerful tool to build up a new systemic model of genome ..**



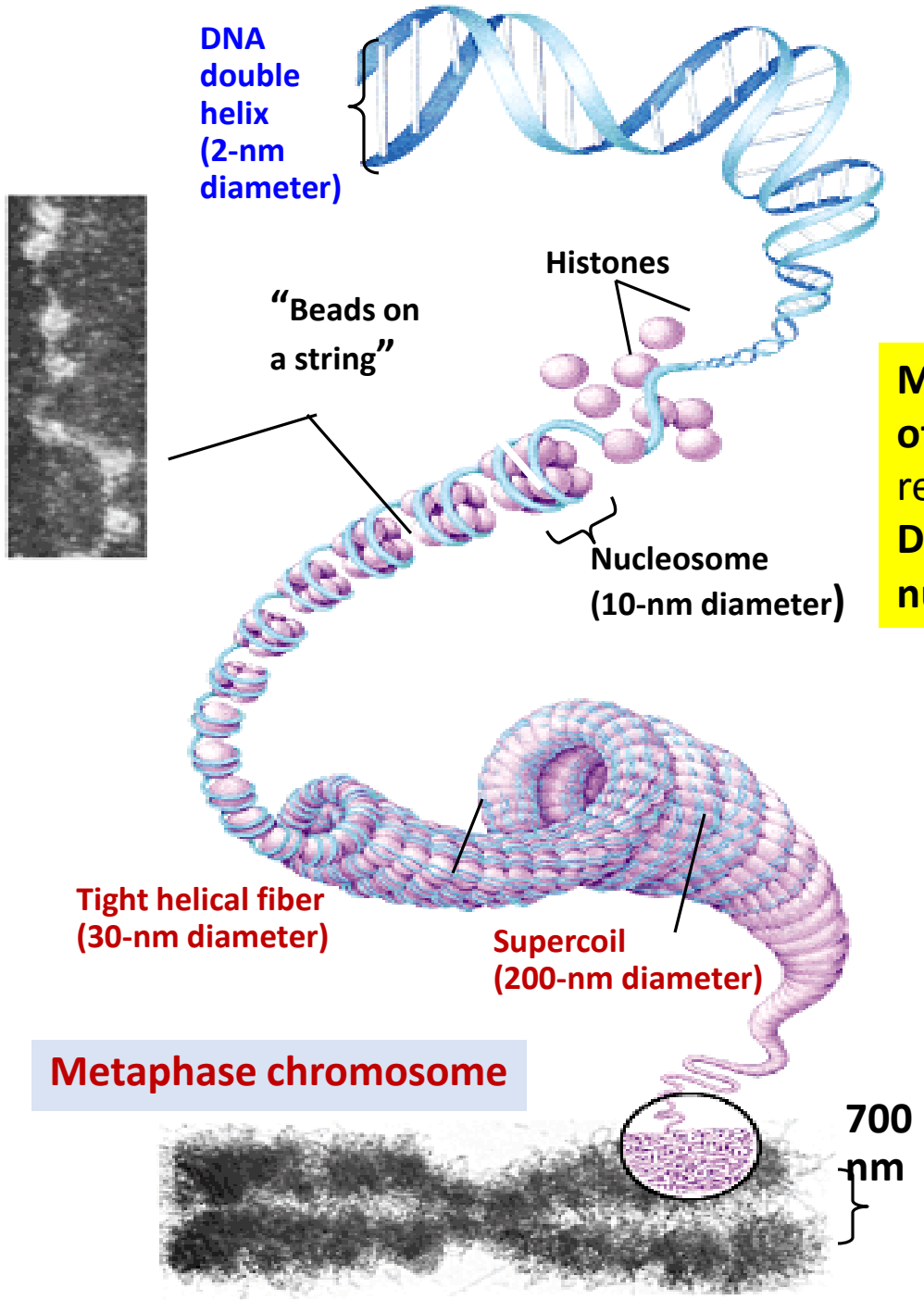

Mitotic chromosome




.. a **dynamic and fluid molecular network** which can interact within itself and with the outside

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

.. it has become evident that the **genome** is a complex **molecular system (*network*)** made up not only by DNA sequence, but also **by a dynamic and responsive structure of histones** and an "**epigenetic" cloud of molecules** (methyl and acetyl groups, **enzymes**, transcription factors, microRNAs )..




**Euchromatin**

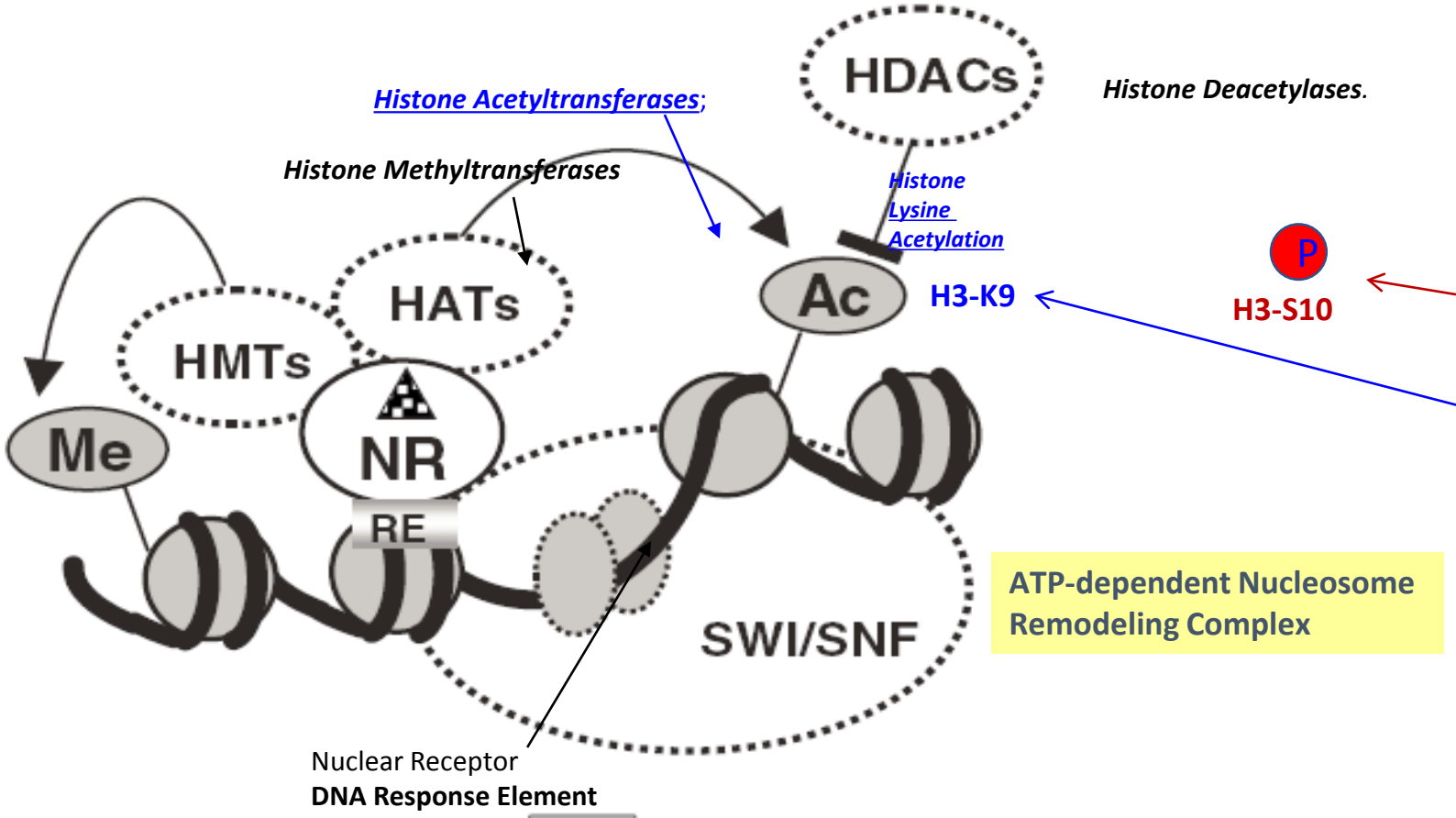
**Multiple levels of packing** are required **to fit the DNA** into the cell **nucleus**

**Heterochromatin**

**Metaphase chromosome**

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

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 **phosphorylation of serine 10 of histone H3** and the **acetylation of lysines 9 and/or 14** take place

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

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

They could be regarded as the **sensory / receptive component** of the genome

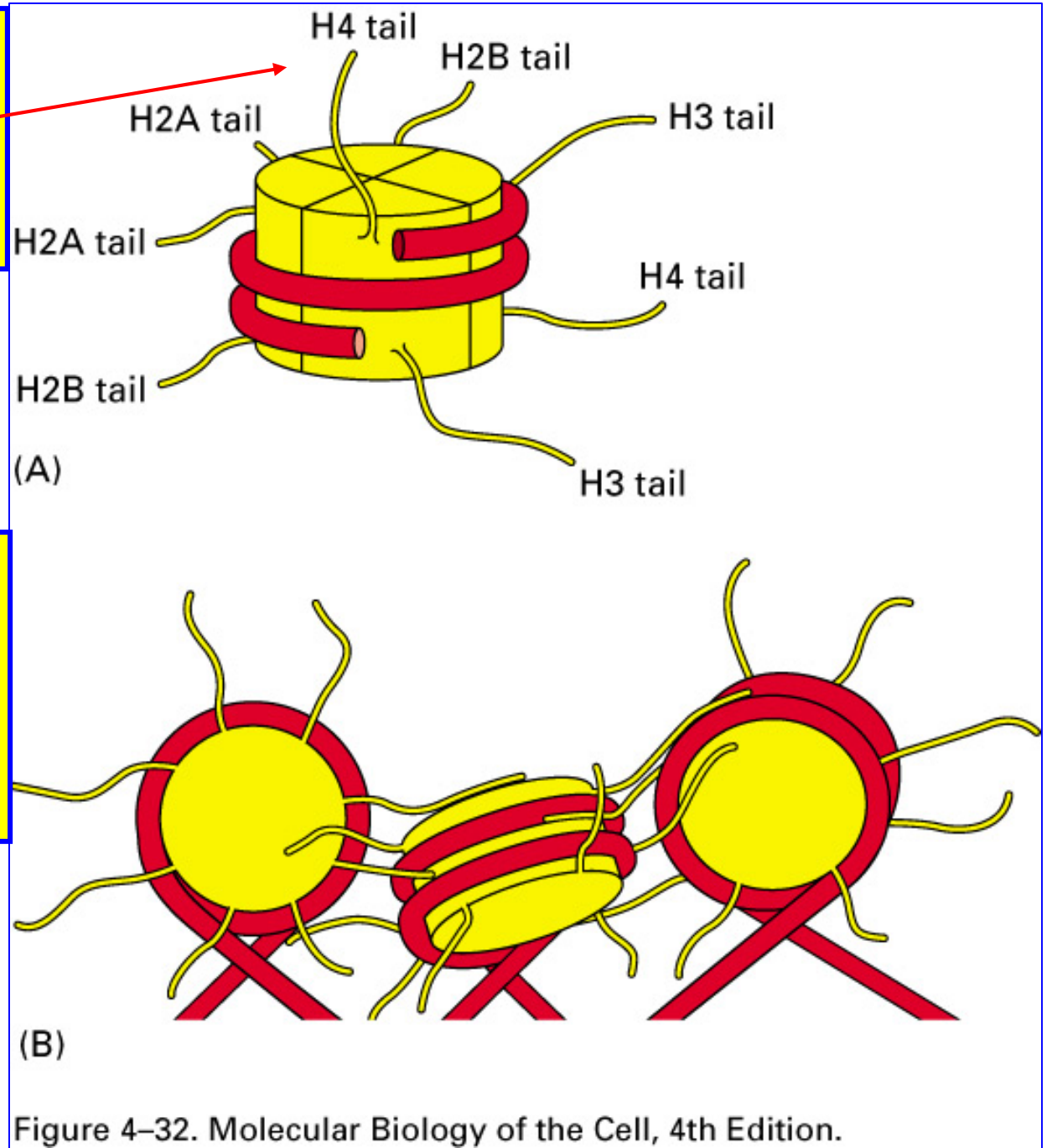



Figure 4–32. Molecular Biology of the Cell, 4th Edition.

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

**The 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 **inactive genes (= gene silencing)**

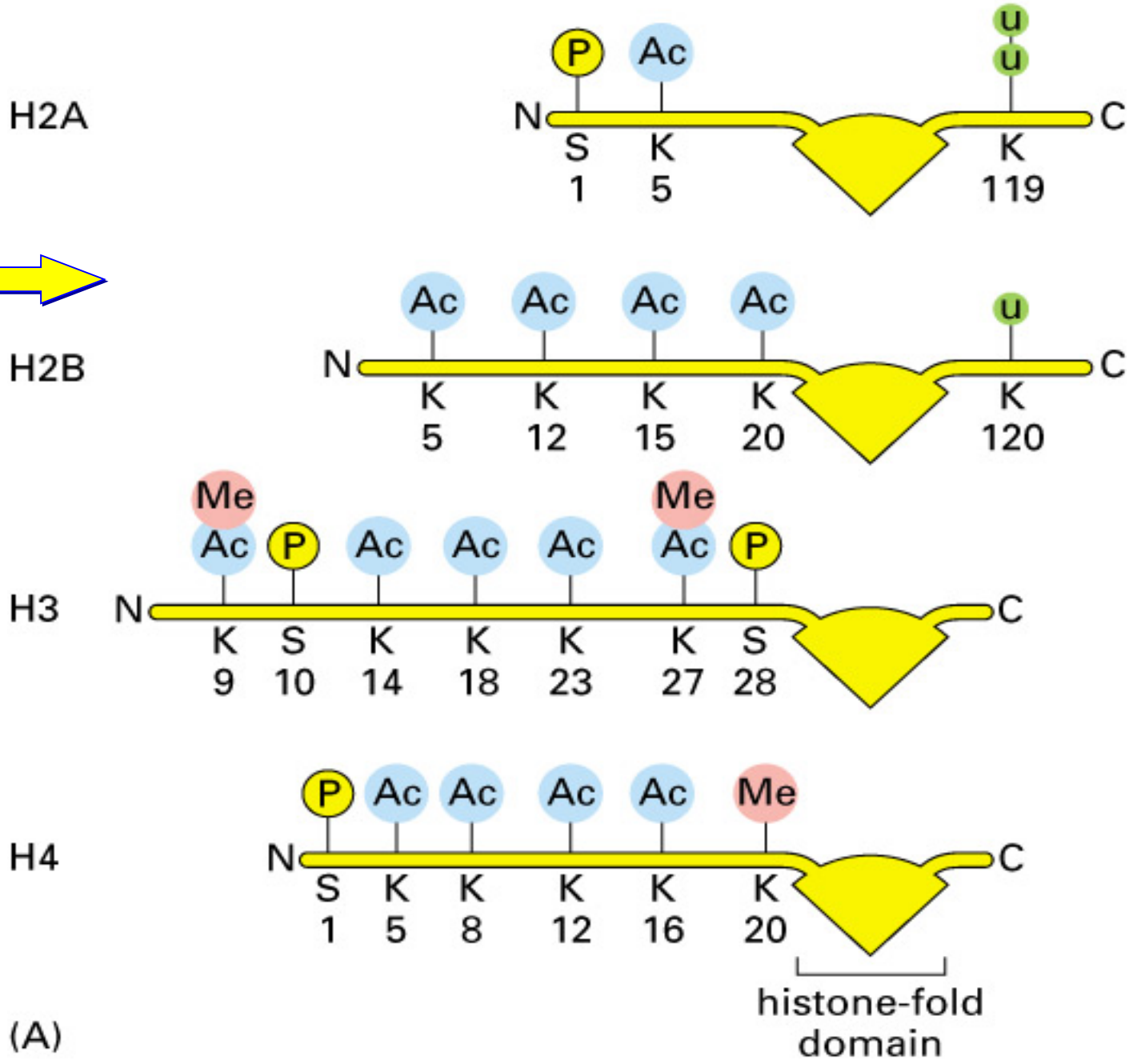
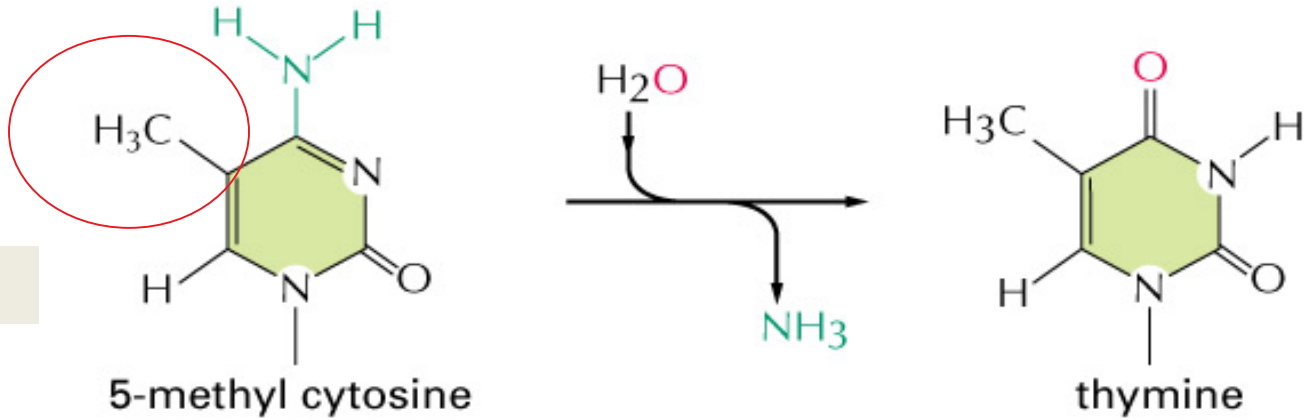


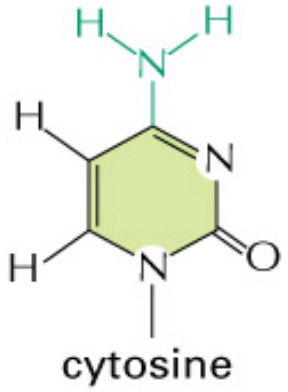

Figure 4–35 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

# DNA methylation

DNA methylation is a very **stable/covalent modification** of the DNA, very important for ***gene silencing*** in human cells. Most genes have **GC rich areas of DNA in their promoter regions,** that are also referred to as ***CpG islands***. **Methylation of the C residues within the CpG islands leads to gene silencing.**

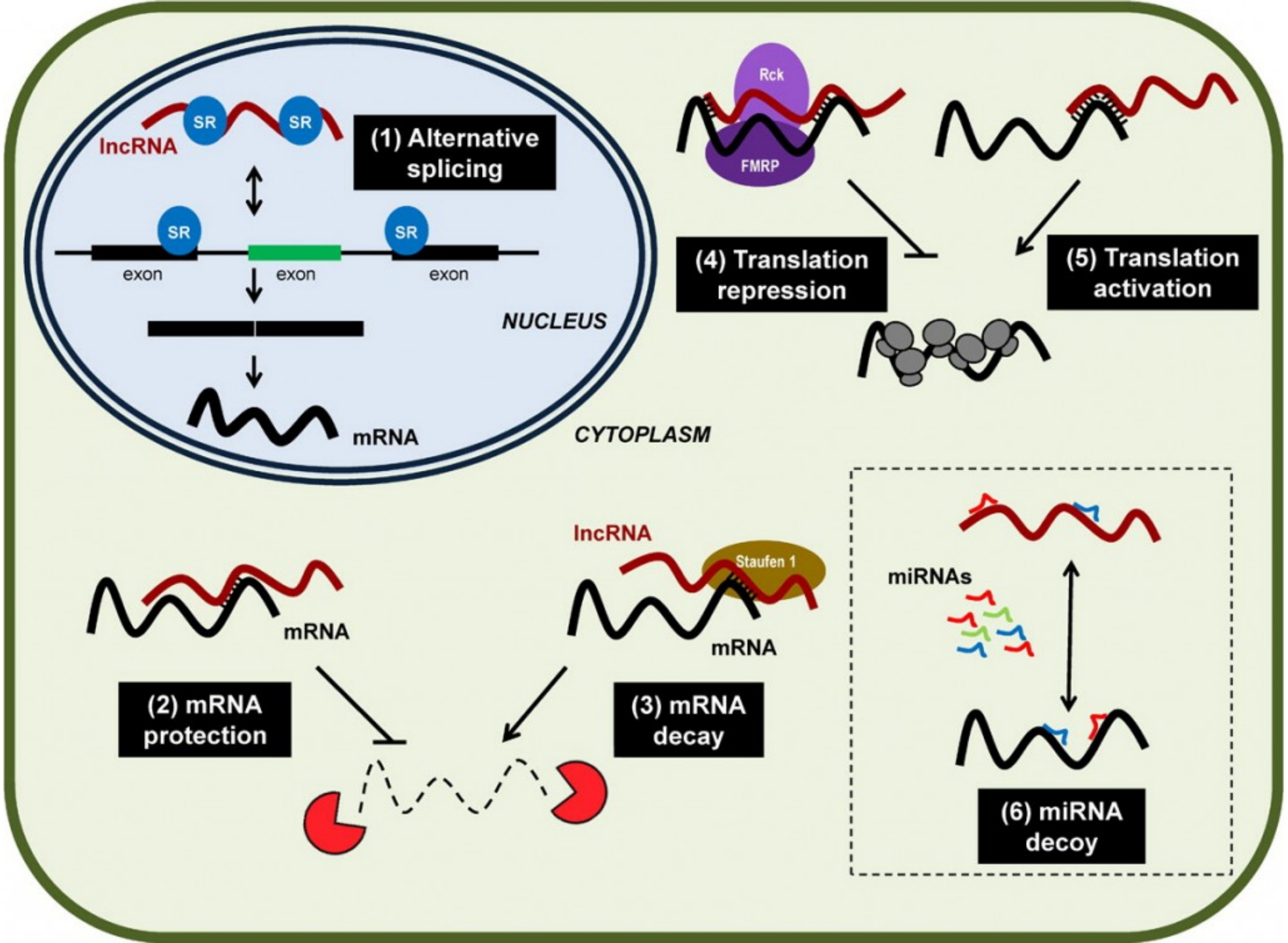
(highly *unstable* base)



3

The **vast majority of human DNA does not encode proteins**, but ***microRNAs:*** hundreds of these ***ncRNAs*** have already been discovered that play roles of ***natural genetic engineering***



**Transposable elements can be seen as a natural genetic engineering system capable of acting** not just on one location at a time but **on the genome as a whole** ..This dynamic view of the genome has been illustrated most impressively by *Shapiro* who stated that **the genome is composed of modular units arranged in a "Lego-like" manner that can be altered under circumstances**

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Gene 345 (2005) 91–100

GENE
SECTION
EVOLUTIONARY GENOMICS

www.elsevier.com/locate/gene

Review

# A 21st century view of evolution: genome system architecture, repetitive DNA, and natural genetic engineering

James A. Shapiro

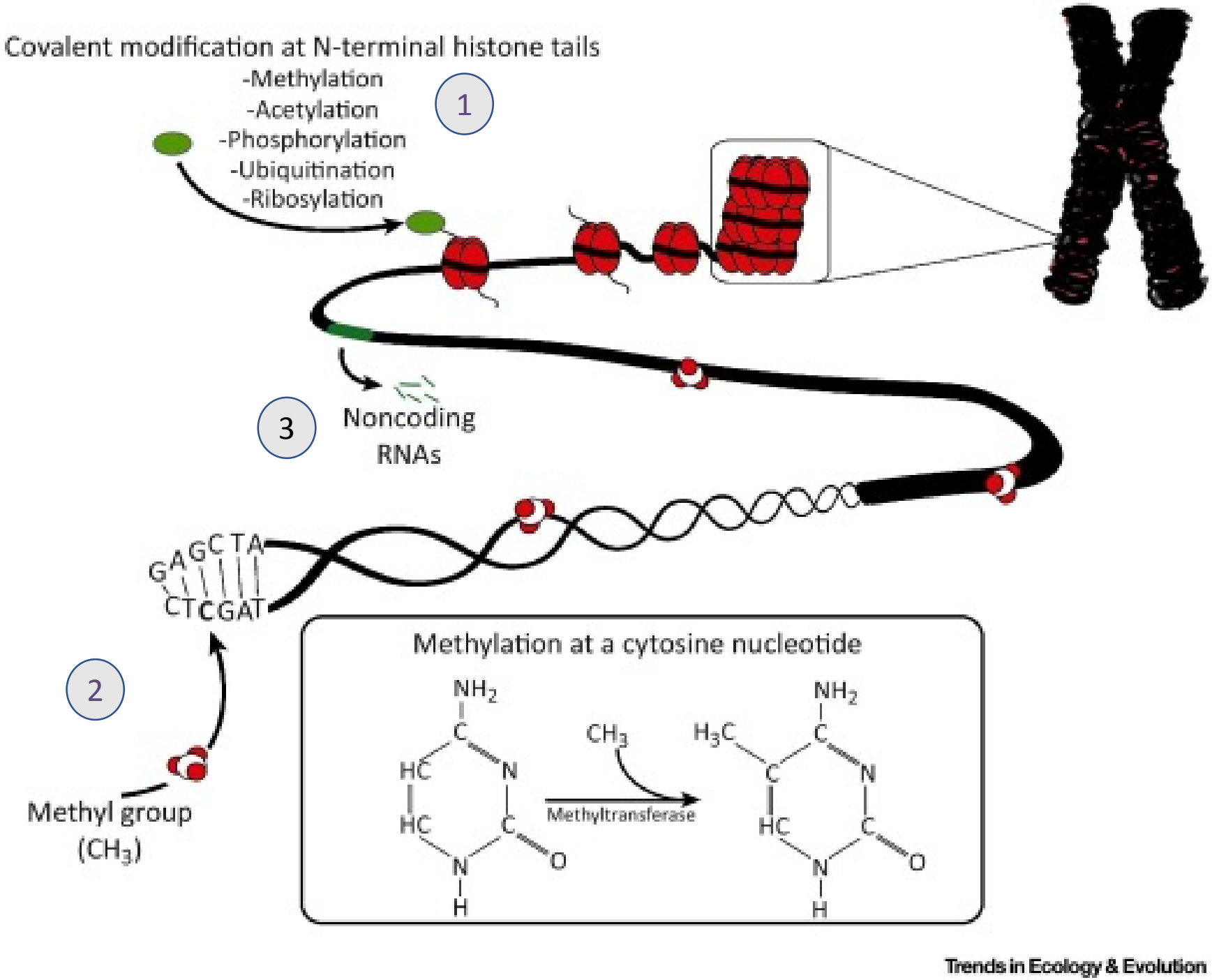
*Department of Biochemistry and Molecular Biology, University of Chicago, 920 E. 58th Street, Chicago, IL 60637, United States*

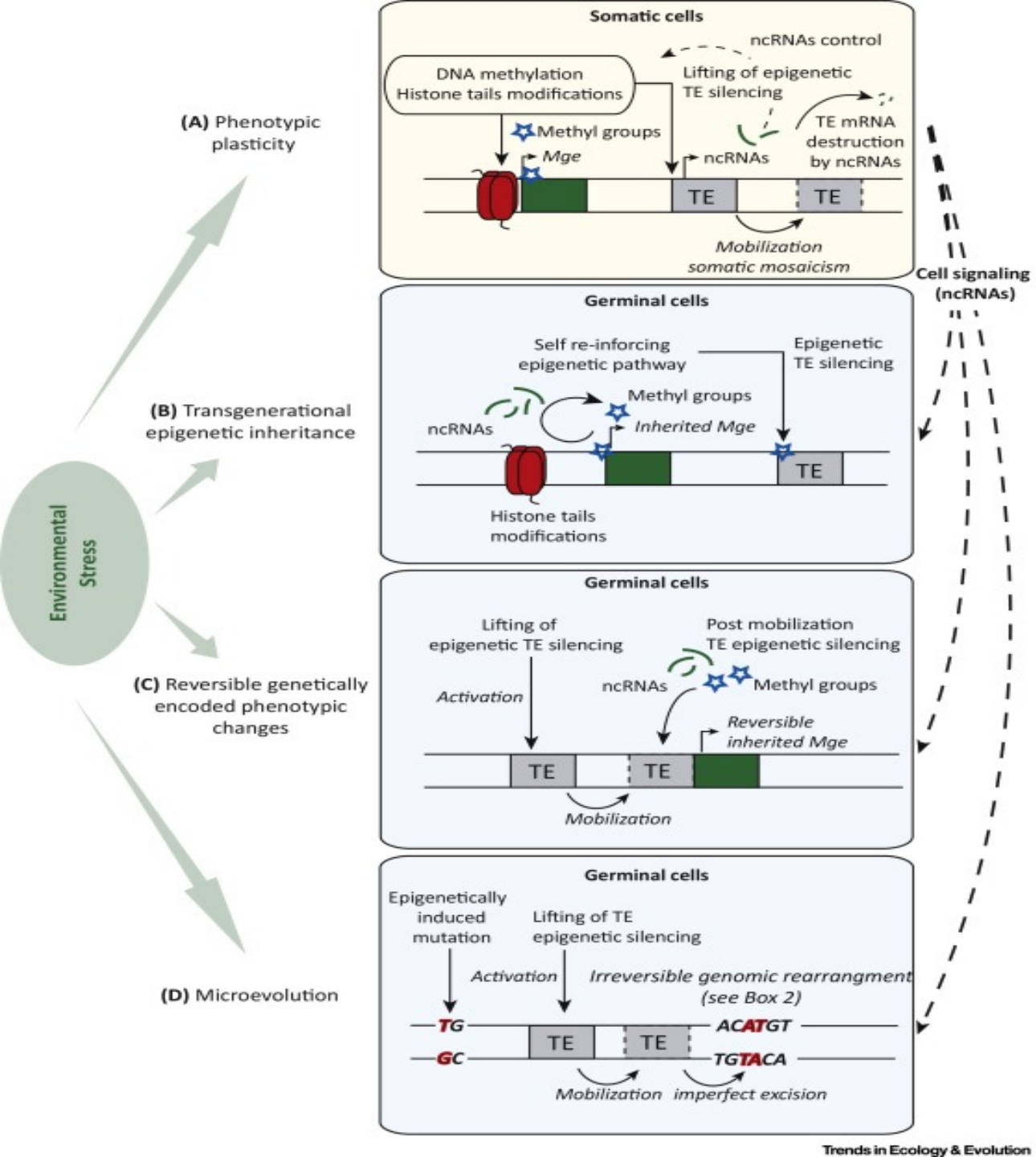
The last 50 years of molecular genetics have produced an abundance of new discoveries and data that make it useful to revisit some basic concepts and assumptions in our thinking about genomes and evolution. Chief among these observations are the complex modularity of genome organization, biological ubiquity of mobile and repetitive DNA sequences, and the fundamental importance of DNA rearrangements in the evolution of sequenced genomes. This review will take a broad overview of these developments and suggest some new ways of thinking about genomes as sophisticated informatic storage systems and about evolution as a systems engineering process.

1 2 3 4 5

**Adaptation to Global Change: A Transposable Element–Epigenetics Perspective**

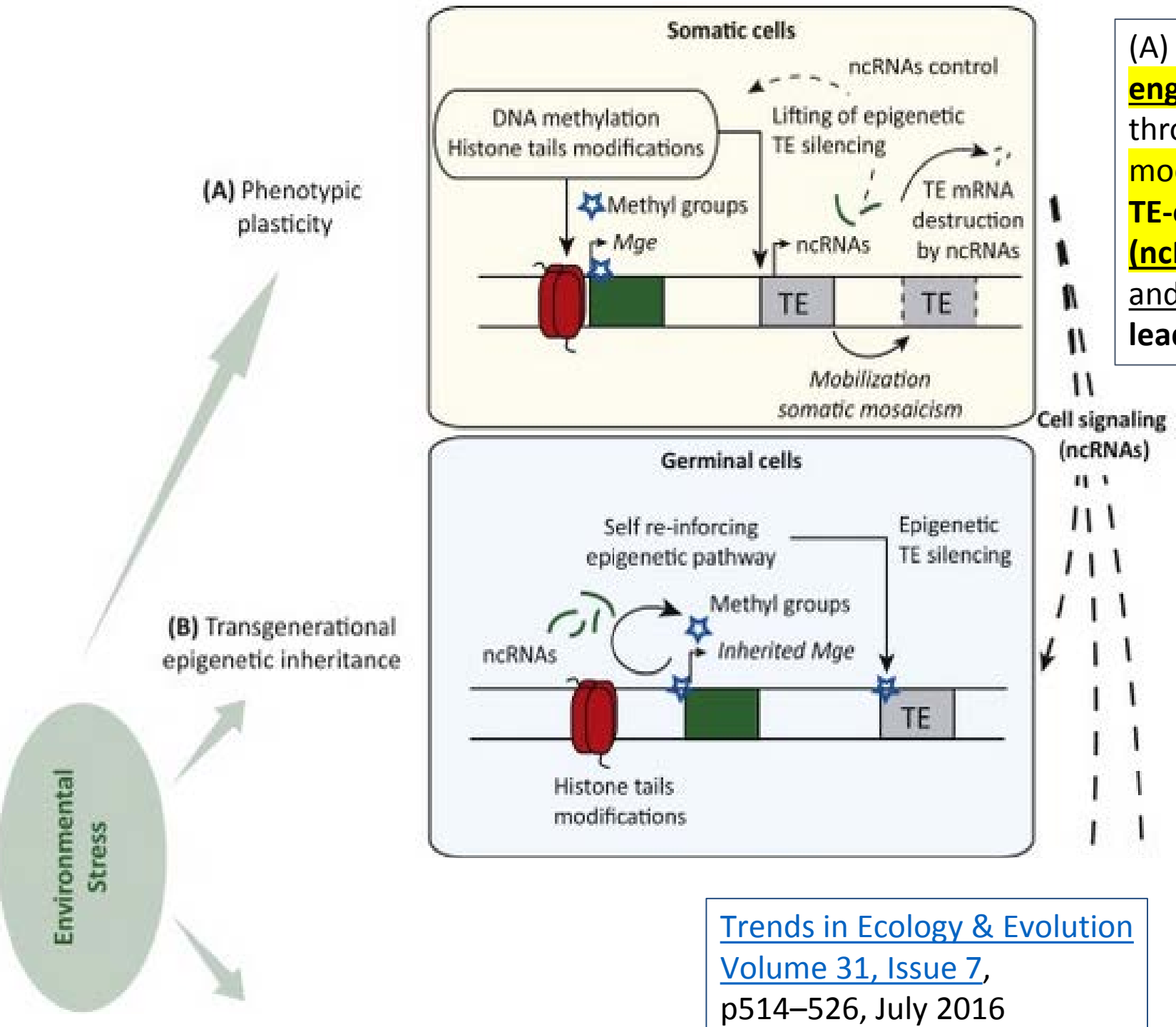
Trends in Ecology & Evolution
Volume 31, Issue 7,
p514–526, July 2016






Evolutionary Outcomes of **Activation of the TE–EC Engine in Somatic and Germinal Cells in Response to Stress**. Mge, modified gene expression.

Trends in Ecology & Evolution
Volume 31, Issue 7,
p514–526, July 2016



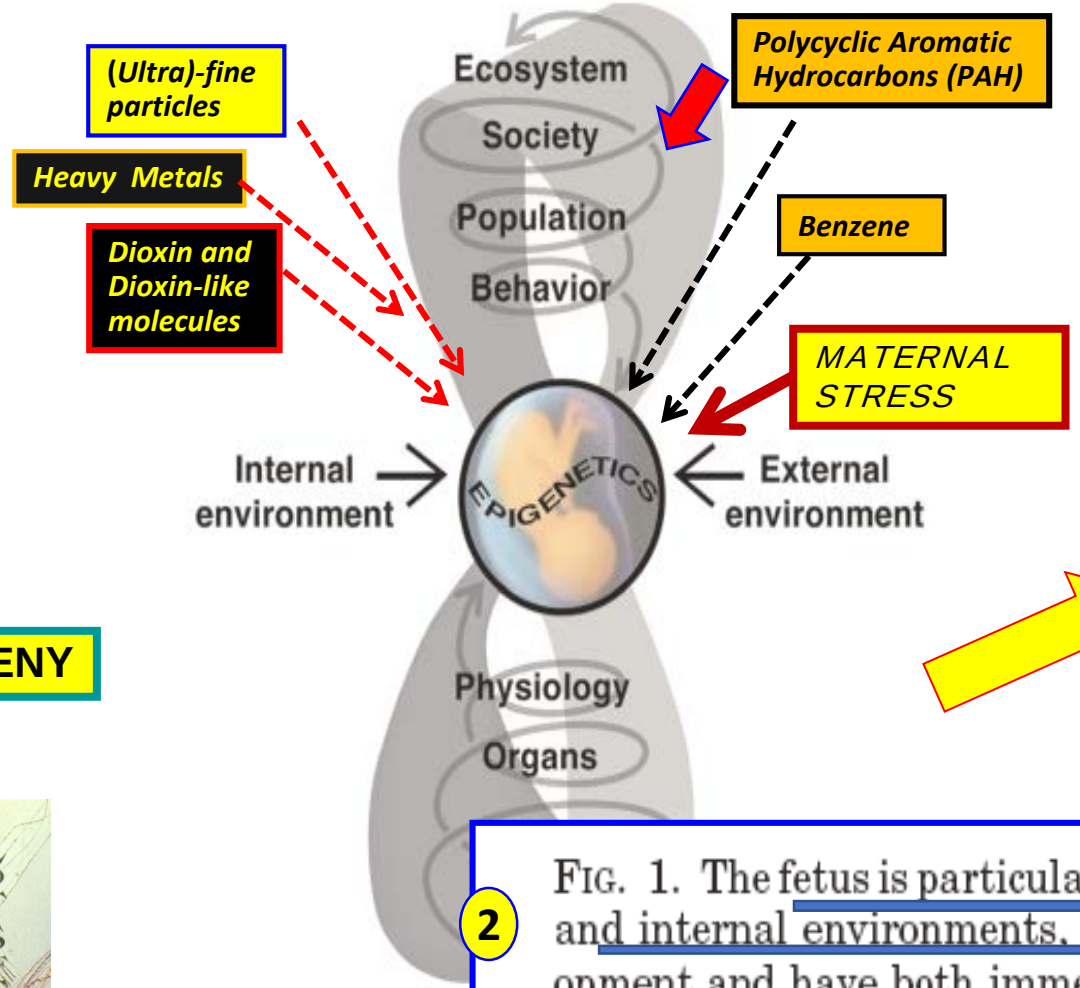

(A) **Under stress, the activation of the TE–EC engine** in somatic cells induces **plastic responses** through: (i) DNA methylation and/or modifications of histone tails; (ii) **transcription of TE-encoded regulatory noncoding RNAs (ncRNAs)**; and (iii) lifting of epigenetic silencing and **mobilization of TEs in somatic cells, leading to somatic mosaicism.**

(B) **Stress induces epigenetic modifications in germline cells**. The resulting **phenotypes can be stabilized over generations (transgenerational epigenetic inheritance) through self-reinforcing epigenetic pathways**.

**Stress perceived in somatic cells** can also induce the **production of circulating ncRNAs that may modify the epigenome of remote germline cells** [dashed arrow from (A) to (B)].

Trends in Ecology & Evolution
Volume 31, Issue 7,
p514–526, July 2016

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

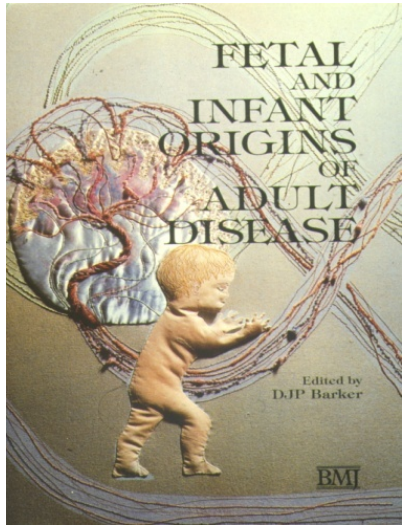



**ONTOGENY**

1

… a technical term that refers to the ***capability*** and, at the same time, the ***requirement***, for **embryo-foetal cells to define their epigenetic setting in a predictive and adaptive way** , in relation to the information coming from the mother and, through her, from the outer world ..

A ***predictive adaptive response (PAR)*** is a developmental trajectory taken by an organism during a period of ***developmental plasticity*** in response to perceived environmental cues..




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

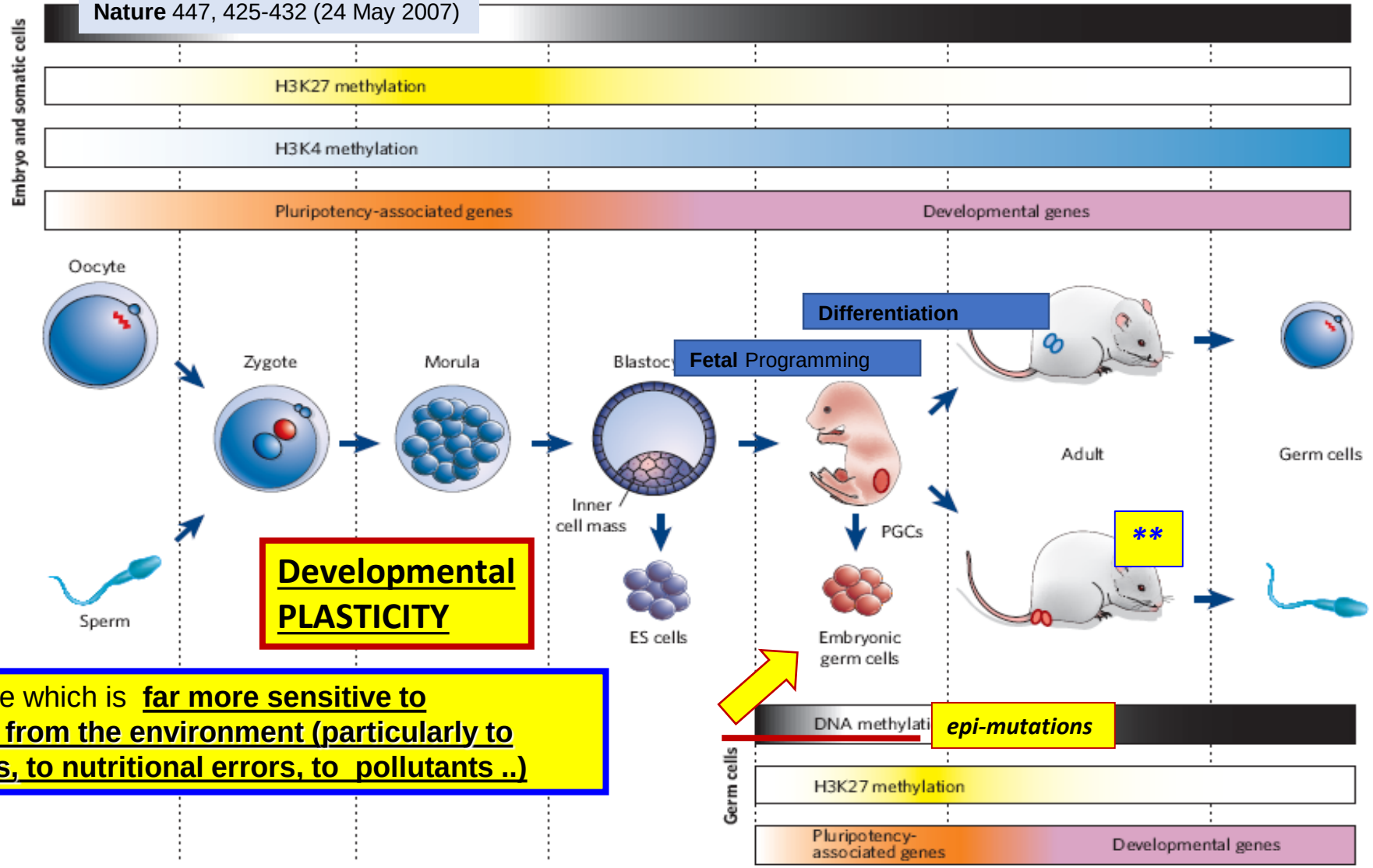
The **fourth** keyword is ***developmental plasticity***

***Cellular Differentiation*: an *epigentic process***

**The actual genetic program of a single multicellular organism is the product of nine months of epigenetic adaptive-predictive "formatting" of trillions of cells)**

# Stability and flexibility of epigenetic gene regulation in mammalian development

**Nature** 447, 425-432 (24 May 2007)




**Developmental PLASTICITY**

1 → 2

**Differentiation is the process through wich** the organism changes **from a zygote to a complex system** of **tissues** and **200 cell types (genetically identical.. each with its own epigenetic and morpho-functional characteristics) ..**

3

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 ..)**

The ***brain**** is by far the ***most plastic organ*** during all (human) life

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

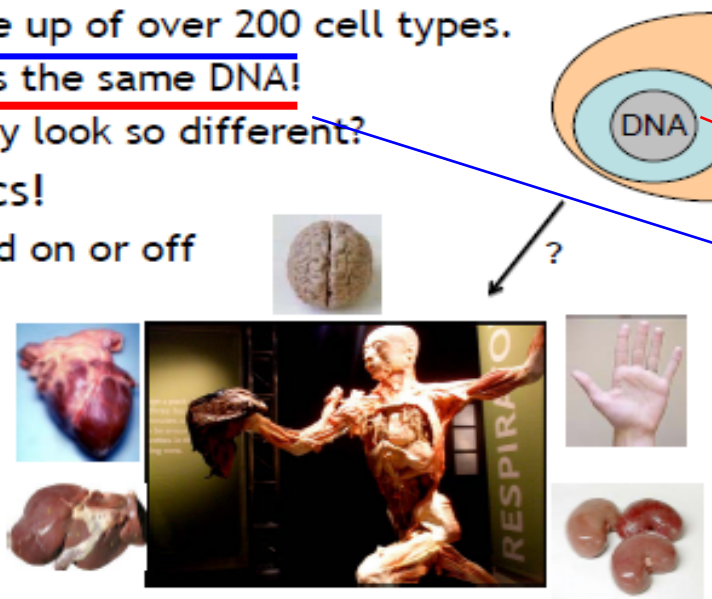
The **fourth** keyword is ***developmental plasticity***

## 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?

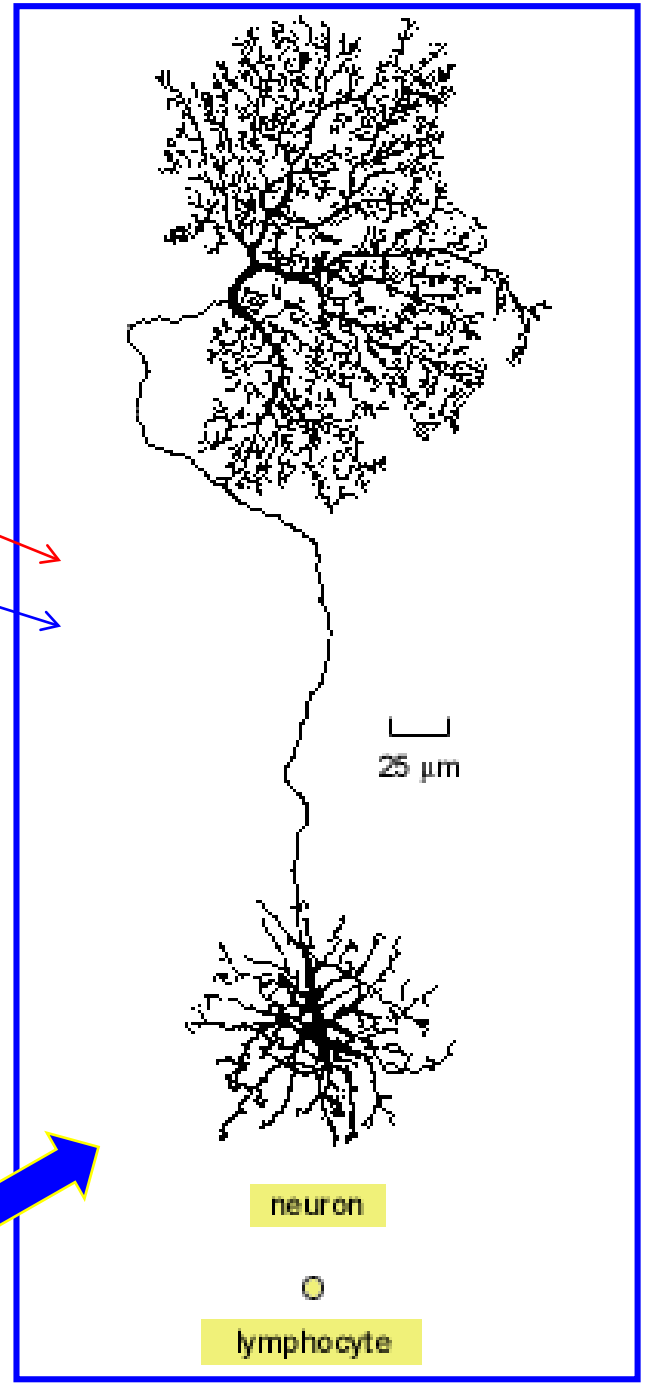
Epigenetics!

- Genes turned on or off



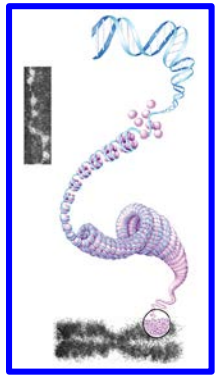

Wikimedia Commons, ORNL.gov, Flickr: richdelux

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**


***Phylogeny***



**of 4 billion years of molecular coevolution** * (in particular, our **DNA** is the **product** of this long journey) ..

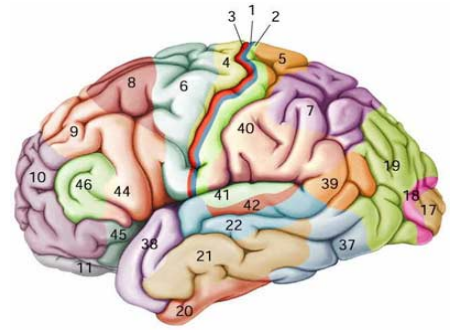
We should never forget that **we are at the same time the product**

***Mismatch***

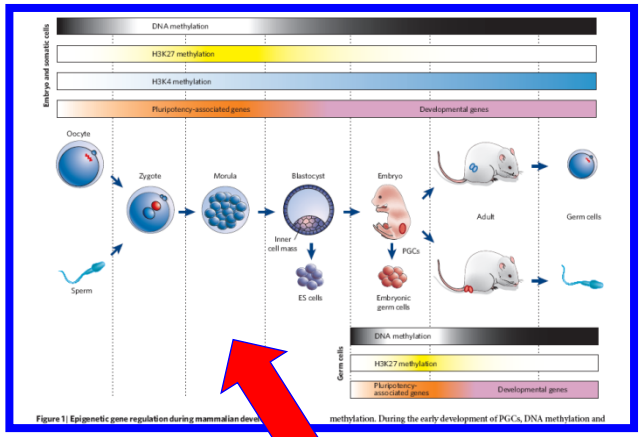
and of **9 months of an individual development**

***Ontogeny***

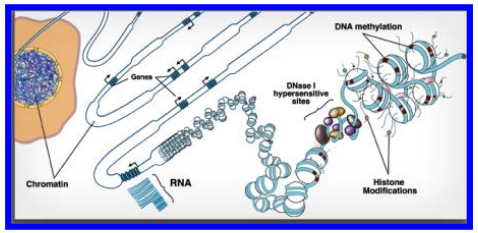
***Devo-Evo***

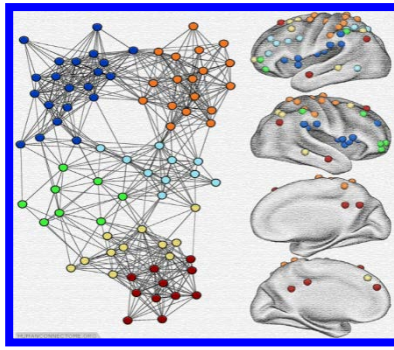


The **epigenome** being the product of nine months of ***cellular and tissue programming*** (**adaptive** to an environment that is rapidly changing)..



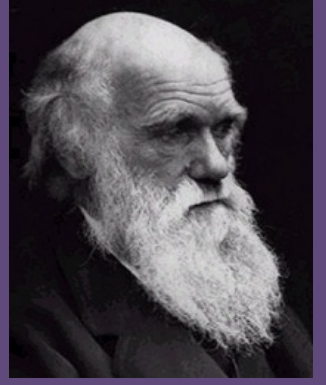

***Ontogeny*** Recapitulates (***anticipates***) ***Phylogeny***



A ***major risk***: the **EDCs** and other ***xenobiotics*** (***not*** being the product of ***molecular coevolution***) can interfere at this level, acting as ***pseudo-morphogens***

# *Chimpanzee-human divergence*



***Evo***

**Brain:**
**a *rapidly evolving Organ ?***

***6-8 million years***

The ***ancestral*** **wiring**

***Hominids or hominins***

The ***Individual*** wiring !!

***+ Soft Wired-memory***

***Chimpanzees***

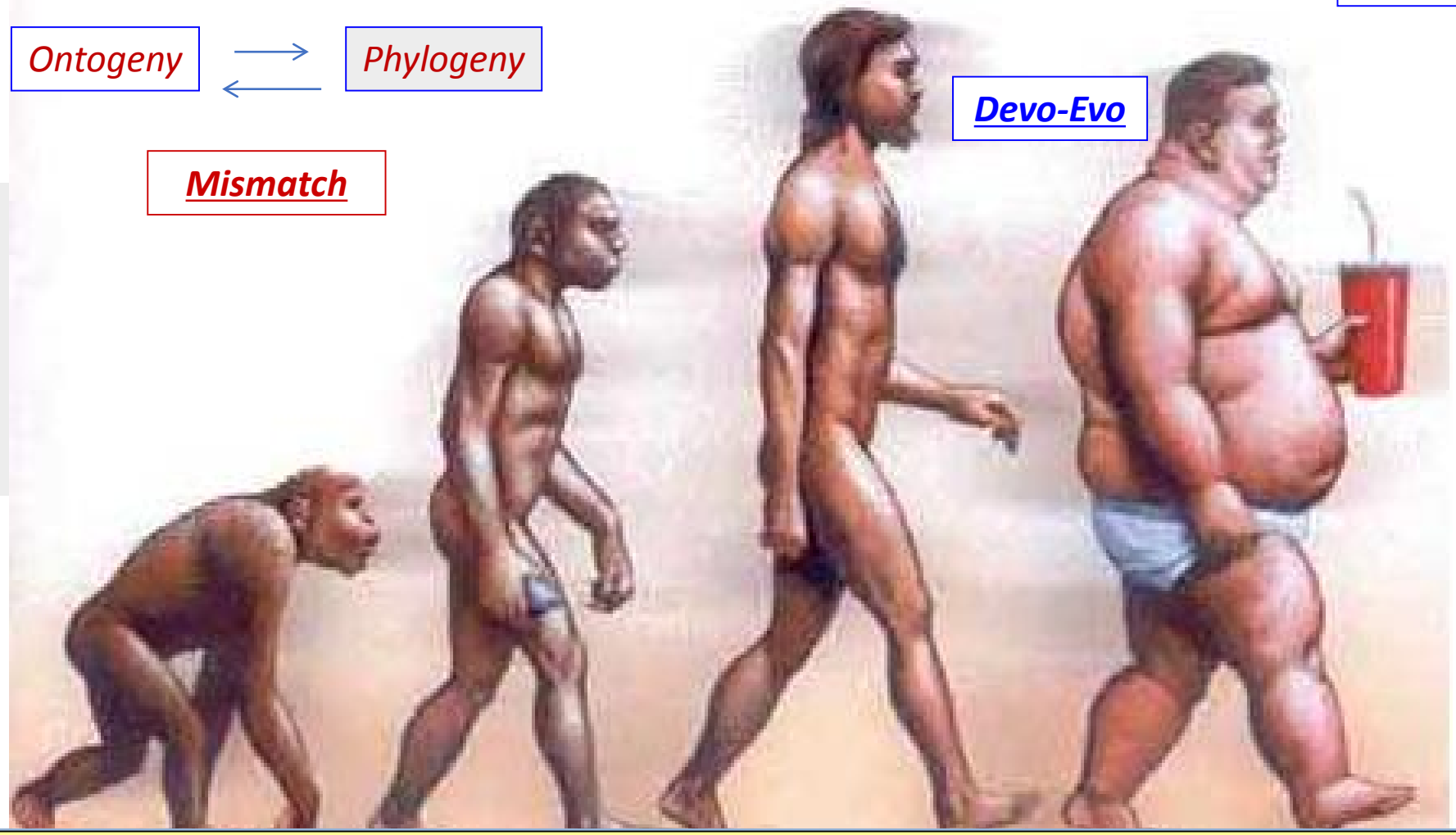
***Humans***

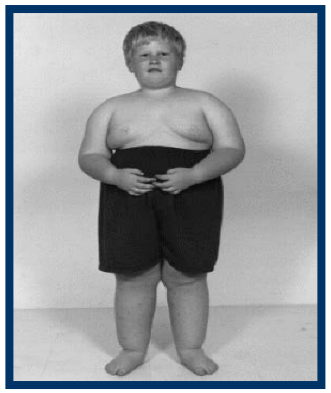
Ontogeny ⇄ Phylogeny

Devo-Evo

Mismatch

*The Obesity pandemics is the very **first phenotypical transformation** of an **entire species***





We can summarize all this by saying that **the main phenotypic (in particular behavioural) differences between *Homo sapiens* and the other primates (and between single individuals) have epigenetic rather than genetic origins**: **in the actual, epigenomic programming and in its ongoing transformations**.

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

# Relative frequency of articles with *epigenetic* or *epigenetics* in their title

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

International Journal of Epidemiology

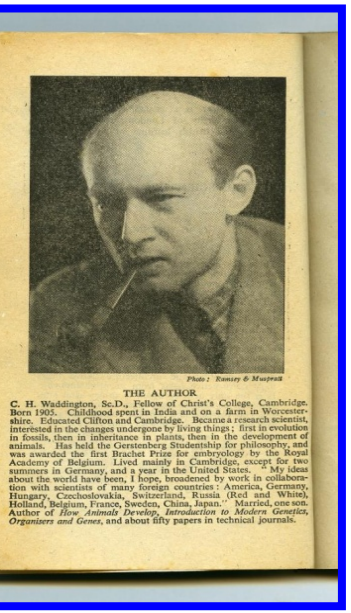
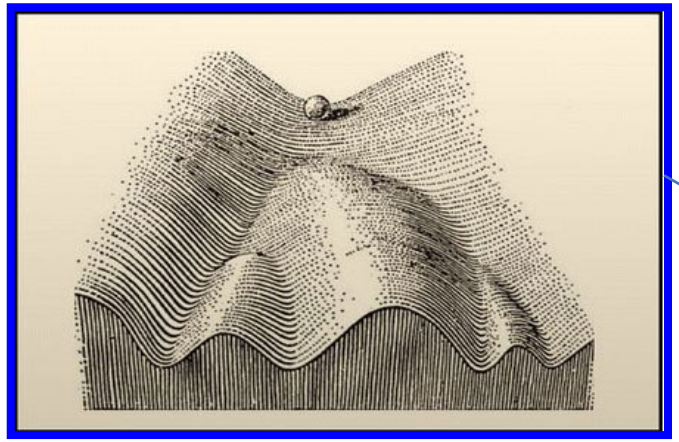
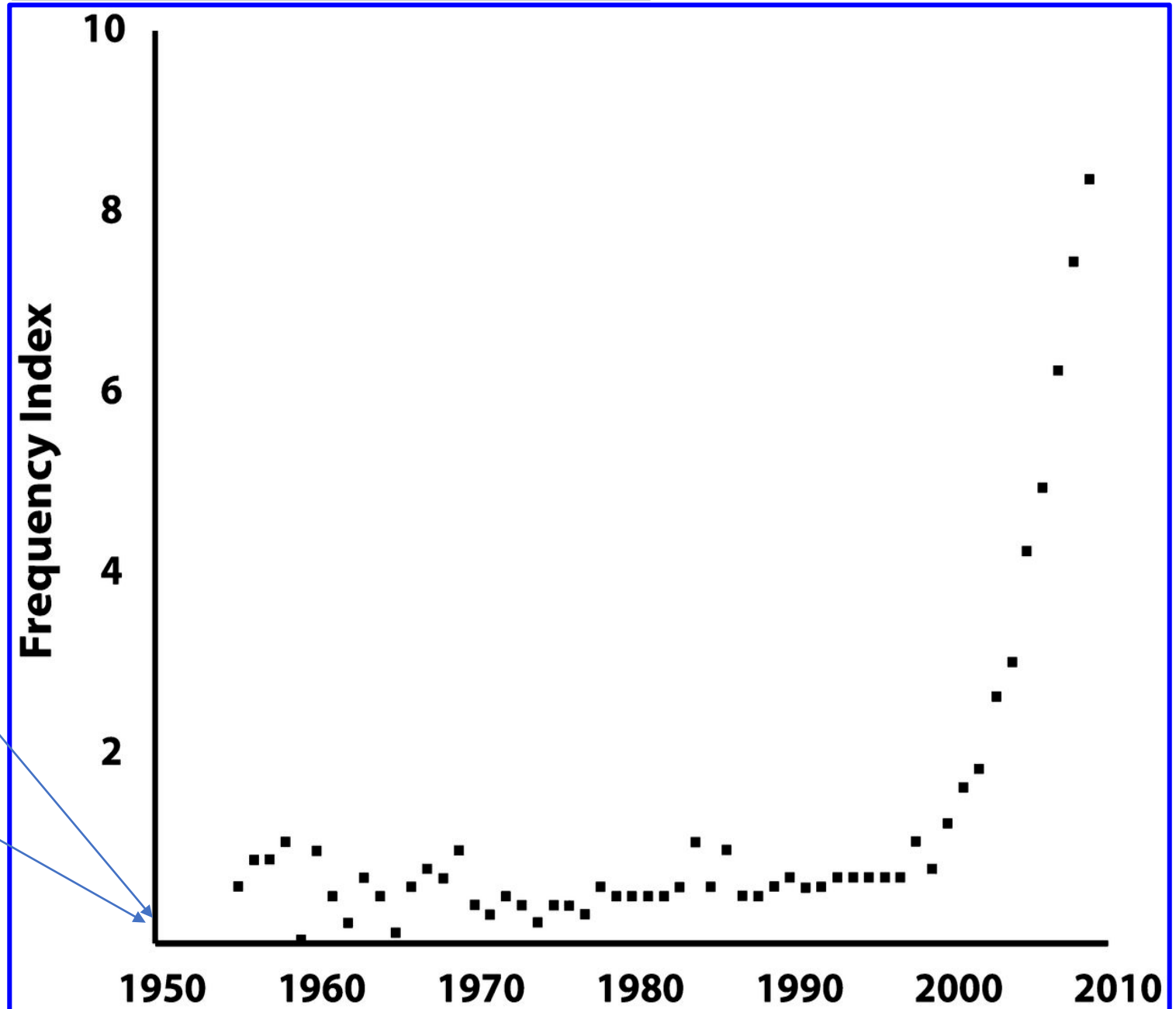


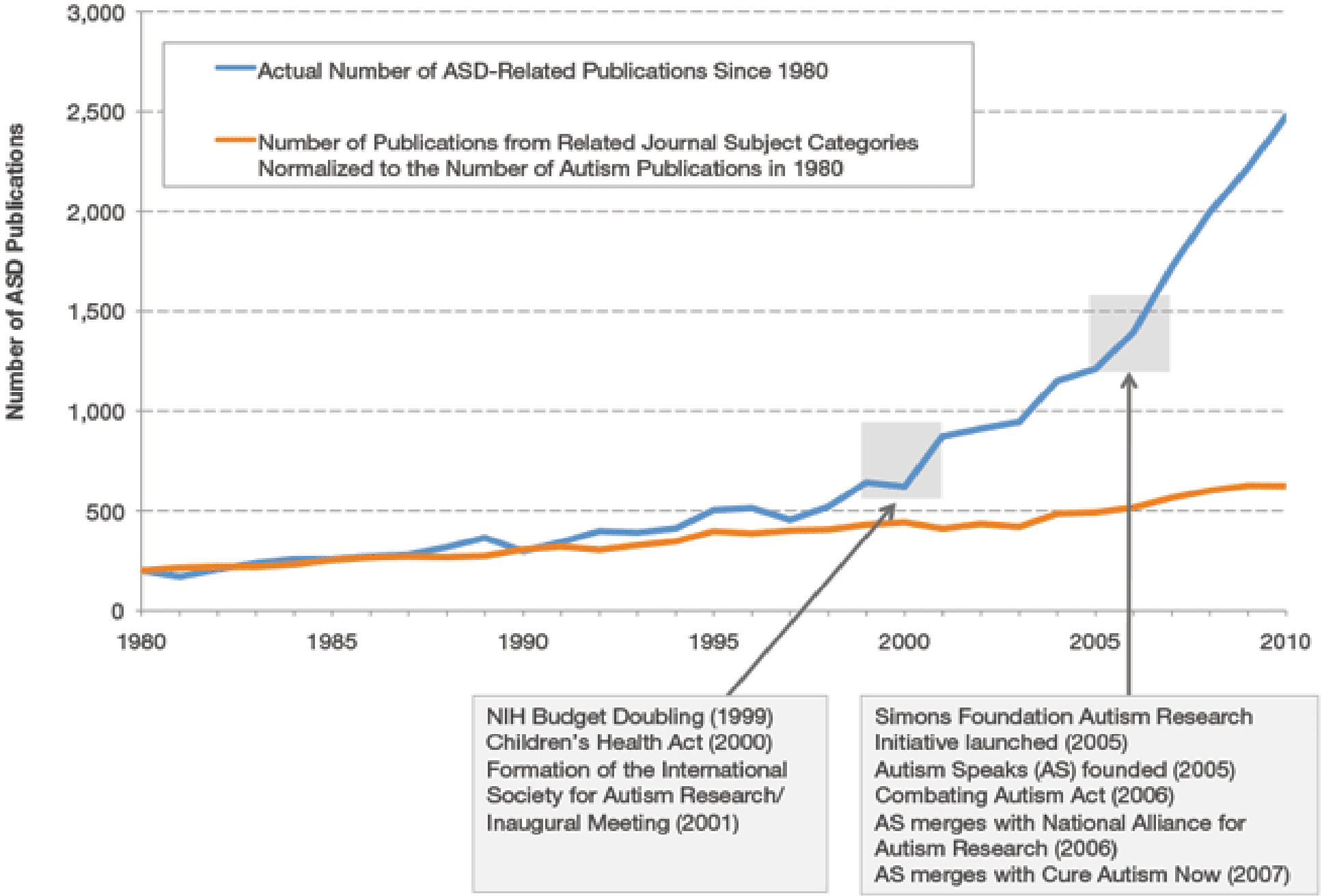
Photo: Ramsey & Muspratt

THE AUTHOR

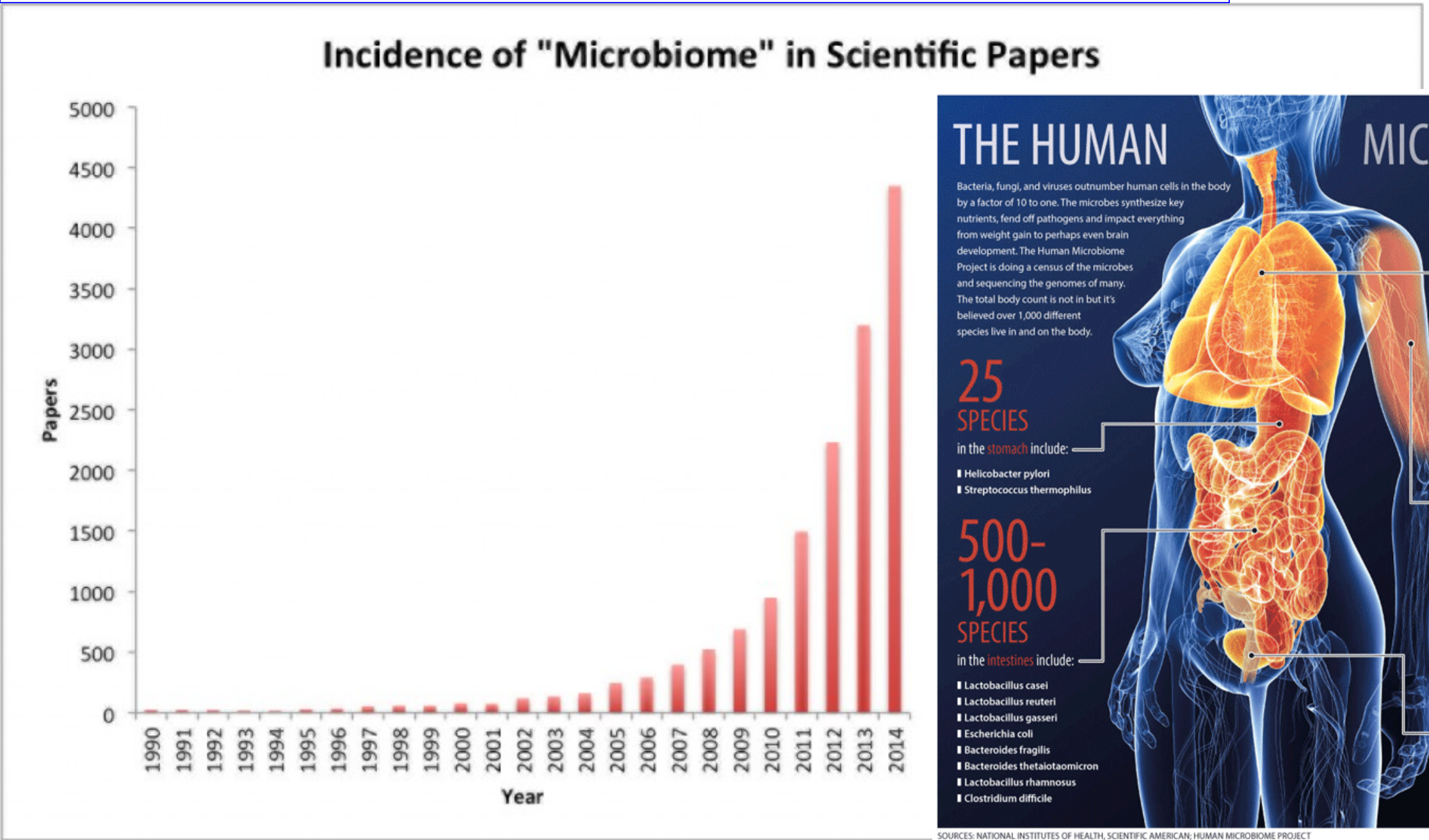
C. H. Waddington, Sc.D., Fellow of Christ's College, Cambridge. Born 1905. Childhood spent in India and on a farm in Worcestershire. Educated Clifton and Cambridge. Became a research scientist, interested in the changes undergone by living things; first in evolution in fossils, then in inheritance in plants, then in the development of animals. Has held the Gerstenberg Studentship for philosophy, and was awarded the first Brachet Prize for embryology by the Royal Academy of Belgium. Lived mainly in Cambridge, except for two summers in Germany, and a year in the United States. "My ideas about the world have been, I hope, broadened by work in collaboration with scientists of many foreign countries: America, Germany, Hungary, Czechoslovakia, Switzerland, Russia (Red and White), Holland, Belgium, France, Sweden, China, Japan." Married, one son. Author of *How Animals Develop*, *Introduction to Modern Genetics*, *Organisers and Genes*, and about fifty papers in technical journals.





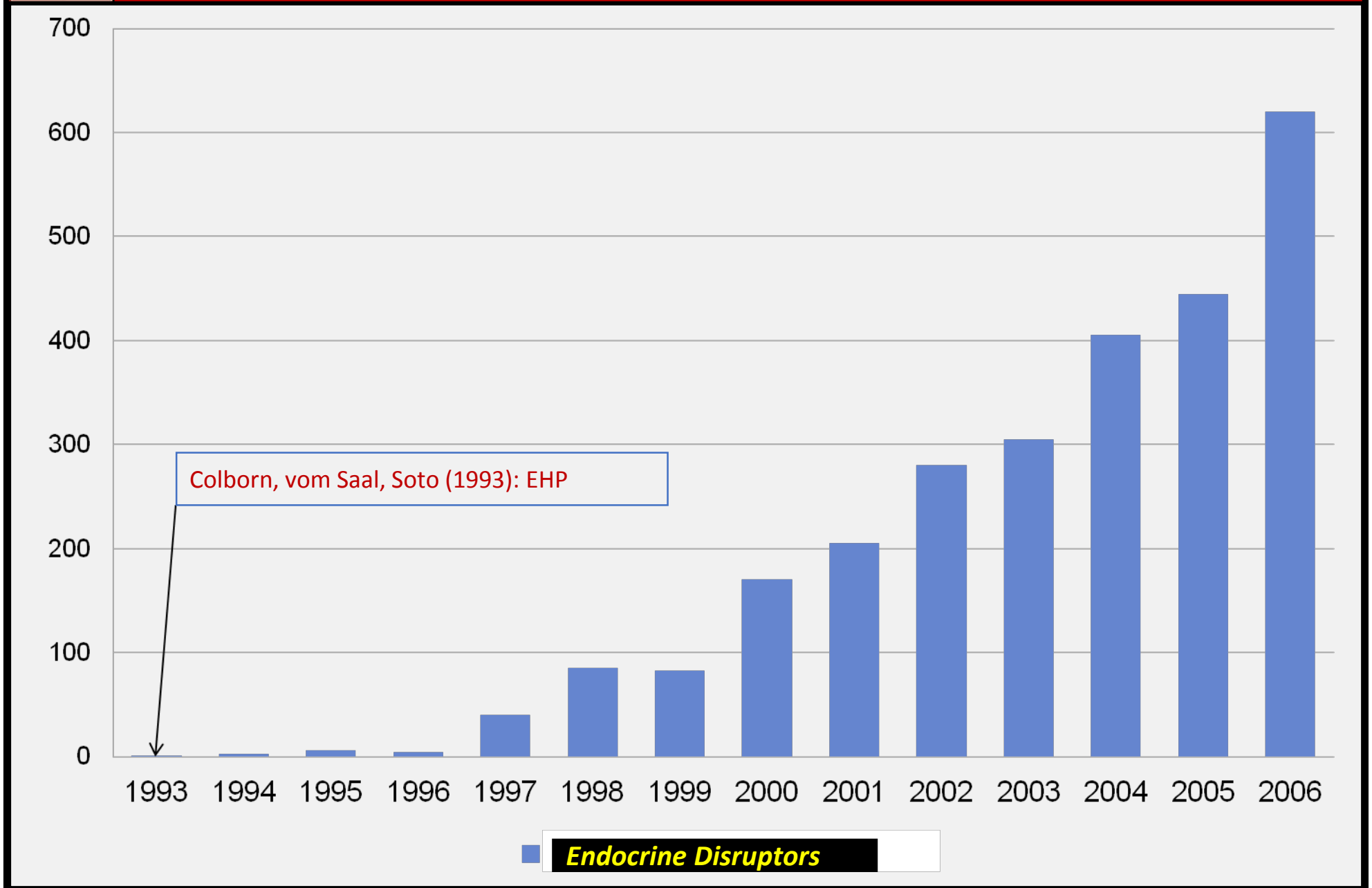

Number of ASD Publications
3,000
2,500
2,000
1,500
1,000
500
0
1980
1985
1990
1995
2000
2005
2010
Actual Number of ASD-Related Publications Since 1980
Number of Publications from Related Journal Subject Categories Normalized to the Number of Autism Publications in 1980
NIH Budget Doubling (1999)
Children's 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***

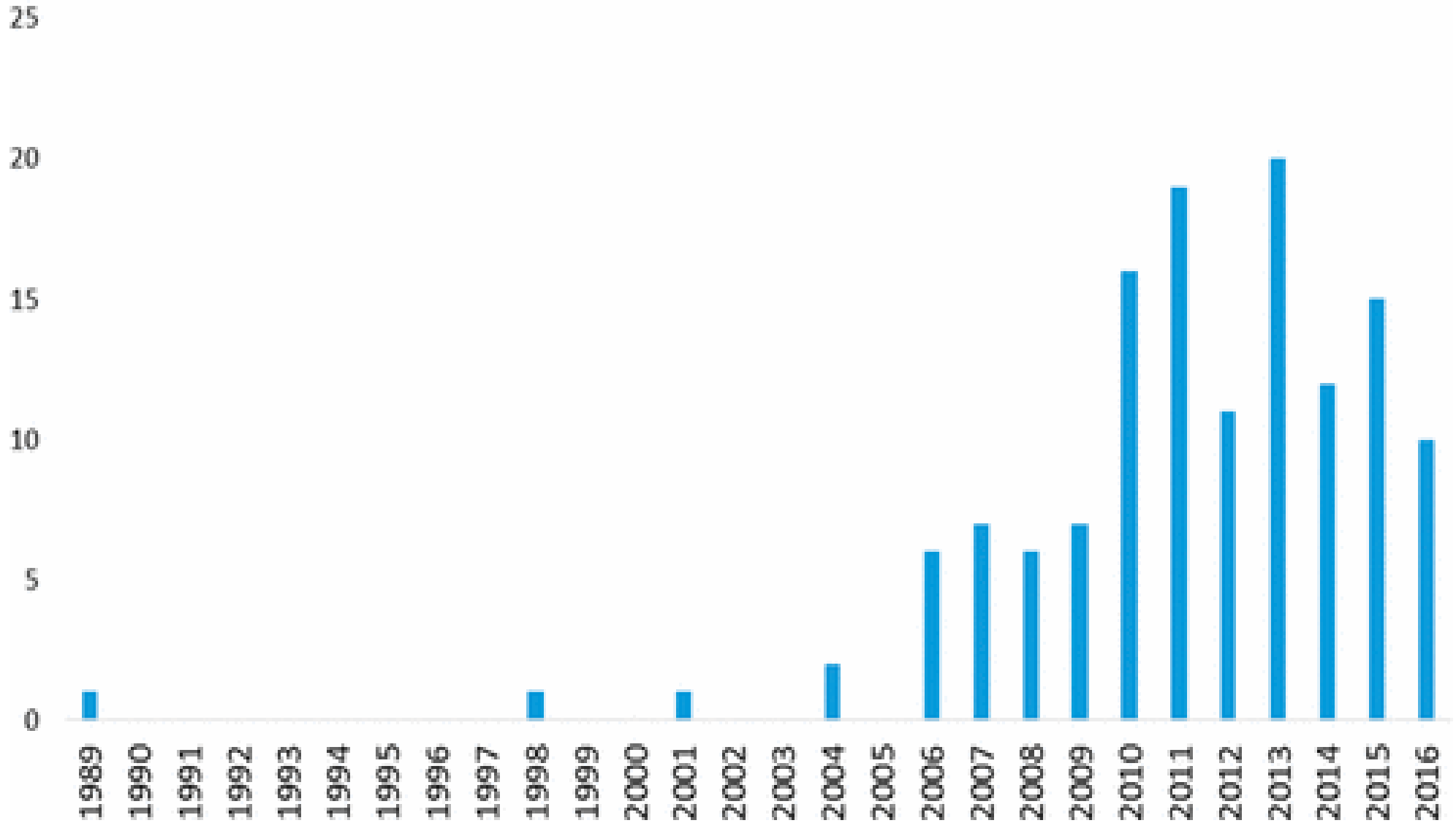


ACADEMY FOR ENVIRONMENTAL MEDICINE

# Published papers about ***Endocrine Disruptors*** between 1993 and november 2006 (Gies)



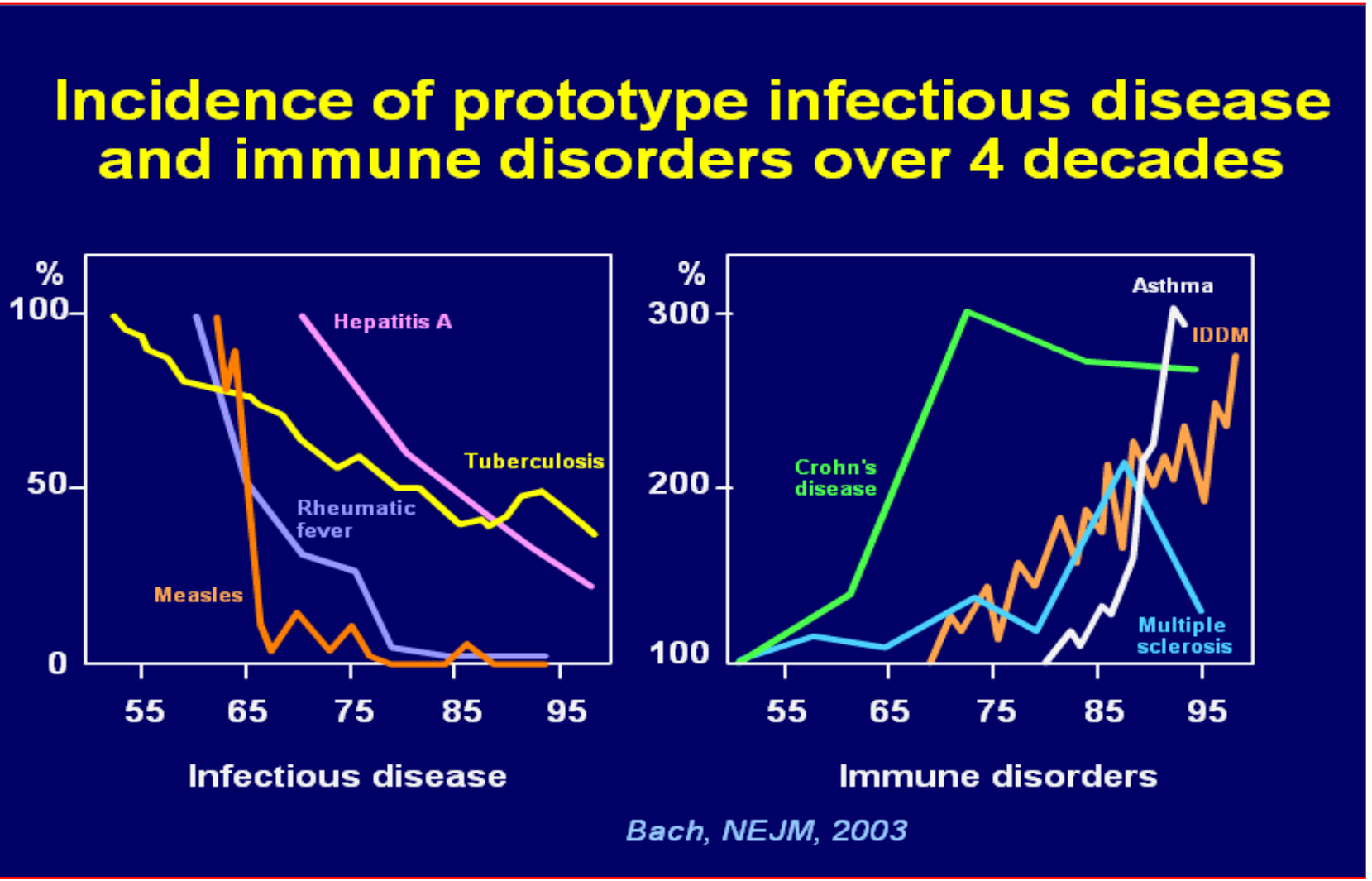
# Articoli scientifici su PFAS e rischi per la salute umana




http://pubs.acs.org/doi/pdf/10.1021/acs.jafc.6b04683

Vincenzo Cordiano

# La ***transition épidémiologique*** du XX siècle




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

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

Athérosclérose

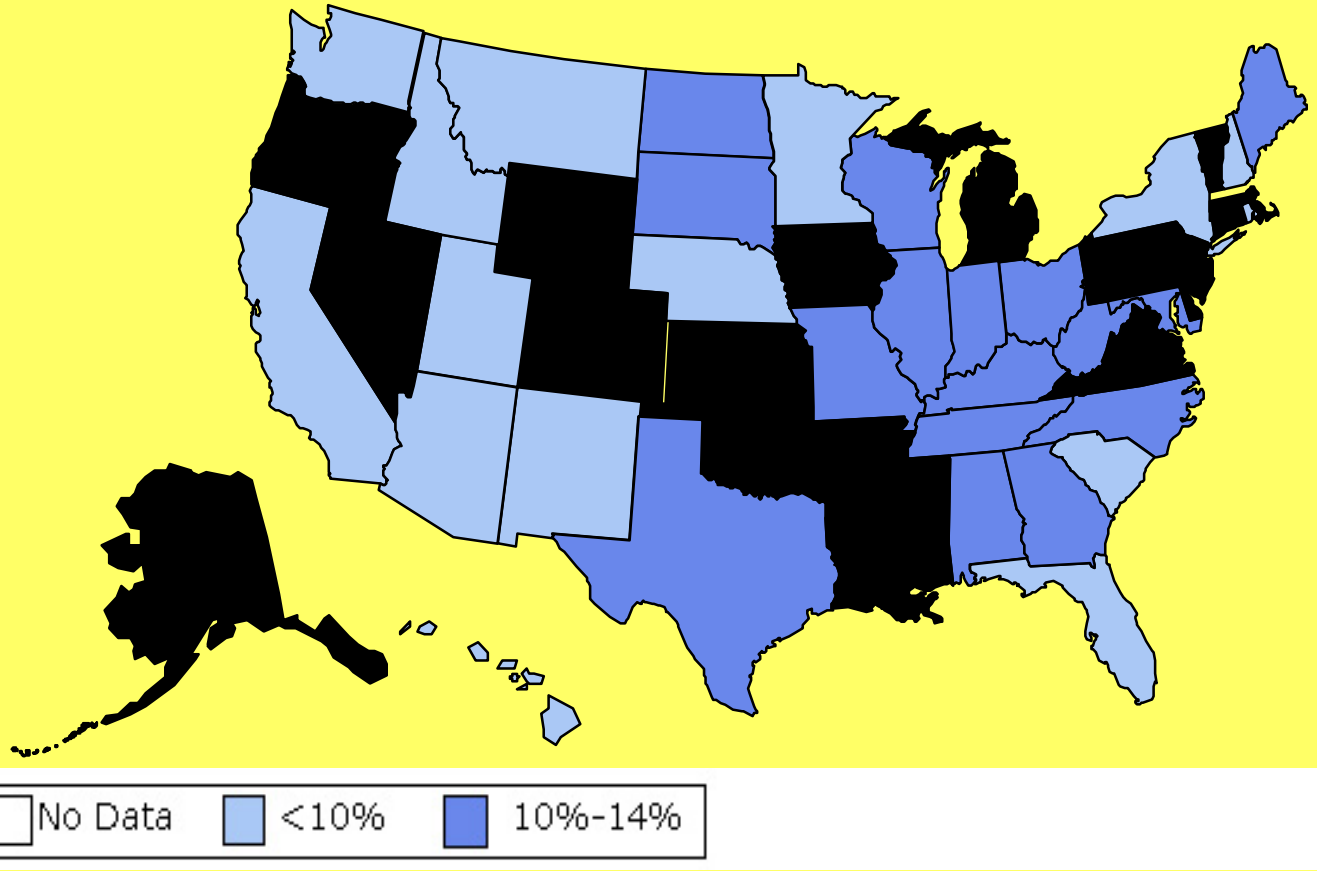
Troubles du **neurodéveloppement**
**neurodegeneratives**

**Cancer**.

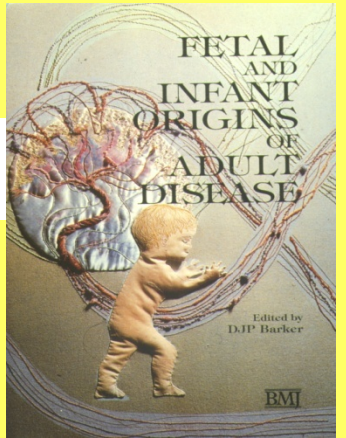
Ceci est un **graphique tiré d'un article publié il y'a 10 ans sur le NEJM**, qui montrait la diminution rapide des maladies infectieuses / aigues et **l'augmentation simultanée des maladies chroniques / inflammatoires** dans le Nord du monde

# Obesity Trends* Among U.S. Adults 1987

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

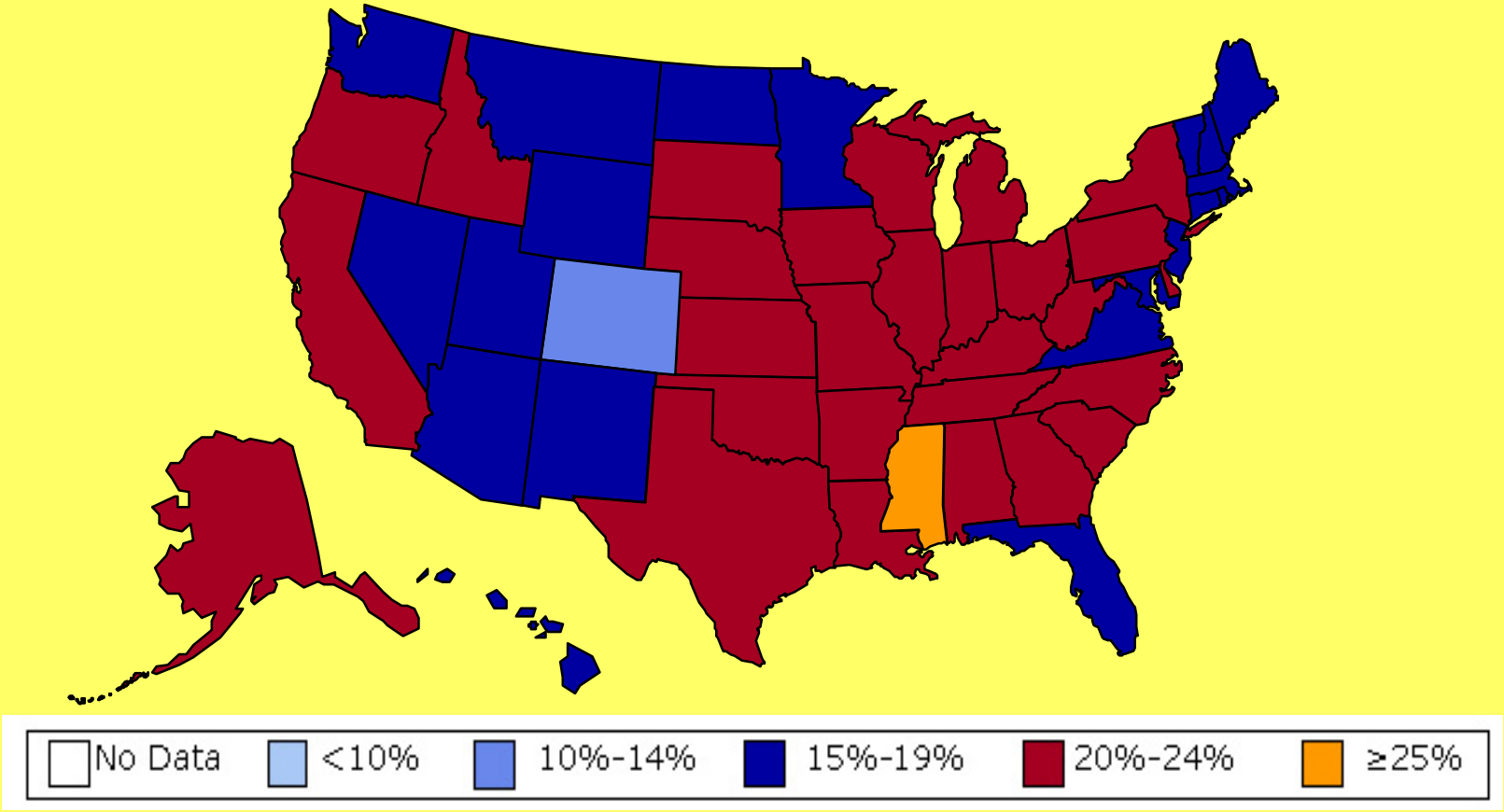



Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.



# Obesity Trends* Among U.S. Adults 2001

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




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

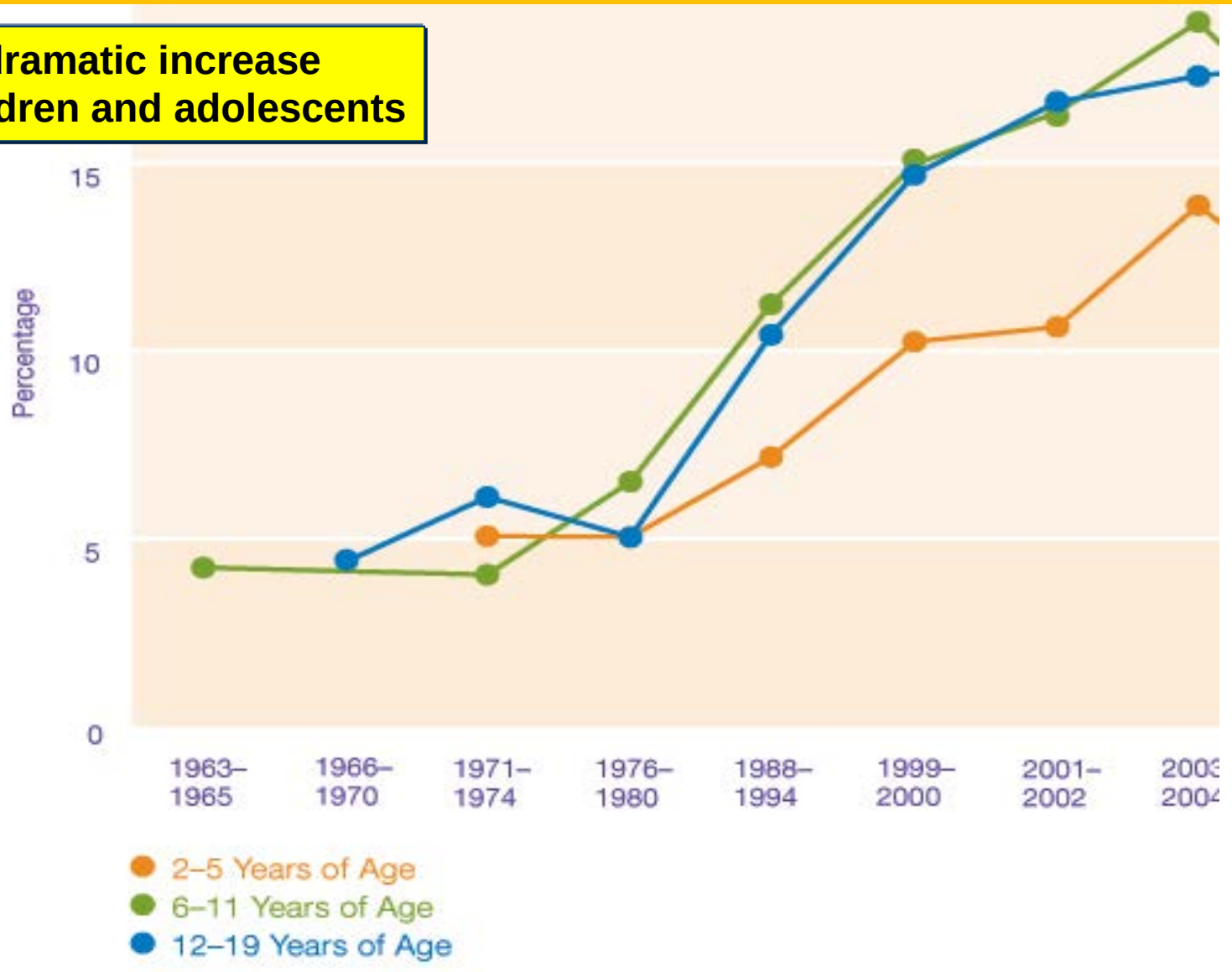
Today the situation has **<u>further deteriorated:</u>**
**65%** of Americans are overweight, **35%** morbidly obese

# The Childhood Obesity Epidemic

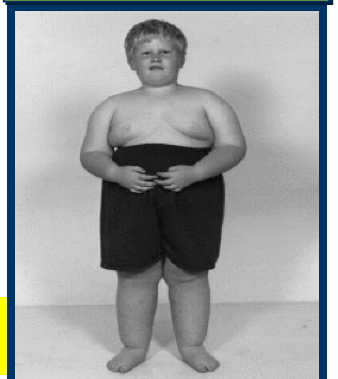
Matthew W. Gillman, MD, SM

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

BMI >95$^{th}$ %'ile




**<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**



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

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

# Obesity and diabetes: from genetics to epigenetics

Ernesto Burgio · Angela Lopomo · Lucia Migliore

Recent researches point out the **continuous increase of "obesogens", in the environment and food chains**, above all *endocrine disruptors*, that may have an important role in the obesity and diabesity pandemics.

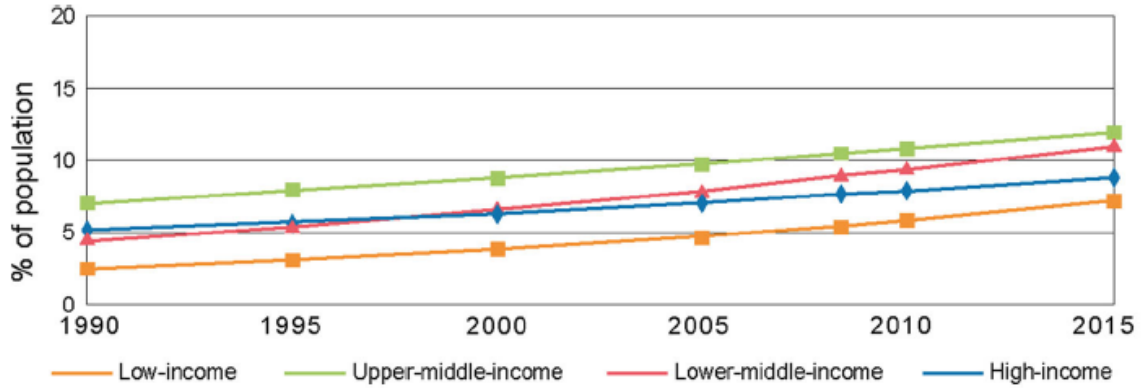



**Fig. 1** Infant and young child overweight trends from 1990 to 2015, by World Bank income group (Adapted from WHO, 2010)

**Genetic factors in obesity and diabetes**

**The obesogen hypothesis**

**Epigenetic biomarkers**

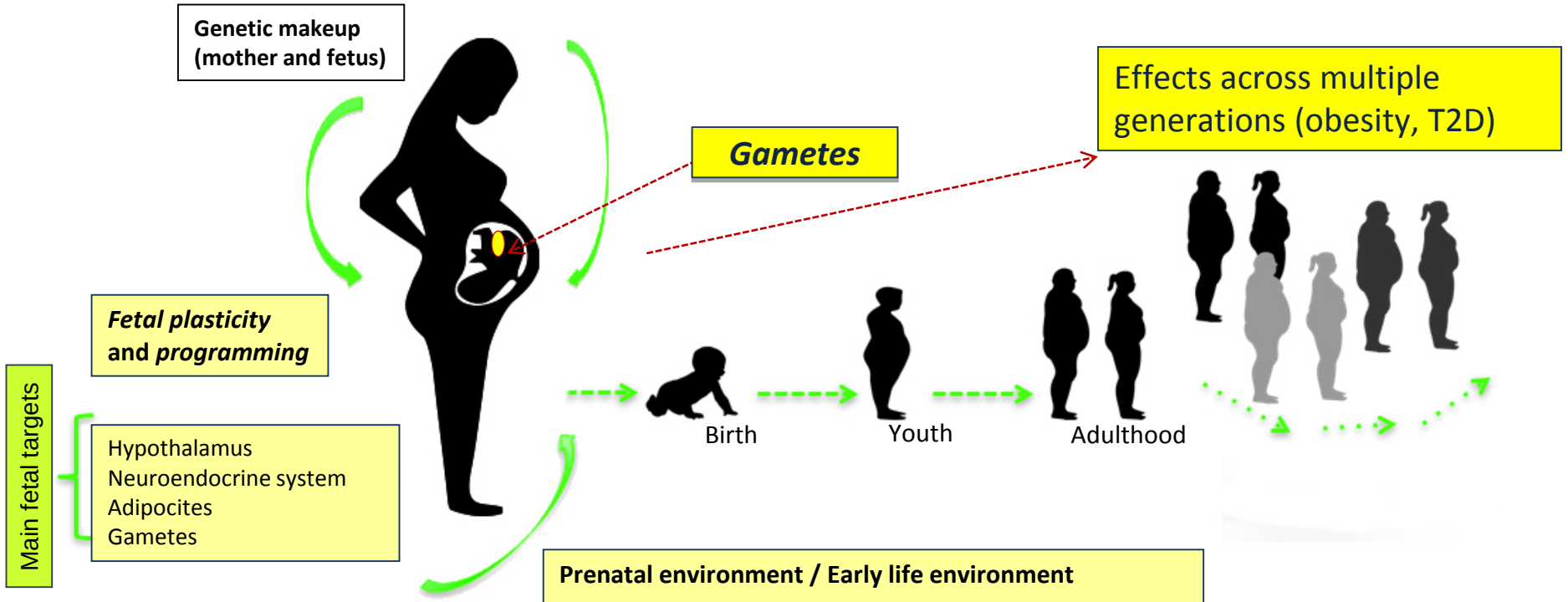
**Beyond genetics**

**Diabetogens and diabetes epidemic**

**From genetics to epigenetics: fetal programming alterations**

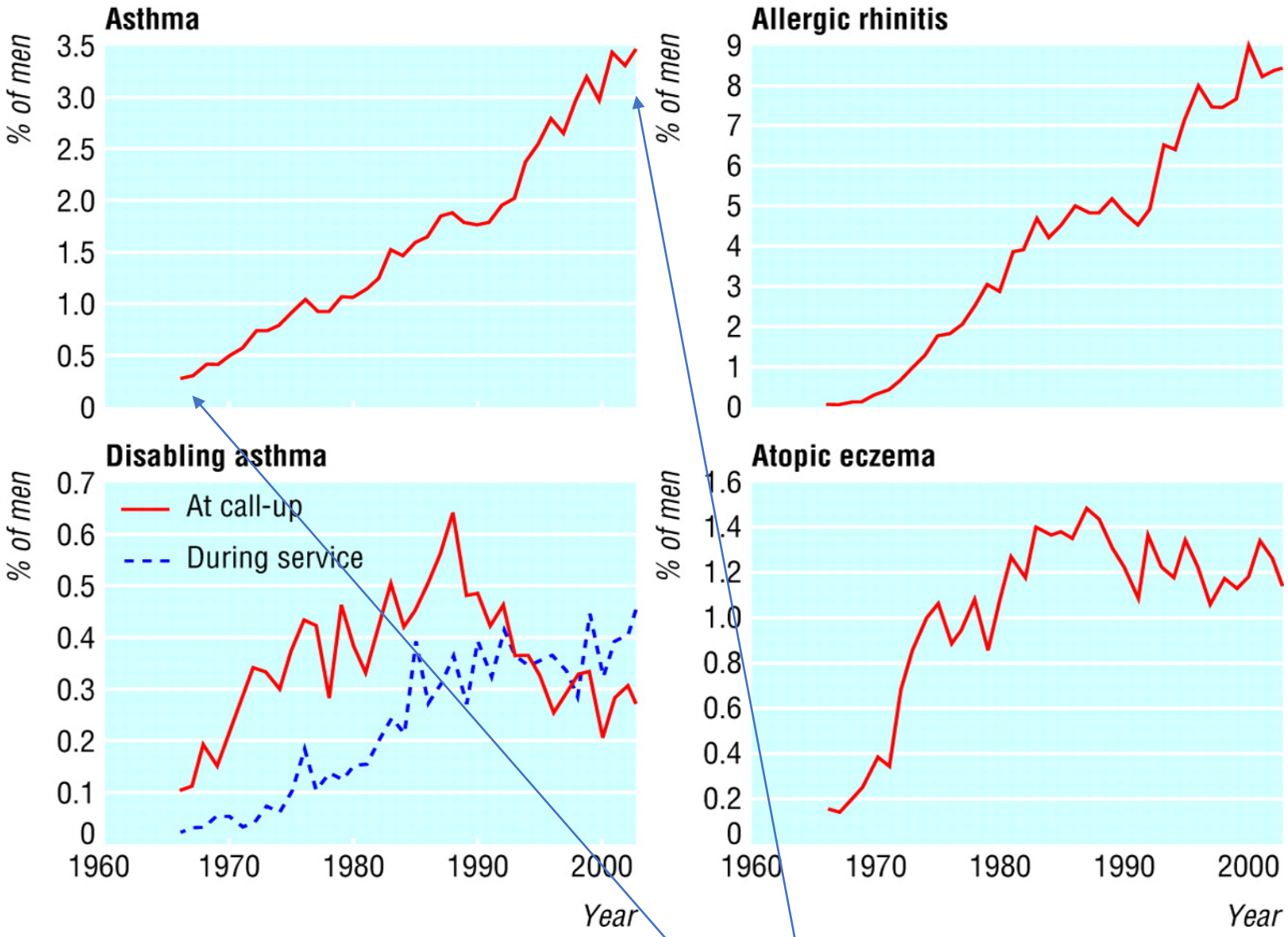
**Is there a role for gut microbiota?**

# Environmentally driven epigenetic effects




**Epigenetic modifications can be passed across generations – a "memory" of environmental influence** that occurred many years previously.

**OBESITY AND DIABETES: FROM GENETICS TO EPIGENETICS (Mol Rep 2015)**
Ernesto Burgio[1,2], Angela Lopomo[3,4] and Lucia Migliore[3]




*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**

WHAT IS EPIGENETICS

# Could Epigenetics Explain the Origins of Allergic Disease?

**Hypersensitivity begins in the womb**

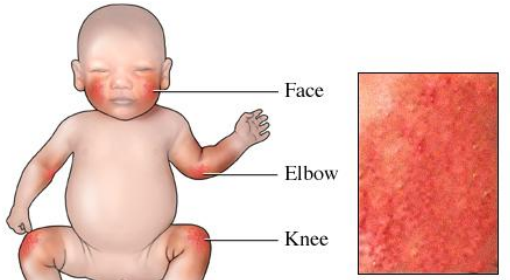
In a study examining **umbilical cord blood**, it was shown that **babies born to allergic mothers had a reduced number of Tregs**…and were at **high risk to develop sensitivity to food allergens and *atopic dermatitis*** (the start of atopic march) **during the first year of life**

Hinz D, (2012). ***Cord blood tregs with stable foxp3 expression are influenced by prenatal environment and associated with atopic dermatitis at the age of one year***. Allergy. 67:380-389

**Parental atopy history, particularly maternal hay fever and paternal asthma** were **related to lower Treg numbers in cord blood**

**Children with lower Treg numbers at birth** had a higher risk to develop ***atopic dermatitis*** (adj. OR = 1.55, 95% CI = 1.00–2.41) ***and sensitization to food allergens*** (adj. OR = 1.55, 95% CI = 1.06–2.25) during the first year of life.

**Maternal cytokines (IL-13, IL-17E and IFN-γ)** and **maternal smoking/exposure to tobacco smoke during pregnancy** were also associated with **decreased cord blood Treg numbers**



COPD: Journal of Chronic Obstructive Pulmonary Disease

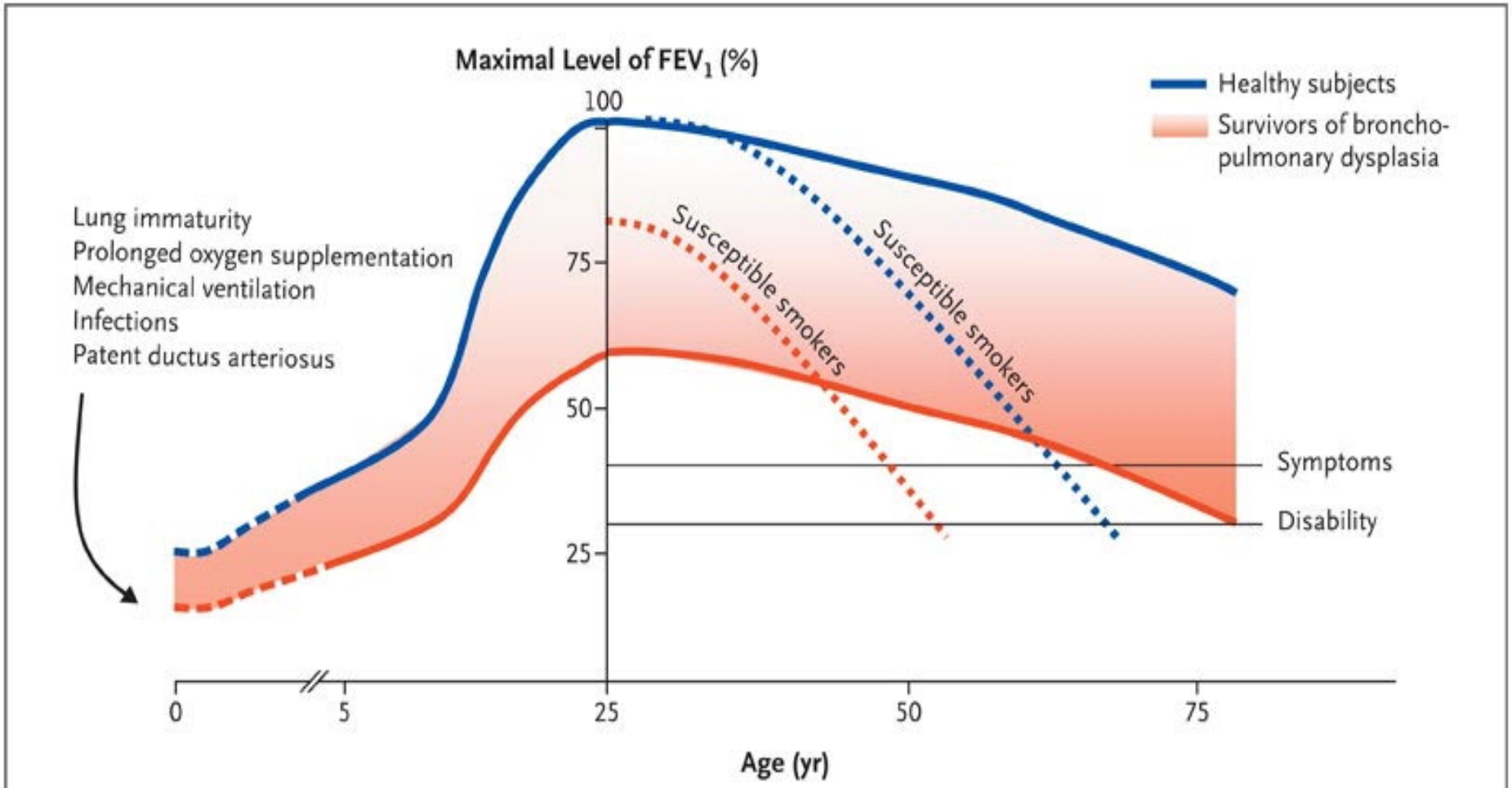
Volume 5, Issue 1, 2008


CLINICAL REVIEW

# COPD: A Pediatric Disease

Chronic obstructive pulmonary disease (COPD) is conventionally thought of as a disease of adult smokers, related to airway inflammation and structural airway changes (remodeling). However, there is important epidemiological evidence, from a series of studies with overlapping age groups from birth to late middle age that early life events, including antenatal influences on lung growth, program the child to be at increased risk for future COPD. This paper reviews the evidence for potential gene: environment interactions in this process, in particular with respect to the maternal genotype of the COPD patient. It explores the hypothesis that genes important in early lung development are also important in determining adult risk for COPD. Although the major preventable factor adversely impacting on child lung health is maternal smoking, the effects of viral infection, nutrition, and indoor and outdoor pollution are reviewed. The survivors of preterm birth are another important cohort who may develop premature COPD in adult life. Early life events provide the substrate for COPD, with later cigarette smoking, and occasionally other exposures, pulling the trigger to produce COPD. Although a rigorous anti-smoking program is necessary to halt this spiral of lung destruction leading to COPD, a focus on early (including prenatal) lung health is also important. Any model of COPD which does not take into account early life influences is likely to be fatally flawed.

# EARLY INSULTS MAY CAUSE FAILURE TO ACHIEVE MAXIMAL LUNG FUNCTION AND EXPOSE INDIVIDUALS TO THE RISK OF COPD LATER IN LIFE




Esiste infatti una serie di **fattori di rischio che possono già intervenire durante la vita fetale: l'immaturità del polmone, le infezioni virali, l'atopia, inquinamento atmosferico e fumo passivo** sono in grado di modificare la curva del **declino di FEV1**.

**Dr. Sandro Rossi**
*U.O. Pneumologia Terni*
*Usl Umbria 2*

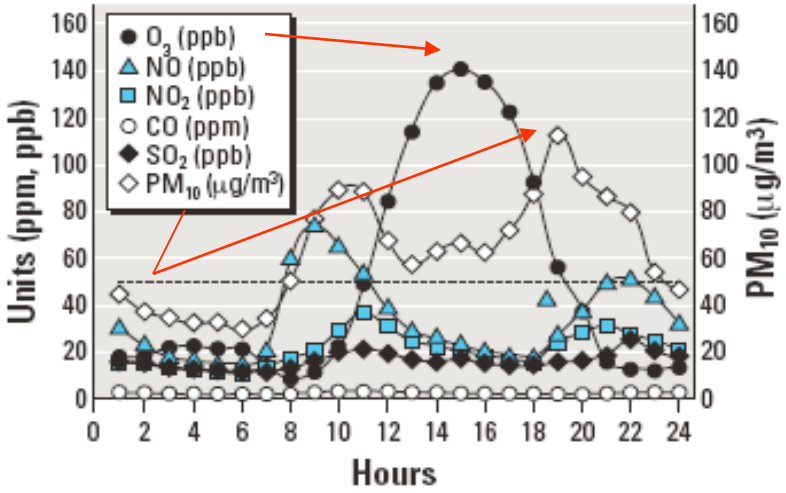



**Figure 1.** The typical 24-hr pattern of key air pollutants in southwest metropolitan Mexico City averaged over 31 days for the month of January 1999. Left scale: $O_3$, nitric oxide, $NO_2$, carbon monoxide, sulfur dioxide; right scale: $PM_{10}$. The horizontal dashed line at 50 μg/m³ represents the current yearly $PM_{10}$ standard. There is an average of 4 ± 1 hr/day with $O_3$ values above 0.08 ppm. The average yearly $PM_{10}$ level is 48 μg/m³, and that for $PM_{2.5}$ is 21 μg/m³.

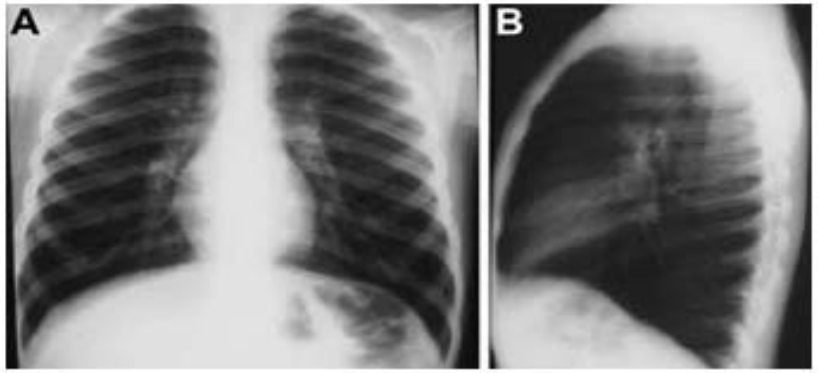



**Figure 2.** Eleven-year-old boy with frontal (*A*) and lateral (*B*) CXRs that demonstrate hyperinflation. The lateral film shows an increase in the anterior clear space, increased anterior–posterior diameter, and flattening of the hemidiaphragms.

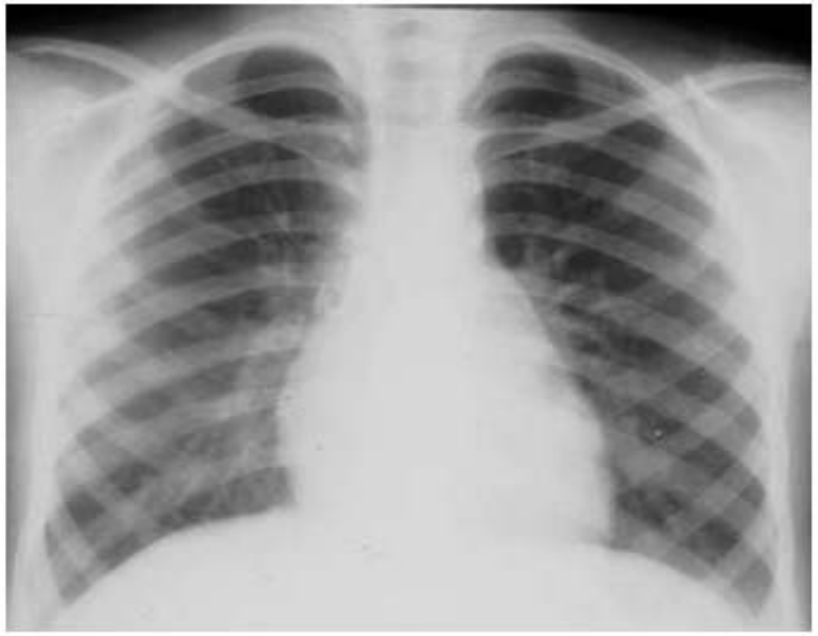


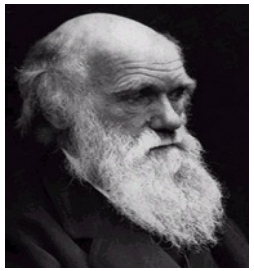
**Figure 3.** Ten-year-old boy with a frontal CXR that demonstrates subtle increased linear markings.

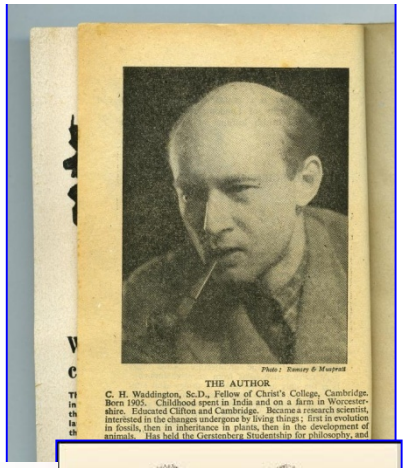
C.H.U. DE NICE

XXIVème SEMINAIRE NICOIS D'ENDOCRINOLOGIE
DIABETOLOGIE ET REPRODUCTION

*Professeur Patrick FENICHEL*

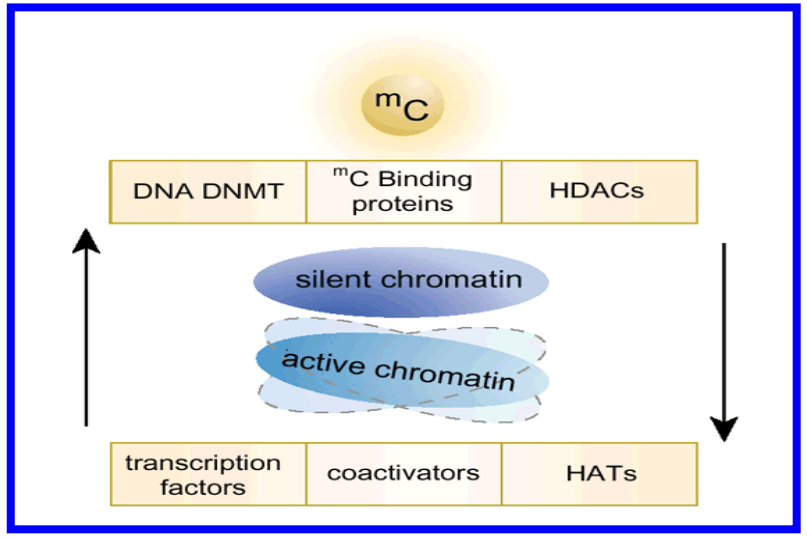
*Sous le patronage de la Société Française d'Endocrinologie*






# Cancer des enfants: de la génétique à l'épigénétique

**(vers un paradigme épigénétique dans la carcinogenèse)**



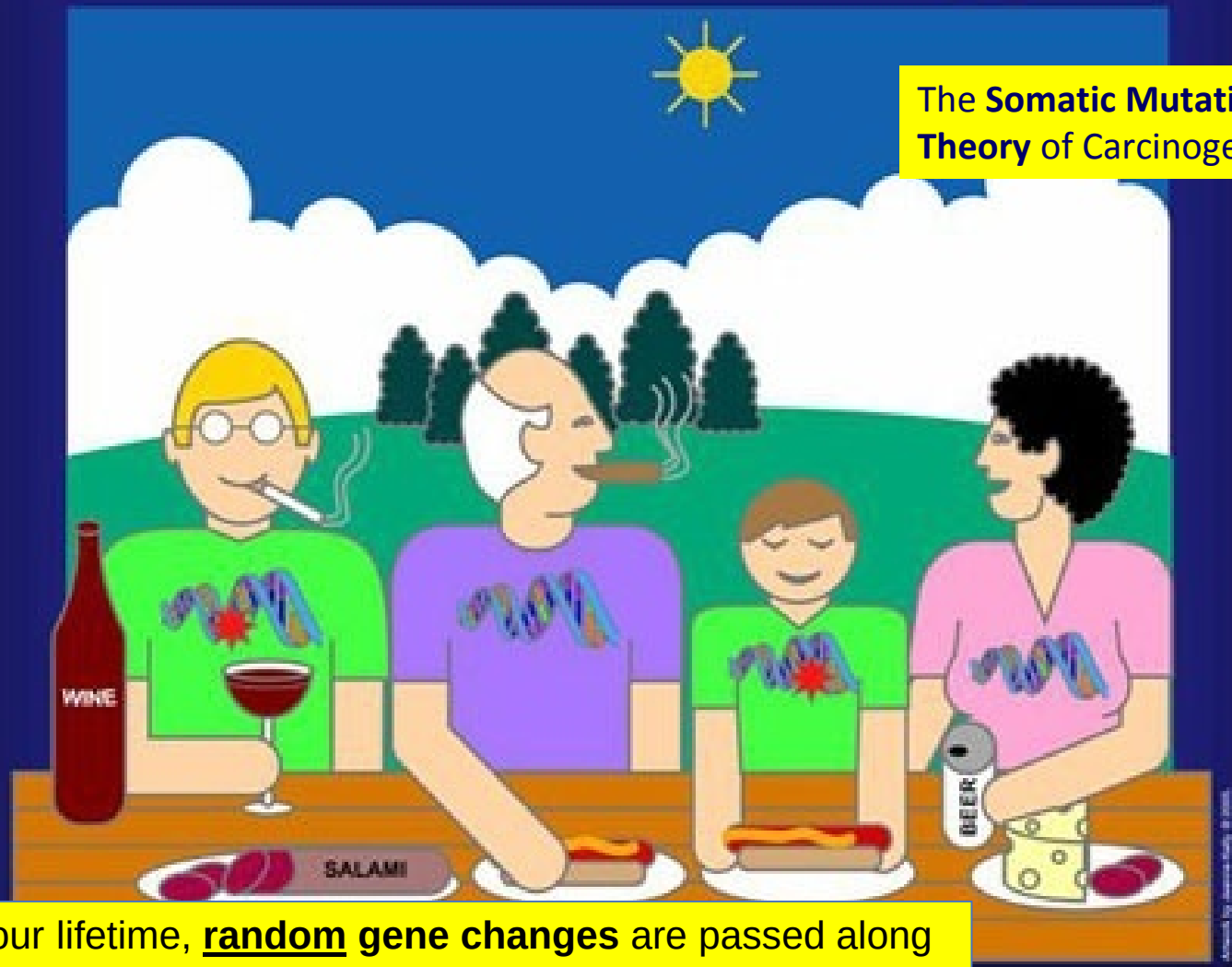

ECERI
European Cancer and Environment Research Institute

**ERNESTO BURGIO**
**ECERI - European Cancer and Environment Research Institute (Bruxelles)**

# The Inside Matters: Random Gene Changes

**What is Cancer ?**

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**

CELEBRATING OUR TENTH YEAR

HISTORICAL PERSPECTIVE

nature medicine

## What's *Cancer* ?

# Cancer genes and the pathways they control

Bert Vogelstein & Kenneth W Kinzler

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

The revolution in cancer research can be summed up in a single sentence: cancer is, in essence, a genetic disease. In the last decade, many important genes responsible for the genesis of various cancers have been discovered, their mutations precisely identified, and the pathways through which they act characterized. The purposes of this review are to highlight examples of progress in these areas, indicate where knowledge is scarce and point out fertile grounds for future investigation.

**Alterations in three types of genes** are responsible for tumorigenesis:
***oncogenes***, ***tumor-suppressor genes*** and ***stability genes***
Unlike diseases such as cystic fibrosis or muscular dystrophy,
wherein mutations in one gene can cause disease, no single gene defect 'causes' cancer. Mammalian **cells have multiple safeguards to protect them against the potentially lethal effects of cancer gene mutations**,
and **only when several genes are defective does an invasive cancer develop**

Vogelstein B, Kinzler KW. ***Cancer genes and the pathways they control*** Nat Med. 2004 Aug;10(8):789-99.

**Table 1 Cancer predisposition genes**

| Gene (synonym(s))[a] | Syndrome | Hereditary pattern | Second hit | Pathway[b] | Major heredity tumor types[c] |
|---|---|---|---|---|---|
| **Tumor-suppressor genes** | | | | | |
| *APC* | FAP | Dominant | Inactivation of WT allele | APC | Colon, thyroid, stomach, intestine |
| *AXIN2* | Attenuated polyposis | Dominant | Inactivation of WT allele | APC | Colon |
| *CDH1* (E-cadherin) | Familial gastric carcinoma | Dominant | Inactivation of WT allele | APC | Stomach |
| *GPC3* | Simpson-Golabi-Behmel syndrome | X-linked | ? | APC | Embryonal |
| *TP53* (*p53*) | Li-Fraumeni syndrome | Dominant | Inactivation of WT allele | p53 | Breast, sarcoma, adrenal, brain... |
| *WT1* | Familial Wilms tumor | Dominant | Inactivation of WT allele | p53 | Wilms' |
| *STK11* (*LKB1*) | Peutz-Jeghers syndrome | Dominant | Inactivation of WT allele | PI3K | Intestinal, ovarian, pancreatic |
| *PTEN* | Cowden syndrome | Dominant | Inactivation of WT allele | PI3K | Hamartoma, glioma, uterus |
| *TSC1, TSC2* | Tuberous sclerosis | Dominant | Inactivation of WT allele | PI3K | Hamartoma, kidney |
| *CDKN2A* ($p16^{INK4A}$, $p14^{ARF}$) | Familial malignant melanoma | Dominant | Inactivation of WT allele | RB | Melanoma, pancreas |
| *CDK4* | Familial malignant melanoma | Dominant | ? | RB | Melanoma |
| *RB1* | Hereditary retinoblastoma | Dominant | Inactivation of WT allele | RB | Eye |
| *NF1* | Neurofibromatosis type 1 | Dominant | Inactivation of WT allele | RTK | Neurofibroma |
| **Stability genes** | | | | | |
| *MUTYH* | Attenuated polyposis | Recessive | ? | BER | Colon |
| *ATM* | Ataxia telangiectasia | Recessive | ? | CIN | Leukemias, lymphomas, brain |
| *BLM* | Bloom syndrome | Recessive | ? | CIN | Leukemias, lymphomas, skin |
| *BRCA1, BRCA2* | Hereditary breast cancer | Dominant | Inactivation of WT allele | CIN | Breast, ovary |
| *FANCA, C, D2, E, F,G* | Fanconi anemia | Recessive | ? | CIN | Leukemias |
| *MSH2, MLH1, MSH6, PMS2* | HNPCC | Dominant | Inactivation of WT allele | MMR | Colon, uterus |
| *XPA, C; ERCC2–5; DDB2* | Xeroderma pigmentosum | Recessive | ? | NER | Skin |
| **Oncogenes** | | | | | |
| *KIT* | Familial gastrointestinal stromal tumors | Dominant | ? | RTK | Gastrointestinal stromal tumors |
| *MET* | Hereditary papillary renal cell carcinoma | Dominant | Mutant allele duplication | RTK | Kidney |

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] Department of Biochemistry and Biophysics and, Hormone Research Institute, University of California at San Francisco, San Francisco, California 94143, USA

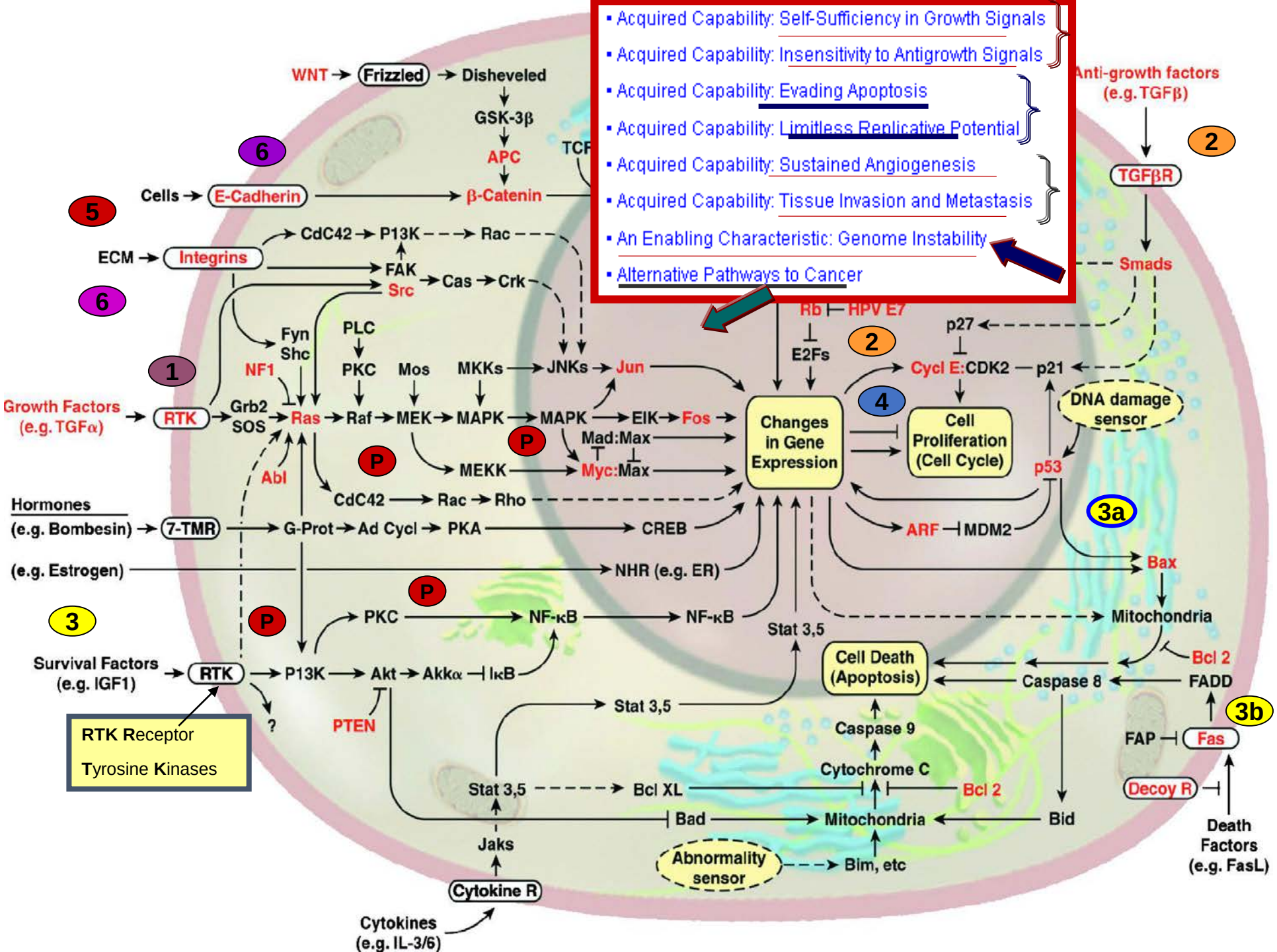
[2] Whitehead Institute for Biomedical Research and, Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02142, USA

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 dictate malignant growth:**

- 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
▪ Acquired Capability: Insensitivity to Antigrowth Signals
▪ Acquired Capability: Evading Apoptosis
▪ 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
NF1
PLC
PKC
Mos
MKKs
JNKs
Jun
Growth Factors
(e.g. TGFα)
RTK
Grb2
SOS
Ras
Raf
MEK
MAPK
MAPK
ElK
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)
Survival Factors
(e.g. IGF1)
RTK
P13K
Akt
Akkα
IκB
PKC
NF-κB
NF-κB
PTEN
?
Stat 3,5
Stat 3,5
Jaks
Cytokine R
Cytokines
(e.g. IL-3/6)
Stat 3,5
Bcl XL
Bad
Abnormality
sensor
Bim, etc
Cytochrome C
Bcl 2
Mitochondria
Bid
Caspase 9
Cell Death
(Apoptosis)
Caspase 8
Bcl 2
FADD
FAP
Fas
Decoy R
Death
Factors
(e.g. FasL)
Anti-growth factors
(e.g. TGFβ)
TGFβR
Smads
Rb
HPV E7
E2Fs
p27
Cycl E:CDK2
p21
DNA damage
sensor
Changes
in Gene
Expression
Cell
Proliferation
(Cell Cycle)
p53
ARF
MDM2
Bax
Mitochondria
RTK Receptor
Tyrosine Kinases
1
2
2
3
3a
3b
4
5
6
6
P
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.

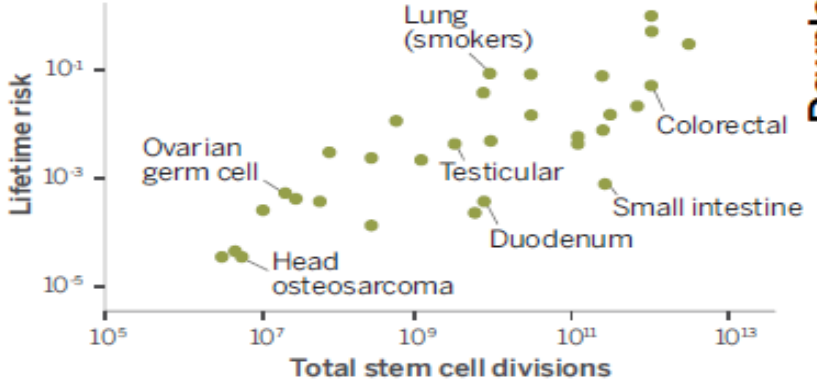
CANCER ETIOLOGY

# 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.



# 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***

**The only distinguishing feature (HALLMARK) of cancer** is its **ability to metastasize** (which is **not the result of mutations**, but the **reactivation of an embryonic genetic program !!)**

NEWS FEATURE

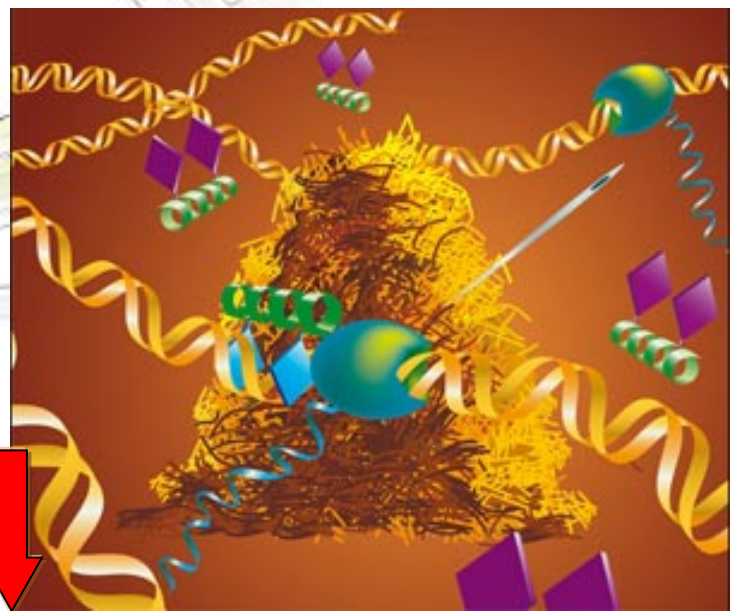
NATURE|Vol 464|15 April 2010

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.

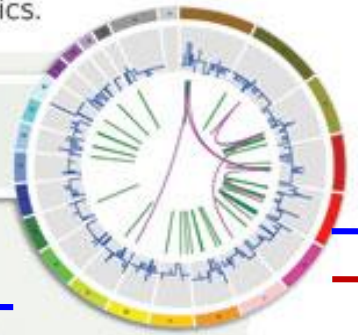
In a recent **editorial** on *Nature* Heidi Ledford stated that **the millions of genetic sequences and SNPs accumulated** in an attempt to **decipher the genetics of cancer** have built **giant haystacks in which researchers have gone lost …**



**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.



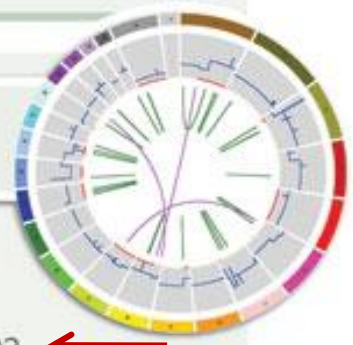
## LUNG CANCER

**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).



## 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).

## 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).

## BRAIN CANCER

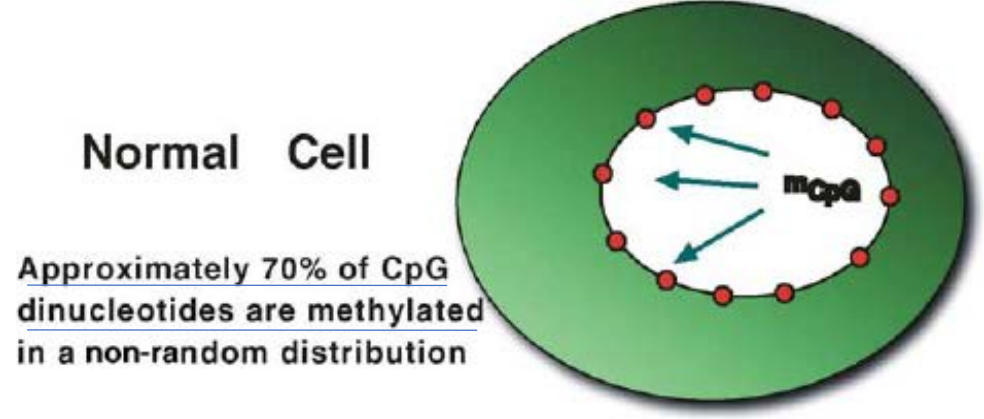
**Cancer: glioblastoma multiforme**

- 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.

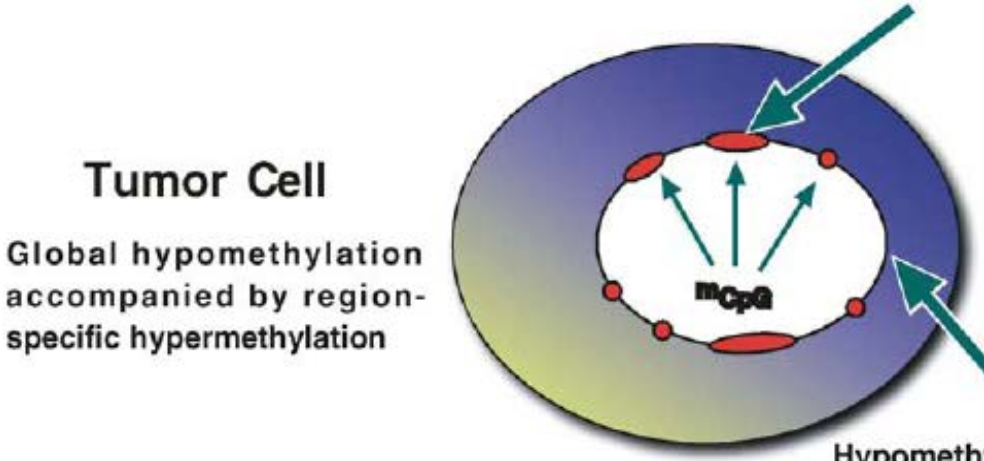
Source: E. R. Mardis *et al. N. Engl. J. Med.* **361,** 1058–1066 (2009).

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




Trigger (?)

Hypermethylation:
- Silencing of tumor suppressor genes
- Gene mutation




Hypomethylation:
- Potential activation of oncogenes
- Genome instability

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)*,**

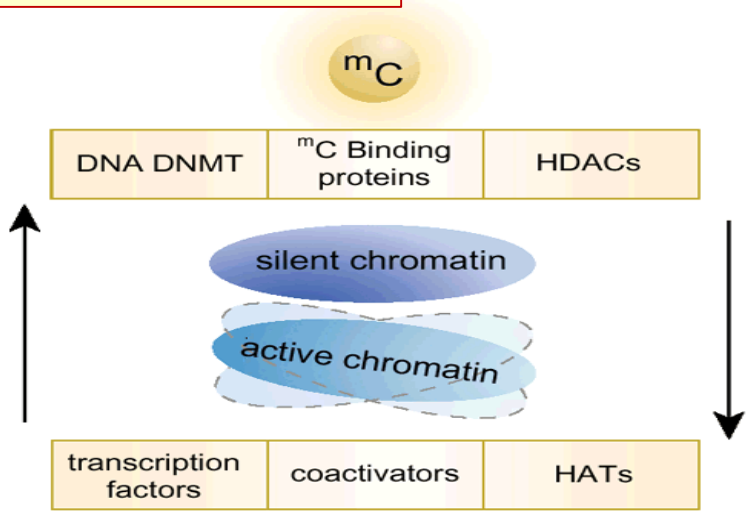
***Retrosequences activation***

R Villa, F De Santis, A Gutierrez, S Minucci, PG Pelicci, L Di Croce
***Epigenetic gene silencing in acute promyelocytic leukemia*** Biochem Pharmacol (2004) 68: 1247-54

# Towards an epigenetic model in carcinogenesis

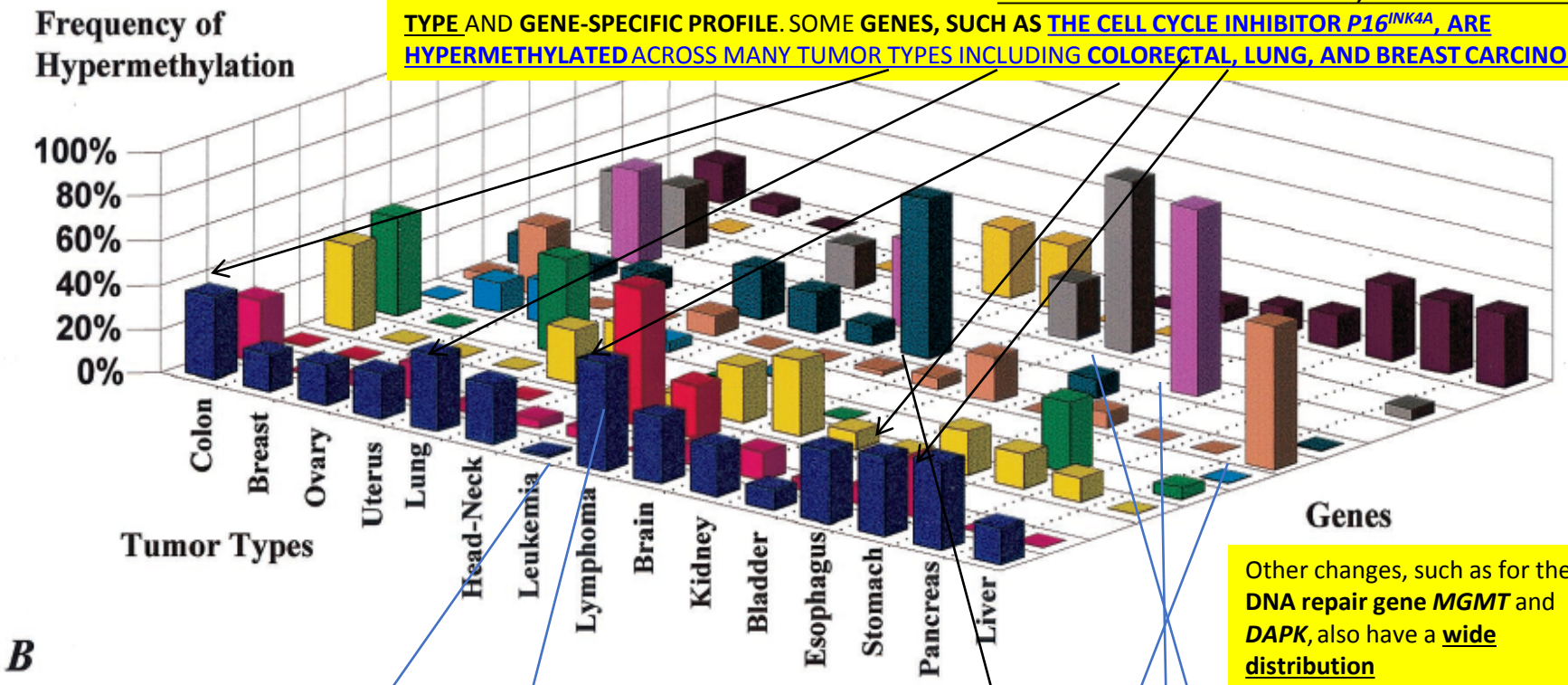
- .. there is ***now ample evidence*** that some **specific epigenetic alterations,** (primarily the ***hypomethylation*** **of DNA**, with **activation of oncogenes** and **increased mobility of mobile sequences**) ** **are the result of protracted genomic *stress* (eg chronic inflammation and persistent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

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



**ONE OR MORE** OF THE GENES STUDIED IS **HYPERMETHYLATED IN EVERY TUMOR TYPE**. **HOWEVER, THE PROFILE** OF **PROMOTER HYPERMETHYLATION FOR THE GENES DIFFERS FOR EACH CANCER TYPE, PROVIDING A TUMOR-TYPE** AND **GENE-SPECIFIC PROFILE**. SOME **GENES, SUCH AS THE CELL CYCLE INHIBITOR *P16*$^{INK4A}$, ARE HYPERMETHYLATED** ACROSS MANY TUMOR TYPES INCLUDING **COLORECTAL, LUNG, AND BREAST CARCINOMAS**

***A***




Other changes, such as for the **DNA repair gene *MGMT*** and ***DAPK***, also have a **wide distribution**

***B***

| | *p16* $^{INK4a}$ | *p14* $^{ARF}$ | *p15* $^{INK4b}$ | *MGMT* | *hMLH1* | *BRCA1* | *GSTP1* | *DAPK* | *CDH1* | *TIMP-3* | *p73* | *APC* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Colon | 37%,41/110 | 28%,37/132 | 0%,0/19 | 39%,127/323 | 44%,15/34* | 0%,0/18 | 4%,1/23 | 13%,2/23 | N.D. | 27%,6/22 | 0%,0/10 | 18%,20/108 |
| Breast | 17%,11/66 | 0%,0/20 | 0%,0/16 | 0%,0/36 | 0%,0/10 | 13%,11/84 | 31%,24/77 | 7%,1/15 | 42%,37/88 | 27%,8/29 | 0%.0/15 | 5%,1/19 |
| Ovary | 18%,4/22 | 5%,1/20 | N.D. | 0%,0/23 | N.D. | 19%,11/58 | 0%,0/10 | 9%,2/23 | N.D. | N.D. | N.D. | 0%,0/20 |
| Uterus | 20%,6/29 | 16%,4/25 | N.D. | 0%,0/17 | 43%,24/56* | N.D. | 0%,0/20 | N.D. | N.D. | N.D. | N.D. | N.D. |
| Lung | 31%,28/89 | 6%,4/62 | 0%,0/21 | 21%,18/83 | 0%,0/20 | 4%,1/22 | 9%,2/21 | 16%,10/64 | N.D. | 19%,4/21 | 0%,0/22 | 0%,0/17 |
| Head-Neck | 27%,26/95 | 4%,1/25 | N.D. | 32%,37/116 | N.D. | N.D. | 0%,0/106 | 18%,17/92 | N.D. | N.D. | N.D. | 0%,0/10 |
| Leukemia | 1%,1/150 | 5%,1/20 | 62%,93/150 | 6%,2/31 | 6%,3/51 | 0%,0/19 | 0%,0/10 | 9%,8/86 | 40%,30/75 | N.D. | 31%,11/35 | N.D. |
| Lymphoma | 48%,12/25 | 0%,0/22 | 24%,6/25 | 25%,15/61 | N.D. | N.D. | 2%,1/47 | 72%,21/29 | N.D. | N.D. | 30%,3/10 | N.D. |
| Brain | 30%,3/10 | 9%,2/22 | N.D. | 34%,74/213 | 0%,0/15 | N.D. | 5%,1/20 | N.D. | N.D. | 26%,20/77 | 0%,0/22 | 0/10 |
| Kidney | 23%,6/25 | 13%,5/38 | N.D. | 8%,1/12 | N.D. | N.D. | 20%,8/35 | N.D. | N.D. | 78%,28/36 | 0%,0/10 | 8%,1/12 |
| Bladder | 9%,1/11 | 5%,1/20 | N.D. | 4%,2/44 | N.D. | N.D. | 0%,0/24 | 9%,1/11 | N.D. | N.D. | N.D. | 10%,2/19 |
| Esophagus | 33%,5/15 | 8%,3/37 | N.D. | 20%,3/14 | N.D. | N.D. | 7%,1/14 | N.D. | 84%,26/31 | N.D. | N.D. | 15%,4/27 |
| Stomach | 36%,8/22 | 26%,31/118 | N.D. | 16%,10/60 | 32%,21/65* | N.D. | 0%,0/22 | N.D. | N.D. | N.D. | N.D. | 34%,13/38 |
| Pancreas | 39%,7/18 | 0%,0/20 | N.D. | 11%,2/18 | N.D. | N.D. | 0%,0/18 | N.D. | N.D. | N.D. | N.D. | 33%,6/18 |
| Liver | 15%,3/20 | 0%,0/20 | N.D. | 0%,0/59 | 5%,2/20 | 0%,0/18 | 65%,13/20 | 0%,0/20 | N.D. | 5%,1/20 | N.D. | 33%,6/18 |

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 and 2) — with particular focus on their functional consequences and their implications (actual or potential) for the development of effective anticancer therapies.

**Are *TRANSLOCATIONS* chromosomal aberrations or reactive/positive rearrangements ??**

THE CAUSES OF **CHROMOSOMAL ABNORMALITIES** REMAINS POORLY UNDERSTOOD.
STUDIES OF VARIOUS TYPES OF LEUKEMIA HAVE SHOWN THAT CERTAIN ENVIRONMENTAL AND OCCUPATIONAL EXPOSURES AND THERAPY WITH CYTOTOXIC DRUGS CAN INDUCE **CHROMOSOMAL ABERRATIONS**.
FOR EXAMPLE, CASES OF MYELODYSPLASTIC SYNDROME OR AML THAT ARISE AFTER TREATMENT WITH *ALKYLATING AGENTS* ARE FREQUENTLY ASSOCIATED WITH UNBALANCED ABNORMALITIES, PRIMARILY DELETION OR LOSS OF CHROMOSOME 5 OR 7 (OR BOTH), WHEREAS **THERAPY WITH TOPOISOMERASE II INHIBITORS** IS TYPICALLY ASSOCIATED WITH BALANCED ABNORMALITIES, **MOST COMMONLY TRANSLOCATIONS INVOLVING THE *MLL GENE ON CHROMOSOME* BAND 11Q23.1**

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

Published by Oxford University Press 2006
Received November 28, 2005
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.**

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

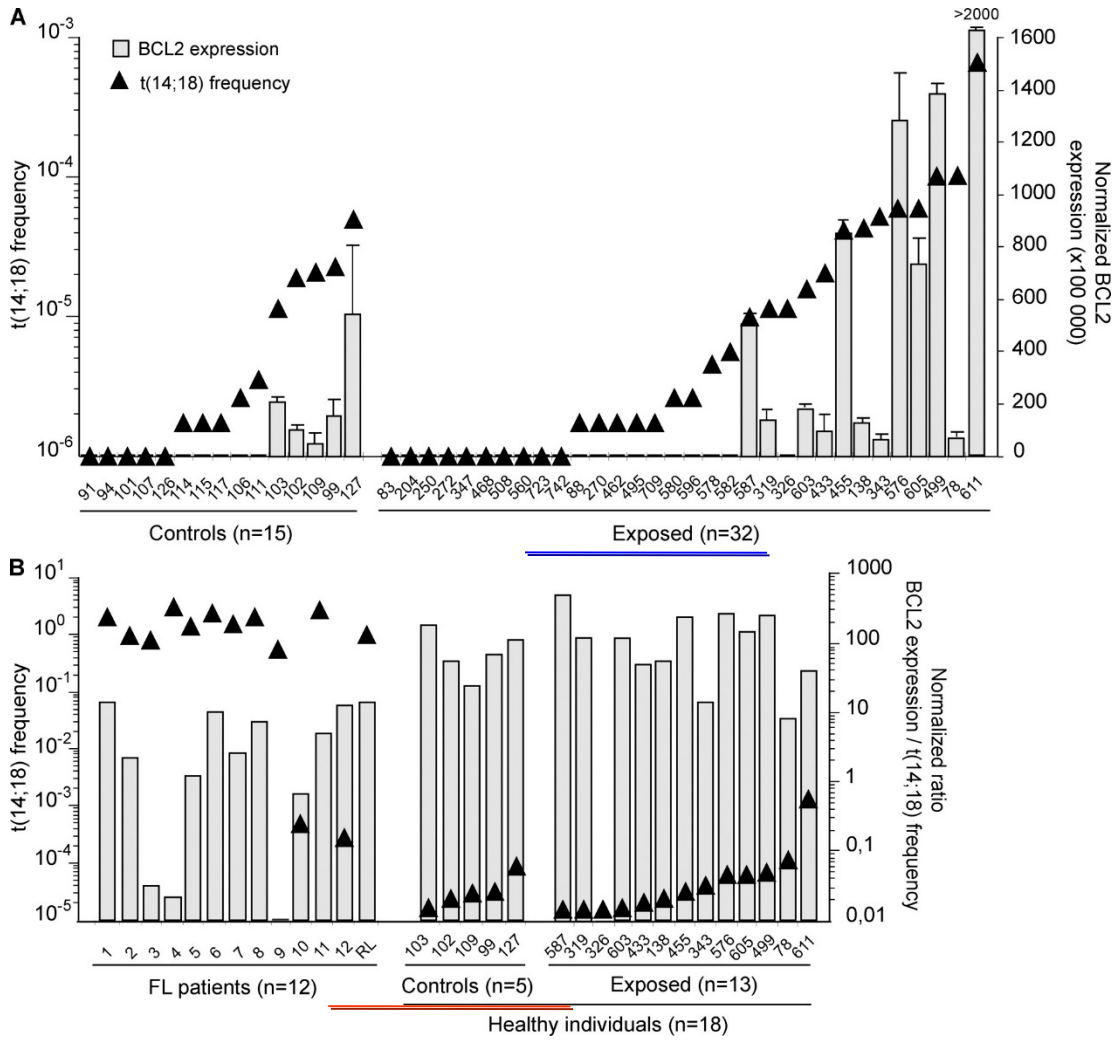
# t(14;18) translocations in lymphocytes of healthy dioxin-exposed individuals from Seveso, Italy

**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

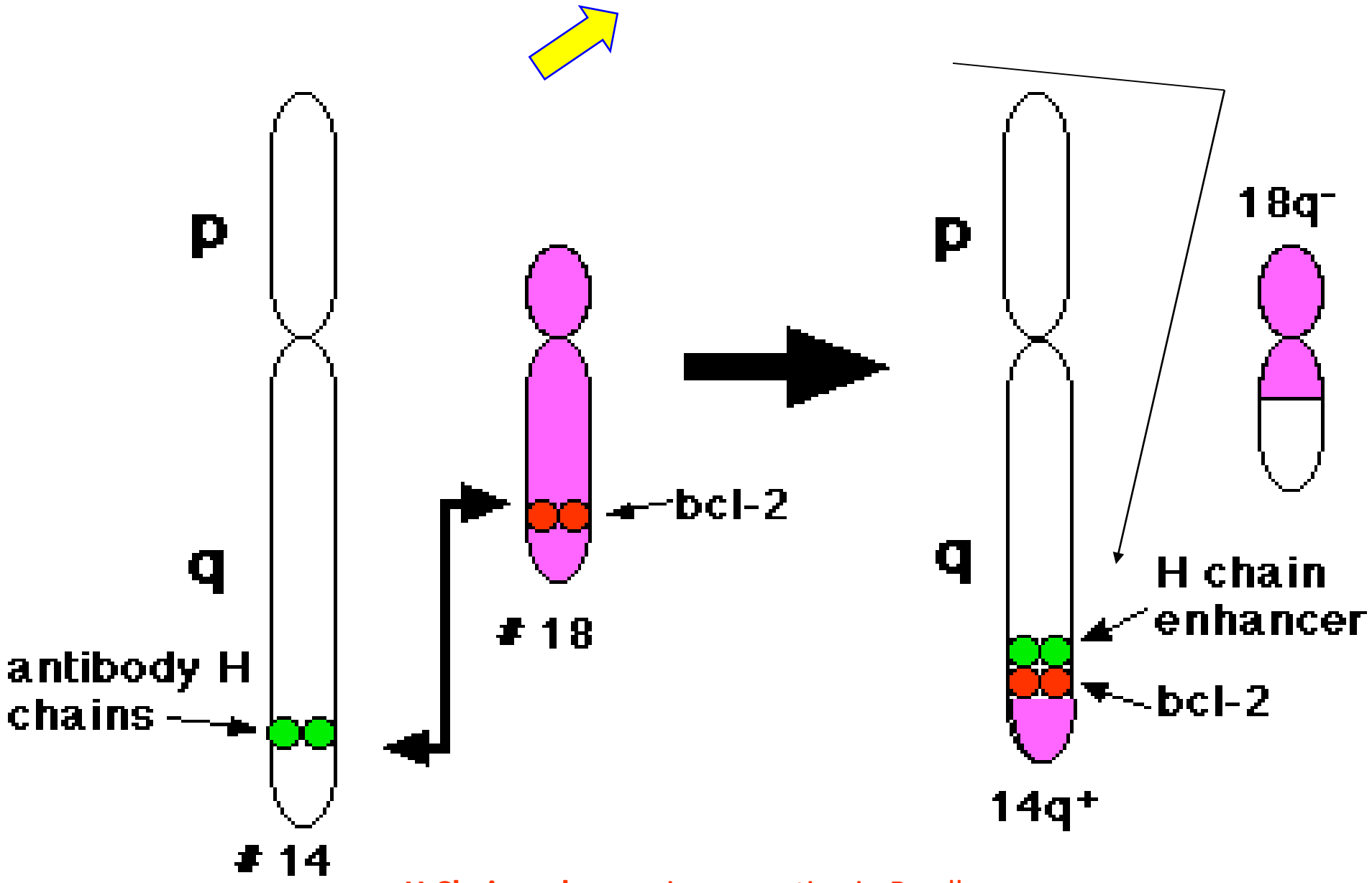



We can find exactly the **same (reactive) translocation** (++ expression of the **anti-apoptotic gene BCL-2**) in many **subjects chronically exposed to pesticides ..**

Agopian et al. Journal of Experimental Medicine 2009:206:1473-1483

JEM

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.

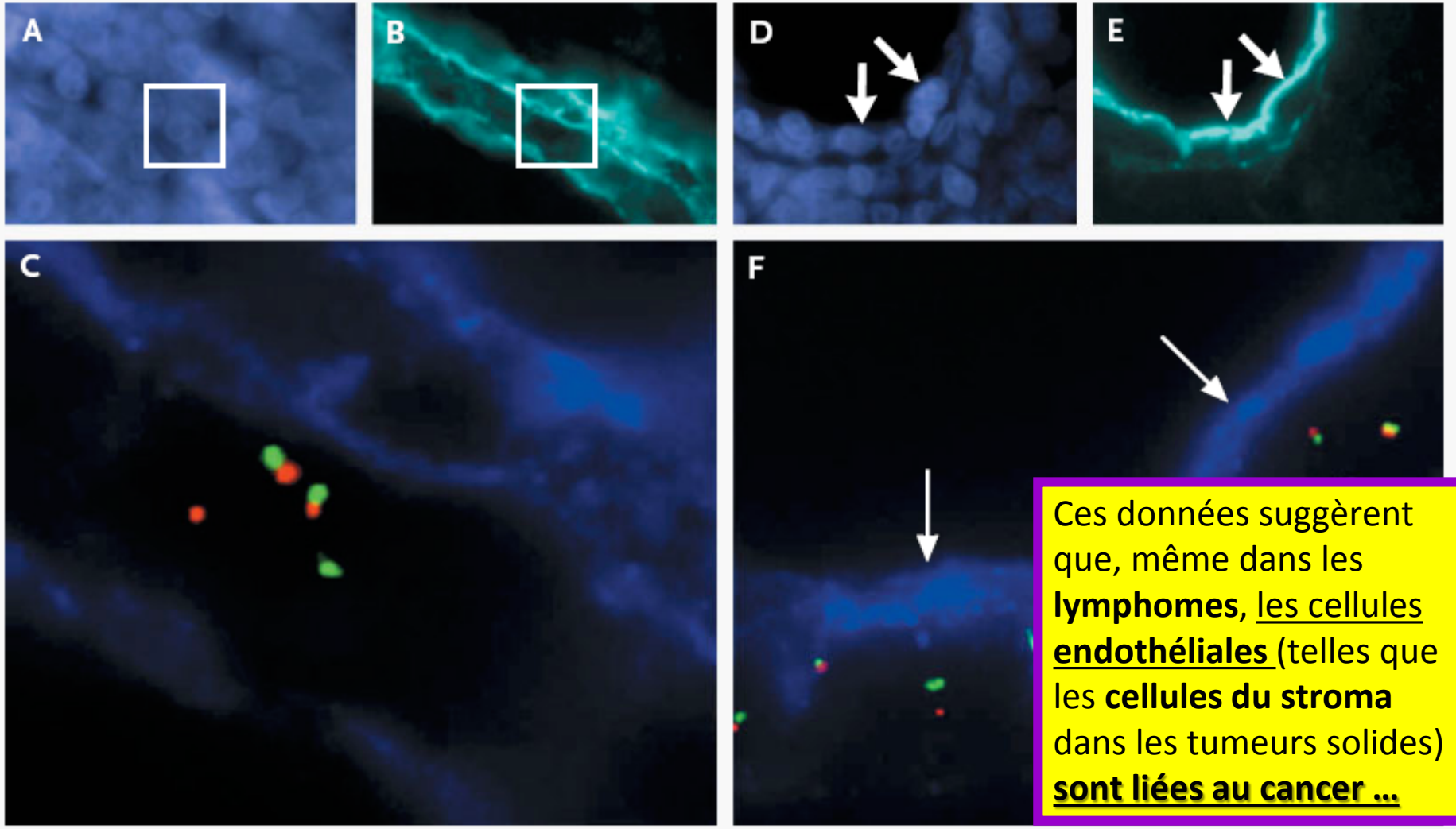
**CONCLUSIONS**

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.*

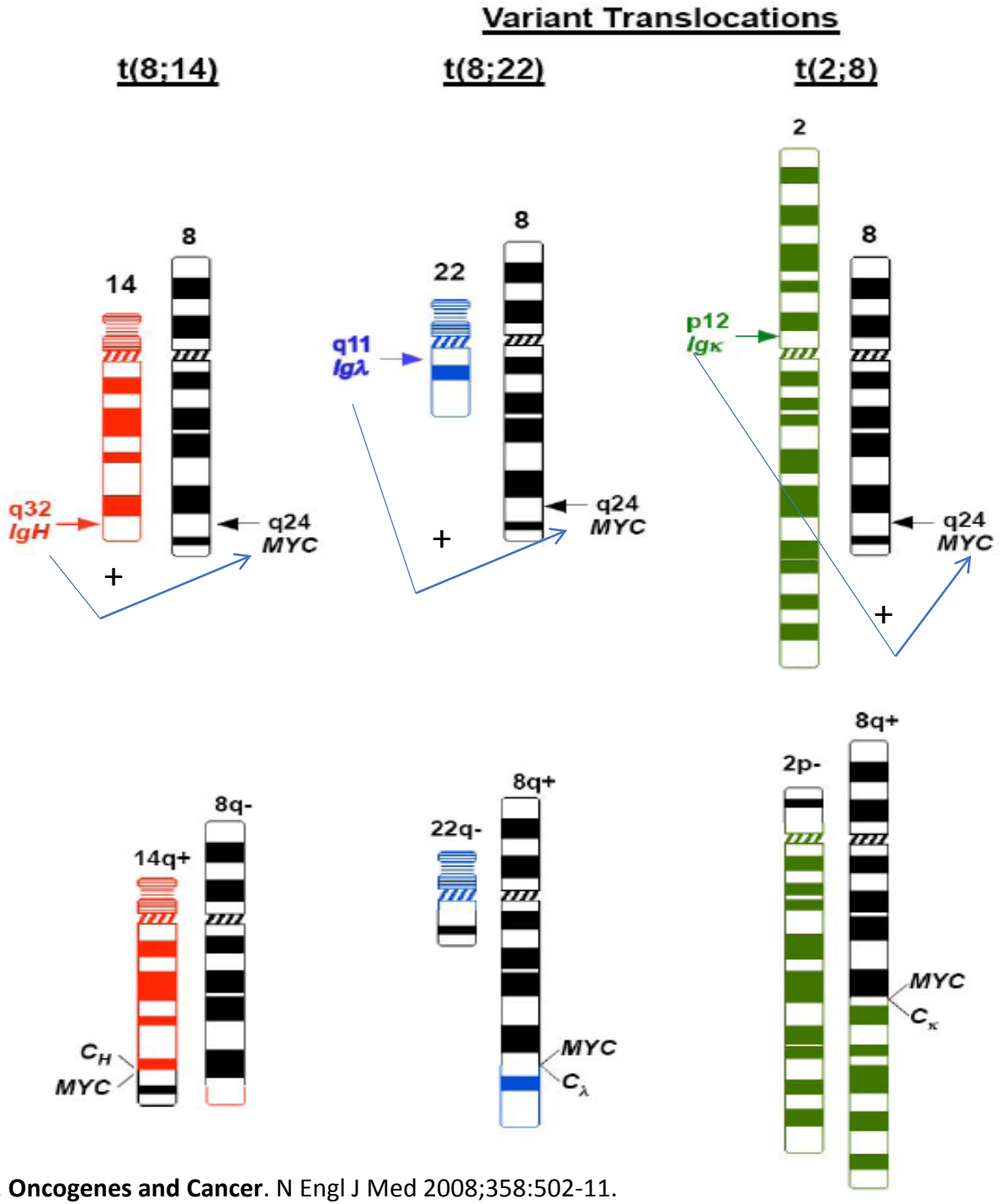
| Case No. | Diagnosis | Site | Patient's Age and Sex | Cytogenetic Aberrations | | Endothelial-Cell Markers | Endothelial Cells with Genetic Aberrations |
|---|---|---|---|---|---|---|---|
| | | | | In Lymphoma Cells (Stem-Cell Line) | In Endothelial Cells | | |
| | | | | | | | % |
| 1 | FL 1† | Lymph 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.




THE FIRST EVIDENCE THAT CANCER ARISES FROM SOMATIC GENETIC ALTERATIONS CAME FROM STUDIES OF **BURKITT'S LYMPHOMA**, IN WHICH ONE OF **THREE DIFFERENT TRANSLOCATIONS** JUXTAPOSES AN **ONCOGENE, *MYC*, ON CHROMOSOME 8q24** TO ONE OF THE **LOCI FOR IMMUNOGLOBULIN GENES**. CHROMOSOMES **14q, 22q, AND 2q — THE TRANSLOCATION PARTNERS — EACH CARRIES ENHANCER ELEMENTS IN THE IMMUNOGLOBULIN LOCI, THEREBY ACTIVATING THE JUXTAPOSED *C-MYC ONCOGENE***

Are the ***antibody gene loci*** **quite *"dangerous places"* for *proto-oncogenes*** to take up residence ?

Croce CM. **Oncogenes and Cancer**. N Engl J Med 2008;358:502-11.

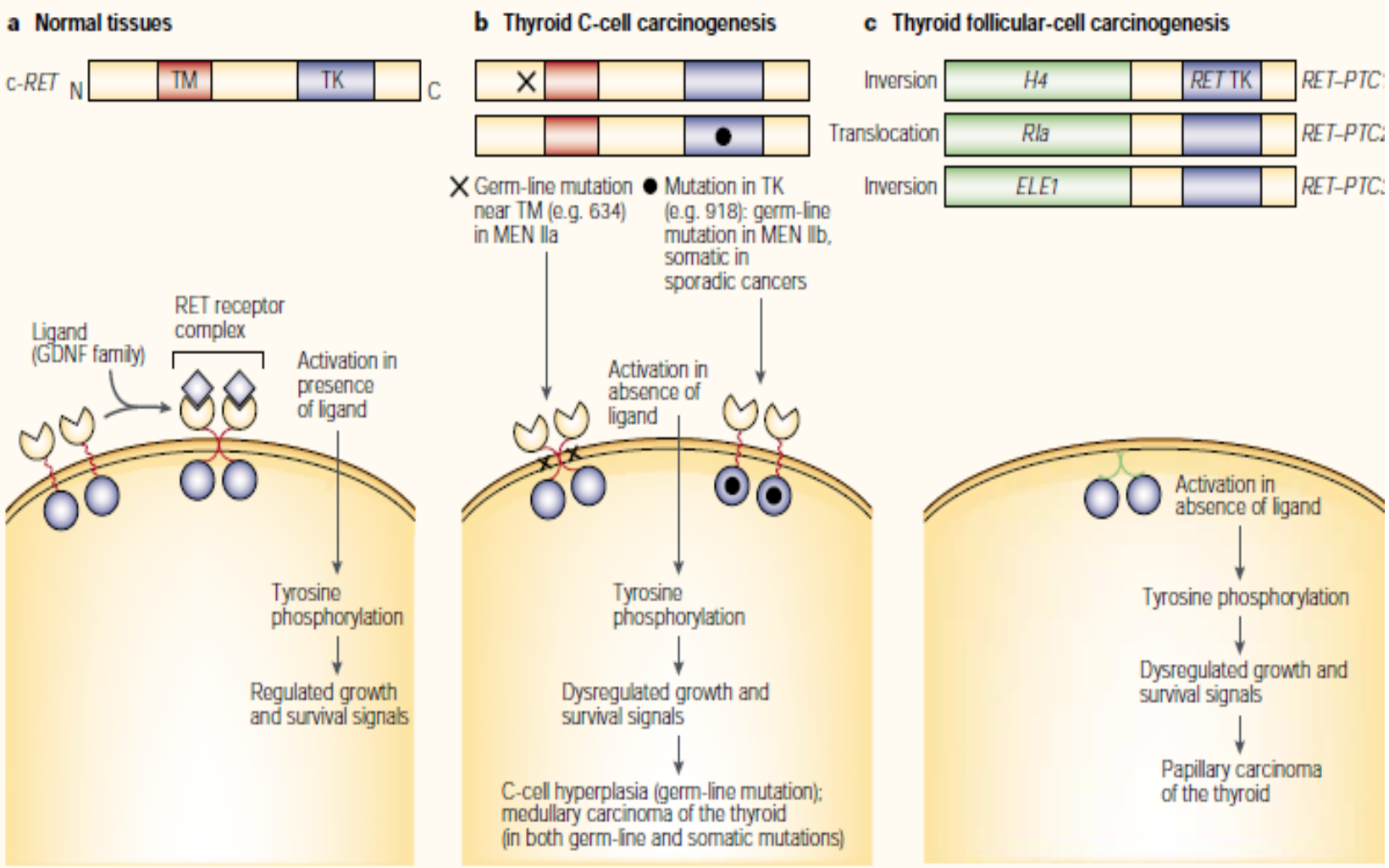



Figure 3 | **The role of *RET* in thyroid carcinogenesis. a** | The receptor tyrosine kinase c-*RET* is normally expressed in the developing neural-crest-derived tissues, including thyroid C cells. It binds to members of the glial-derived neurotrophic factor (GDNF) family of ligands, leading to dimerization of c-RET and

**… in Bielorussia l'incidenza aumentò di 30 volte nel '95 e nelle zone più vicine a Chernobyl di 100 volte**…

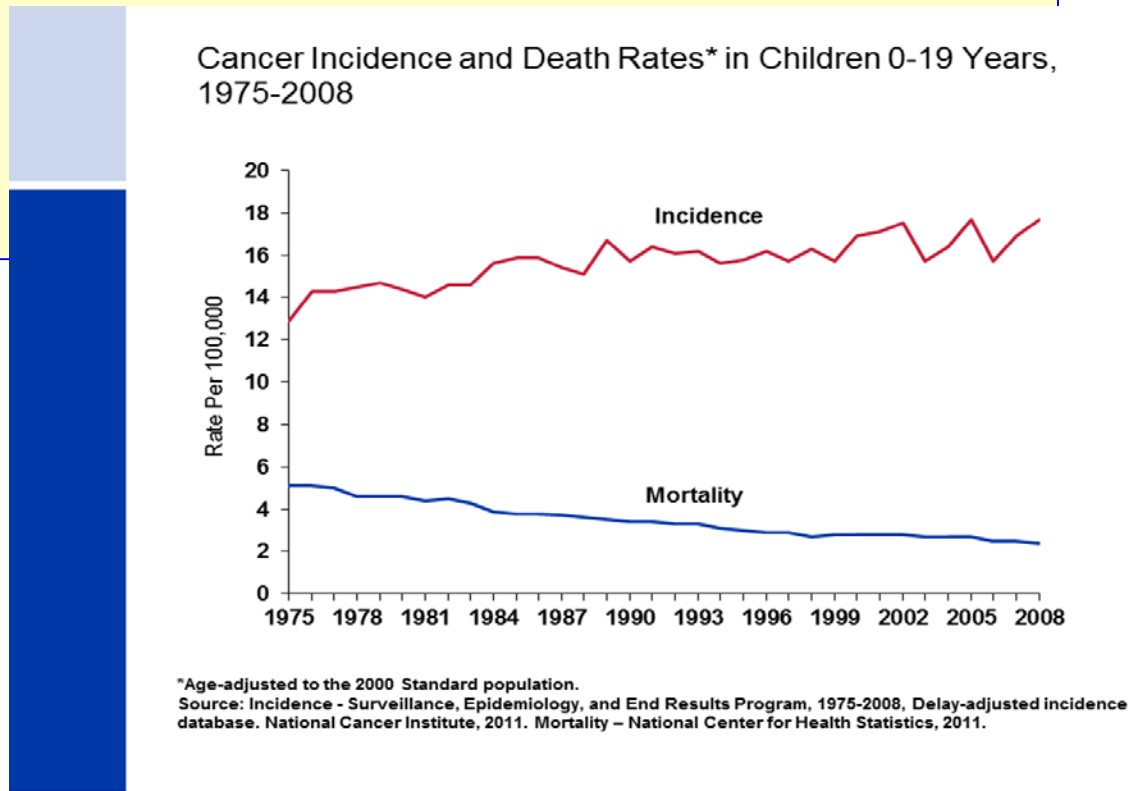
inoltre, **per dosi molto alte il rischio di CA diminuiva, mentre aumentava il rischio di ipotiroidismo,** per distruzione di tessuto tiroideo…

nella quasi totalità dei casi era implicato uno **specifico oncogène (c-RET),** coinvolto in **traslocazioni** interpretabili come **reattivo-adattative** …

# Children cancer increase

**Child cancers** are generally considered as a **rare disease**. **But** it is worth remembering

- *that*, statistically, **about 1 in 5-600 children will develop cancer before the age of 15**;
- *that*, in spite of the decisive improvement in diagnosis and therapy in the last decades, **cancer** is **the leading cause of death due to diseases among children over the first year of age**;
- *that*, **even at this age, a continuous and significant increase has been seen during the last decades.**



# TEN LEADING CAUSES OF DEATH

(Childre

| RANK | CAUSE OF DEATH | NO. OF DEATHS | % OF TOTAL DEATHS | DEATH RATE* |
|---|---|---|---|---|
| | ALL CAUSES | 10780 | 100.0 | 19.0 |
| 1 | Accidents (unintentional injuries) | 3868 | 35.9 | 6.8 |
| 2 | Cancer | 1284 | 11.9 | 2.3 |
| 3 | Congenital anomalies | 859 | 8.0 | 1.5 |
| 4 | Assault (homicide) | 756 | 7.0 | 1.3 |
| 5 | Heart diseases | 414 | 3.8 | 0.7 |
| 6 | Intentional self-harm (suicide) | 219 | 2.0 | 0.4 |
| 7 | Influenza & pneumonia | 193 | 1.8 | 0.3 |
| 8 | Septicemia | 172 | 1.6 | 0.3 |
| 9 | Chronic lower respiratory diseases | 158 | 1.5 | 0.3 |
| 10 | Cerebrovascular disease | 149 | 1.4 | 0.3 |
| | All other causes | 2708 | 25.1 | - |



* Rates are per 100,000 population and age adjusted to the 2000 US standard population.

*Based on US Mortality Data, 2006, National Center for Health Statistics, Centers for Disease Control and Prevention, 2009*

# Incidenza di tumori (anno/100.000)

Alberto Tommasini,
Laboratorio Immunologia Pediatrica, IRCCS Burlo Garofolo

It is generally argued that **childhood cancers** are a **rare condition**.

But **it should be reminded**

that CANCER is **the main cause of death by disease** in **childhood**

that there is a **constant and significant increase** of tumors in the world for this age group

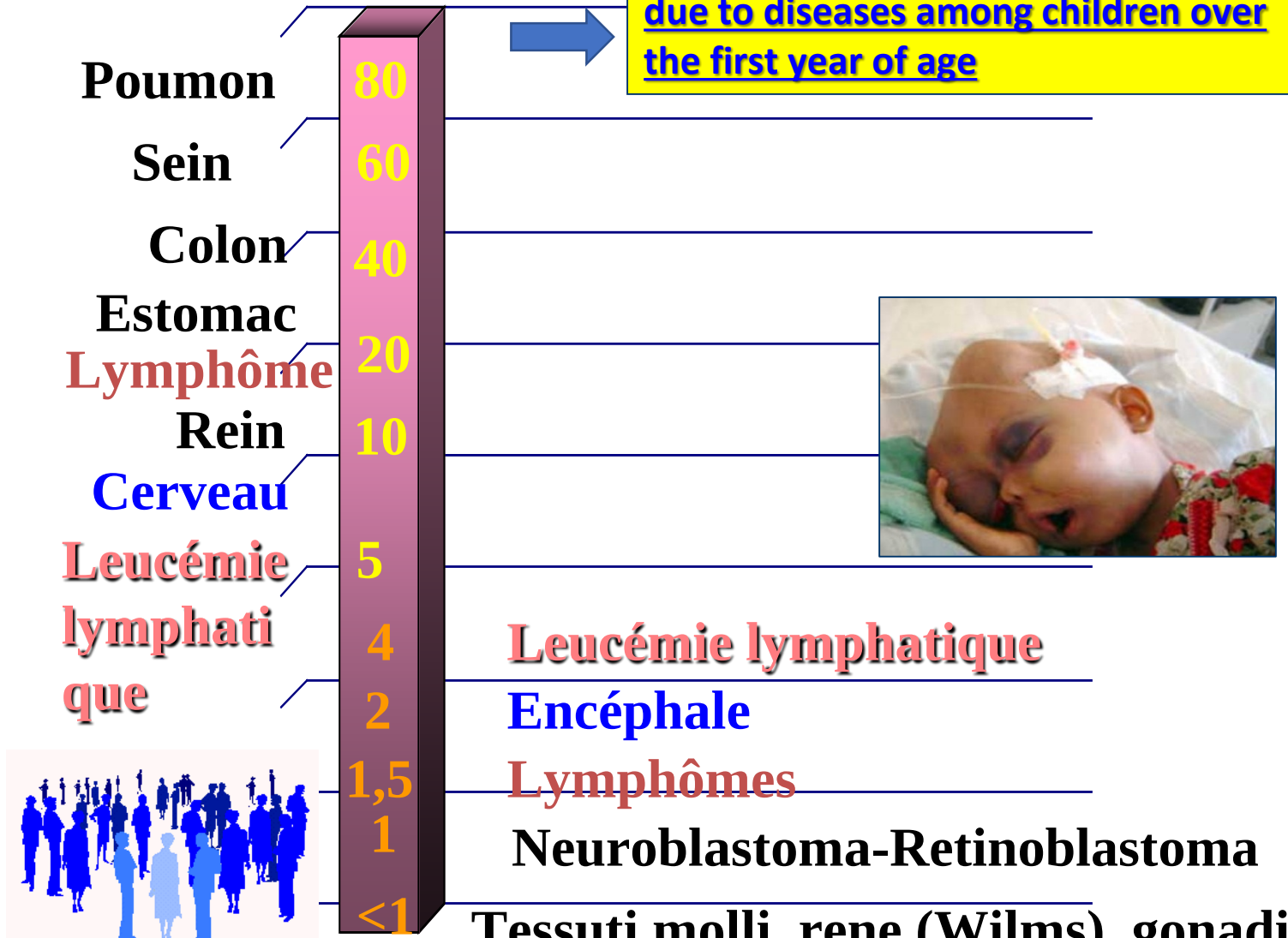
that **1 : 5-600 children falls ill with cancer**

That more than

**13 000 children fall ill with cancer each year in the U.S.**

Bleyer A, O'Leary M, Barr R, Ries LA, editors. ***Cancer epidemiology in older adolescents and young adults 15-29 ears of age, including SEER incidence and survival: 1975-2000***. NIH Pub. No. 06-5767. Bethesda (MD): National Cancer Institute; 2006. Jemal A, Siegel R, Ward E, et al***. Cancer statistics***, 2008. CA Cancer J Clin 2008;58:71 – 6.

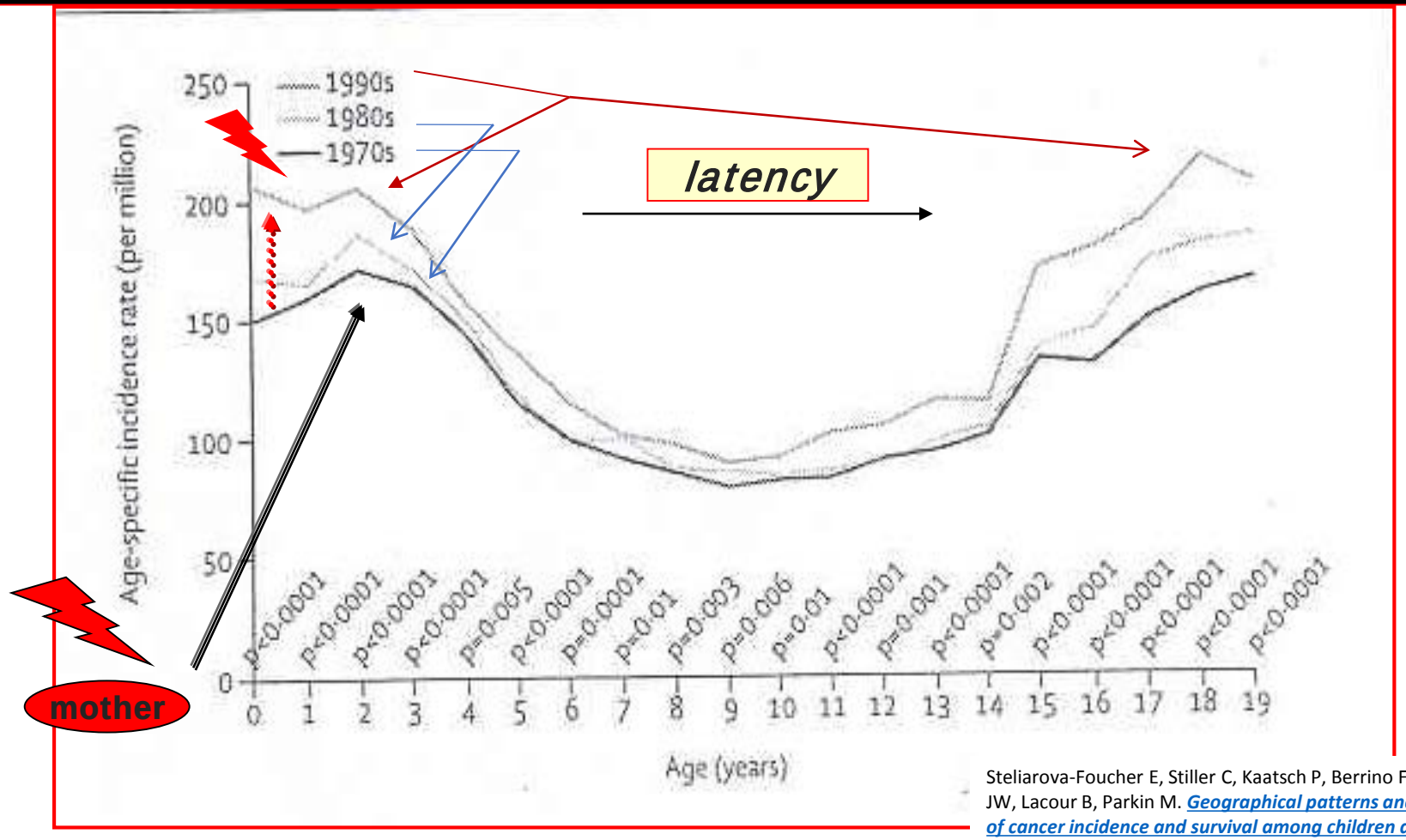
Cancer is **the leading cause of death due to diseases among children over the first year of age**



**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)**

# CA incidence in childhood and adolescence IN EUROPE ( 1970-1999)

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




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 ACCISproject): an epidemiological study.*** Lancet. 2004 Dec 11-17;364(9451):2097-105

NCBI

PubMed www.pubmed.gov

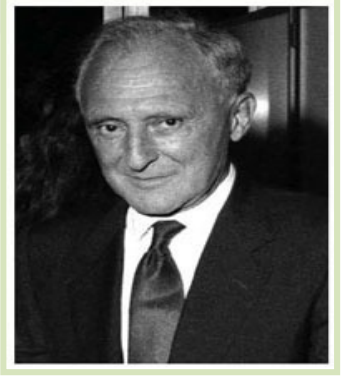
A service of the U.S. National Library of Medicine and the National Institutes of Health

**(4) Tomatis legacy**

All Databases | PubMed | Nucleotide | Protein | Genome | Structure | OMIM | PMC | Journa

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]

Early Human Development (2005) 81, 123–129

ELSEVIER

Early Human Development

e/earlhumdev

## (5) Pro-leukemic translocations in foetuses

# 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

2

**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 **postnatal latency** of disease (1—15 years).

.. 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 ...

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

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

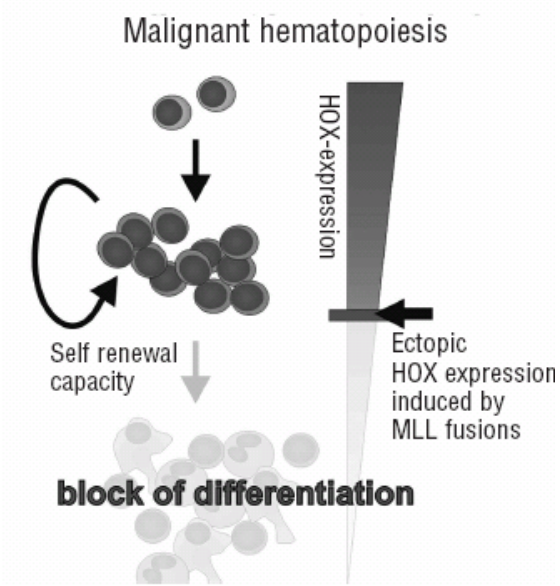
3

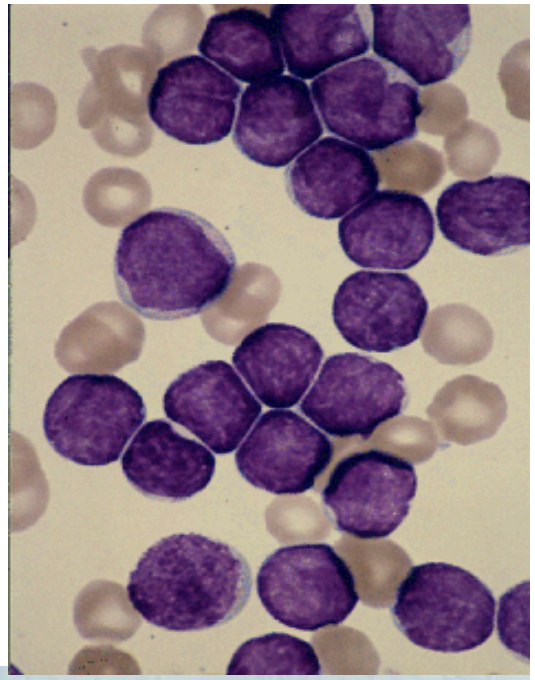
**Adult leukaemia (ALL/ AML),** in contrast, has a **very low rate of concordance (< 1%).**

**~1% of newborns had TEL-AML1 positive B lineage** clones...
which represents **100 times** the incidence of **TEL-AML1 positive ALL (~1 in 12,000).**

**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 Sci. 2006 Sep;1076:1-14

Interestingly, **the typical translocations of leukemias of the first year (those with the highest increase and worse prognosis) concern a histone methyltransferase**, that is, **a key enzyme of epigenetic programming**



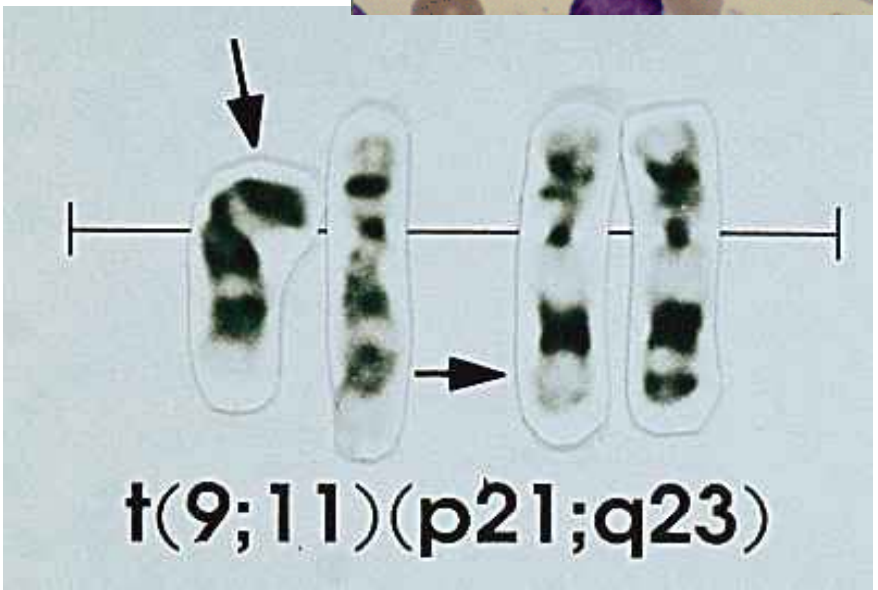
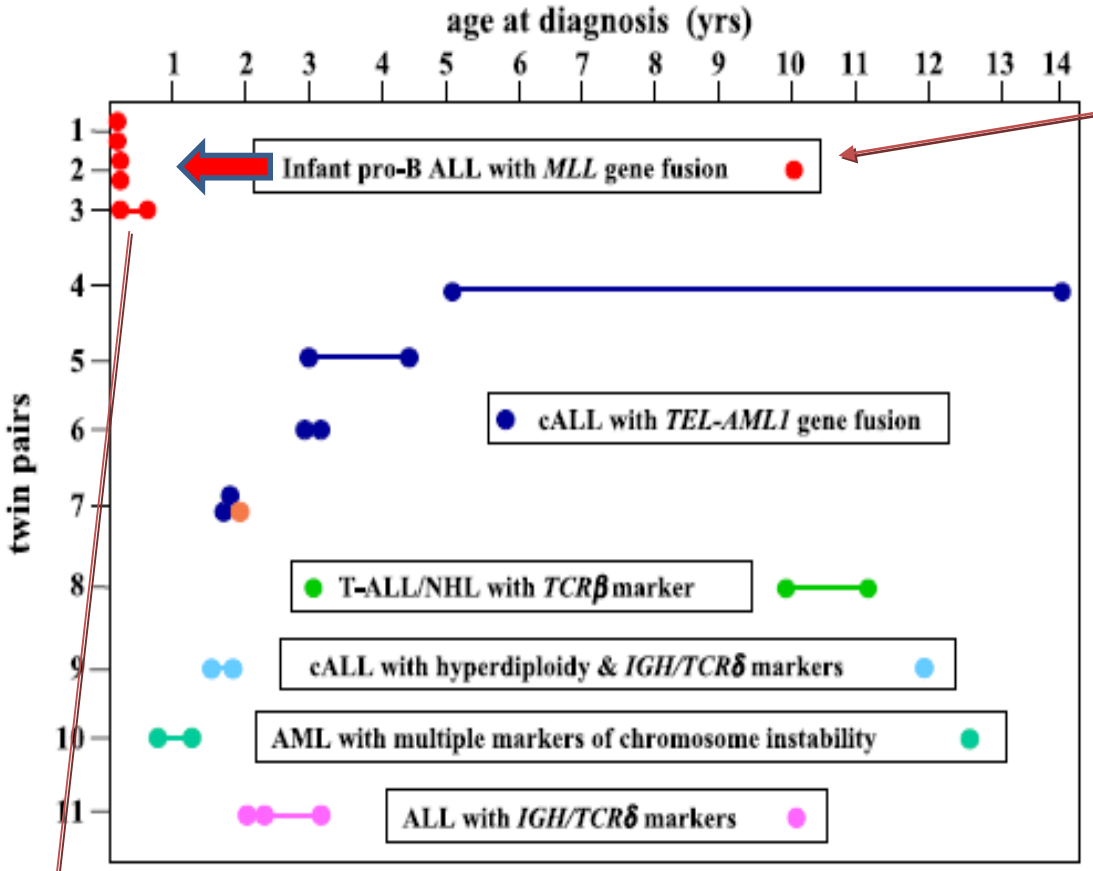


Figure 1 Concordant leukaemia in identical twins: the LRF Series (1993–2003). Figure illustrates age at diagnosis for each twin in the 11 pairs studied, the biological subtype of leukaemia and the molecular markers of clonality used.




**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,

!

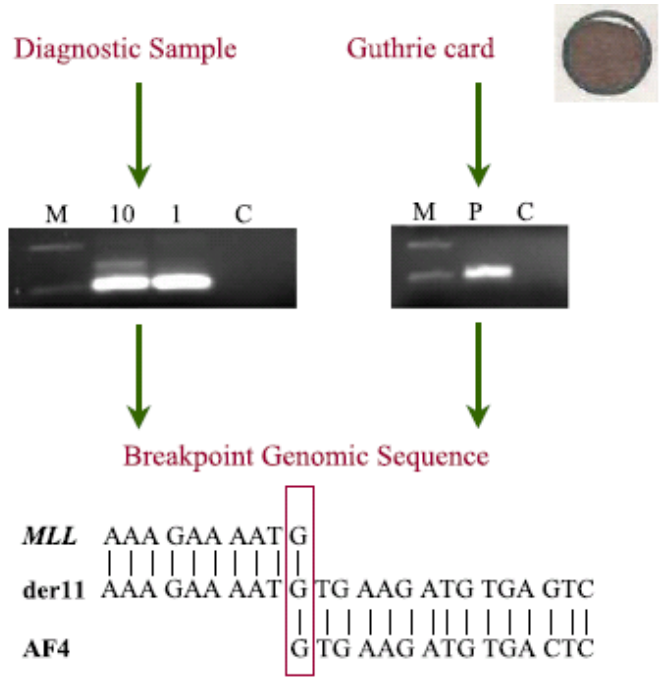



Figure 3 Detection of clonotypic fusion gene sequences (*MLL-AF4*) in neonatal blood spots (Guthrie card). 10, 1 μg DNA; C, control DNA; M, marker. Diagnostic DNA amplified by long-range PCR or long-distance inverse PCR [21]. Guthrie card DNA amplified by short-range (conventional) PCR using primers 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 leukaemia ..**

!!

# 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** (WHICH ENCODE TRANSCRIPTIONS FACTORS)..and micro**RNAs GENES SUCH AS *MIR191*.**

The first and most striking property of MLL fusion proteins is their incredible diversity. MLL has been found in **73 different translocations** and **54 partner genes** have been cloned (*http://atlasgeneticsoncology.org/Genes/MLL.html).*

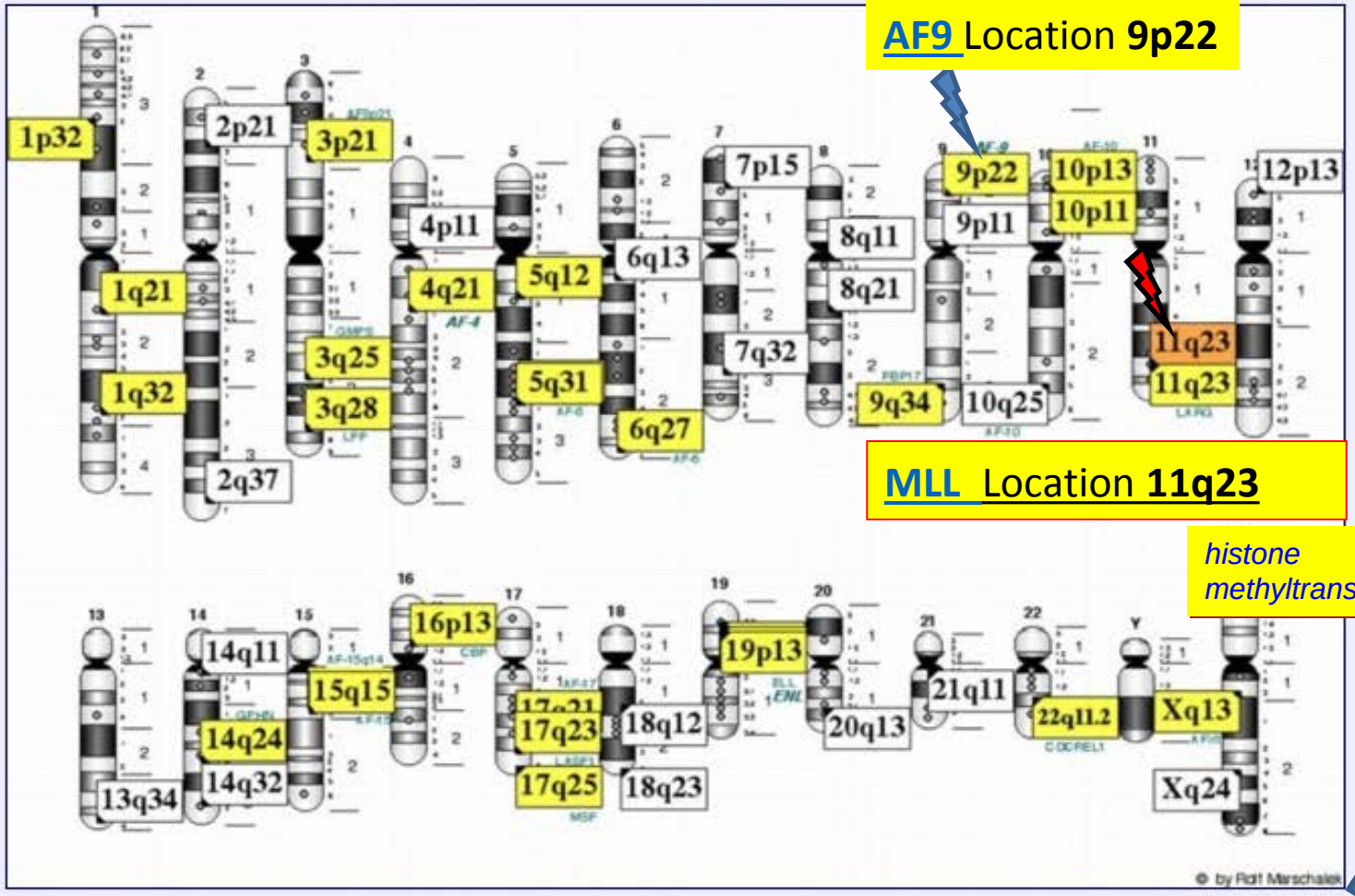
## ALL1, HRX, Htrx (human trithorax), TRX1

**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 Cell 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 for 11q23 translocations.**

[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 $MLL^{+ve}$ (but not $MLL^{-ve}$) leukemias (2.31 for DNA-damaging drugs, $P = 0.03$; 5.84 for 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

# Childhood cancers and atmospheric carcinogens

E G Knox

J Epidemiol Community Health 2005; [illegible]: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.

# The dynamic (epi)-genome

In fact **only in a genome conceived as a *unitary* and *complex* (at the same time, *dynamic* and *responsive*) *molecular network*,**



it is possible to suggest that all the ***epigenetic*** (*global DNA hypomethylation, hyper-methylation of promoter sequences of tumor suppressor genes, ncRNA networks modifications..*), ***genetic*** (*genomic instability, mobilization of transposable sequences..*), and ***chromosomal*** (*translocations*) ***mutations***,

determining the **cancer progression**

should be seen as **steps in a (failed or distorted) evolutionary/adaptive and defensive process ….**

Esteller M. ***Cancer epigenomics***: ***DNA methylomes*** **and** ***histone-modification maps*** Nat Rev Genet (2007);8(4):286-98; Karpinets TV, Foy BD. ***Tumorigenesis: the adaptation of mammalian cells to sustained stress environment by epigenetic alterations and succeeding matched mutations.*** Carcinogenesis. (2005); 26(8):1323-34; Hauptmann S., Schmitt W.D. ***Transposable elements - Is there a link between evolution and cancer?*** Medical Hypotheses (2006), 66 (3):580-591;

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, alth… variably deleterious and unpredictably important in deter-mining the establishment of the ne… not the primary origin for a ma… attempt to describe the inadequa… demonstrate that epigenetics is a … carcinogenesis.

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

… and 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*)**

Mol Biol Rep
DOI 10.1007/s11033-014-3806-3

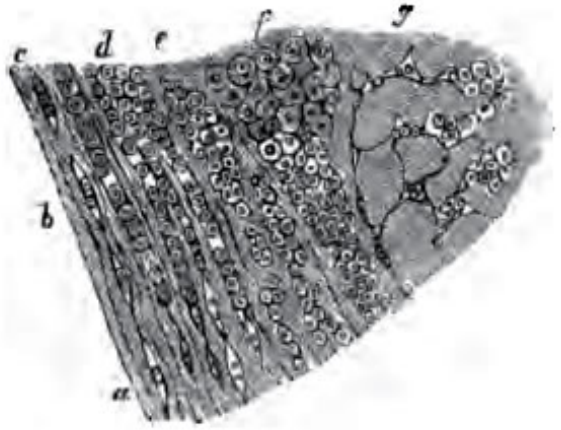
# The Embryonic Rest Theory and the field theories of cancer

## Towards a systemic paradigm in carcinogenesis: linking epigenetics and genetics

Ernesto Burgio · Lucia Migliore

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

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




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*).**



**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

E. Burgio (✉)
European Cancer and Environment Research Institute (ECERI), Brussels, Belgium
e-mail: erburgio@libero.it

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### Cancer as a genetic disease: the somatic mutation theory

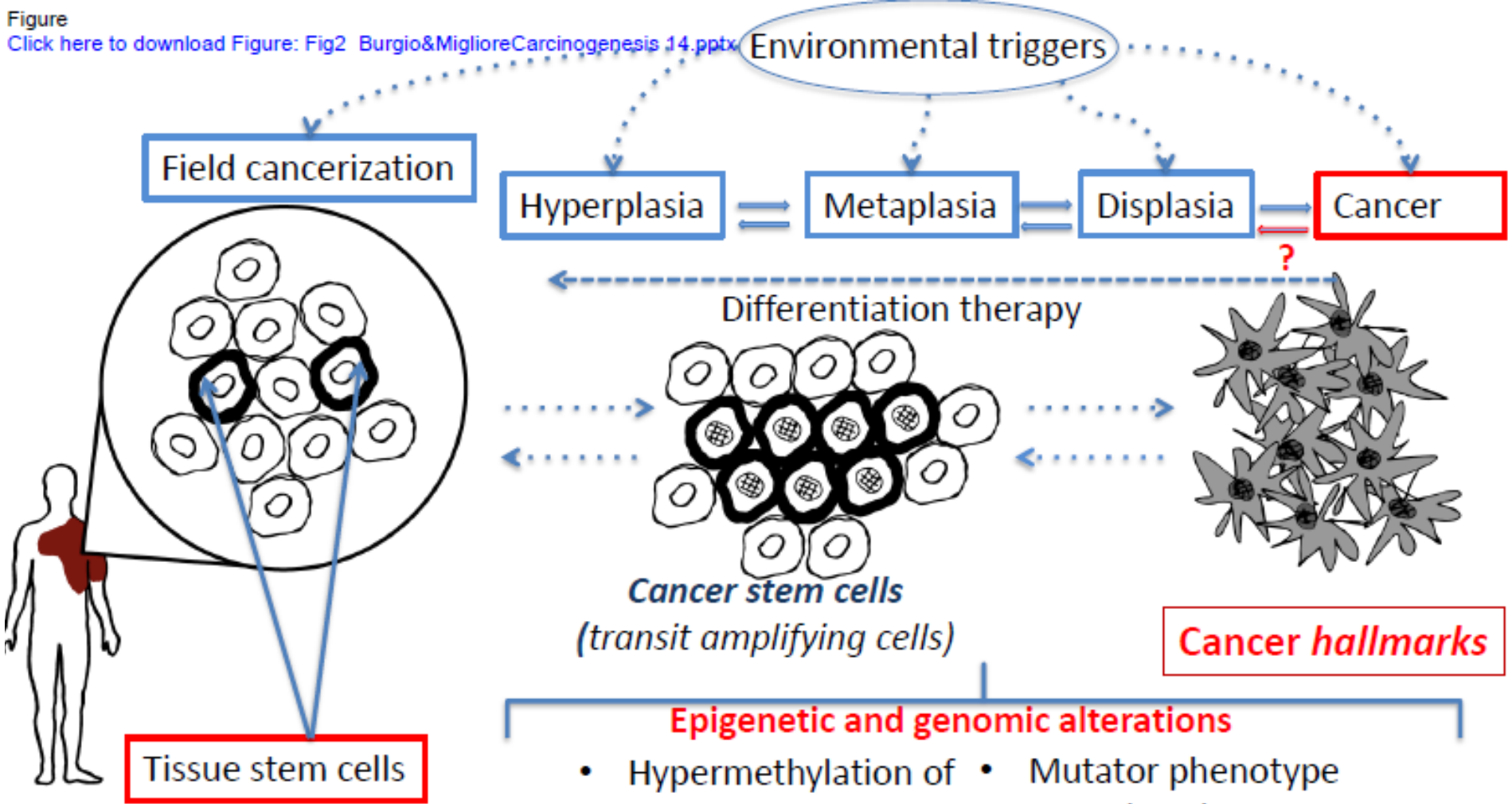
> The revolution in cancer research can be summed up in a single sentence: cancer is, in essence, a genetic disease [1]

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 or promoted by radiation, physical or chemical insults or

## The great lesson of *teratocarcinoma* and the stem cell theory of cancer

- the **transplantation of pluripotent or embryonic stem cells into adult mammals**, frequently leads to the growth of **teratocarcinomas**
- the **microenvironment** was central to this paradigm-breaking findings: the origin of the teratoma was a "dissonance"..
- intriguingly, **putting the teratocarcinoma cells into an early mammal embryo at the blastocyst stage**.. they can **generate normal tissues in viable mosaic individuals ..**
- **normal offspring** could result from a… cancer cell
- normal germinal **stem cells who became cancerous, showed the potential to revert to normal cells if placed in embryo**

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




**Epigenetic and genomic alterations**

- Hypermethylation of oncosuppressor genes
- Global DNA Hypomethylation (protooncogenes and mobile sequences activation)
- miRNAs activation
- Mutator phenotype
- Mutations in oncosuppressor genes (*TP53*)
- LOH
- Microsatellite alterations
- Chromosomal instability
- Chromotripsis

**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

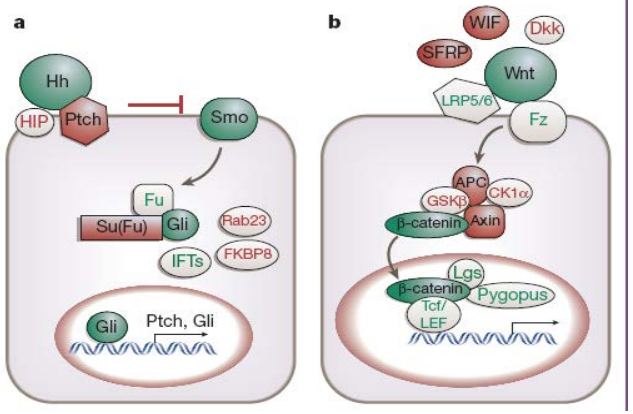
Nature. 2004 Nov 18;432(7015):324-31.

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

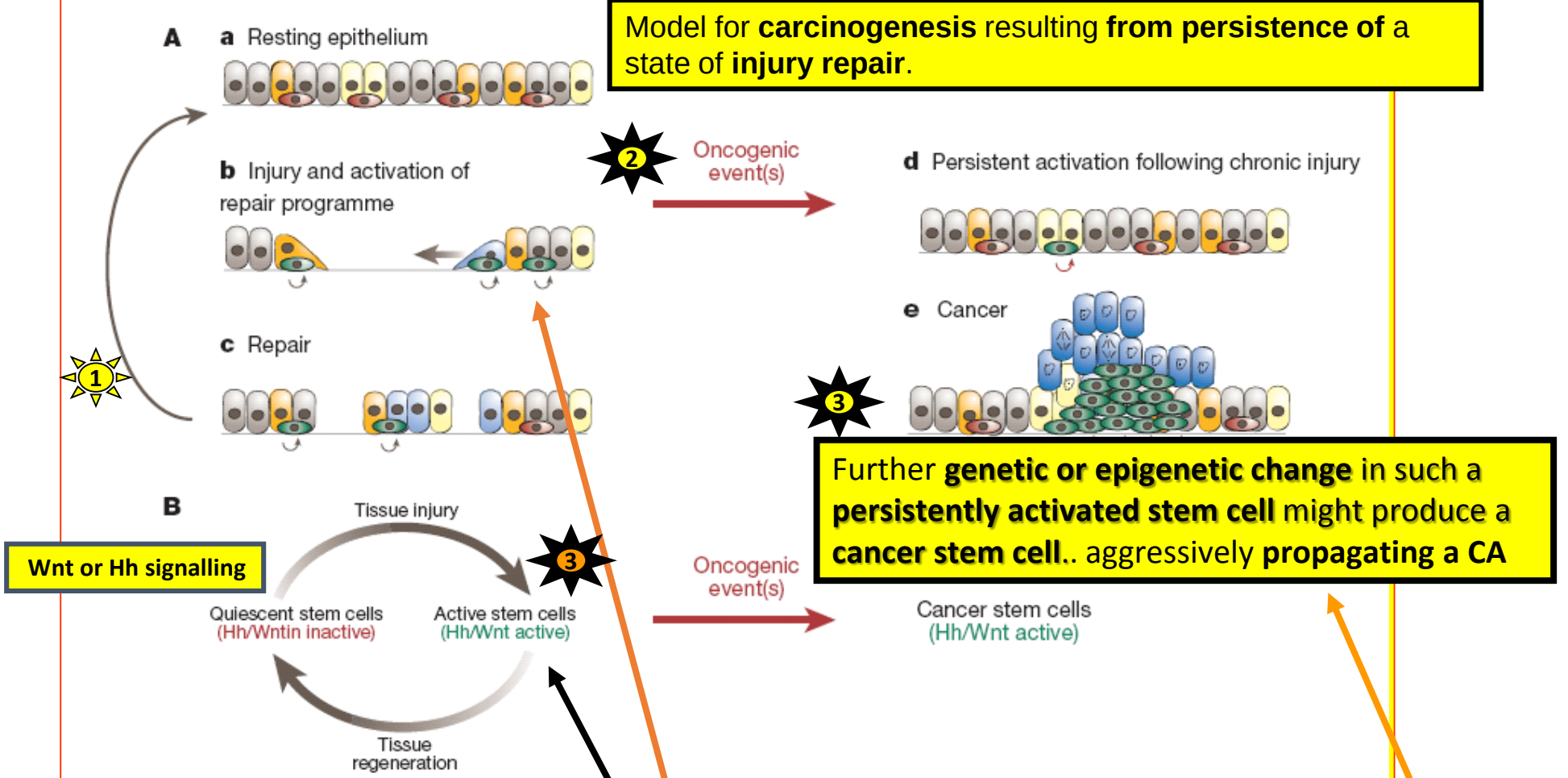
[1]Department of Molecular Biology and Genetics, The Howard Hughes Medical Institute, [2]Department of Pathology, [3]Department of Urology and [4]Department of Oncology, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA (e-mail: pbeachy@jhmi.edu)

**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.**

**Cancer** is increasingly being viewed as a **stem cell disease**.. 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**
suggest that **carcinogenesis proceeds by misappropriating homeostatic mechanisms that govern tissue repair and stem cell self-renewal.**



Model for **carcinogenesis** resulting **from persistence of** a state of **injury repair**.




Further **genetic or epigenetic change** in such a **persistently activated stem cell** might produce a **cancer stem cell**.. aggressively **propagating a CA**

**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):1417–1419.

# EMT: When epithelial cells decide to become mesenchymal-like cells

**Cancer is a wound which never heals**

*Rudolf Virchow*

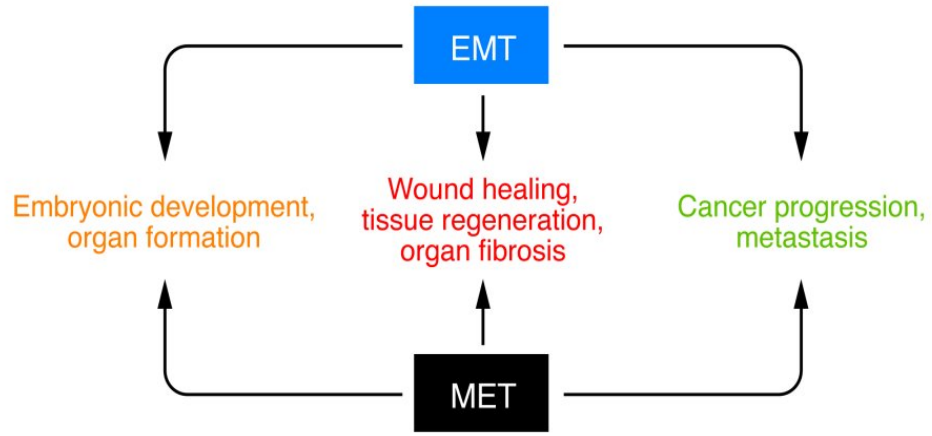
Raghu Kalluri[1,2]

[1]Division of Matrix Biology, Beth Israel Deaconess Medical Center, and Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts, USA. [2]Harvard-MIT Division of Health Sciences and Technology, Boston, Massachusetts, USA.

**Epithelial-mesenchymal transition (EMT) is critical for appropriate embryonic development, and this process is re-engaged in adults during wound healing, tissue regeneration, organ fibrosis, and cancer progression. Inflammation is a crucial conspirator in the emergence of EMT in adults but is absent during embryonic development. As highlighted in this Review series, EMT is now a recognized mechanism for dispersing cells in embryos, forming fibroblasts/mesenchymal cells in injured tissues, and initiating metastasis of epithelial cancer cells. Also discussed**

During **embryogenesis**, **epithelia** are considered to be **highly plastic** and able to **switch back and forth between epithelia and mesenchyme**, via the processes of **EMT** and mesenchymal-epithelial transition (**MET**), respectively

.. **terminally differentiated epithelia can change their phenotype (EMT ⇆ MET) under the influence of repair-associated or pathological stress**

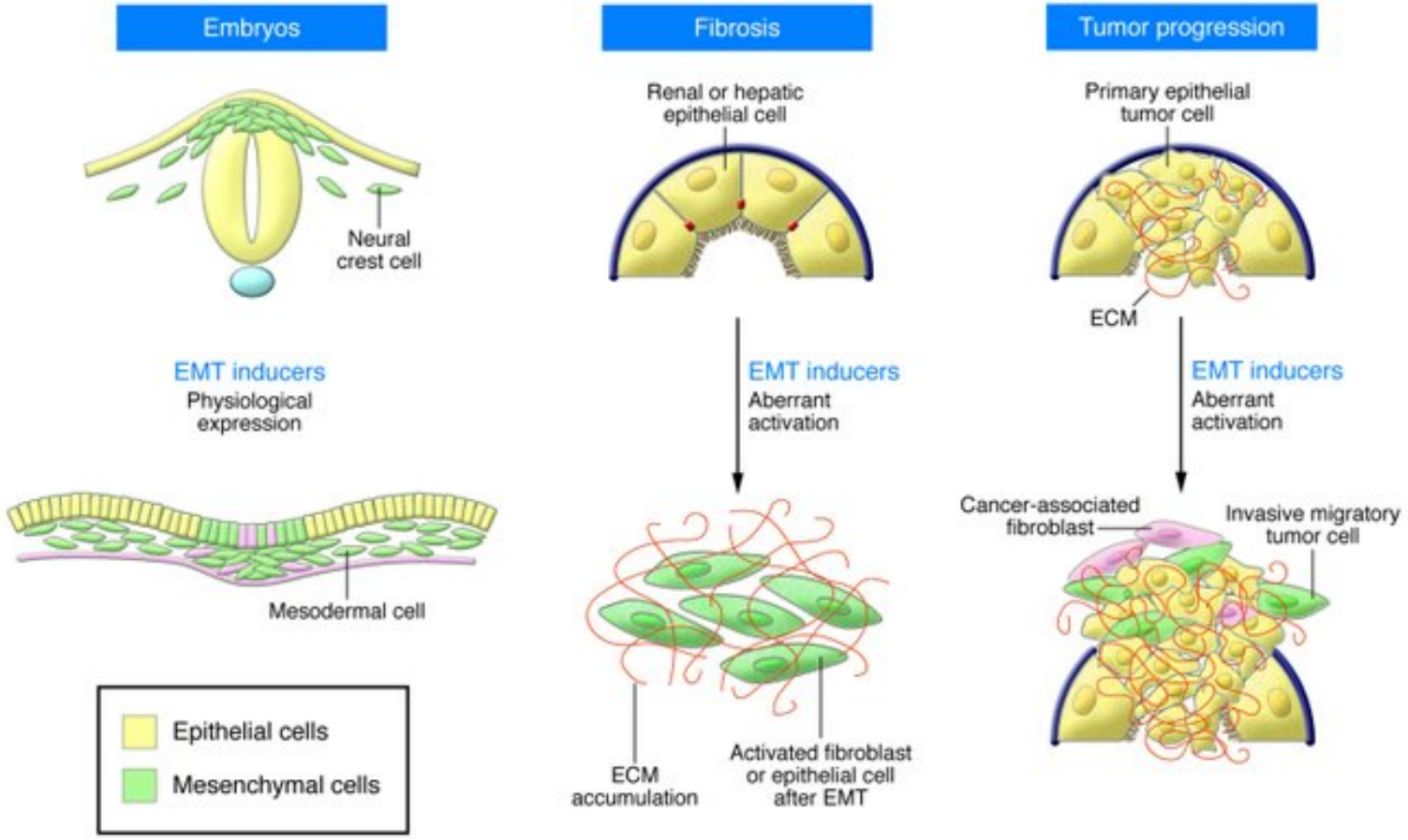



Epithelial-mesenchymal transition (**EMT**) is critical for **appropriate embryonic development… re-engaged** in adults during **wound healing, tissue regeneration, organ fibrosis**, and **cancer progression**.

Review series

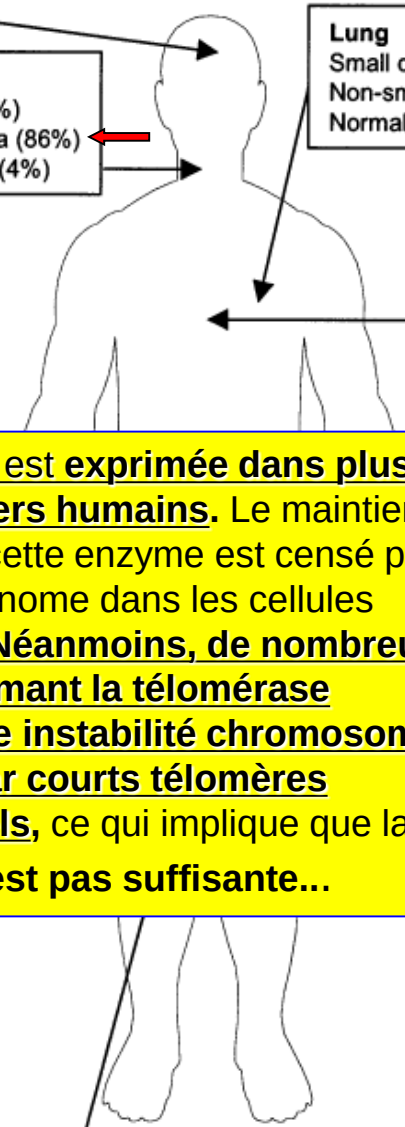
# Epithelial-mesenchymal transitions: the importance of changing cell state in development and disease

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




*J Clin Invest.* 2009;119(6):1438–1449.

# Telomerase in Human Cancer



**Nervous System**
Normal retina/brain (0%)
Retinoblastoma (50%)
Glioblastoma multiforme (75%)
Oligodendroglioma (100%)
Anaplastic astrocytoma (10%)
Meningioma
Ordinary (17%)
Atypical (92%)
Malignant (100%)
Adrenal, neonate (0%)
Ganglioneuroma (0%)
Neuroblastoma (94%)
Normal tissue adjacent to tumor (0%)

**Head and Neck**
Normal oral mucosa (3%)
Squamos cell carcinoma (86%)
Normal adjacent tissue (4%)

**Lung**
Small cell lung carcinoma (100%)
Non-small cell carcinoma (78%)
Normal tissue adjacent to tumor (4%)

**Breast**
Normal breast tissue (0%)
Fibrocystic disease (0%)
Fibroadenoma (28%)
Carcinoma in situ (75%)
Carcinoma, ductal and lobular (88%)
Normal tissue adjacent to tumor (5%)
FNA benign lesions (9%)
FNA malignant lesions (81%)

**Hepatic**
Normal tissue (0%
Liver Disease, nor
Hepatocellular car
Normal tissue adja

La ***télomérase*** est **exprimée dans plus de 90% des cancers humains.** Le maintien des télomères par cette enzyme est censé protéger l'intégrité du génome dans les cellules néoplasiques. **Néanmoins, de nombreuses tumeurs exprimant la télomérase présentent une instabilité chromosomique déclenchée par courts télomères dysfonctionnels,** ce qui implique que la **télomérase n'est pas suffisante...**

**strointestinal**
stric adenoma (27%)
stric carcinoma (85%)
mal tissue adjacent to tumor (5%)
orectal adenoma (45%)
orectal carcinoma (89%)
mal tissue adjacent to tumor (25%)
ncreatic carcinoma (95%)

**Reproductive Tract - Female**
Fetal ovary (100%)
Adult ovary (33%)
Normal endometrium (0%)
Leiomyoma (0%)
Leiomyosarcoma (100%)
Endometrial adenocarcinoma (100%)
Cervical carcinoma (100%)
Vaginal carcinoma (100%)
Ovarian Carcinoma (91%)

**Urinary Tract**
Normal bladder endothelium (0%)
Dysplastic bladder endothelium (43%)
Bladder carcinoma (92%)
washings (73%)
voided urine (29%)
Renal carcinoma (83%)
Normal tissue adjacent to tumor (0%)
Wilm's tumor (100%)
Normal tissue adjacent to tumor (33%)

Reproductive Tract - male
Testis (100%)
Mature spermatozoa (0%)
Normal prostate (0%)
BPH without carcinoma (5%)
BPH with carcinoma (11%)
High grade PIN (60%)
Prostate carcinoma (90%)

**Skin**
Normal epidermis (44%)
Squamous cell carcinoma (83%)
Basal cell carcinoma (95%)
Melanoma (86%)

# REMARK

- Those who adhere to the **paradigm of stochastic mutations**
- and more generally **to a linear and gene-centric model of DNA have obviously some difficulty to accept all this…**

# INC DAY 2017
# BRAIN & EPIGENETICS

OCT 16 2017

KEYNOTE LECTURE BY :
Edith Heard (Collège de France, Paris)
Epigenetics in development and disease : lessons from the x chromosome

INVITED SPEAKERS :
Tracy Bale (UPenn)
Bérénice Benayoun (UC Davies)
Ernesto Burgio (Brussels)
Giacomo Cavalli (Montpellier)
Johannes Gräff (Lausanne)
Claudine Junien (Paris)
Francesca Merlin (Paris)
Marc Potenza (USA)
Jonathan Weitzman (Paris)

Organizers : J. Fagard, V. Lallemand-Mezger, C. Legay, C. Meunier
In partnership with the BCPP, BME-Paris, Cogmaster and PCFA Masters

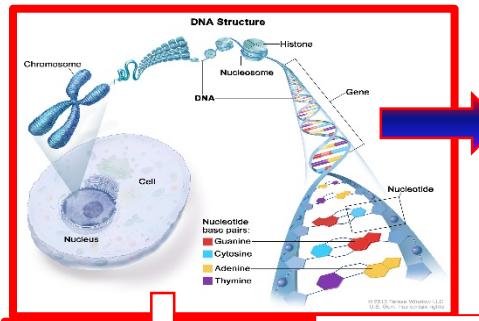
UNIVERSITÉ PARIS DESCARTES
AMPHITHÉÂTRE VULPIAN
12 RUE DE L'ECOLE DE MÉDECINE 75006 PARIS

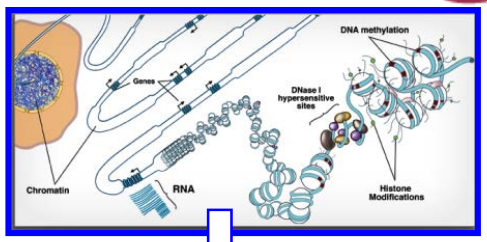
INSTITUT NEUROSCIENCES COGNITION
UNIVERSITÉ PARIS DESCARTES
USPC Université Sorbonne Paris Cité
bme paris BioMedical Engineering Master Program

Categories: EVENTS, INC MEETINGS

## INC Day 2017 : Brain and Epigenetics – Oct 16th.

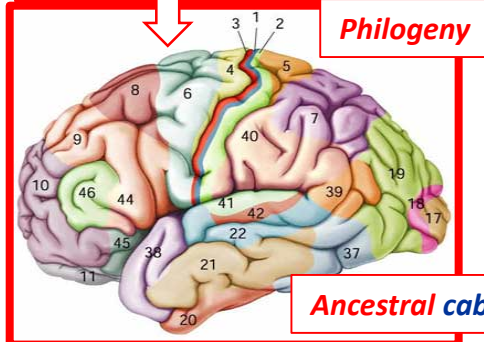
INSTITUT PARIS DESCARTES NEUROSCIENCES COGNITION



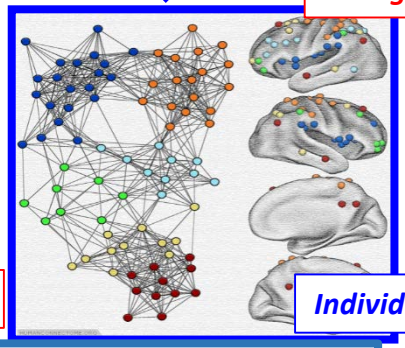




*Philogeny*

*Ontogeny*



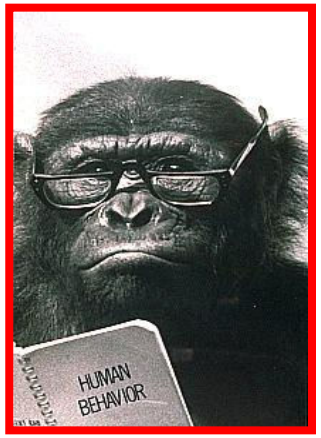
*Ancestral cablage*



*Individual cablage*

*Brodmann areas*

*The human Connectome*




(I) The building of the ***hardware*** is under ***genetic control***

(Ib) The building of the ***software*** (the ***connectome***) is ***epigenetically*** modulated

*Neurodegenerative diseases*

*Neurodevelopmental disorders*

*Neuropsychiatric diseases*

## *Brain Evolution and Neurodevelopmental Disorders*

ECERI
European Cancer and Environment Research Institute

*From Genetics to Epigenetics*

**Ernesto Burgio** (ECERI, Brussels, Belgium

Executive Healthcare Management
www.executivehm.com

EHM Executive Healthcare

# autism the great modern health concern

CDC Centers for Disease Control and Prevention

**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 (PPD-NOS; also called "atypical autism")

1980 1 : 1500

## 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 communication challenges. People with PDD-NOS usually have fewer and milder symptoms than those with autistic disorder.

2002 1 : 150

**1 in 150** children in the US have an ASD CDC estimated ave...

meaning

2014 1 : 68

**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

2006 1 : 110

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

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

2008 1 : 88

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

Reports of autism cases per 1,000 children

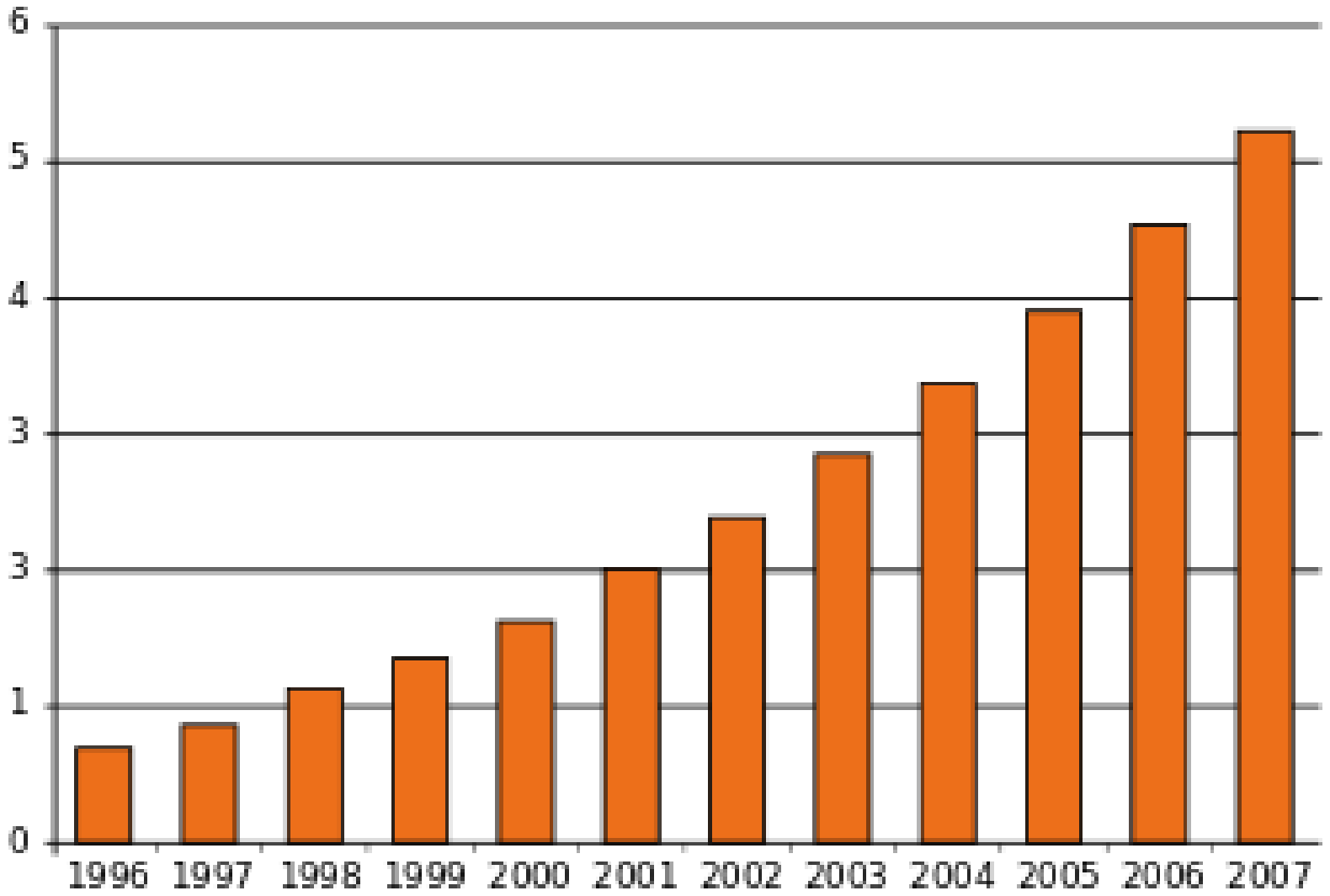

Lifetime cost to care for an individual with an ASD Estimated from recent studies **$3.2m** with **$4,110–$6,200** per year of medical expenditures for an individual with an ASD than one without

2014 1 : 68

Sources: CDC | www...

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

Newschaffer CJ, Croen LA, Daniels J et al. The epidemiology of autism spectrum disorders . Annu Rev Public Health. 2007;28:235–58.




**Reports of autism cases per 1,000 children grew dramatically in the U.S. from 1996 to 2007**

# Autism Prevalence Since 2000


Many scientists and researchers claim that Autism is **the fastest-growing developmental disorder**

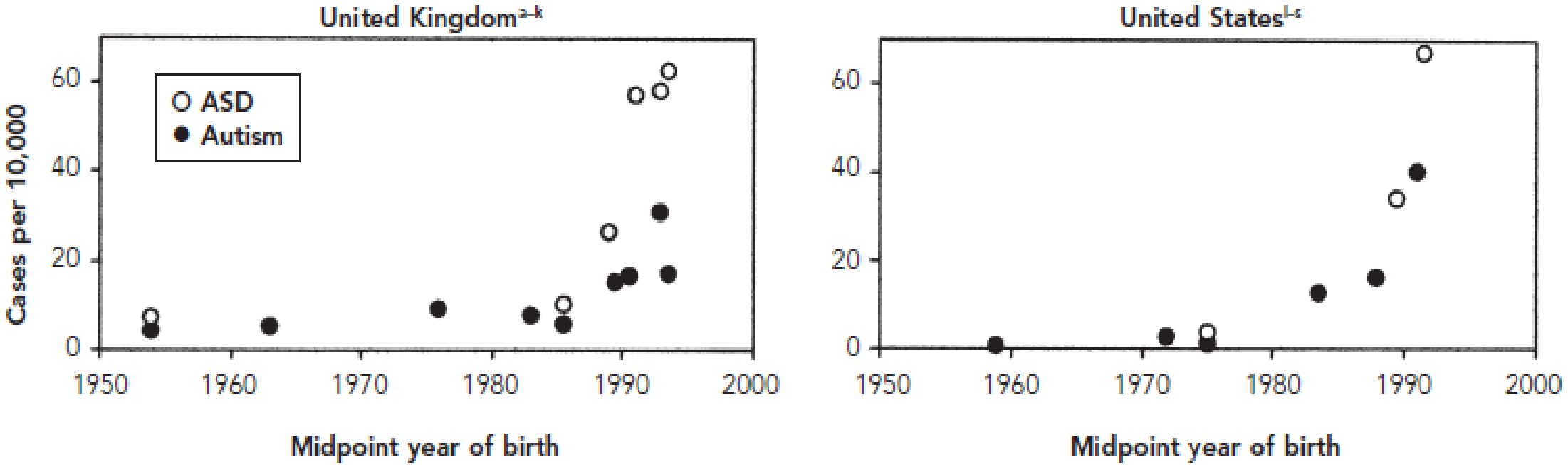
# AUTISM
# (ASD :Autism Spectrum Disorders)

**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 (**incidence**) in US increased **from 15,580 in 1992 to 163.773 in 2003**

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

**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]

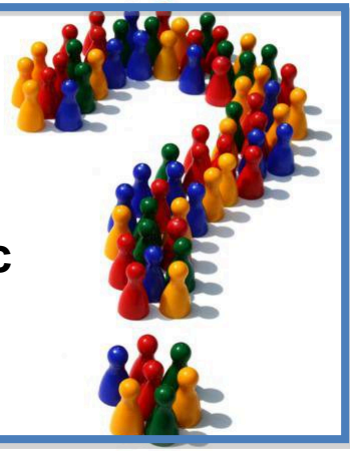
[m]Ritvo et al. 1989[53]

[n]Burd et al. 1987[45]

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

**Centre for Disease Control (CDC)**
***Autism and Developmental Disabilities Monitoring Network 2014***

**1 of 68 children aged 8 years had been diagnosed as autistic**



*Prevalence of Autism Spectrum Disorders in EU*: 0,62 - 0,7%

***Autism*. Lai MC, Lombardo MV, Baron-Cohen S. Lancet. 2014 Mar.**

1:119 Finlandia *Mattila et al., 2011*

1:87 Svezia *Idring et al., 2012*

1:59 Gran Bretagna Russel et al., 2014

# Community Report on Autism 2018

Centers for Disease Control and Prevention

National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention

HELPING CHILDREN

Community Report from the
**Autism and Developmental Disabilities Monitoring (ADDM) Network**

ADDM Network

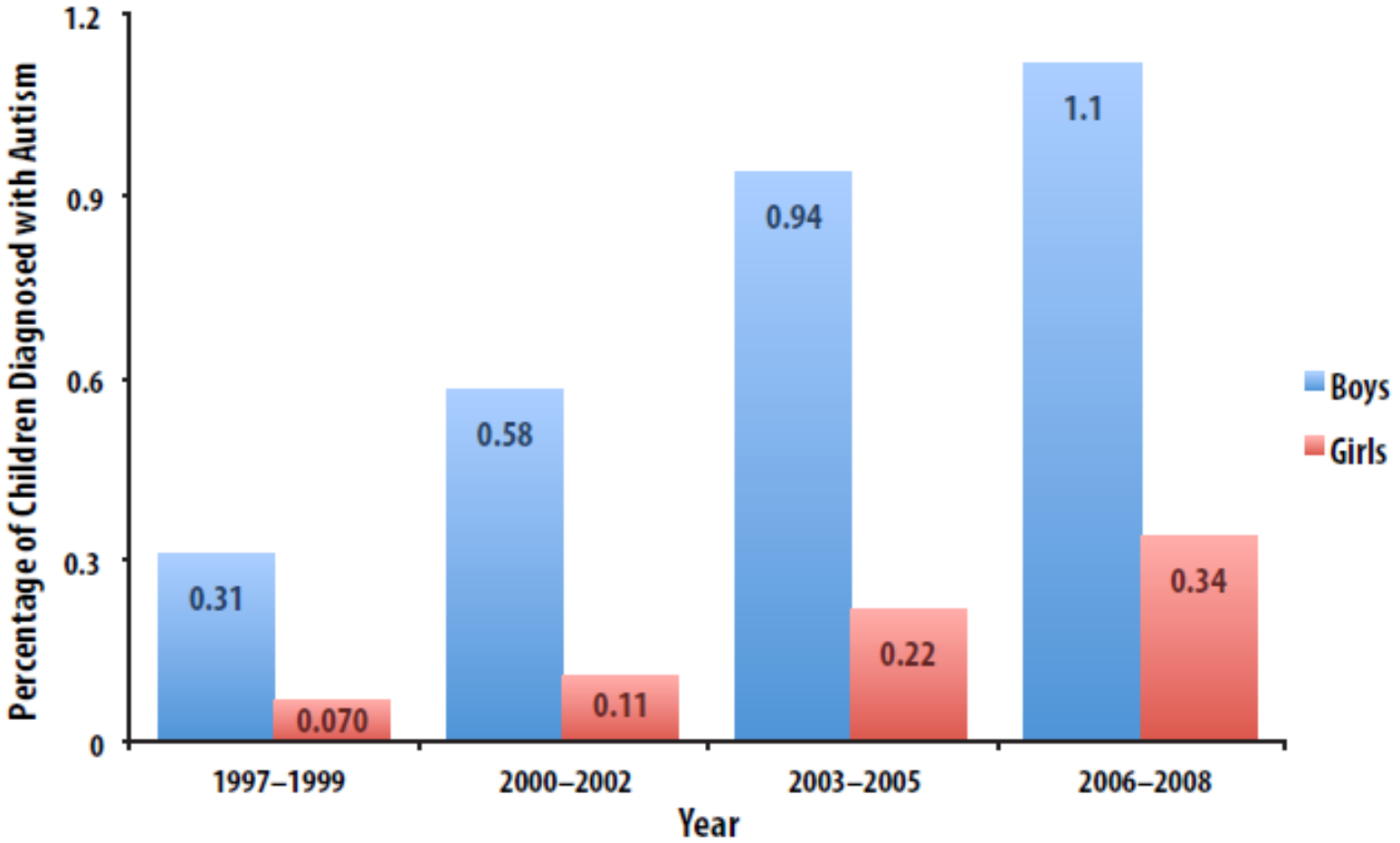
**1.7%**
is the average percentage identified with ASD

**1 in 59**
8-year-old children were identified with ASD by ADDM in 2014

## Why is this information important and how can it be used?

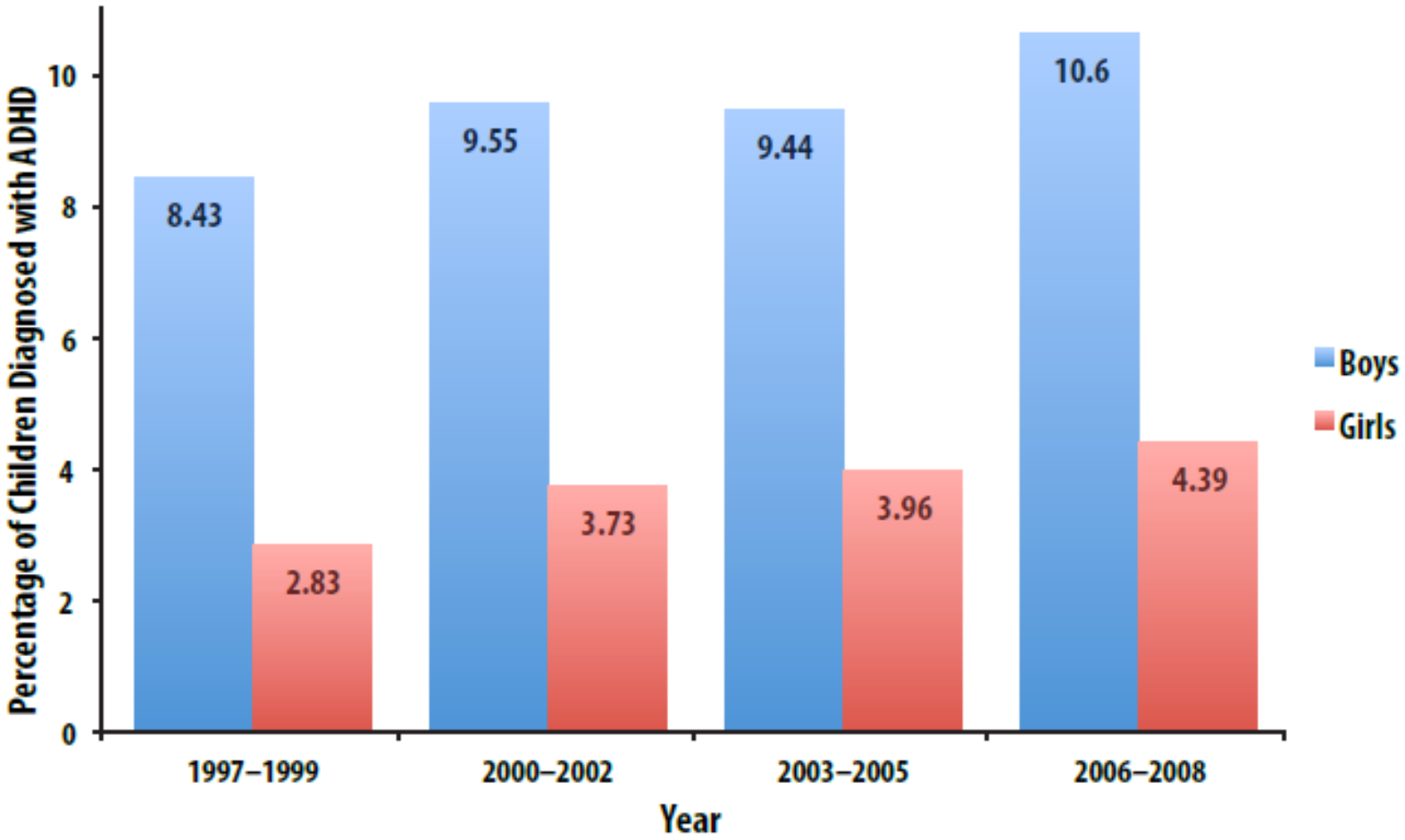
1. Lower the age of first evaluation by community providers; and
2. Increase awareness of ASD among black and Hispanic families, and identify and address barriers in order to ensure that all children with ASD are evaluated, diagnosed, and connected to services.

**Figure 3:** Autism Prevalence among Children Ages 3 to 17, from 1997–2008




Rates of autism have risen dramatically in the past decade. While overall prevalence is higher among boys, the rate of increase is higher among girls. Source: C. Boyle et al, "Trends in the Prevalence of Developmental Disabilities in U.S. Children, 1997–2008."

**Figure 2:** ADHD Prevalence among Children Ages 3 to 17, from 1997–2008




The number of children diagnosed with ADHD increased an average of 3 percent every year from 1997 to 2008. Boys are much more likely to be affected. Source: C. Boyle et al., "Trends in the Prevalence of Developmental Disabilities in U.S. Children, 1997– 2008."

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.

A few industrial chemicals (eg, **lead, methylmercury, polychlorinated biphenyls [PCBs], arsenic**, and **toluene**) are recognised causes of neurodevelopmental disorders and subclinical brain dysfunction.

**…**

Seven years ago two well known experts in Environmental Health, a pediatrician and an epidemiologist, launched an alarm from the pages of *the Lancet*, saying that a ***silent pandemic*** of ADHD, autism and other neurodevelopmental disorders was spreading also due to the ***shortage of funds in this area of research***

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

# Neurobehavioural effects of developmental toxicity

*Lancet Neurol* 2014; 13: 330–38

Published Online
February 15, 2014
http://dx.doi.org/10.1016/S1474-4422(13)70278-3

Department of Environmental Medicine, University of Southern Denmark, Odense, Denmark (P Grandjean MD); Department of Environmental Health, Harvard School of Public Health, Boston, MA, USA (P Grandjean); and Icahn School of Medicine at Mount Sinai, New York, NY, USA (P J Landrigan MD)

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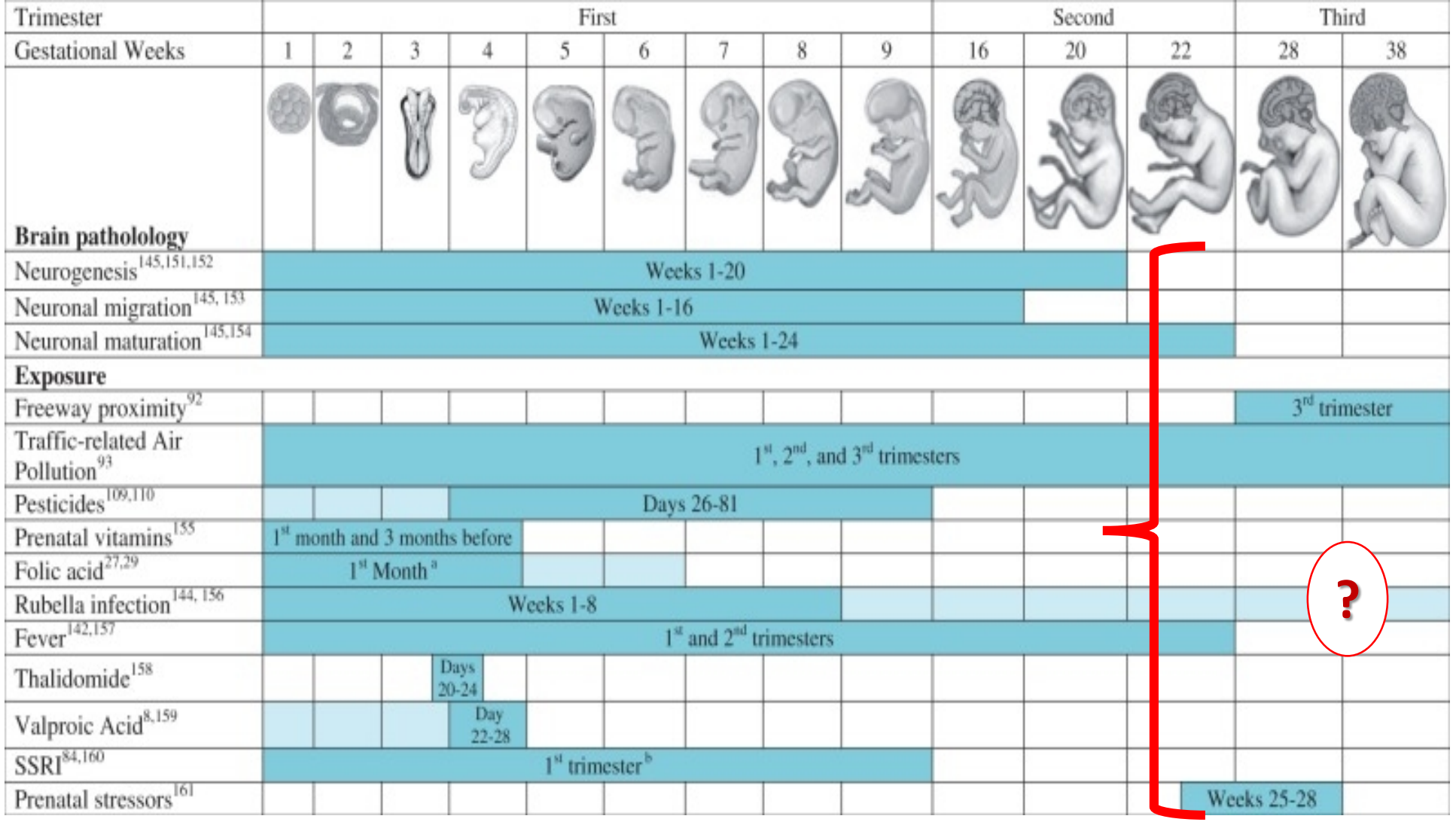
pgrand@hsph.harvard.edu

*Philippe Grandjean, Philip J Landrigan*

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




**Neuropathology (autopsy and imaging) studies** of brains of individuals with autism found evidence of **dysregulated neurogenesis, neuronal migration and neuronal maturation** .. processes that generally occur **in the first half of pregnancy**. Figure shows **windows of critical periods indicated by evidence from epidemiological studies of environmental factors demonstrating an association with ASDs**.
Int J Epidemiol. 2014 Apr; 43(2): 443–464.

# Neurodevelopmental Disorders and Prenatal Residential Proximity to Agricultural Pesticides: The CHARGE Study

Janie F. Shelton,[1] Estella M. Geraghty *Environ Health Perspect*; DOI:10.1289/ehp.1307044: 23 June 2014

970 participants, **California Pesticide Use Report** (1997-2008) linked to the ***addresses during pregnancy***. *Pounds of active ingredient …*
aggregated within 1.25km, 1.5km, and 1.75km buffer distances from the home



- **Organophosphates** higher 3rd trimester expos: **60% increased risk ASD**
- **Pyrethroid insecticide** just prior to conception or for 3rd trimester at **greater risk for both ASD and DD** (developmental delay)
- **Carbamate**: risk for **DD** increased (Arprocarb : Undene, **Propoxur = Baygon**).

**De grandes études de cohorte** ont documenté le lien entre
**l'exposition précoce aux pesticides et les troubles du spectre autistique**

Giuseppe Giordano
ISDE Palermo

Environmental Health

Environmental Health 2008, 7:50 doi:10.1186/1476-069X-7-50

Review

Open Access

# Potential developmental neurotoxicity of pesticides used in Europe

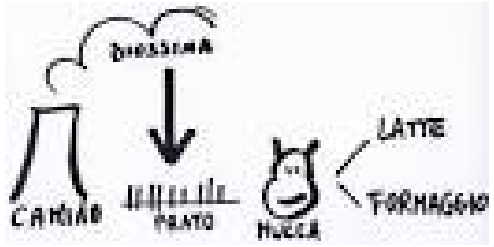
Marina Bjørling-Poulsen*[1], Helle Raun Andersen[1] and Philippe Grandjean[1,2]

Pesticides used in agriculture are designed to protect crops against unwanted species, such as weeds, insects, and fungus. Many compounds target the nervous system of insect pests. Because of the similarity in brain biochemistry, such pesticides may also be neurotoxic to humans. Concerns have been raised that the developing brain may be particularly vulnerable to adverse effects of neurotoxic pesticides. Current requirements for safety testing do not include developmental neurotoxicity. We therefore undertook a systematic evaluation of published evidence on neurotoxicity of pesticides in current use, with specific emphasis on risks during early development. Epidemiologic studies show associations with neurodevelopmental deficits, but mainly deal with mixed exposures to pesticides. Laboratory experimental studies using model compounds suggest that many pesticides currently used in Europe – including organophosphates, carbamates, pyrethroids, ethylenebisdithiocarbamates, and chlorophenoxy herbicides – can cause neurodevelopmental toxicity. Adverse effects on brain development can be severe and irreversible. Prevention should there
other types of human ex
known to be neurotox
vulnerability of the deve
for investment in target
should be considered in light of the need for precautionary action to protect brain development.

**Estimating Burden and Disease Costs of Exposure to EDCs in the EU**:
" The ***neurodevelopment panel*** estimated a strong probability (70–100%) that **each year in Europe, 13.0 million IQ points are lost** (sensitivity analysis, 4.24–17.1 million) **due to prenatal organophosphate exposure**"

# Pre or postnatal exposure ?

## *Dioxines & Furans*





**Incinerators, landfills.. 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).**

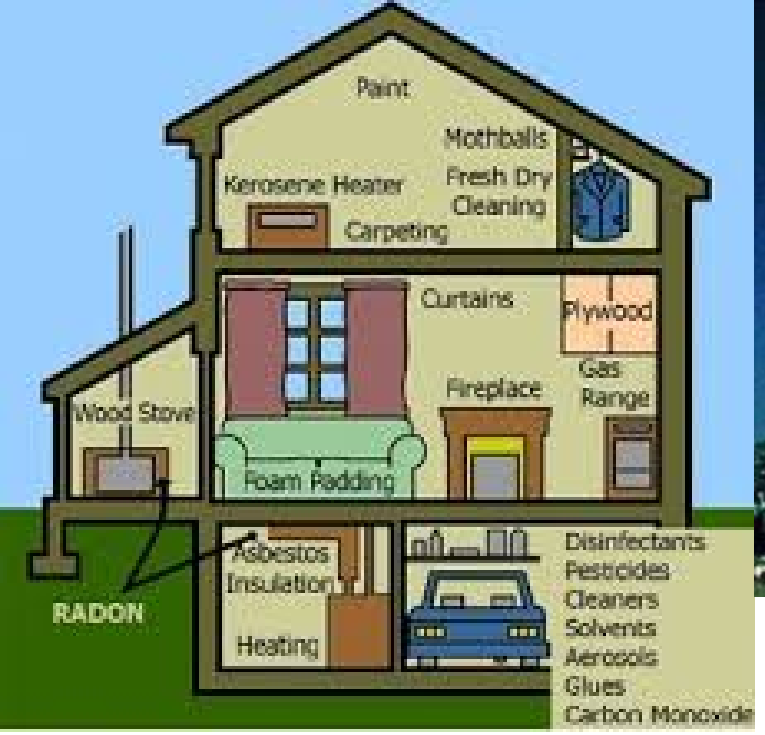
Chemosphere. 2004 Mar;54(10):1459-73. *Infant exposure to polychlorinated dibenzo-p-dioxins, dibenzofurans and biphenyls (PCDD/Fs, PCBs)--correlation between prenatal and postnatal exposure*. Wang SL, Lin CY, Guo YL, Lin LY, Chou WL, Chang LW.

# Pre or postnatal exposure ?

## PCBs


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)

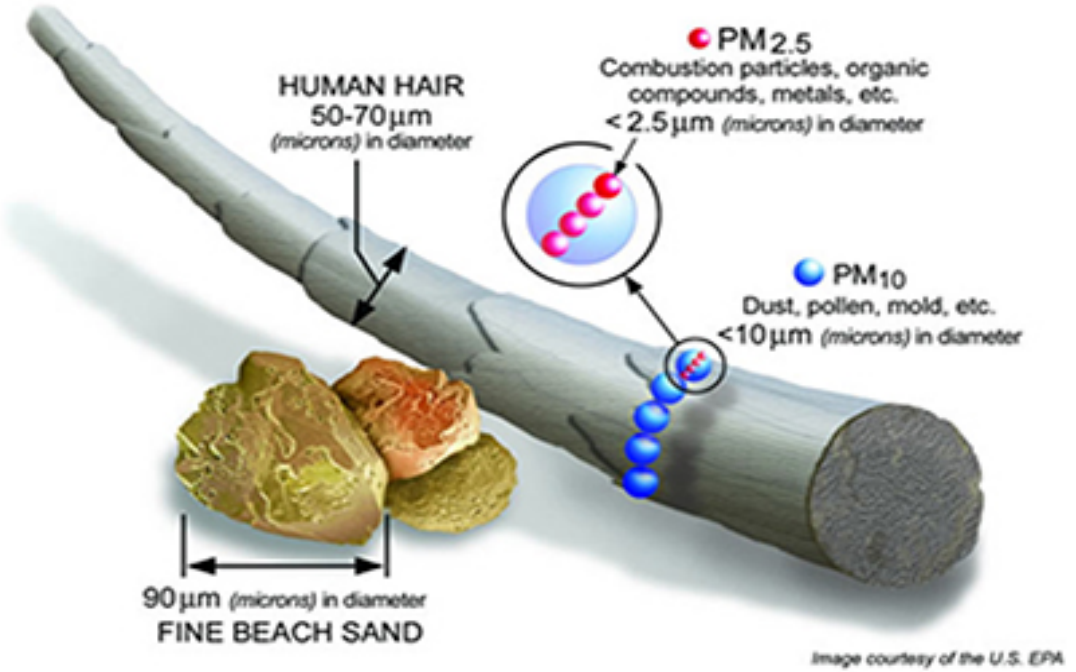
**J Expo Anal Environ Epidemiol. 2000 May-Jun;10(3):285-93. PCB exposure in utero and via breast milk. A review. DeKoning EP, Karmaus W. Et al.**





## House dust mites

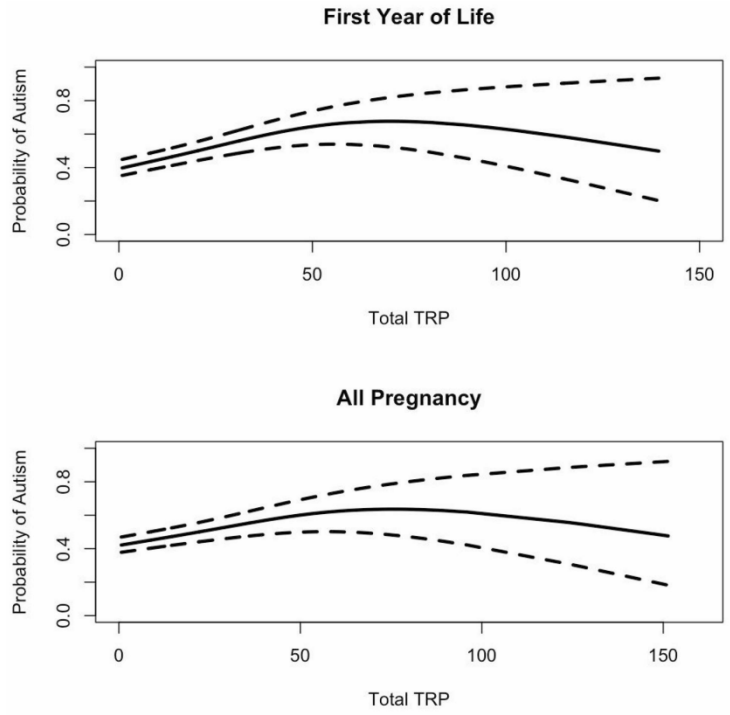
- House dust mites produce *Der p 1* allergen, a potent sensitizer
- Good evidence of increased risk of sensitization with increasing allergen exposure, but this does not necessarily lead to asthma
- Small reductions in exposure will not necessarily lead to reduced incidence and/or symptoms
- Indoor humidity is important



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

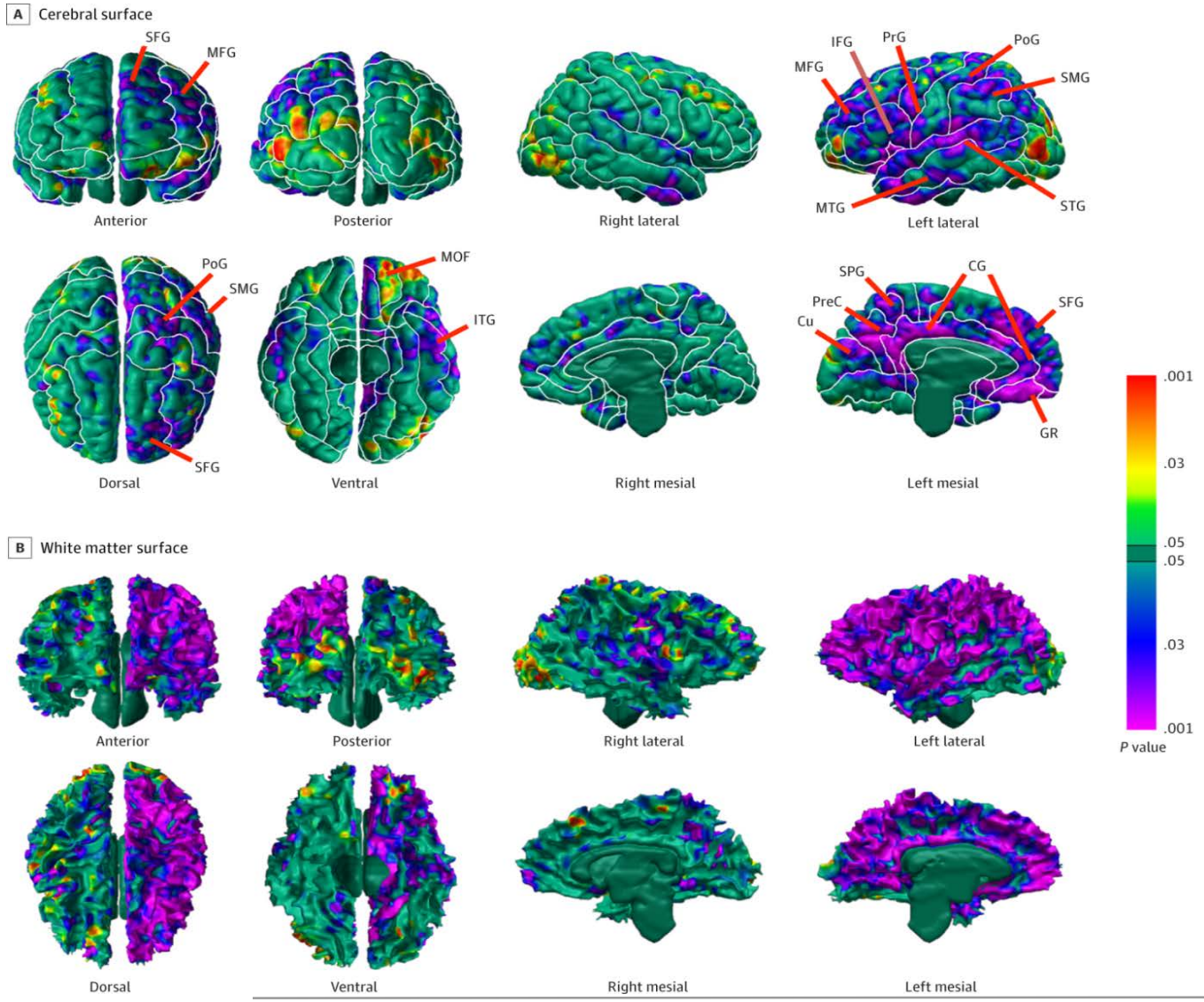
PM2.5, PM10, and NO2 at residences were higher in children with autism.

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 1.20–3.31)




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

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




We detected a **dose-response relationship between increased prenatal PAH exposure** (measured in the **third trimester** but thought to index **exposure for all of gestation**) and **reductions of the white matter surface in later childhood** that were confined almost exclusively to the **left hemisphere of the brain** and that involved almost its entire surface

genes

**Genes** 2017, 8, 150; doi:10.3390/genes8060150

MDPI

*Review*

# Maternal Factors that Induce Epigenetic Changes Contribute to Neurological Disorders in Offspring

Avijit Banik [1], Deepika Kandilya [1], Seshadri Ramya [1], Walter Stünkel [2], Yap Seng Chong [3] and S. Thameem Dheen [1,*]

It is well established that **the regulation of epigenetic factors**, including **chromatin reorganization, histone modifications, DNA methylation, and miRNA regulation, is critical for the normal development and functioning of the human brain**.
There are a number of **maternal factors influencing epigenetic pathways** such as **lifestyle, including diet, alcohol consumption, and smoking**, as well as **age and infections** (viral or bacterial).

Genetic and metabolic alterations such as **obesity, gestational diabetes mellitus (GDM), and thyroidism alter epigenetic mechanisms, thereby contributing to neurodevelopmental disorders (NDs) such as embryonic neural tube defects (NTDs), autism, Down's syndrome, Rett syndrome, and later onset of neuropsychological deficits**.

This review comprehensively describes the recent findings in the epigenetic landscape contributing to altered molecular profiles resulting in NDs. Furthermore, we will discuss potential avenues for future **research to identify diagnostic markers and therapeutic epi-drugs to reverse these abnormalities in the brain as epigenetic marks are plastic and reversible in nature.**

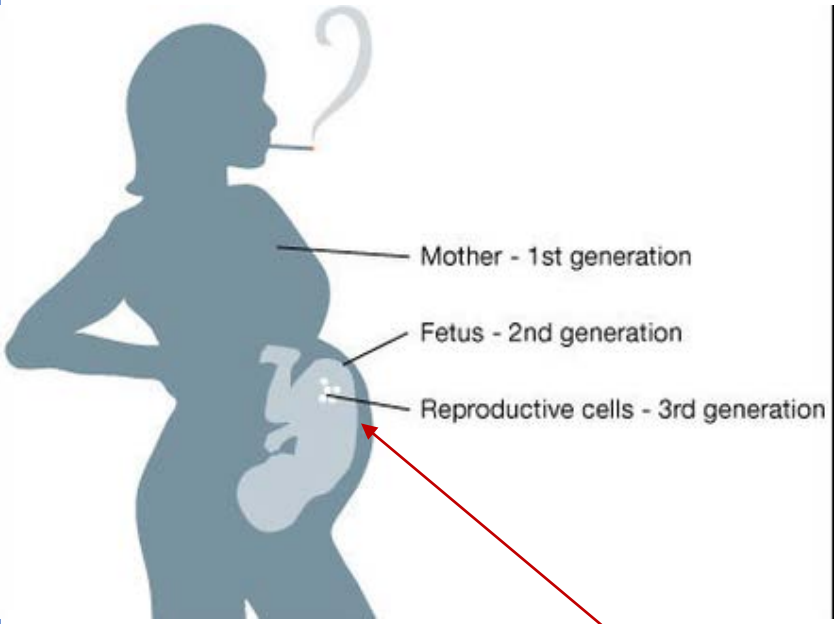
**Figure 1 Smoking in mothers alters neurodevelopmental processes in the fetus. Maternal smoking alters the DNA methylation of genes involved in placental and fetal development, leading to neurodevelopmental disorders** in the offspring.

## Maternal Smoking

### Alteration in DNA methylation pattern of fetal gene pools

- Placental Function: *LINE-1* [43], *AluYb8* [9]
- Neurodevelopment: *NR3C1* [50], *HSD11B2* [51], *GPR13, LRFN3* [53]
- Neurotransmission: *HTR2A, ADA* [47,48]
- Immune development: *ADA, PTPN22* [48]
- Transcriptome regulator: *RUNX3* [46], *PURA, GTF2H2, HKR1* [49]
- Calcium binding: *GCA* [45]
- Metabolism of aromatic hydrocarbon: *CYP1A1* [49]

- Placental abruption, Miscarriage, stillbirth, preterm delivery
- Neurobehavioral disorders: ADHD, Autism, Tourette's syndrome, Tic disorder , Obsessive-compulsive disorder




***Exposure of the germline*** *to* ***nicotine*** *produces* ***epigenetic changes in the germline…*** *they are* ***permanent, and passed from one generation to the next***

**F2** Epigenetic targets of alcohol exposure in the fetus. **Gestational alcohol exposure induces histone modification, alteration in DNA methylation pattern and miRNA targets, and expression of genes associated with fetal developmental process**, leading to neurodevelopmental disorders.

## Gestational Alcohol Exposure

### Susceptible targets in the fetus

**1 Gene targets**

- Developmental: Plunc, Neurofilament, Pale ear [68], *Hoxa1* [87]
- Cell Proliferation: *Oct4, Sox2, Nanog* [72], *Bub1, Cdc20, CcnB1, Plk1* [74]
- Cell Differentiation: *Sox1, Zic1, Cxcl12, BMP8b, Dmrt1, Meis1, Mef2c* [72], *Sh3bp2, Tnf, Adra1a, Pik3r1* [75]
- Brain development: *Pten, Otx2, Slitrk2, Nmnat1* [79]
- Imprinting: *H19* [76], *POMC* [80], *Sfmbt2, Dlk1, Ube3a* [79]
- Learning & Memory: *PNOC, PDYN* [82]

**2 miRNA targets**

miR-9, miR-21, miR-153, miR-335 [73]; miR-10a, miR-10b, miR-30a-3p, miR-145, miR-152, miR-29c, miR-30e-5p, miR-154, miR-200a, miR-296, miR-339, miR-362, miR-496 [87]

**3 Histone modifying targets**

H3K9ac [81]
H3K27me3 [82]
CBP [83]

**4 DNA methylation targets**

DNMT, MeCP2 [67]


### Phenotypic outcomes in the offspring

**Fetal alcohol spectrum disorder (FASD)**

- Attention and memory deficit
- Craniofacial malformation
- Motor function abnormalities
- Auditory and language problem

**F3** Effect of **maternal dietary deficiency** on fetal development.

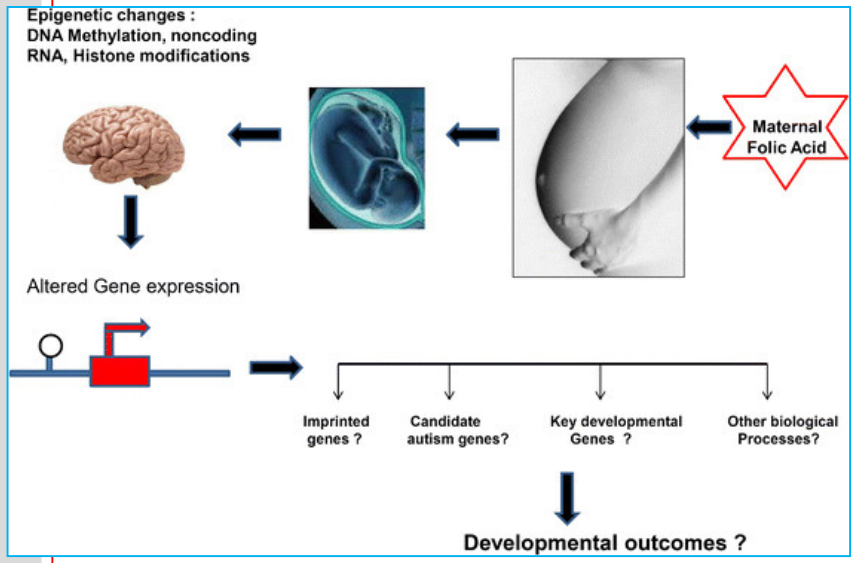
**The absence of essential dietary supplements in maternal diet during gestation leads to a disruption in metabolic pathways and several epigenetic alterations in the fetus**, triggering **abnormal uterine development** and **neurodevelopmental disorders**.

## Maternal dietary deficiency

Absence of dietary methyl group donors such as folate, choline, methionine, betain and methylcobalamine

- Imbalance in folate-mediated one-carbon metabolism (FOCM) pathway [98]
- Mutation in methionine synthase reductase (*Mtrr*) gene, essential for deployment of methyl groups from the folate cycle [104]
- Down-regulation of genes related to fetal brain development: *BDNF*, *CREB*, *NGF* and *TrkB* [105]
- H3K9 and H4K20 methylation [114]
- Altered expression of miRNAs linked to FOCM pathway : miR-29c, miR-183, miR-422b, miR-189 [115]; miR-22, miR-24, miR-29b, miR-34a, miR-125, miR-344-5p/484, miR-488 [116-118]

Abnormal uterine development and congenital malformation [104]



**F4** Effect of **maternal metabolic conditions** on fetal development.

**Metabolic conditions at gestation such as GDM, obesity, and hypothyroidism induce epigenetic alterations in the fetus**, leading to a series of **metabolic and immunogenic changes triggering neuroanatomical and neuropsychological deficits in the developing brain**.

## Maternal metabolic conditions

- Gestational Diabetes Mellitus (GDM)
- Maternal Obesity
- Maternal Hypothyroidism

Trigger epigenetic imbalance in the fetus [149,150,157,158,172]

- Induces oxidative stress [148]
- ROS accumulation [148]
- Inflammatory response [155]
- Cytokine production [156]
- Decreased T3 levels [169]
- Altered levels of metabolic genes [172]

Neuroanatomical /neuropsychological deficits in developing brain

**F5** Several **lifestyle-related metabolic factors and infection at gestation play a critical role in the epigenetic modification** and in turn the **altered expression of many genes associated with abnormal fetal development**. This may lead to a series of neurodevelopmental disorders in the offspring.

## Maternal Factors

| Life Style | Metabolic | Infection |
|---|---|---|
| • Smoking<br>• Alcohol consumption<br>• Malnutrition<br>• High fat diet<br>• Late parental age | • Gestational diabetes mellitus (GDM)<br>• Thyroidism<br>• Obesity | • Viral<br>• Bacterial |

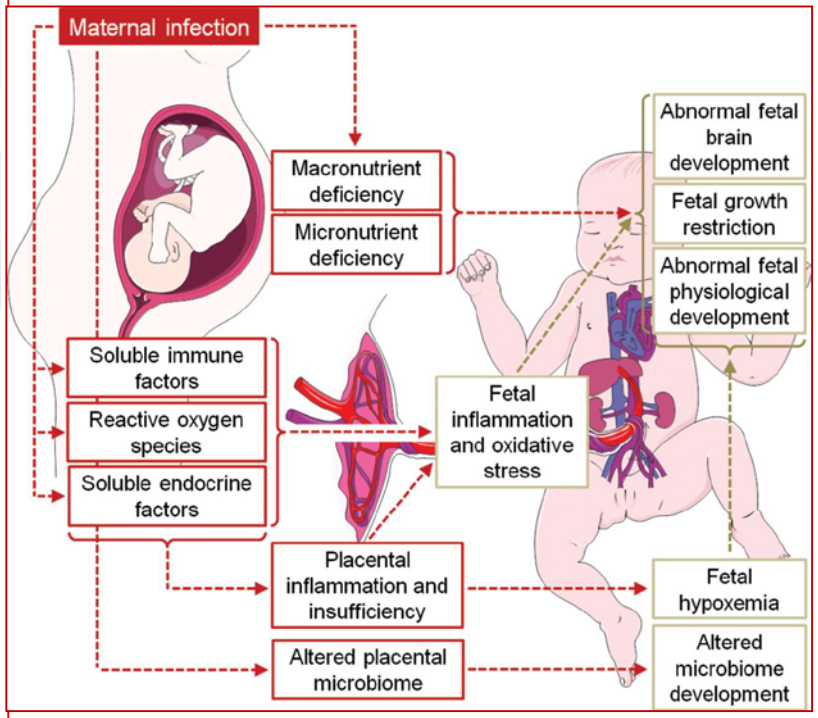
Induce imbalance in the epigenetic mechanisms in early developmental process

| DNA Methylation | Histone Modification | Chromatin Remodelling | Differential expression of mi-RNAs |
|---|---|---|---|

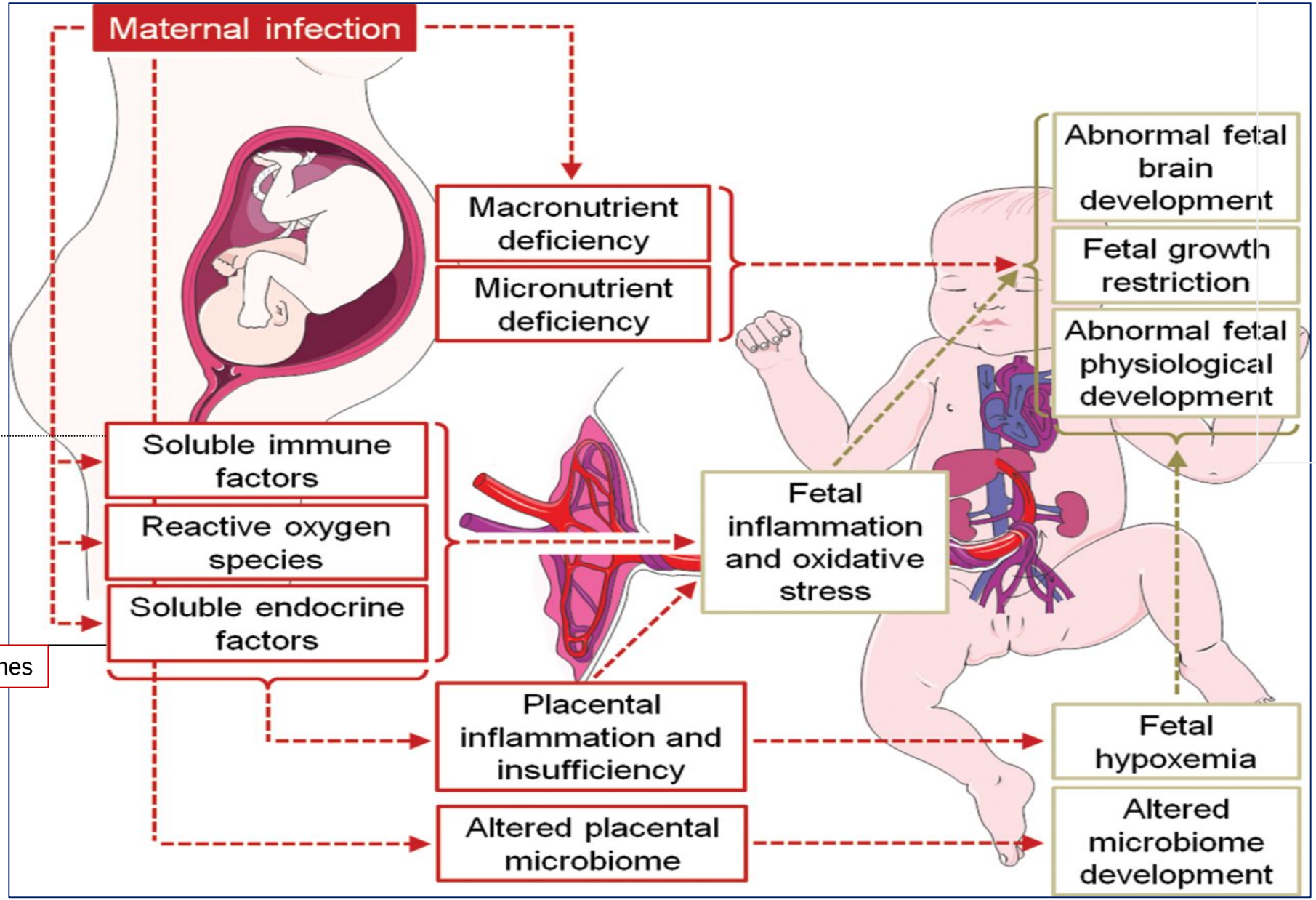
Altered expression of genes critical for normal fetal development

### Neurodevelopmental Disorders

| Genetic | Multifactorial |
|---|---|
| • Down's syndrome<br>• Prader–Willi syndrome<br>• Rett syndrome<br>• Fragile-X syndrome<br>• ICF syndrome | • Neural tube defects<br>• ADHD<br>• Autistic disorders<br>• Epilepsy<br>• Tourette's syndrome<br>• Fetal alcohol syndrome<br>• Schizophrenia |



**Possible mechanisms mediating the pathological effects of maternal infection on the developing organism in utero**

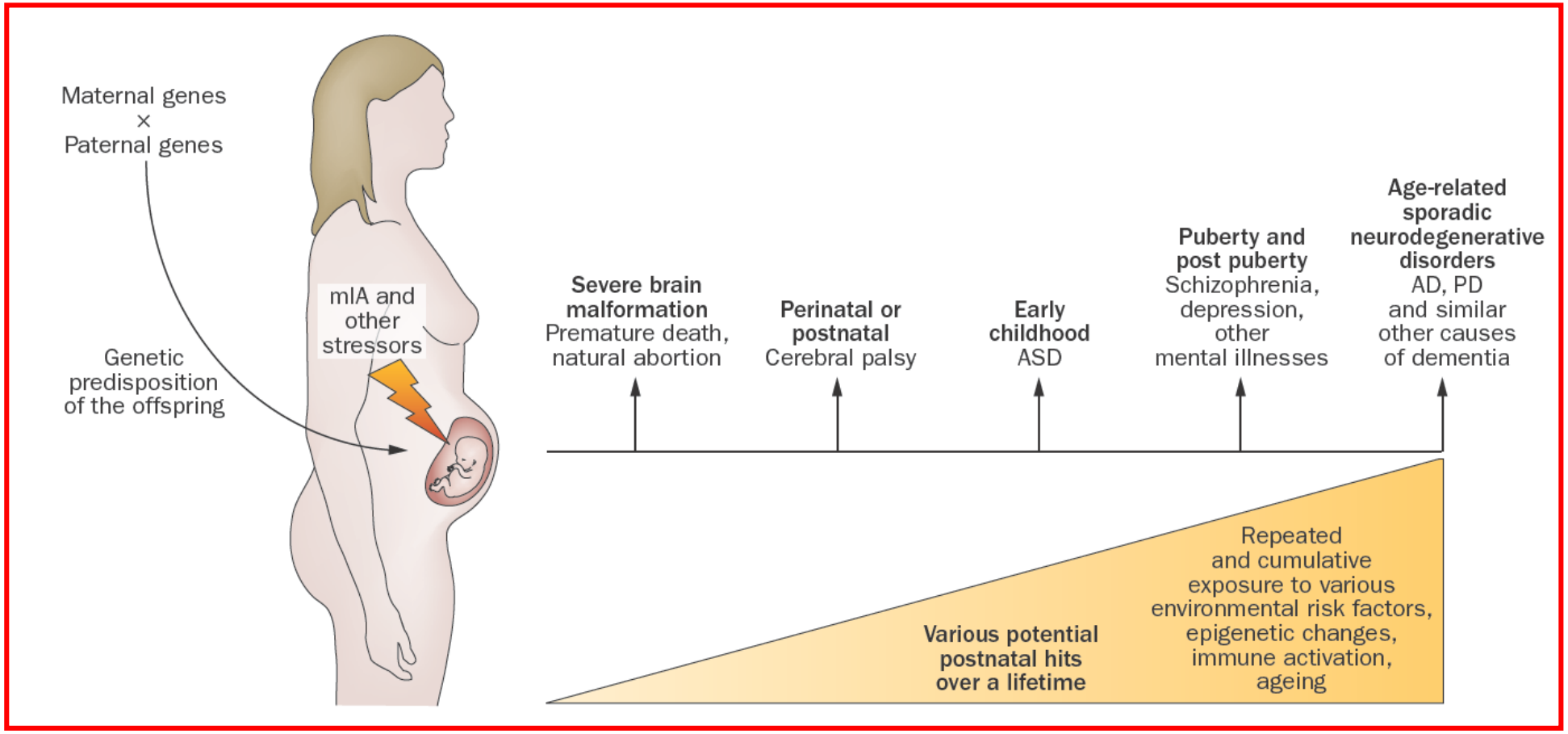



AMERICAN JOURNAL OF PHYSIOLOGY
Regulatory, Integrative and Comparative Physiology

Marie A. Labouesse et al. Am J Physiol Regul Integr Comp Physiol 2015;309:R1-R12

# Maternal immune activation and abnormal brain development across CNS disorders

Nature Reviews Neurology 10, 643–660 (2014)




**Epidemiological studies** have shown a clear association between **maternal infection and schizophrenia or autism** in the progeny.

**Animal models** have revealed **maternal immune activation (mIA) to be a profound risk factor for neurochemical and behavioural abnormalities in the offspring**.

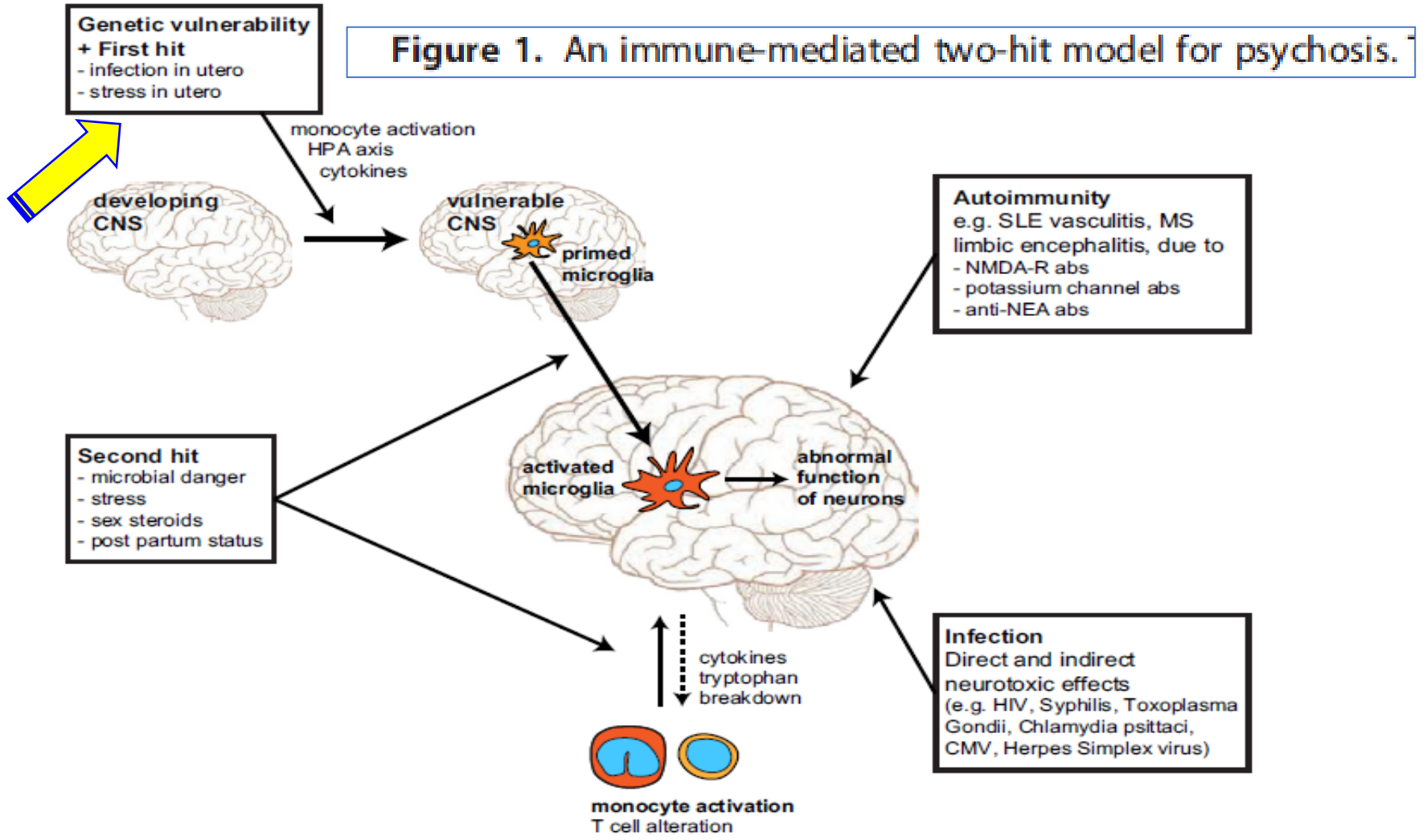



**Figure 1.** An immune-mediated two-hit model for psychosis.

Infection **but also environmental stressors during gestation/early life activate microglia, perturbing neuronal development, thereby setting the stage for vulnerability for later psychotic disorders.**

A **second hit, such as endocrine changes, stress, or infection, could further activate microglia, leading to functional abnormalities of the neuronal circuitry in the brain and psychosis**

Clinical Therapeutics

Volume 35, Issue 5, May 2013, Pages 584–591

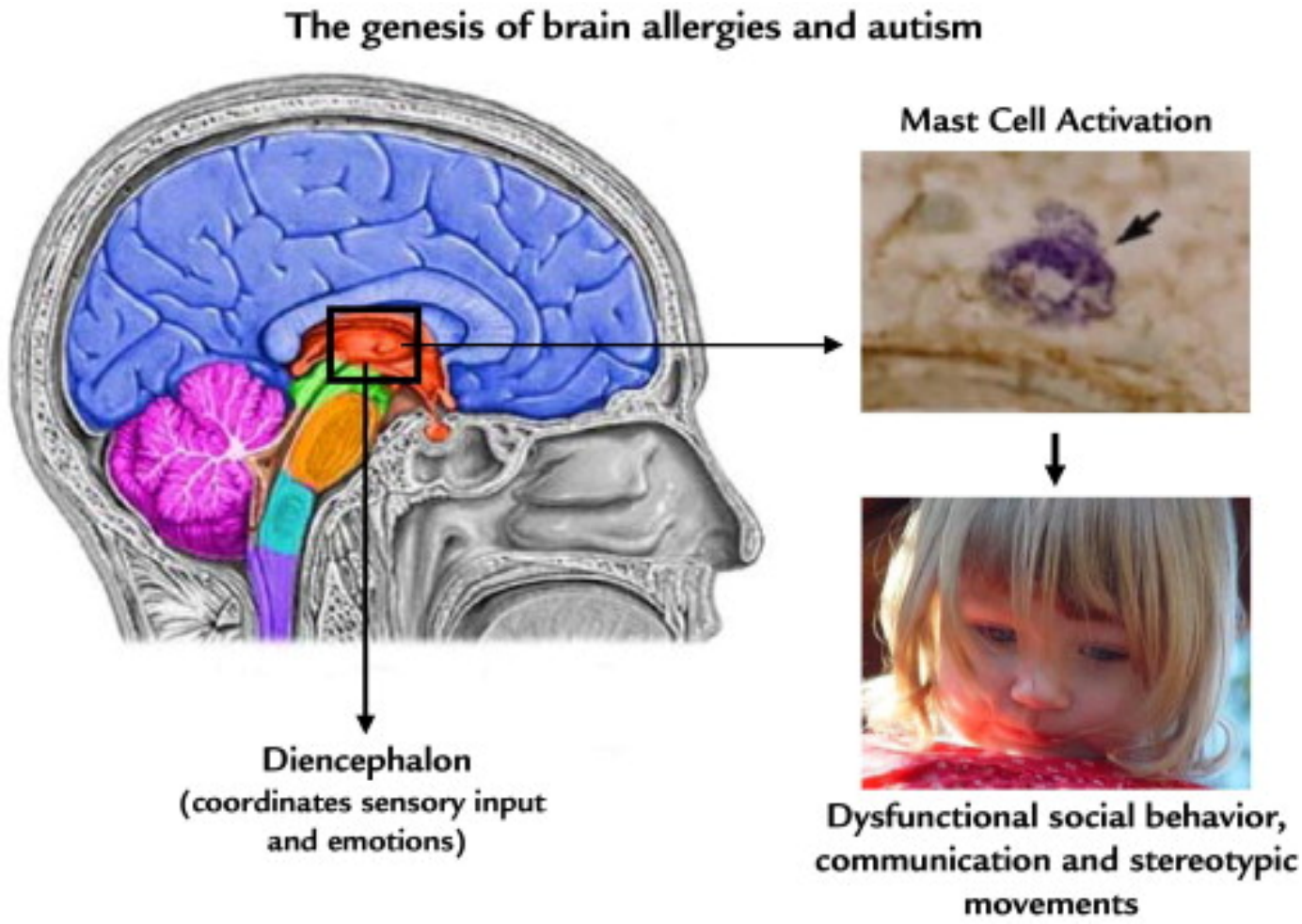
New "atopic" clinical entities in search of pathogenesis and treatment

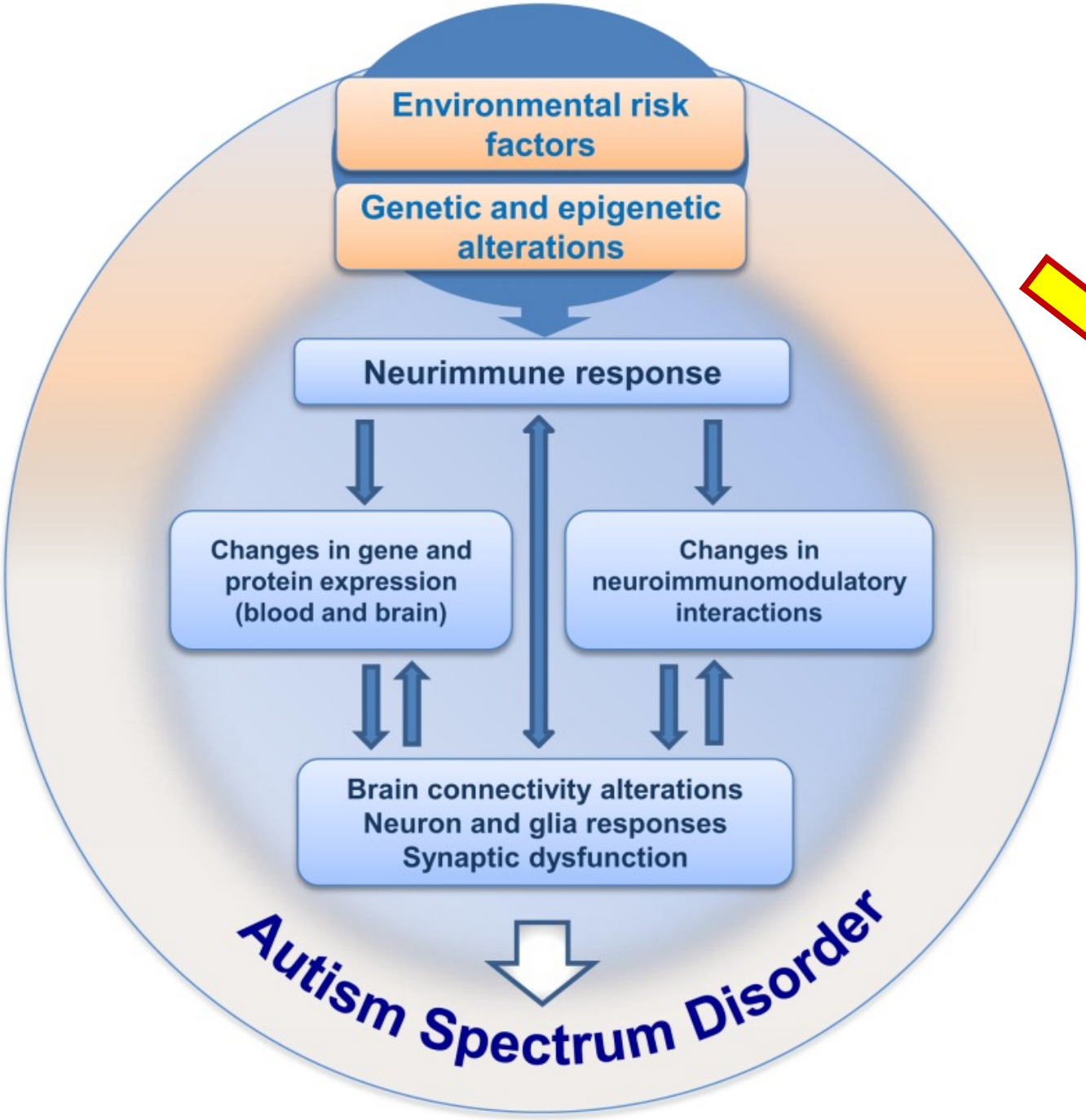
# Is a Subtype of Autism an Allergy of the Brain?

Theoharis C. Theoharides, MS, MPhil, PhD, MD

Show more

doi:10.1016/j.clinthera.2013.04.009

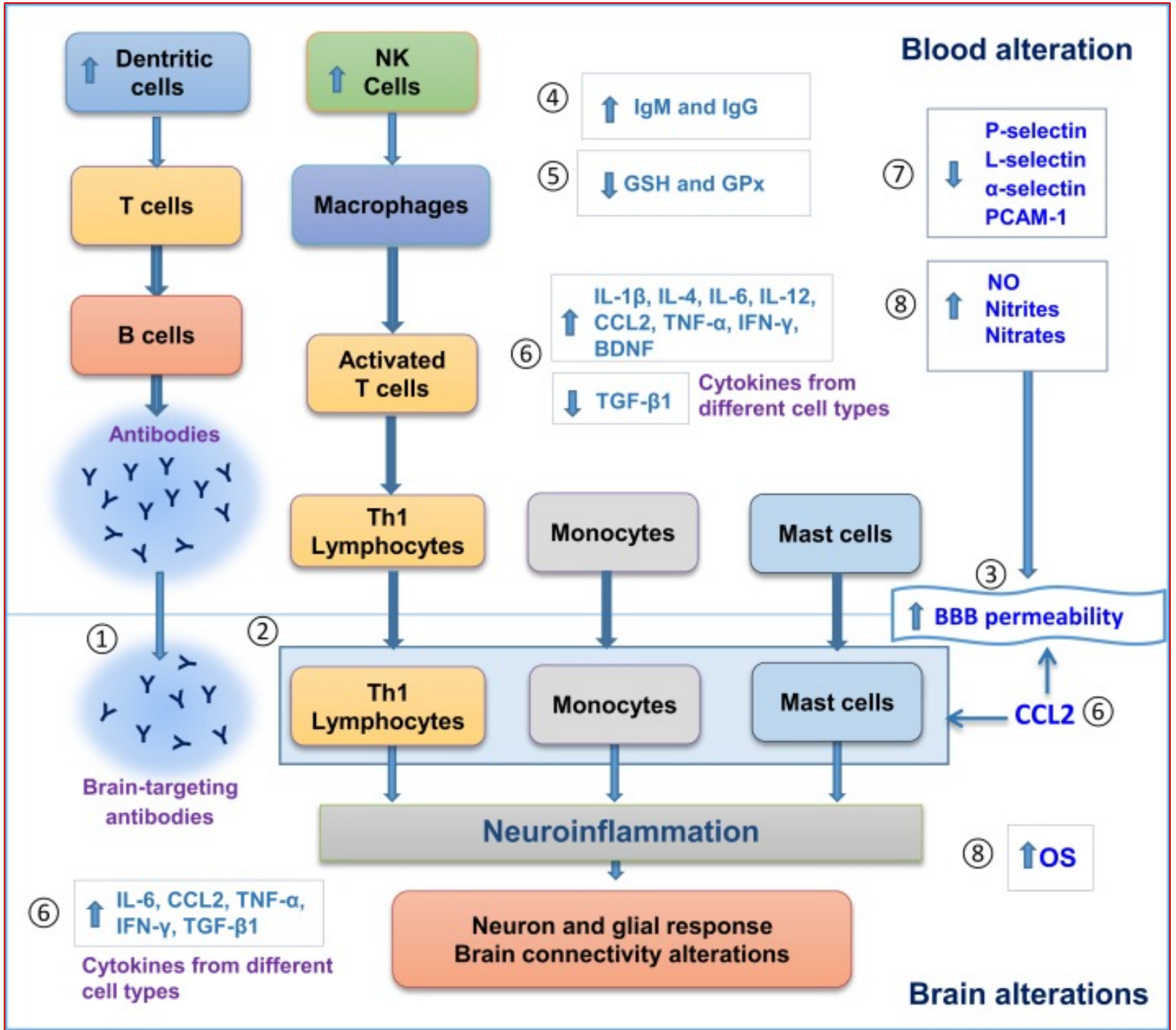





**Hypothesis for neuroimmune interactions in triggering the development of ASD**.

This hypothesis considers the presence of **environmental risk factors during pregnancy**, followed by **immunoneuroendocrine response from the mother to the developing embryo/fetus**.

The risk factors (such as VPA) would influence central and peripheral neural responses in the context of a crosstalk with the immune system, **followed by gradual changes in neural plasticity and function, resulting in behavioral impairment during development, ultimately leading to ASD.**




**Evidence for neuroimmune interactions in autism spectrum disorder (ASD).**

**Blood and postmortem brain alterations** in individuals with ASD.

(1) **Antibody production** in blood **against brain antigens.**

(2) **Brain cell infiltration of Th1 lymphocytes, monocytes and mast cells**.

(3) **Increase in blood brain barrier (BBB) permeability.**

(4) Increase in IgG and IgM levels.

(5) **Less antioxidant defenses**. Increase in **oxidative stress**.

(6) **Changes in cytokine levels**.

(7) **Decrease in cell adhesion molecules**, such as Selectins and PCAM-1.

All these alterations can promote **neuroinflammation, followed by neuron–glial response and brain connectivity dysfunction** that ultimately can influence behavioral features in ASD.

# The Microglia Hypothesis of Schizophrenia

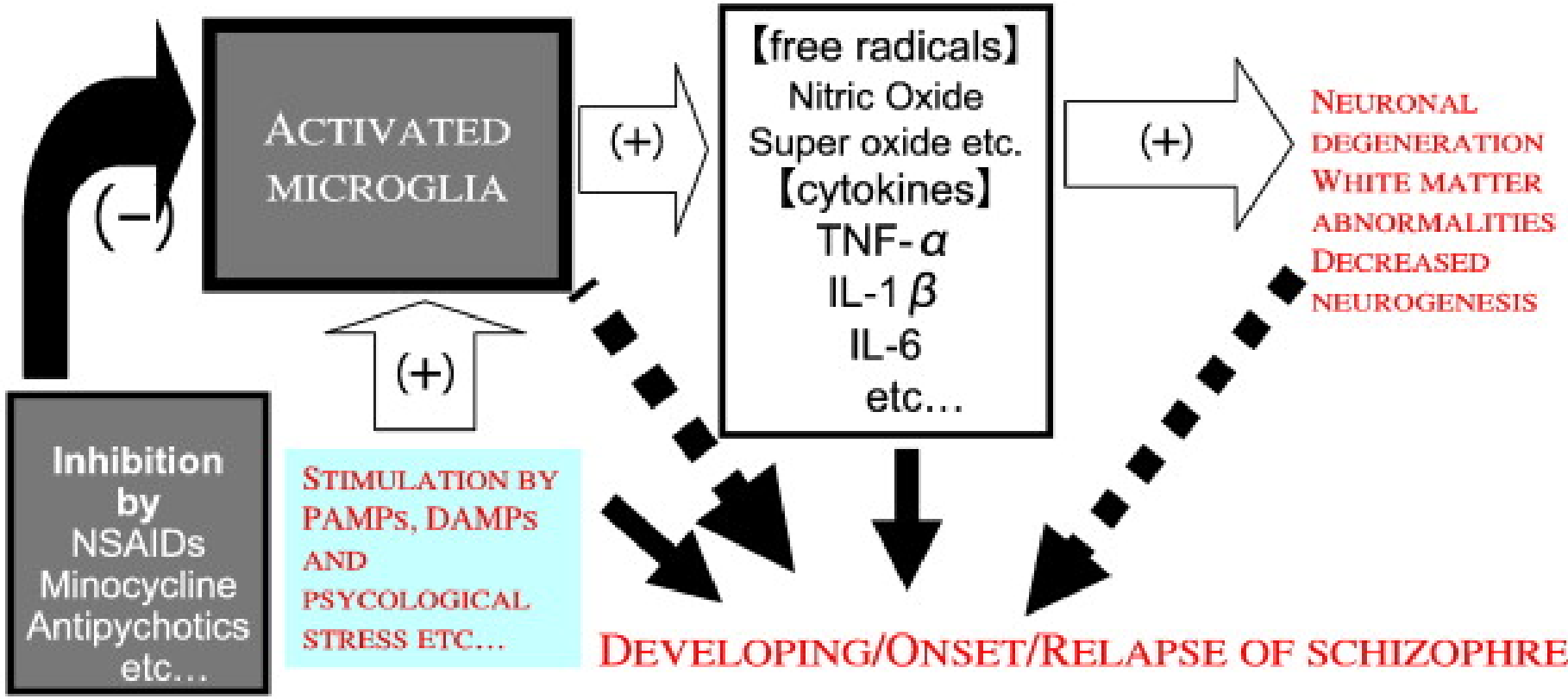
(Recent clinical findings on the neurobiology of schizophrenia)

Progressive brain atrophy and its inhibition by some atypical antipsychotics

Microglial activation revealed by PET in the brains of patients with schizophrenia

Antipsychotic effect of anti-inflammatory drugs such as NSAIDs and minocycline

## The neuron-glia interaction in the pathphysiology of schizophrenia




THERAPEUTIC STRATEGY OF SCHIZOPHRENIA THROUGH THE INHIBITION OF MICROGLIAL

Hindawi Publishing Corporation
Neural Plasticity
Volume 2015, Article ID 708306, 12 pages
http://dx.doi.org/10.1155/2015/708306

*Review Article*

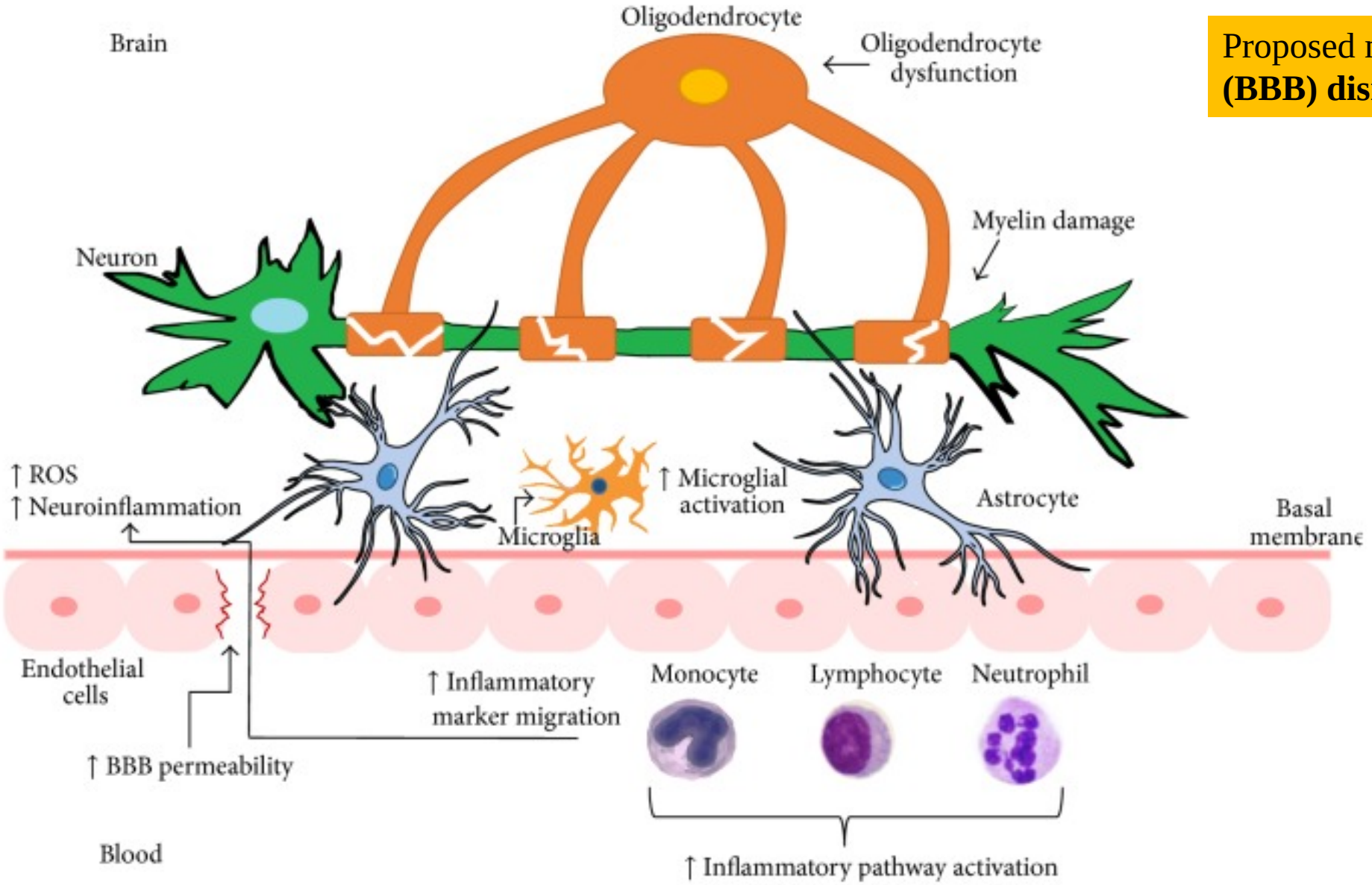
# Disruption in the Blood-Brain Barrier: The Missing Link between Brain and Body Inflammation in Bipolar Disorder?

Jay P. Patel[1] and Benicio N. Frey[1,2,3]

There has been growing evidence that **BBB disruption is associated with brain inflammatory conditions such as Alzheimer's disease and multiple sclerosis**.
Considering the increasing role of **inflammation and oxidative stress in the pathophysiology of bipolar disorder (BD),** here we propose a novel model wherein **transient or persistent disruption of BBB integrity is associated with decreased CNS protection and increased permeability of proinflammatory (e.g., cytokines, reactive oxygen species) substances** from the peripheral blood into the brain.

These events would **trigger the activation of microglial cells and promote localized damage to oligodendrocytes and the myelin sheath,** ultimately **compromising myelination and the integrity of neural circuits.**

Proposed model of **blood-brain barrier (BBB) disruption** in **bipolar disorder**




**Increased BBB permeability through the endothelial cells (pink) and basal membrane (dark pink)** may facilitate increased **migration of inflammatory molecules** into the brain. Acti**vation of microglial cells (light orange) and an increase in reactive oxygen species (ROS)** would amplify neuroinflammatory processes and ultimately induce **damage in the myelin sheath**, either directly **via lipid/protein oxidation** or indirectly via **oligodendrocyte dysfunction** (dark orange)

# THE *SINS* OF THE FATHER

*The roots of inheritance may extend beyond the genome,*

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

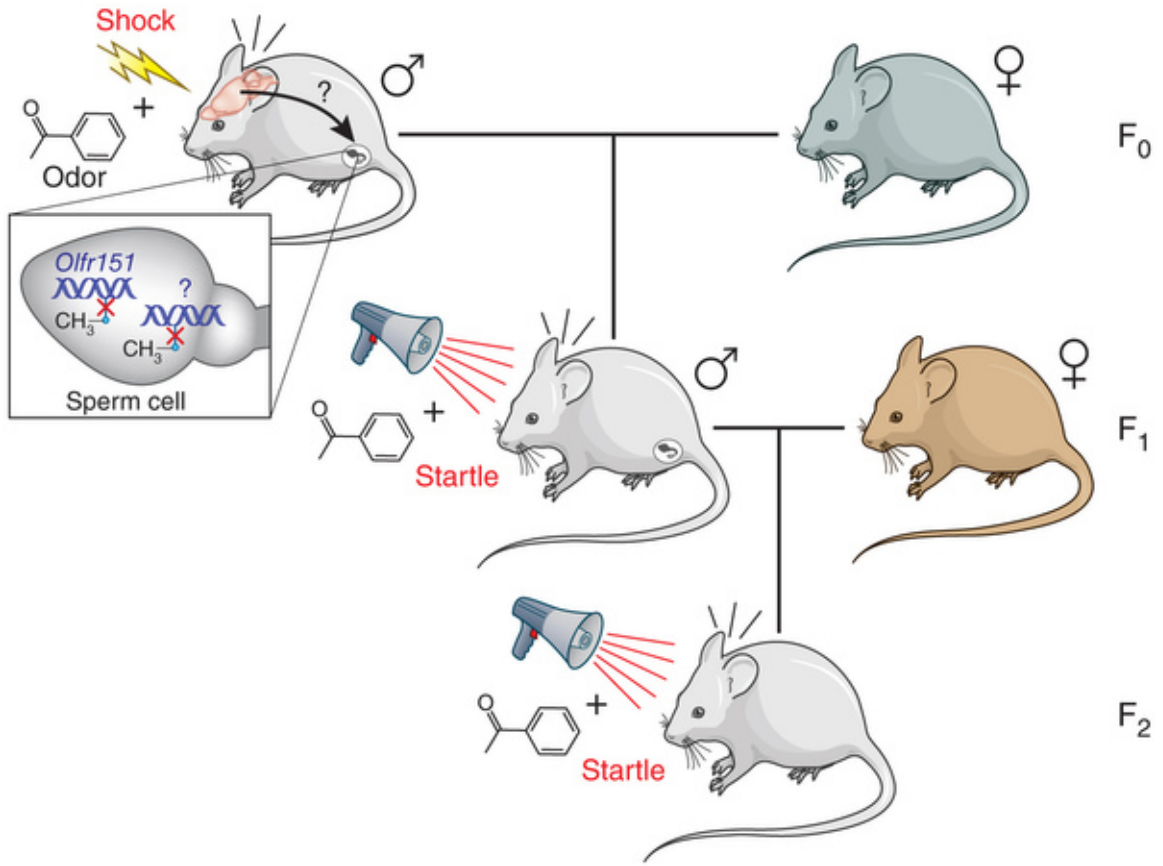
# Lamarck revisited: epigenetic inheritance of ancestral odor fear conditioning

Nature Neuroscience 17, 2–4 (2014)

Moshe Szyf

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

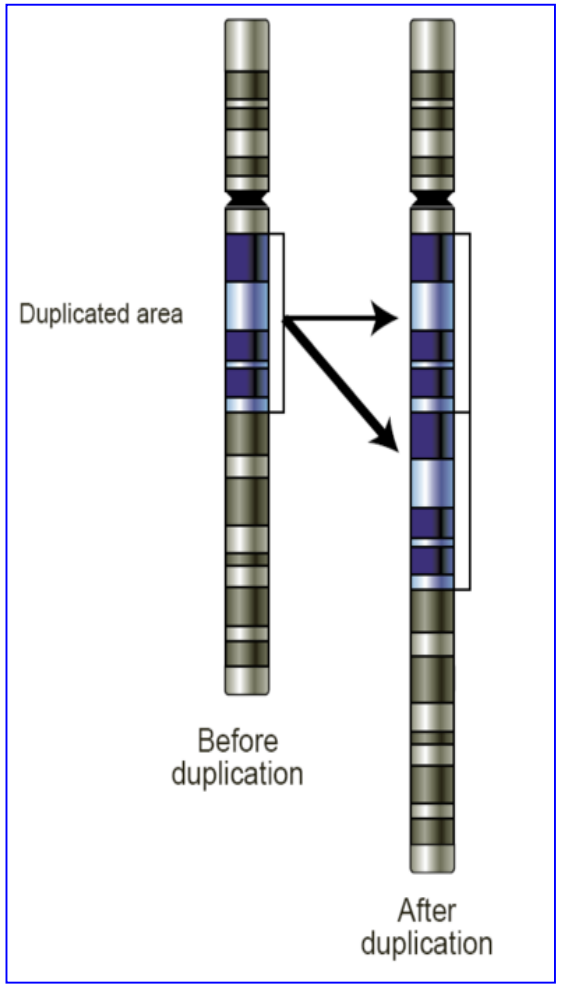
A study shows that **when mice are taught to fear an odor, both their offspring and the next generation are born fearing it.**
The **gene for an olfactory receptor activated by the odor**
**is specifically demethylated in the germ line** and **the olfactory circuits for detecting the odor are enhanced**



**What is most striking is that the same CNVs have been found, at least in some cases, in the semen of parents, showing that autism could be the consequence**

**of a parental exposure to pollutants**

**and a transgenerational transmission:** which could provide **an explanation for the unremitting "pandemic" increase of these disorders.**




All that said .. it **is absolutely necessary to reconsider the problem of many early environmental exposures or even gametic, and their possible synergy .. which can induce an epigenetic instability**,

Update

Trends in Neuroscience Vol 32, 2, 2009, 69–72

Research Focus

# Contact in the genetics of autism and schizophrenia

J. Peter H. Burbach and Bert van der Zwaag

Rudolf Magnus Institute of Neuroscience, Department of Neuroscience and Pharmacology, University Medical Center Utrecht, P.O. Box 85060, 3508 AB Utrecht, The Netherlands

Although autism and schizophrenia are considered to be distinct neuropsychiatric developmental disorders, recent studies indicate that they share genetic factors. The same chromosomal r
single genes have emerge
disorders. One such ge
protein-2 (*CNTNAP2*). These
that these neuropsychiatric
mechanisms and that simila
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A **similar situation is emerging from CNV studies of schizophrenia**. There is **a high frequency of de novo CNVs.. a large heterogeneity in rare variants…**

**Which** indicates that **similar pathways may be involved in phenotypically distinct outcomes**

SCIENCE sciencemag.org
2 OCTOBER 2015 • VOL 350 ISSUE 6256

NEURODEVELOPMENT

# Somatic mutation in single human neurons tracks developmental and transcriptional history

Michael A. Lodato,[1*] Mollie B. Woodworth,[1*] Semin Lee,[2*] Gilad D. Evrony,[1] Bhaven K. Mehta,[1] Amir Karger,[3] Soohyun Lee,[2] Thomas W. Chittenden,[3,4]† Alissa M. D'Gama,[1] Xuyu Cai,[1]‡ Lovelace J. Luquette,[2] Eunjung Lee,[2,5] Peter J. Park,[2,5]§ Christopher A. Walsh[1]§

Neurons live for decades in a postmitotic state, their genomes susceptible to DNA damage. Here we survey the landscape of somatic single-nucleotide variants (SNVs) in the human brain. We identified thousands of somatic SNVs by single-cell sequencing of 36 neurons from the cerebral cortex of three normal individuals. Unlike germline and cancer SNVs, which are often caused by errors in DNA replication, neuronal mutations appear to reflect damage during active transcription. Somatic mutations create nested lineage trees, allowing them to be dated relative to developmental landmarks and revealing a polyclonal architecture of the human cerebral cortex. Thus, somatic mutations in the brain represent a durable and ongoing record of neuronal life history, from development through postmitotic function.

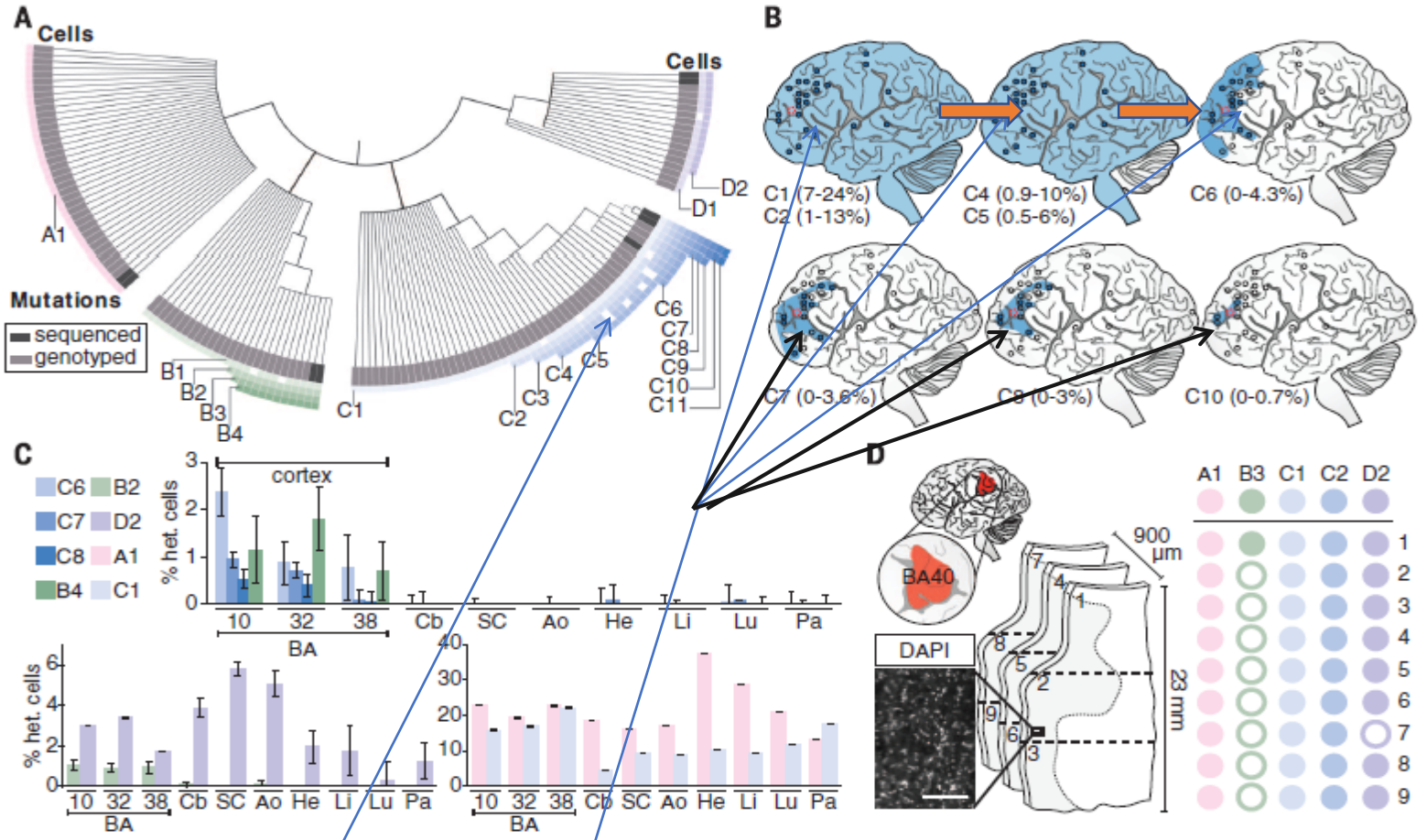


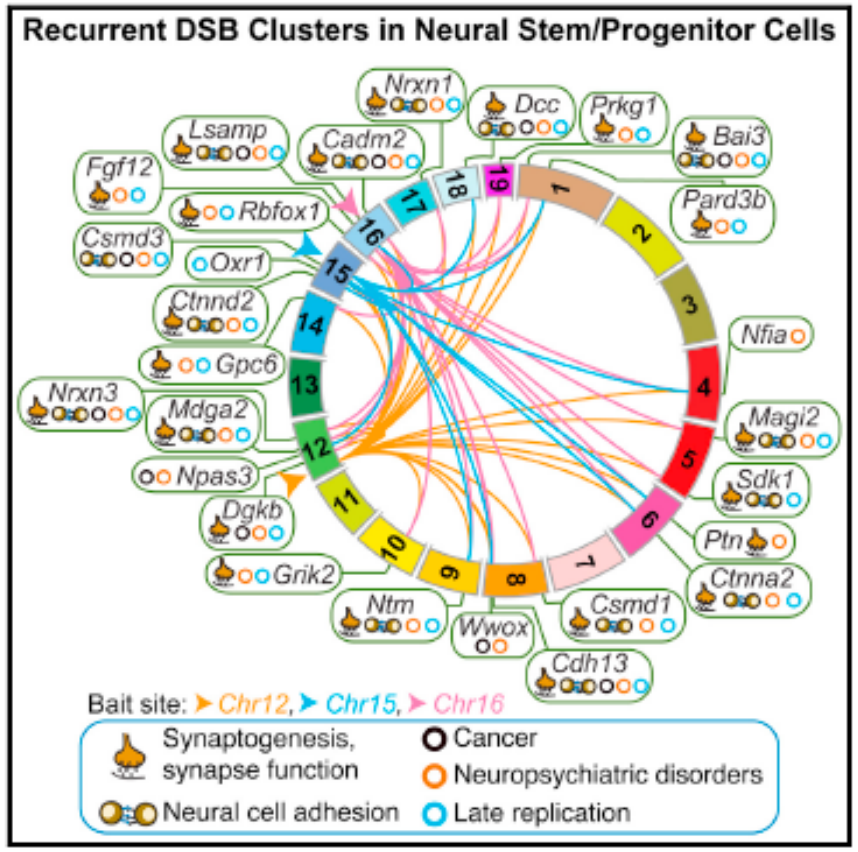

**Fig. 3. Somatic mutations are shared between multiple neurons and demonstrate lineage relationships.** (**A**) Lineage map of 136 human cortical neurons from brain B derived from 18 clonal somatic mutations, including SNVs, long interspersed nuclear element (LINE) insertions, and a TG-dinucleotide expansion. Neurons are placed into four distinct nested clades (pink, green, blue, purple) defined by one or more independent mutations. Cells are ordered within clades according to the presence of multiple somatic mutations. A few cells in each clade fail to manifest individual SNVs shared by other cells of the same clade (indicated by open squares), likely representing incomplete amplification (fig. S2). Dark gray boxes represent cells analyzed by WGS; light gray represents cells analyzed by Sanger-based genotyping. Genomic locations of somatic mutations are given in fig. S11. (**B**) Ultradeep sequencing of mutated loci across the cortex of brain B. Clonal SNVs from a single clade are progressively regionally restricted to frontal cortex and become progressively rarer in bulk tissue, reflecting their later origin during development and neurogenesis. Blue circle, mutation present; empty circle, mutation absent; blue shading, likely spatial distribution of mutation. Percentage range of heterozygous cells is indicated for each SNV. (**C**) Ultradeep sequencing of mutated loci across the brain and body. Some variants are brain-specific (top) and others are shared across germ layers (bottom). Samples sequenced are prefrontal cortex [Brodmann area (BA) 10/BA46], cingulate cortex (BA32/BA8), temporal cortex (BA38), cerebellum (Cb), spinal cord (SC), aorta (Ao), heart (He), liver (Li), lung (Lu), and pancreas (Pa). (**D**) Genotyping shared variants in small sections of human cortex. Left: 4′,6-diamidino-2-phenylindole (DAPI) stain of segment of representative section; scale bar, 200 µm. Center: Three consecutive 300-µm coronal sections from BA40 (red, upper left) were dissected into three axial regions each (1 to 9). Right: Genotyping results for dissected sections. Solid circles denote presence of mutation in indicated sample; open circles denote absence. Mutations with high allele fractions are present in all or virtually all regions, whereas only the least prevalent somatic variant (present in <0.5% of cells) is present in one region but not most regions.

Article

Cell

# Long Neural Genes Harbor Recurrent DNA Break Clusters in Neural Stem/Progenitor Cells

## Graphical Abstract




## Authors

Pei-Chi Wei, Amelia N. Chang, Jennifer Kao, Zhou Du, Robin M. Meyers, Frederick W. Alt, Bjoern Schwer

## Correspondence

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## In Brief

Neural stem and progenitor cells undergo massive genomic alterations in a very restricted set of genes involved in synapse function and neural cell adhesion, processes that are likely to govern the special behavior of brain cells. Many of these genes have also been implicated in mental disorders.

## Highlights

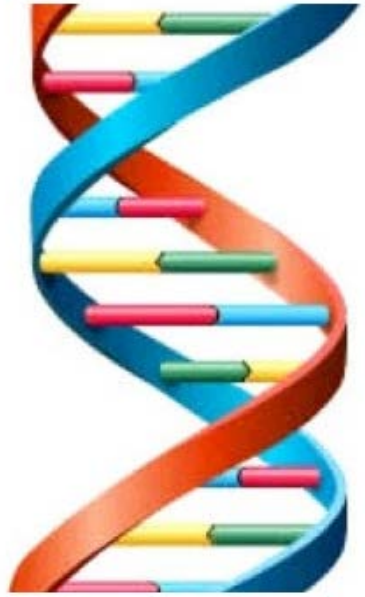
1) **27 Recurrent DSB clusters (RDCs)** are identified **in neural stem/progenitor cells**

**2) All RDCs are within genes**, most of which are long, transcribed, and late replicating

3) Most RDC genes are **involved in synapse function and/or neural cell adhesion**

**4)** A nucleotide-resolution view of **replication stress-associated fragile sites** is provided

# STRESS PROTEINS AND DNA AS A FRACTAL ANTENNA FOR RFR



DNA acts as a 'fractal antenna' for EMF and RFR.

The coiled-coil structure of DNA in the nucleus makes the molecule react like a fractal antenna to a wide range of frequencies.

The structure makes DNA particularly vulnerable to EMF damage.

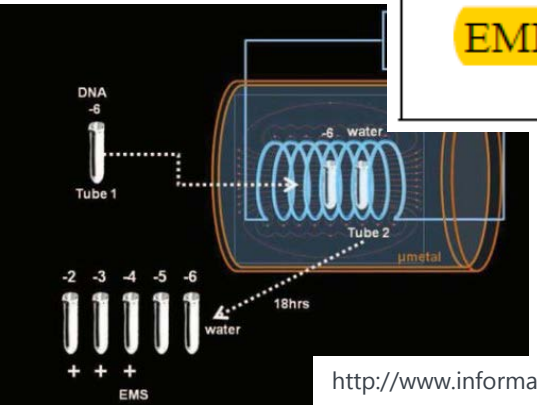
The mechanism involves direct interaction of EMF with the DNA molecule (claims that there are no known mechanisms of interaction are patently false)

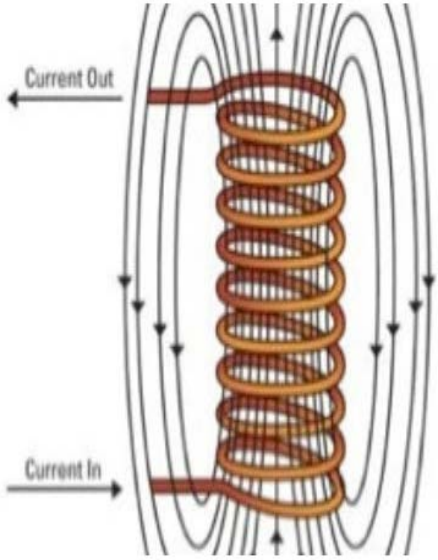
Many EMF frequencies in the environment can and do cause DNA changes.

The EMF-activated cellular stress response is an effective protective mechanism for cells exposed to a wide range of EMF frequencies.

EMF stimulates stress proteins (indicating an assault on the cell).

EMF efficiently harms cells at a billion times lower levels than conventional heating.
Blank, 2012 – Section 7)

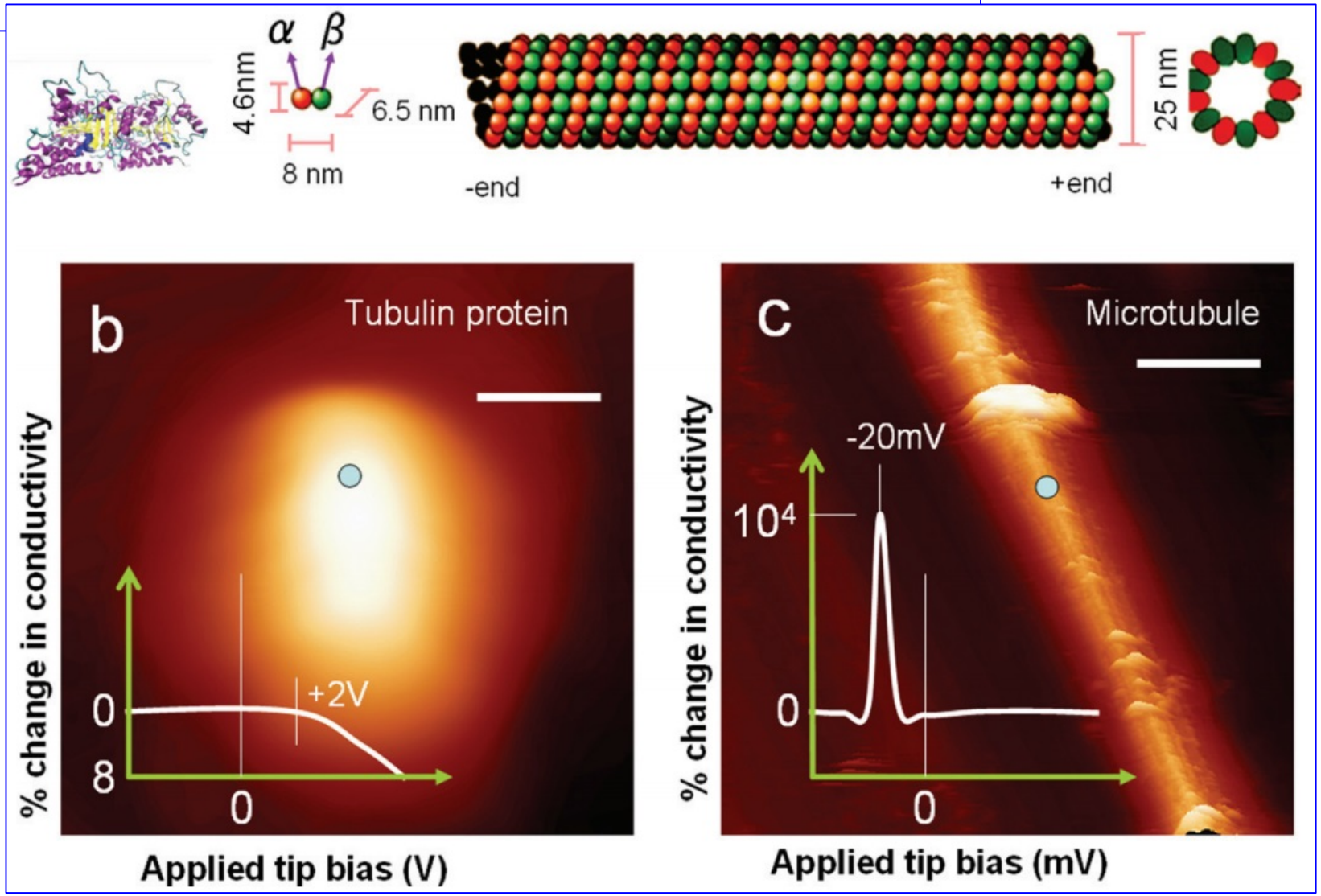


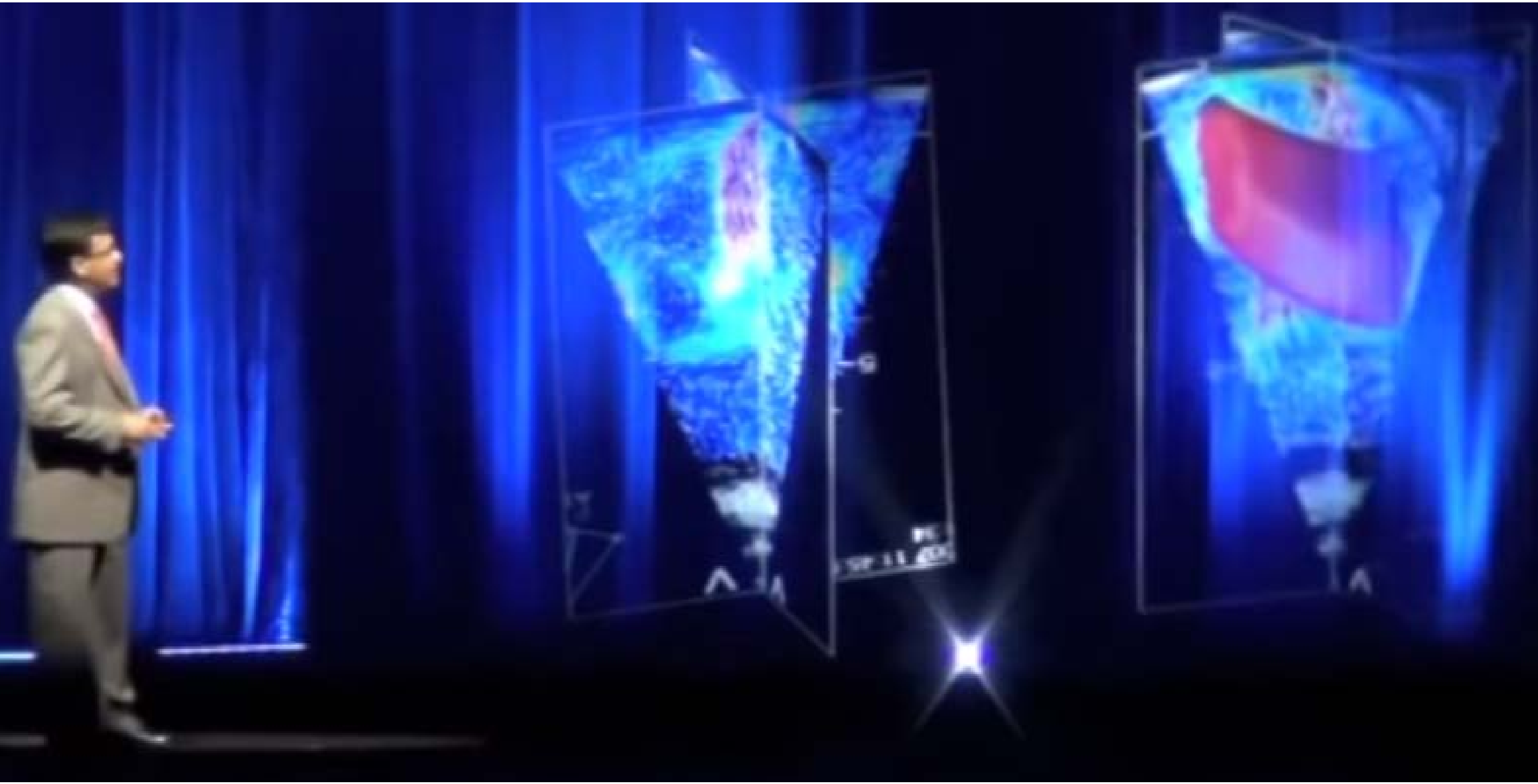



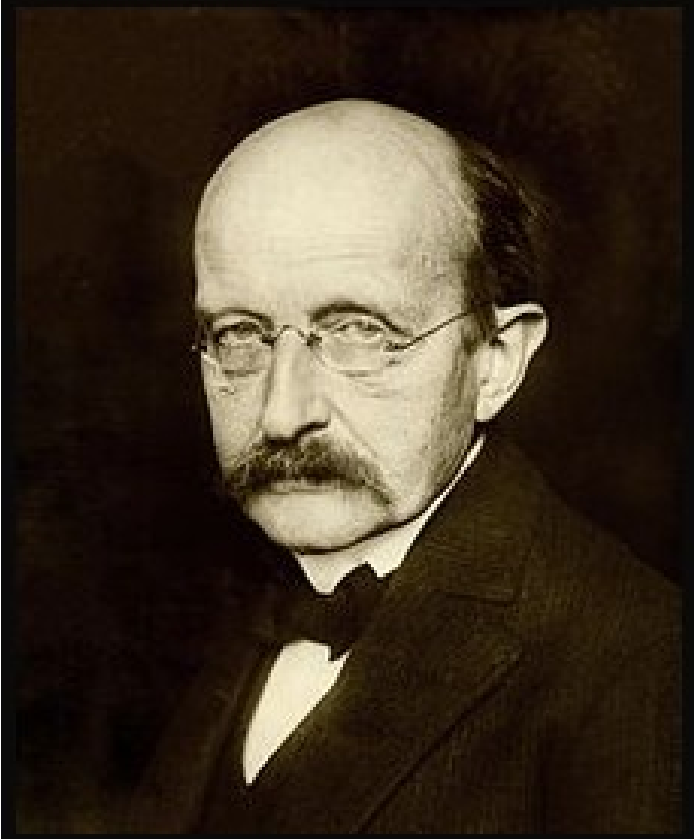

http://www.informationenergymedicine-academy.com/wp-content/uploads/coil-to-generate-7-Hz-carrier-wave-300x228.jpg 300w" sizes="(max-width: 500px) 100vw, 500px" /

# The Penrose–Hameroff theory of "orchestrated objective reduction (Orch OR)"

The Penrose–Hameroff theory of "**orchestrated objective reduction (Orch OR)" identifies discrete conscious moments with quantum computations in microtubules** inside brain neurons



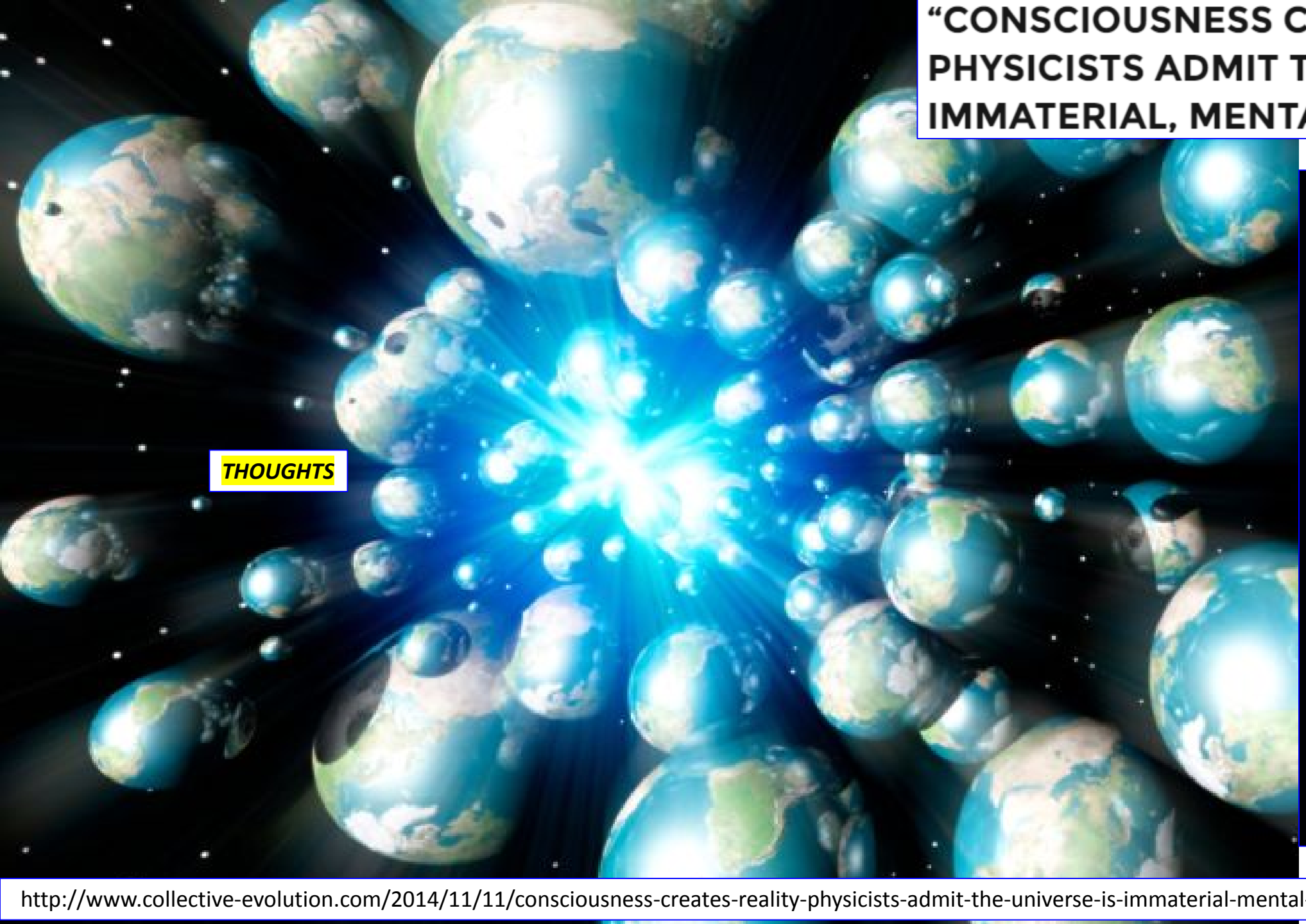




I regard consciousness as fundamental. I regard matter as derivative from consciousness. We cannot get behind consciousness. Everything that we talk about, everything that we regard as existing, postulates consciousness.

(Max Planck)

# "CONSCIOUSNESS CREATES REALITY" PHYSICISTS ADMIT THE UNIVERSE IS IMMATERIAL, MENTAL & SPIRITUAL




As observers involved with the creation

the universe is a "mental" construction

the universe begins to look more like a great thought than like a great machine.

Mind

the creator and governor of the realm of matter

http://www.collective-evolution.com/2014/11/11/consciousness-creates-reality-physicists-admit-the-universe-is-immaterial-mental-spiritual/

*Nature* **436**, 29 (7 July 2005) | doi:10.1038/436029a; Published online 6 July 2005

nature International weekly journal of science

Concept

# The mental Universe

Richard Conn Henry[1]

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**The only reality is mind and observations, but observations are not of things. To see the Universe as it really is, we must abandon our tendency to conceptualize observations as things.**

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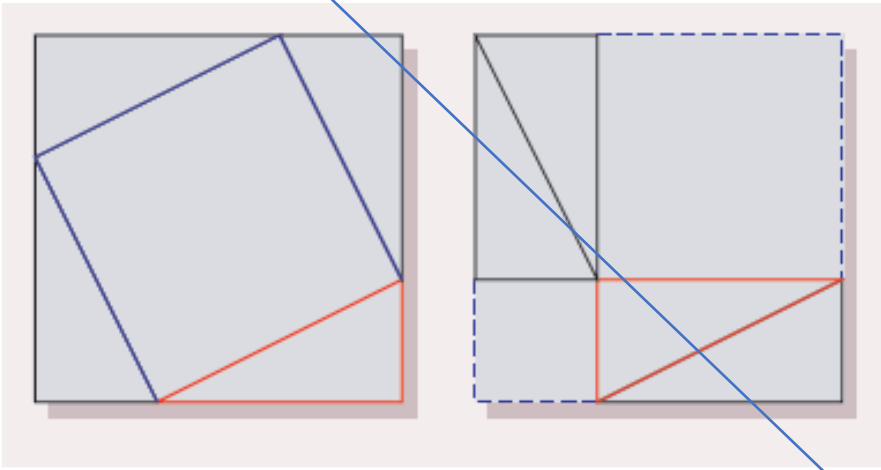
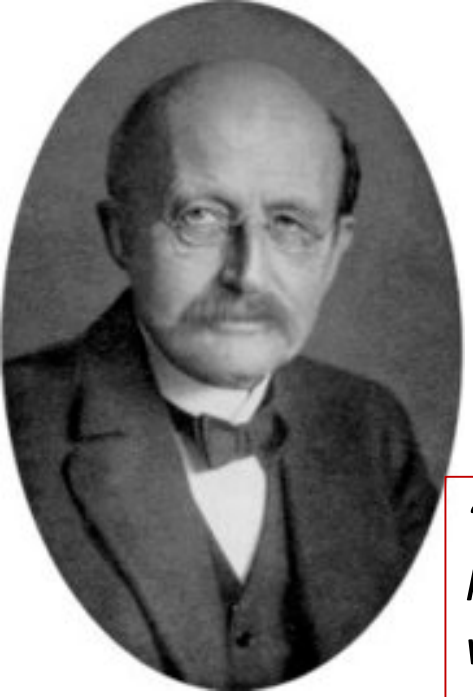
correct understanding of physics was accessible even to Pythagoras. According to Pythagoras, "number is all things", and numbers are mental, not mechanical. Likewise, Newton called light "particles", knowing the concept to be an 'effective theory' — useful, not true. As noted by Newton's biographer Richard Westfall: "The ultimate cause of atheism, Newton asserted, is 'this notion of bodies having, as it were, a complete, absolute and independent reality in themselves.'" Newton knew of Newton's rings and was untroubled by what is shallowly called 'wave/particle duality'.



**Proof without words: Pythagoras explained things using numbers.**

The 1925 discovery of quantum mechanics solved the problem of the Universe's nature. Bright physicists were again led to believe the unbelievable — this time, that the Universe is mental. According to Sir James Jeans: "the stream of knowledge is heading towards a non-mechanical reality; the Universe begins to look more like a great thought than like a great machine. Mind no longer appears to be an accidental intruder into the realm of matter... we ought rather hail it as the creator and governor of the realm of matter." But physicists have not yet followed Galileo's example, and convinced everyone of the wonders of quantum mechanics. As Sir Arthur Eddington explained: "It is difficult for the matter-of-fact physicist to accept the view that the substratum of everything is of mental character."

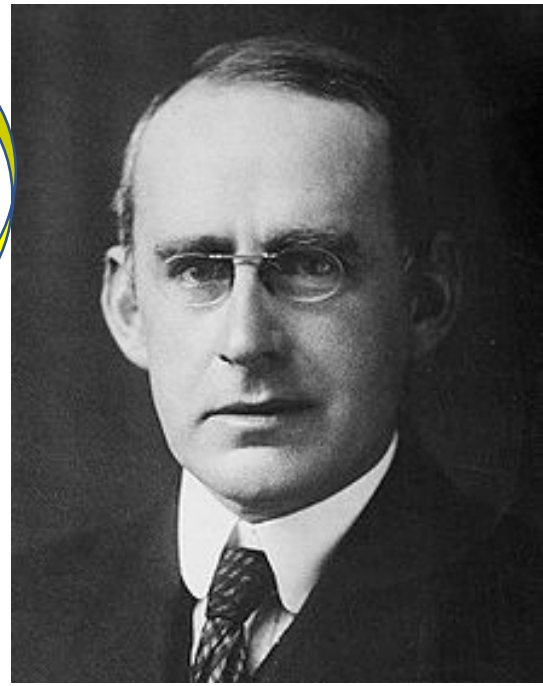
Physicists shy from the truth because the truth is so alien to everyday physics. A common way to evade the mental Universe is to invoke 'decoherence' — the notion that 'the physical environment' is sufficient to create reality, independent of the human mind. Yet the idea that any irreversible act of amplification is necessary to collapse the wave function is known to be wrong: in 'Renninger-type' experiments, the wave function is collapsed simply by your human mind seeing nothing. The Universe is entirely mental.



*"**All matter originates and exists only by virtue of a force** **which brings the particle of an atom to vibration** and holds this most minute solar system of the atom together.*

***We must assume behind this force the existence of a conscious and intelligent mind. This mind is the matrix of all matter."***

*"**The external world of physics has thus become a world of shadows**. In removing our illusions we have removed the substance, for indeed we have seen **that substance is one of the greatest of our illusions**.. In the world of physics we watch a shadowgraph performance of the drama of familiar life. **The shadow of my elbow rests on the shadow table as the shadow ink flows over the shadow paper.***
***It is all symbolic**, and as a symbol the physicist leaves it.*
***Then comes the alchemist Mind who transmutes the symbols.***
***The sparsely spread nuclei of electric force become a tangible solid; their restless agitation becomes the warmth of summer; the octave of aethereal vibrations becomes a gorgeous rainbow…***
*The frank **realization that physical science is concerned with a world of shadows is one of the most significant of recent advances**".*



Eddington A. ***The Nature of the Physical World*** (1928)

*"I regard the physical world as made of **information**, with **energy** and matter as incidentals." - John Wheeler*

http://wsimag.com/science-and-technology/20365-the-intuitive-evidence-of-being-awareness

In science, 'fact' can only mean 'confirmed to such a degree that it would be perverse to withhold provisional assent.' I suppose that apples might start to rise tomorrow, but the possibility does not merit equal time in physics classrooms.

**Stephen Jay Gould** (1941 - 2002)

***MAY GOD US KEEP FROM SINGLE VISION & NEWTON'S SLEEP !***

The most important scientific revolutions all include, as their only common feature, the dethronement of human arrogance from one pedestal after another of previous convictions about our centrality in the cosmos.

**Stephen Jay Gould** (1941 - 2002)

THANK YOU

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