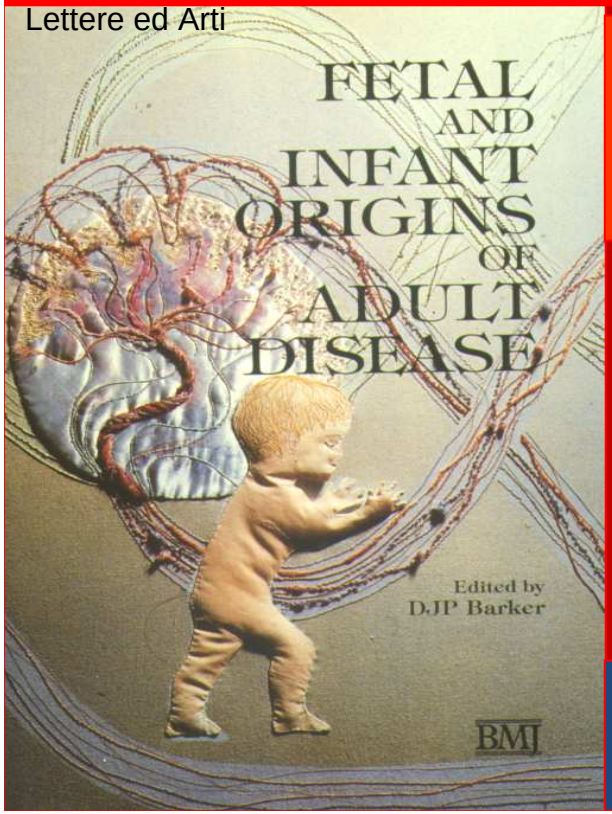
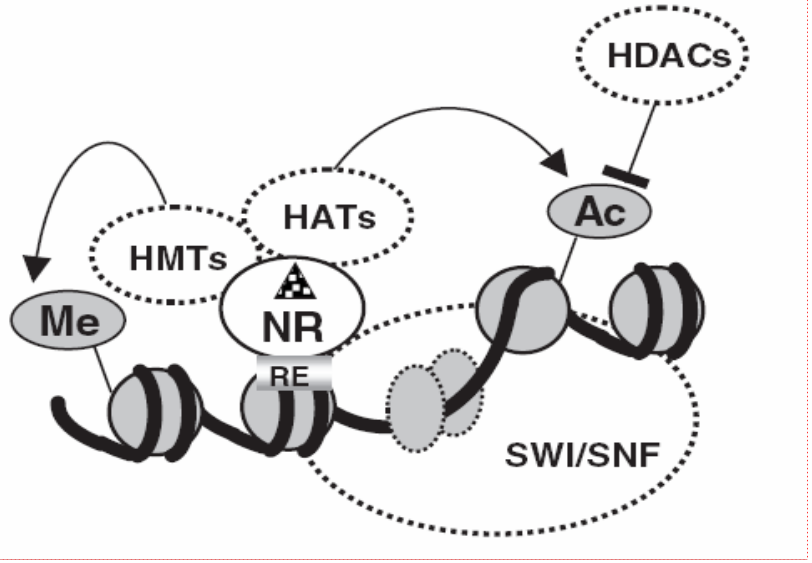
ISDE Salsomaggiore 18/20 - 04 -2008
International Conference
Padova 10 - 05 - 2008
CONVEGNO NAZIONALE "AMBIENTE E SALUTE"
FNOMCeO, ISDE, Accademia Galileiana di Scienze Lettere ed Arti



The Environmental Toxic Burden and the fetal origins of adult diseases

Ernesto Burgio
(ISDE Italy)



Parte I

Summary

- ***ENVIRONMENT*** → HEALTH *Fluid Epigenome*
- **Genome** and **Epi-genome**
- **The *Epidemic Revolution of XXth Century***
- **3 PARADIGMS**

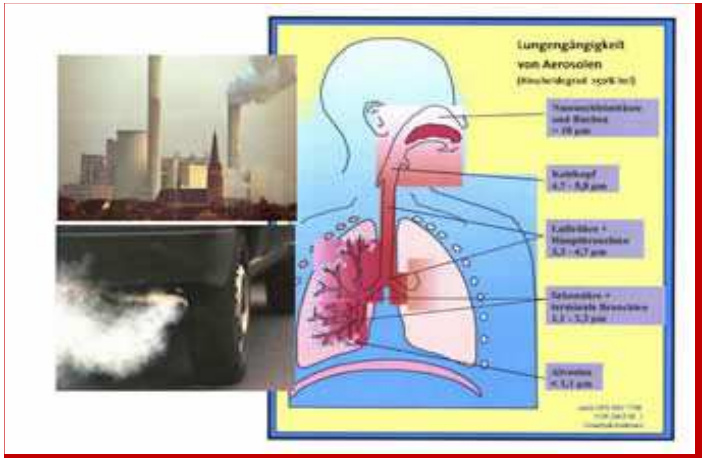
2 **Barker Hypothesis**

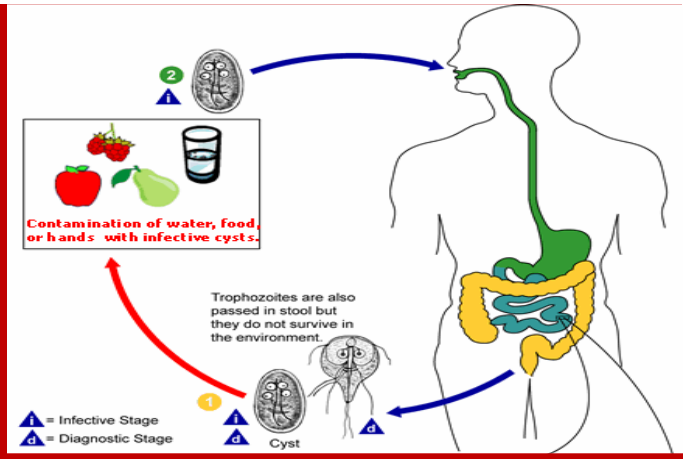
1 **Hygiene Hypothesis**

3 **Systemic-chronic (low grade) Inflammation**

Back to the NEO-LAMARCKIAN PARADIGM

ENVIRONMENT → Epigenetic Changes





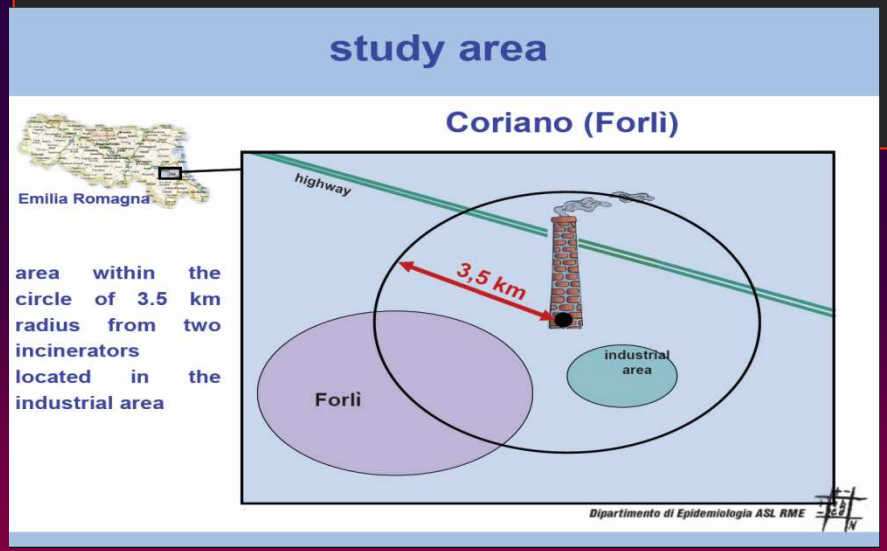
- Generalmente si utilizza il binomio "***ambiente e salute***"
  o si parla di "*epidemiologia ambientale*" in riferimento ad alcuni **problemi specifici**, connessi alla **esposizione diretta o indiretta di singoli individui/popolazioni**
  a "**fonti di inquinamento**" puntuali (grandi impianti) o diffuse sul territorio (traffico veicolare)…
- **trascurando** quello che è il contesto più generale: una **drammatica e rapidamente progressiva trasformazione dell'ambiente fisico-chimico, degli ecosistemi biologici (in particolare micro-biologici) e dei singoli organismi**
  (in tutte le loro componenti e a tutti i livelli: sistemico

- Generalmente si cerca di valutare il **rischio specifico legato a singole fonti di inquinamento**
- essenzialmente **confrontando popolazioni più o meno direttamente esposte**,
- e trascurando il fatto che **oggi l'esposizione agli agenti esogeni (fisici, (bio)chimici, biologici..) più pericolosi concerne, in misura rilevante, l'intera popolazione umana** e **le generazioni future**) (e in un certo senso l'intera biosfera).

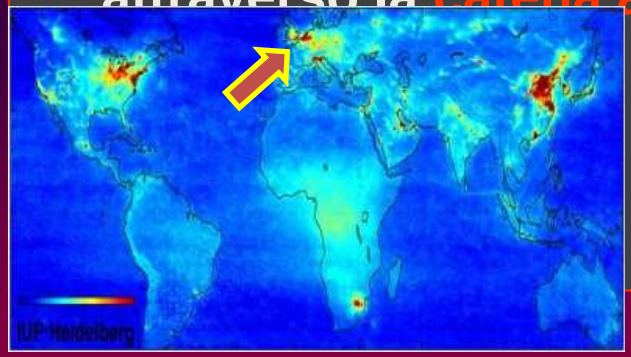
… a causa del **bio-accumulo/biomagnificazione degli *xeno-bi***
in **ambiente**, **catena alimentare** e **tessuti degli organismi comp**
e della trasmissione transgenerazionale delle modifiche epig **ne**

(in genere vengono paragonate **due popolazioni)**

- **una molto esposta..**
  (*id est* direttamente esposta alle emissioni dell'impianto)



- **l'altra un po' meno…**
  (*id est* più distante dall'impianto… ma comunque esposta agli stessi inquinanti (per via diretta o da fonti diffuse, *in primis* il traffico veicolare… o per via indiretta attraverso la catena alimentare)



Né il discorso cambia di molto se si paragonano
l'incidenza locale di una o più patologie (prevalentemente ***neoplastiche***)..
e le **cosiddette patologie attese**, che sono a loro volta il frutto
di una **esposizione massiccia e progressiva agli stessi inquinanti**
(e la cui incidenza aumenta nel tempo di pari passo all'inquinamento);

STUDI EPIDEMIOLOGICI ITALIANI SULLE POPOLAZIONI RESIDENTI IN PROSSIMITÀ DI INCENERITORI

FONTE	AREA	DISEGNO DELLO STUDIO	RISULTATI PRINCIPALI
Biggeri et al. 1996	Trieste	Caso - controllo	Incremento del rischio di cancro polmonare
Michelozzi et al. 1998	Roma	Mortalità micro - geografica	Incremento della mortalità per alcune cause e riduzione della sex – ratio alla nascita
Chellini et al. 2002	Prato	Mortalità micro - geografica	Incremento del rischio di cancro polmonare
Comba et al. 2003	Mantova	Caso - controllo	Incremento del rischio di sarcoma dei tessuti molli
Biggeri e Catelan 2005	Campi Bisenzio	Mortalità comunale	Incremento dei linfomi non Hodgkin
Biggeri e Catelan 2006	17 aree della Toscana con inceneritori	Mortalità comunale	Incremento dei linfomi non Hodgkin
Bianchi e Minichilli 2006	25 comuni italiani con inceneritori	Mortalità comunale	Incremento dei linfomi non Hodgkin
Tessari et al. 2006	Venezia	Caso - controllo	Incremento del rischio di sarcoma dei tessuti molli nelle donne dell'area più esposta
Ranzi et al. 2006	Forlì	Coorte di residenti	Incremento di mortalità nelle donne per tutte le cause, tumore del colon e della mammella, per diabete e malattie cardiovascolari
Zambon et al. 2007	3 ASL Prov. Venezia	Caso – controllo	Incremento di rischio di sarcoma in entrambi i generi e di tumori del connettivo e di altri tessuti molli nelle sole donne

… il che non significa che gli studi epidemiologici perdano di val
anzi le evidenze assumono significato notevolmente maggiore ..

Esposizione ad emissioni di inceneritori: Rischio Relativo (RR)

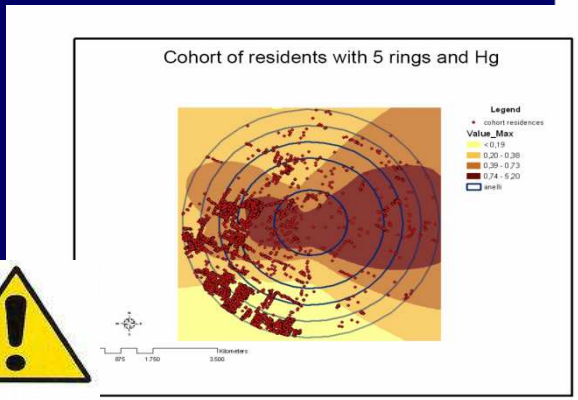
Effetto indagato	RR	Fonte bibliografica
Carcinoma polmonare (mortalità)	2 (small cell) 2.6 (large cell) 6.7	Barbone F., American Journal Epidemiology 1995 Biggeri A., Envirom Health Perspect 1996
Linfomi Non Hodgkin	2.3 (Incidenza) 2 (Mortalità)	Floret N., Epidemiology 2003 A Biggeri Epidemiol. Prevenzione 2005
Sarcomi tessuti molli (incidenza)	8.8 (maschi) 31,4 5.6 (femmine) ?	Comba P., Occupational Enviromental Medicine 2003
Neoplasie infantili (incidenza)	2.1	Knox E. G., International Journal of Epidemiology 2000

… ad esempio, un **RR in rapporto ad un R già alto** assume evidentemente un significato maggiore

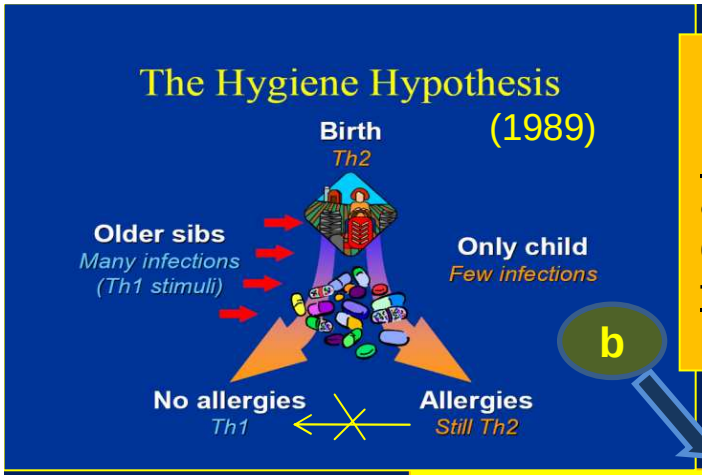
A scientific challenge

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

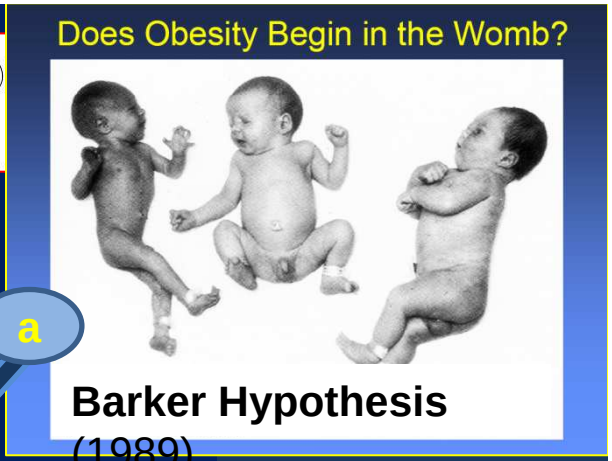
Human epidemiology as it is been traditionally practiced is highly biased toward **false negatives.**



Environmental Health Sciences



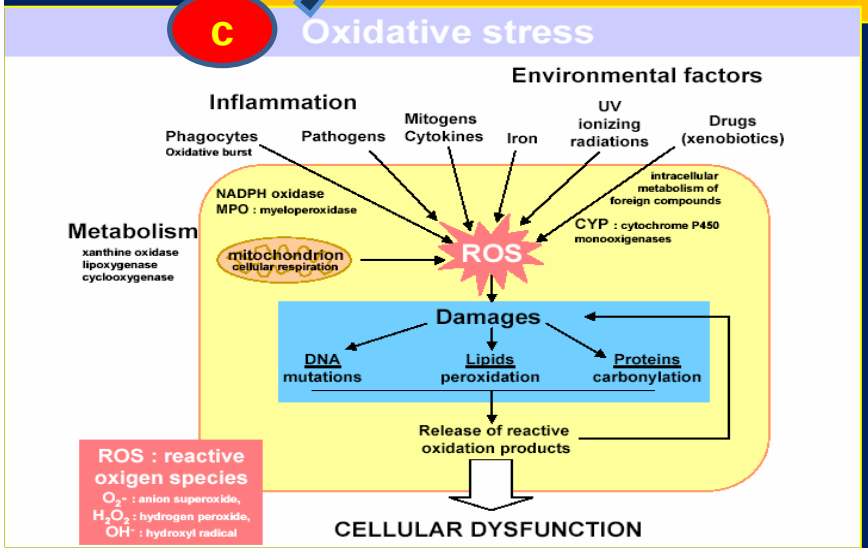
.. ma soprattutto, in questo modo, **ci si "dimentica" della "rivoluzione epidemica"** in atto, … evidentemente connessa alla **drammatica trasformazione ambientale** prodotta dall'uomo in pochi decenni..

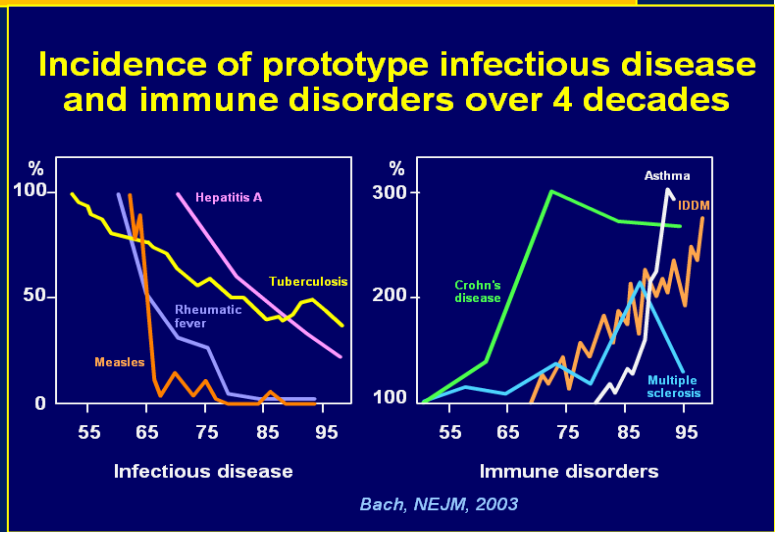


La **Rivoluzione Epidemica** del **XX Secolo**

Insulino-resistance
Diabetes
Cardiovascular Diseases

L'incremento delle patologie cronico-degenerative
[immunomediate, neuro-degenerative, endocrine, neoplastiche, cardiocircolatorie]
quale prodotto di una **drammatica trasformazione ambientale**
di una (conseguente) **alterazione** del ***Programming*** **embrio-fetale**





Devo

Milioni di anni

Evo

I processi filogenetici durano milioni di anni

Ambiente

***Danger* Signals**

Agenti Fisici

***Challenge* "naturale"**

Antigeni

Tolleranza

***Fall-Out* Chimico**

Self

Sistema Immunocompetente

Non self

MHC

(Epi)Genosfera

(Epi)-genomi

virus

Epigenoma

Genoma

Onco-géni

C-onc

Agenti Biologici

HERVs

V-onc

(Retro-viruses)

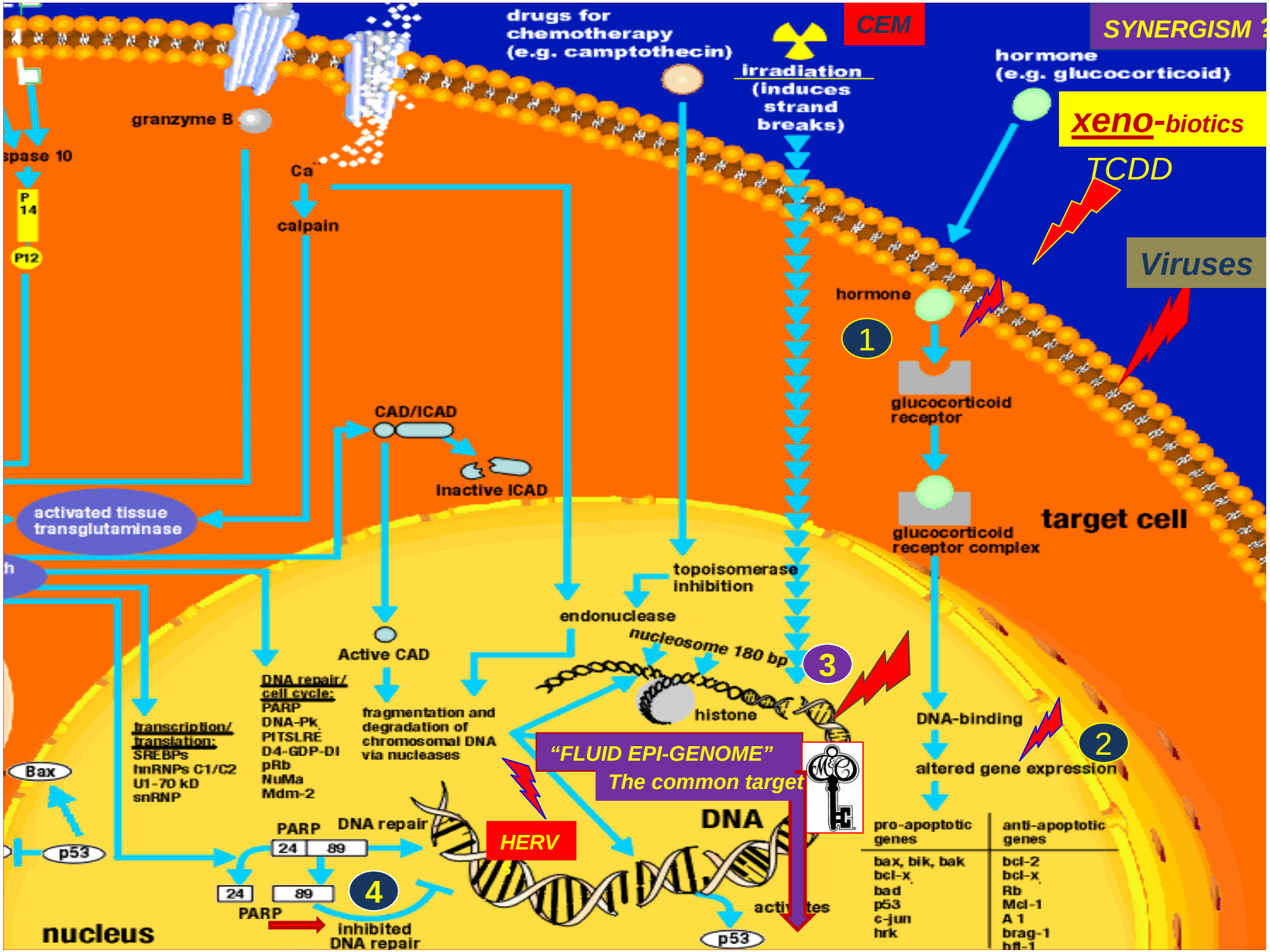
IXX-XX SECOLO

Drammatica alterazione Ambientale e Climatica

Biosfera

Adattamento

Coevoluzione


drugs for chemotherapy (e.g. camptothecin)
irradiation (induces strand breaks)
CEM
SYNERGISM
hormone (e.g. glucocorticoid)
xeno-biotics
TCDD
Viruses
granzyme B
spase 10
P 14
P12
Ca
calpain
hormone
1
glucocorticoid receptor
glucocorticoid receptor complex
target cell
CAD/ICAD
Inactive ICAD
activated tissue transglutaminase
topoisomerase inhibition
endonuclease
nucleosome 180 bp
3
Active CAD
histone
DNA-binding
2
altered gene expression
DNA repair/ cell cycle:
PARP
DNA-Pk
PITSLRE
D4-GDP-DI
pRb
NuMa
Mdm-2
fragmentation and degradation of chromosomal DNA via nucleases
transcription/ translation:
SREBPs
hnRNPs C1/C2
U1-70 kD
snRNP
"FLUID EPI-GENOME"
The common target
HERV
DNA
Bax
p53
PARP
DNA repair
24
89
4
inhibited DNA repair
nucleus
activates
p53
pro-apoptotic genes
anti-apoptotic genes
bax, bik, bak
bcl-x
bad
p53
c-jun
hrk
bcl-2
bcl-x
Rb
Mcl-1
A 1
brag-1

Per interpretare questa trasformazione epidemica, sono stati proposti alcuni grandi **PARADIGMI PATOGENETICI**

Strachan DP. **Hay fever, hygiene and household size** BMJ 1989; 299: 1259-1260

1

Hygiene Hypothesis

Bufford JD, Gern JE **The hygiene hypothesis revisited** Immunol Allergy Clin North Am. 2005 May; 25(2): 247-62

- Il primo è la cosiddetta ***Hygiene Hypothesis*** che, nata da una semplice **constatazione epidemiologica** (il rischio di riniti atopiche e dermatiti allergiche è inversamente correlato alle dimensioni della famiglia, all'ordine di natalità, *id est* all'entità e precocità dei contatti con agenti infettivi)… si è andata via, via trasformando in una **teoria di grande respiro**, secondo cui **l'esposizione sempre più tardiva e ridotta ad agenti microbici e parassitari**, determinerebbe un incremento delle patologie immunomediate: **allergie** *s.stricto,* ma anche ***sclerosi multipla*** ecc …
- Le formulazioni della H. H. sono state numerose..
- Oggi, in estrema sintesi, si può affermare che l'***ipotesi igienica*** sostiene, e in certa misura dimostra, come all'origine dell'*incremento pandemico* di patologie immunomediate sia,
- *da un lato* la **trasformazione ambientale** che si riflette essenzialmente in una **trasformazione degli ecosistemi microbici e parassitari "*naturali*"** (che per **milioni di anni** hanno "allenato" e **modellato** i nostri sistemi difensivi) e, soprattutto, in **un'alterazione dell'ecosistema microbico intestinale** (che non ha soltanto un ruolo maieutico e regolatore dello sviluppo del sistema immunocompetente, ma partecipa attivamente alla sua attività vita natural durante)

N Engl J Med, Vol. 347, No. 12 · September 19, 2002 · www.nejm.org

THE EFFECT OF INFECTIONS ON SUSCEPTIBILITY TO AUTOIMMUNE AND ALLERGIC DISEASES

JEAN-FRANÇOIS BACH, M.D., D.Sc.

The New England Journal of Medicine

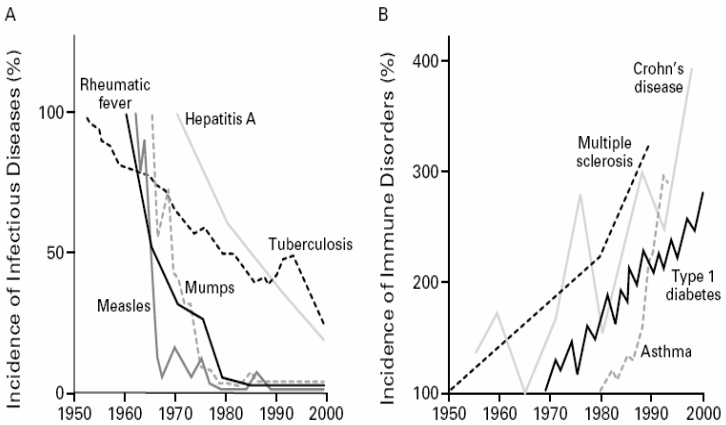


Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

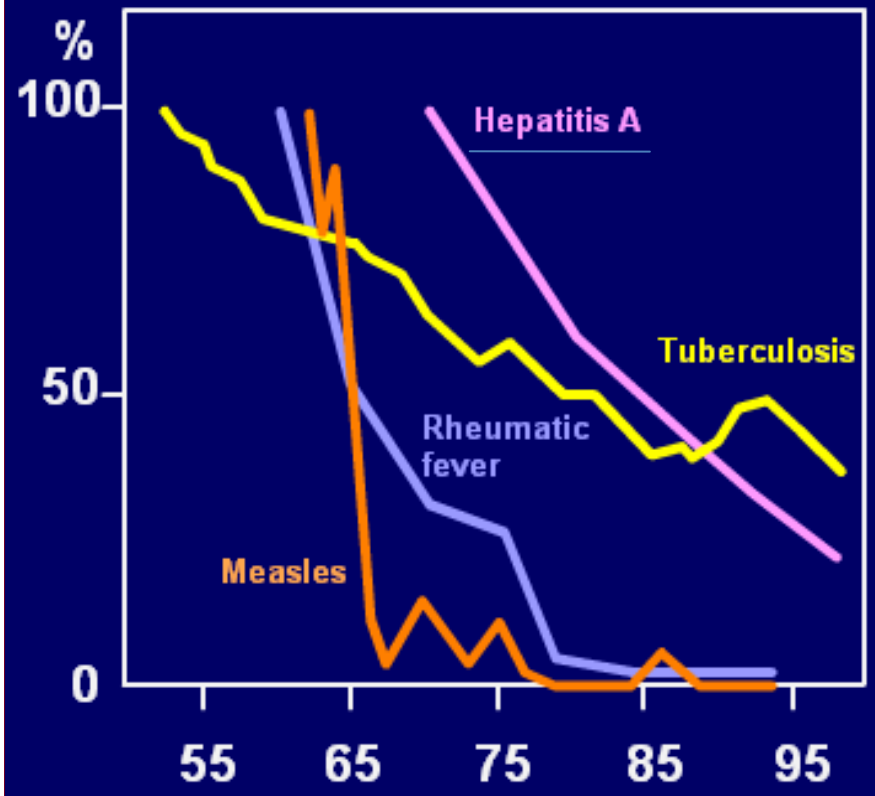
In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Joussemet et al.[12] In Panel B, data on immune disorders are derived from Swarbrick et al.,[10] Dubois et al.,[13] Tuomilehto et al.,[14] and Pugliatti et al.[15]

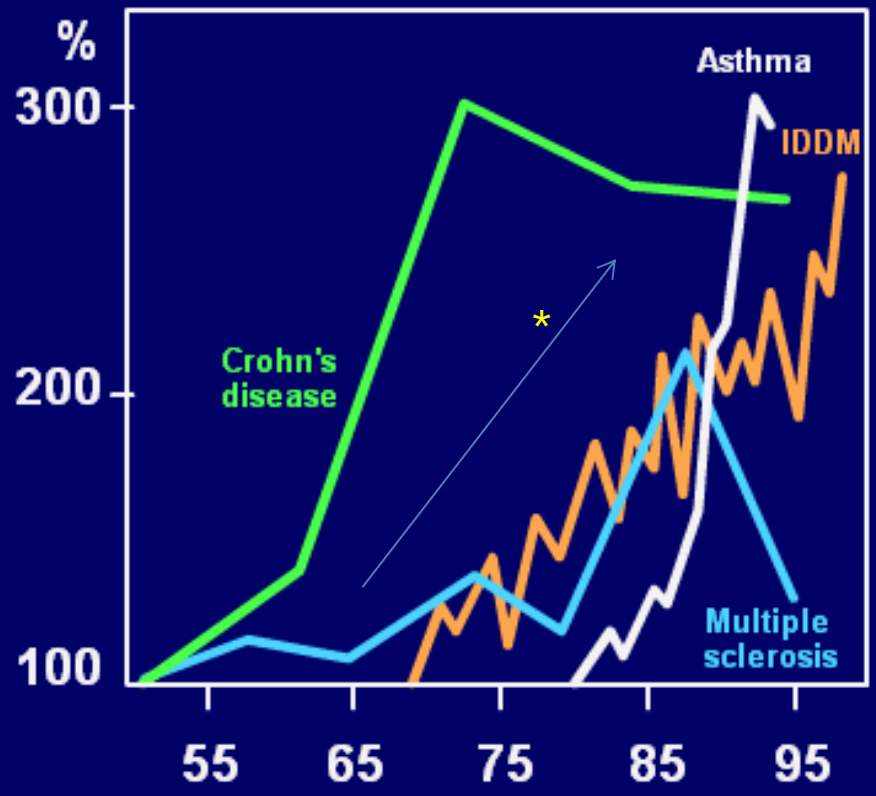
INFECTIOUS agents can induce autoimmune diseases in several experimental settings, some of which have clinical counterparts. A variety of mechanisms have been invoked to explain these observations, including molecular mimicry and an increase in the immunogenicity of autoantigens caused by inflammation in the target organ.[1] Paradoxically, infectious agents can also suppress allergic and autoimmune disorders. In this review, I will summarize the evidence that the main factor in the increased prevalence of these diseases in industrialized countries is the reduction in the incidence of infectious diseases in those countries over the past three decades. This concept is not new. In 1966, for example, Leibowitz et al. suggested that the risk of multiple sclerosis is increased among persons who spent their childhood in a home with a high level of sanitation.[2] About 20 years later, Strachan observed that the risk of allergic rhinitis was inversely linked to birth order and the size of the family. He proposed that infections within households in early childhood have a role in preventing allergic rhinitis.[3] Since then, numerous epidemiologic and experimental studies have sought to clarify and extend this so-called hygiene hypothesis concerning asthma and other allergic diseases and autoimmune disorders.

1

HYGIENE HYPOTHESIS

Incidence of prototype infectious disease and immune disorders over 4 decades



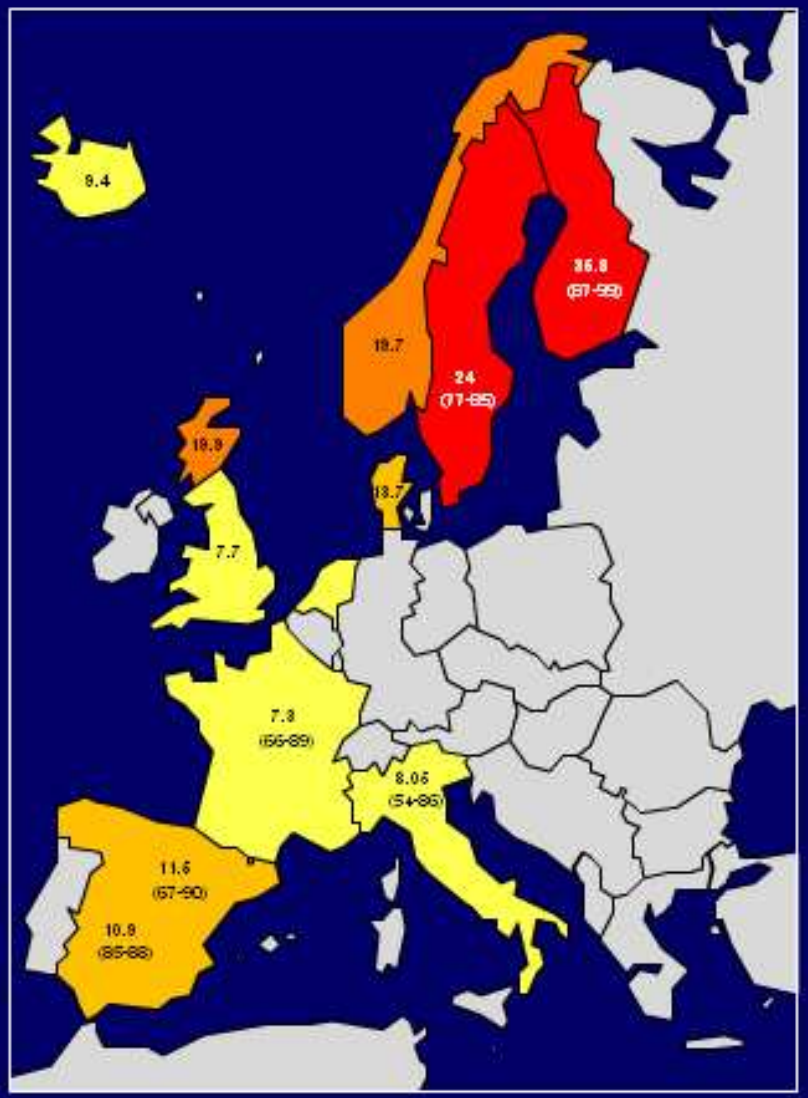


* Hepatitis B -C

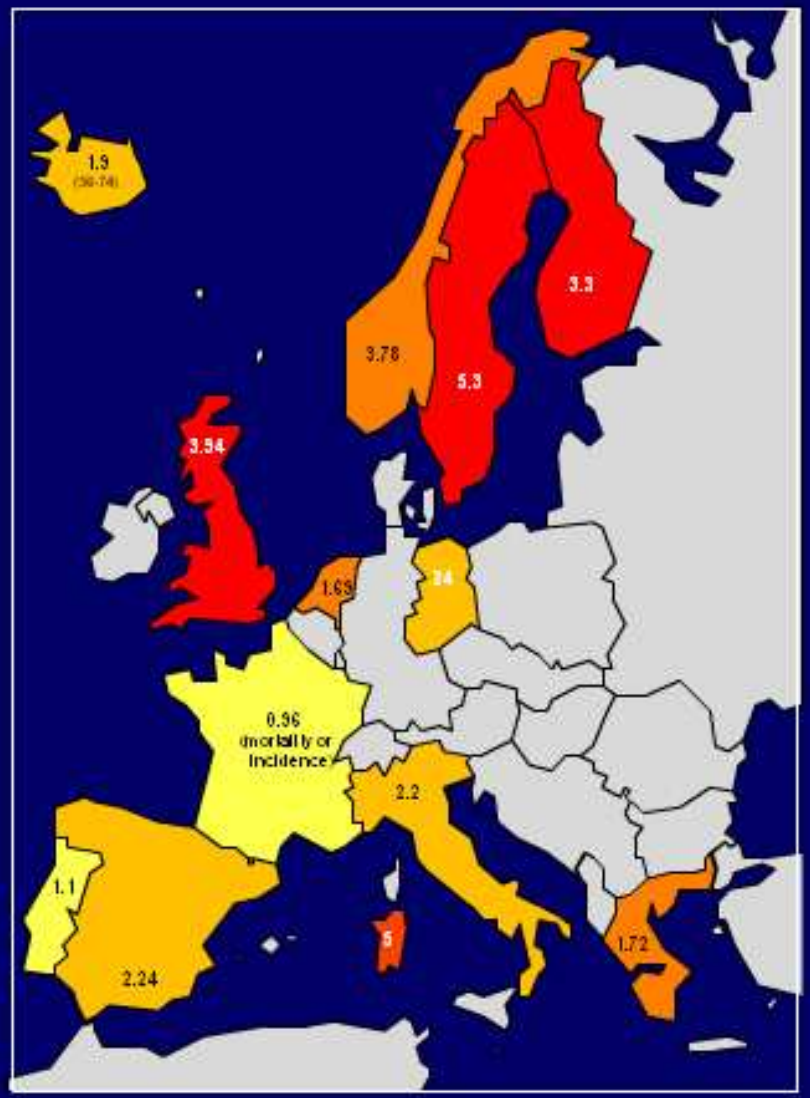
Bach, NEJM, 2003

!

Incidence of IDDM
(per 100,000)



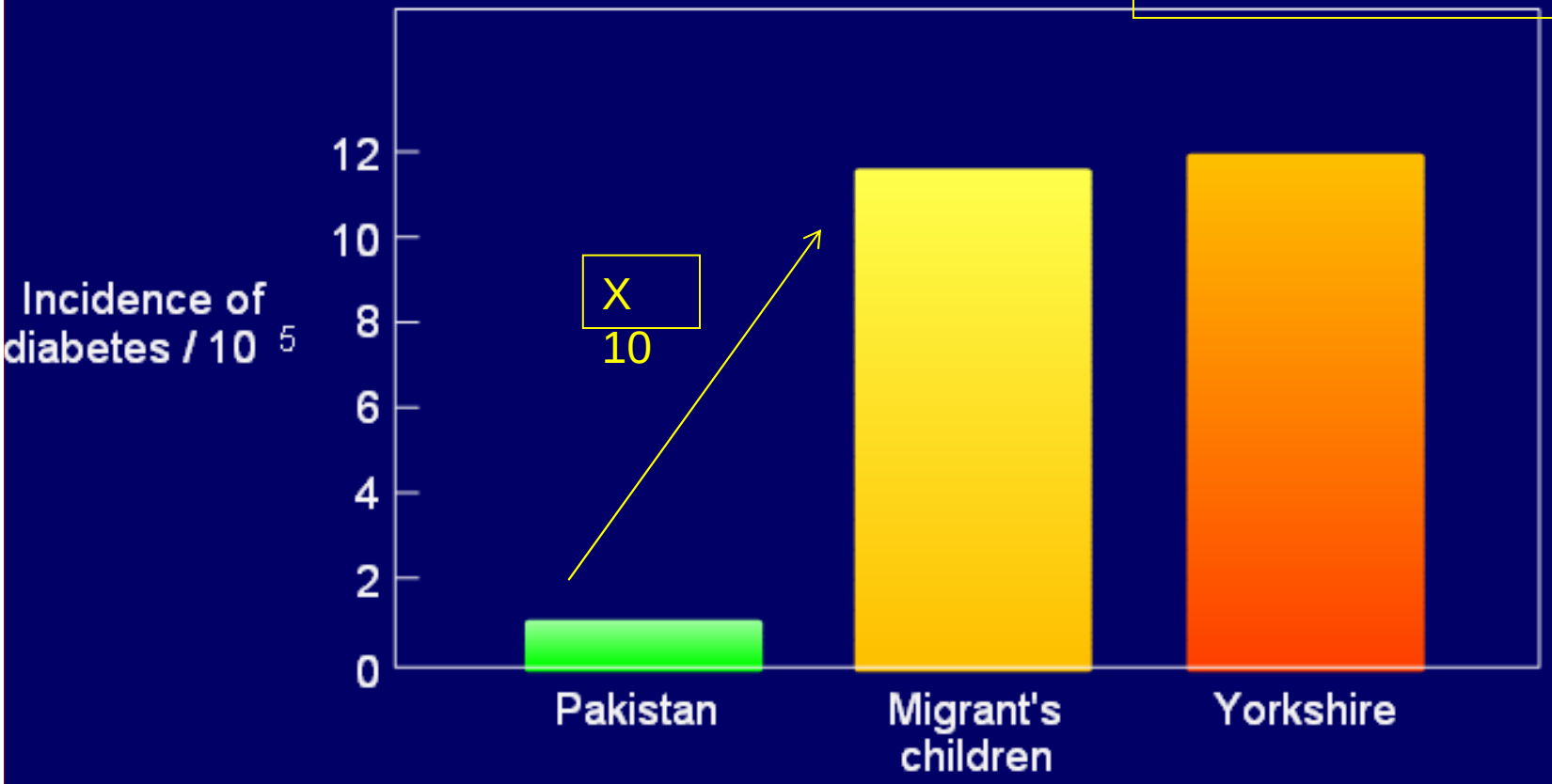
Incidence of multiple sclerosis
(per 100,000)



TIPE I DIABETES

IDDM incidence in children of migrants from Pakistan to Yorkshire

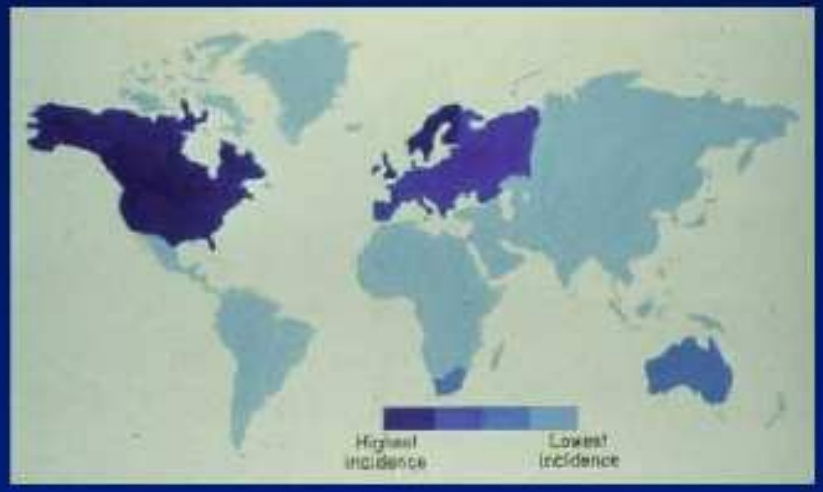
++ ENVIRONMENTAL FACTOR

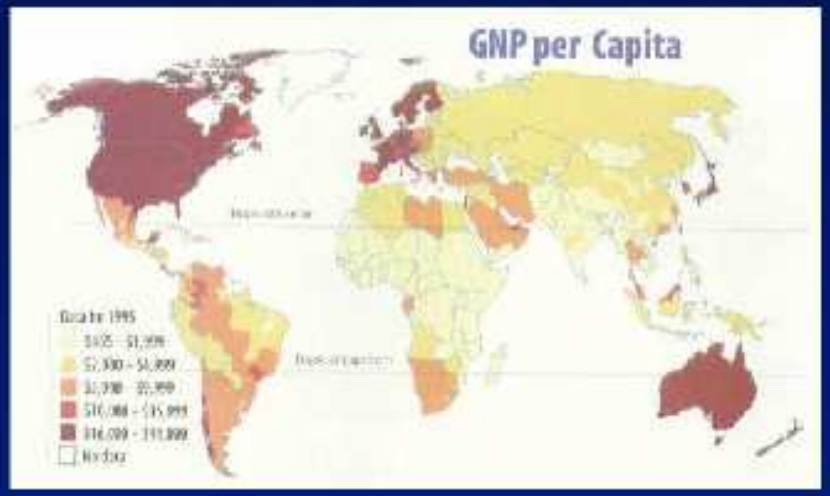


Staines A. (1997) and Bodansky H.J. (1992)

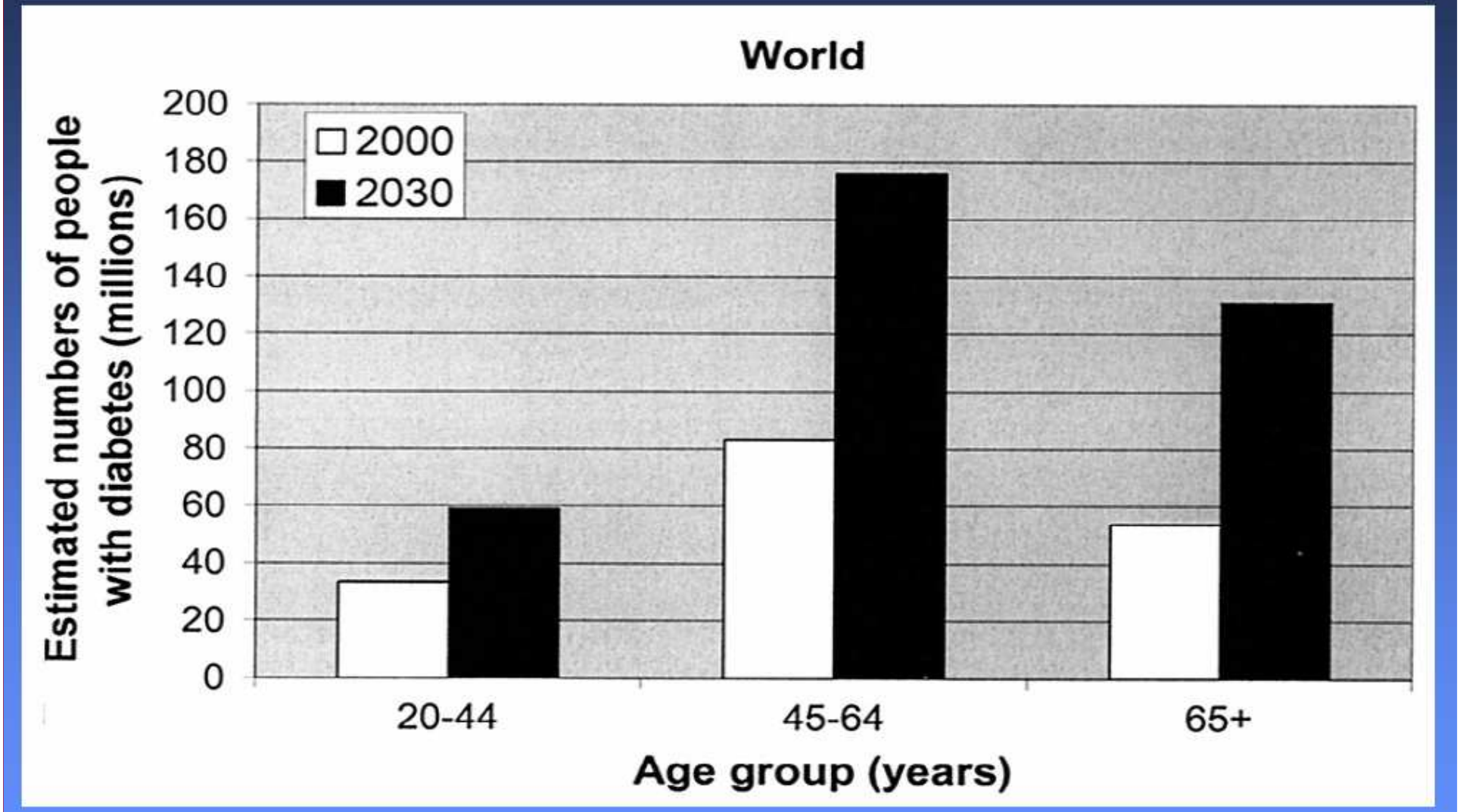
IBD & Industrialization and urbanization

INFLAMMATORY BOWEL DISEASES



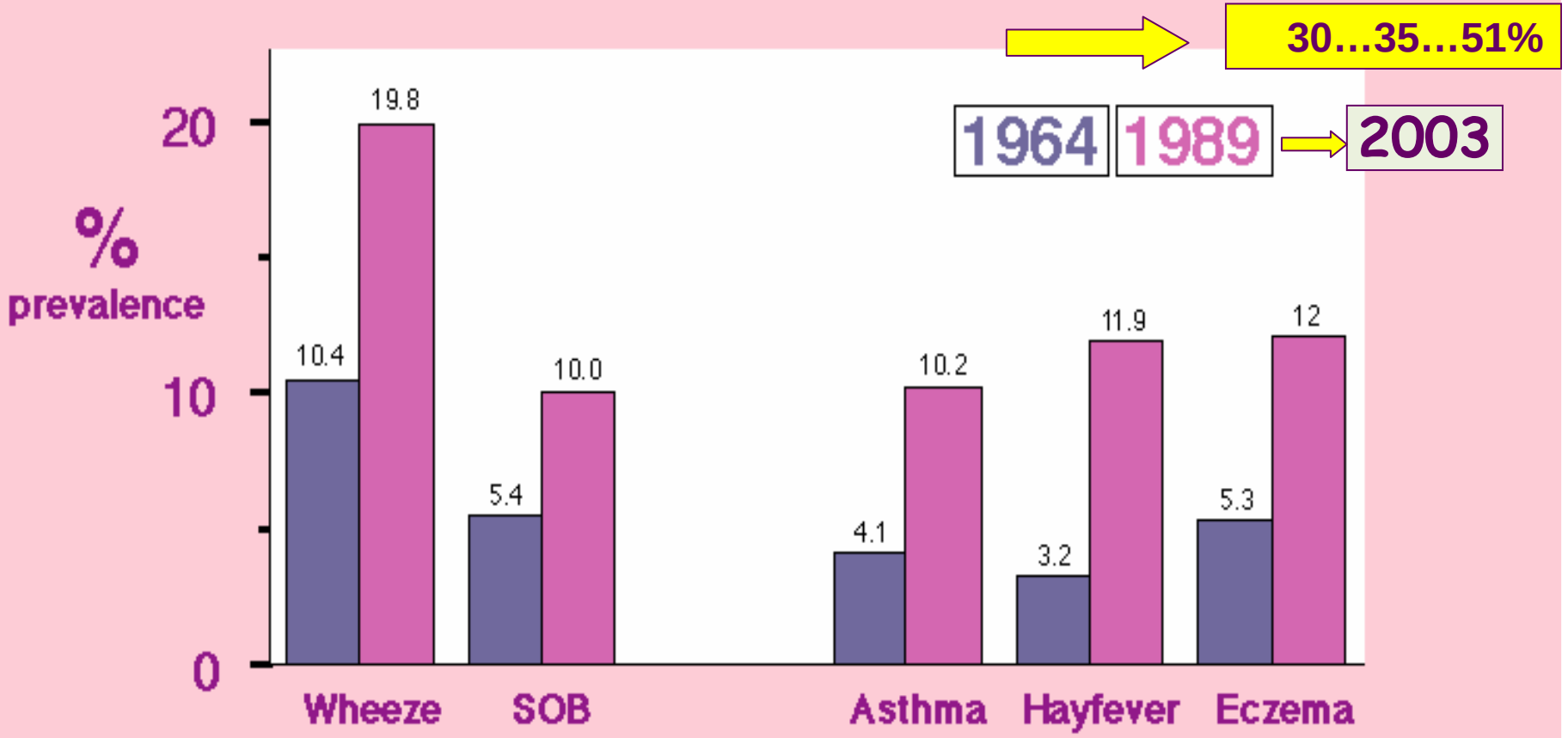


Diabetes Increasing Rapidly Worldwide



Wild S et al. Diabetes Care 2004; 27:1047

Increasing prevalence of asthma & atopy
Aberdeen 1964 - 1989
schoolchildren aged 8 - 13 yrs inclusive



Ninan TK, Russell G. BMJ 1992;304:873-5

Graphic: MAS, Leicester
048.4b

HYGIENE HYPOTHESIS

FACTORS CONTRIBUTING TO THE APPEARANCE OF INFECTIONS

Sources of pathogenic agents

- drinking water
- food (cold storage)
- climate
- housing conditions

Anti-infectious defense

- genetic factors
- nutrition
- antibiotics
- vaccination

CHANGING ***GUT ECOSYSTEM !!***
DECREASING/CHANGING USUAL *ANTIGENIC CHALLENGE*

↑ **ATOPY** (+ TH2?)

↑ **Autoimmunity** (+ TH1?)

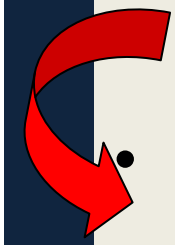
PREVENTION OF IDDM IN NOD MICE BY INFECTIOUS AGENTS

INFECTIONS PREVENT/REDUCE DIABETES I INCIDENCE

Bacteria	streptococci
	salmonella
	mycobacteria (CFA, BCG, ...)
Viruses	LCMV
	MHV
	LDHV
Parasites	schistosoma
	oxyures

GUT ECOSYSTEM

- Many ***chronic diseases***, including ***allergy***, may occur as a result of **genetically based or environmentally induced changes in mechanisms regulating mucosal immunity and tolerance;**
- this leads to **impaired mucosal barrier function, disturbed exclusion** and **increased penetration of microbial, food or airborne antigens into the circulation** and consequently to
- **exaggerated and generalized immune responses to mucosally occurring antigens, allergens,**
- **superantigens and mitogens.**



Tlaskalová-Hogenová H, Tucková L, Lodinová-Zádniková R, Stepánková R, Cukrowska B, Funda DP, Striz I, Kozáková H, Trebichavský I, Sokol D, Reháková Z, Sinkora J, Fundová P, Horáková D, Jelínková L, Sánchez D.
Mucosal immunity: its role in defense and allergy. Int Arch Allergy Immunol. **2002** Jun;128(2):77-89. Review.

..dalla ***Hygienic Hypothesis (1989)***.. alla ***Barker Hypothesis (1989)***

*(CO)**EVO*** → ***DEVO***

Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ **Weight in infancy and death from ischaemic heart disease**. Lancet. **1989** Sep 9;2 (8663):577-80)

Szyf, M. **The Dynamic Epigenome and its Implications in Toxicology**
Toxicol. Sci. 2007 100: 7-23

2

Barker Hypothesis

- Il secondo paradigma, forse meno noto, ma non meno interessante, si ricollega
  alla cosiddetta ***Barker Hypothesis*** che,
- derivata a sua volta da alcune *osservazioni epidemiologiche* (*in primis* l'esistenza di una chiara **relazione tra basso peso alla nascita** in relazione al livello di sviluppo gestazionale e **mortalità per coronaropatia ischemica dell'adulto**)
- si è andata via, via trasformando in una teoria ancora più onnicomprensiva della precedente, secondo cui molte **patologie sistemiche dell'adulto *(aterosclerosi, patologie cardiovascolari, obesità, sindrome metabolica, osteoporosi, insulinoresistenza/diabete, …),*** in costante incremento negli ultimi decenni sarebbero il prodotto di una **inadeguatezza del *programming fetale*** (*id est* dell'***assetto epigenetico programmatico*** concernente i tessuti **destinati** al controllo metabolico-endocrino dell'organismo) secondaria ad **alterazioni del microambiente uterino** (a **carenze nutrizionali** e/o all'esposizione del feto a **stimoli dannosi**, o comunque decodificati come tali, durante i momenti critici ("***finestre***") dello

i **fattori ambientali** sono determinanti dello sviluppo fetale… **prioritari** rispetto ai **fattori genetici**

a Fetal Origin of Adult Disease: The Barker Hypothesis

- 1989 David Barker found an inverse relationship between birthweight and death from heart disease in England and Wales
- Since birthweight is a surrogate for intra-uterine nutrition, individuals who were small at birth experienced poor maternal environment *in utero*

- Studies confirmed by "Dutch Hunger Winter" when food supplies to occupied Netherlands were cut off by Nazis. Individuals born during this time had high incidence as adults of insulin-resistance

- "Fetal Origin of Adult Disease" (FEBAD) now confirmed for
  - **Coronary heart disease**
  - **Hypertension**
  - **Type II diabetes**

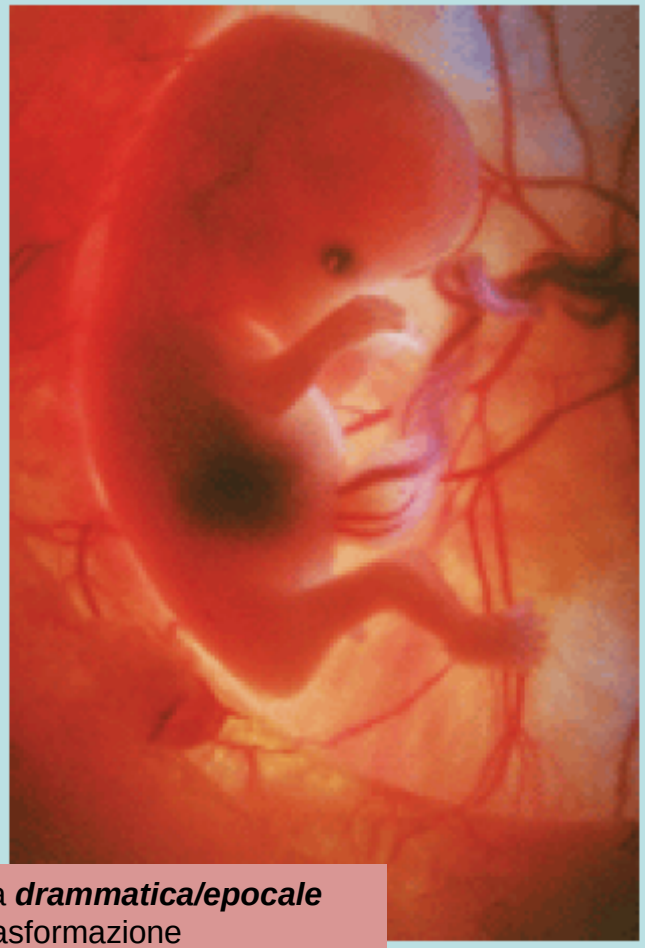
Table 1. Hazard ratios for coronary heart disease acco[illegible] to body size at birth[a]

	Hazard ratio (95% CI)	No. of cases/No. of men
Birthweight (g)		
<2500	3.63 (2.02–6.51)	24/160
–3000	1.83 (1.09–3.07)	45/599
–3500	1.99 (1.26–3.15)	144/1775
–4000	2.08 (1.31–3.31)	123/1558
>4000	1.00	21/538
P for trend	0.006	
Ponderal index (kg m^{-3})		
<25	1.66 (1.11–2.48)	104/1093
–27	1.44 (0.97–2.13)	135/1643
–29	1.18 (0.78–1.78)	84/1260
>29	1.00	31/578
P for trend	0.0006	

From Barker *TRENDS in Endo Met* 2002

SGA : LBW è un **indicatore** importante di sofferenza pre-natale

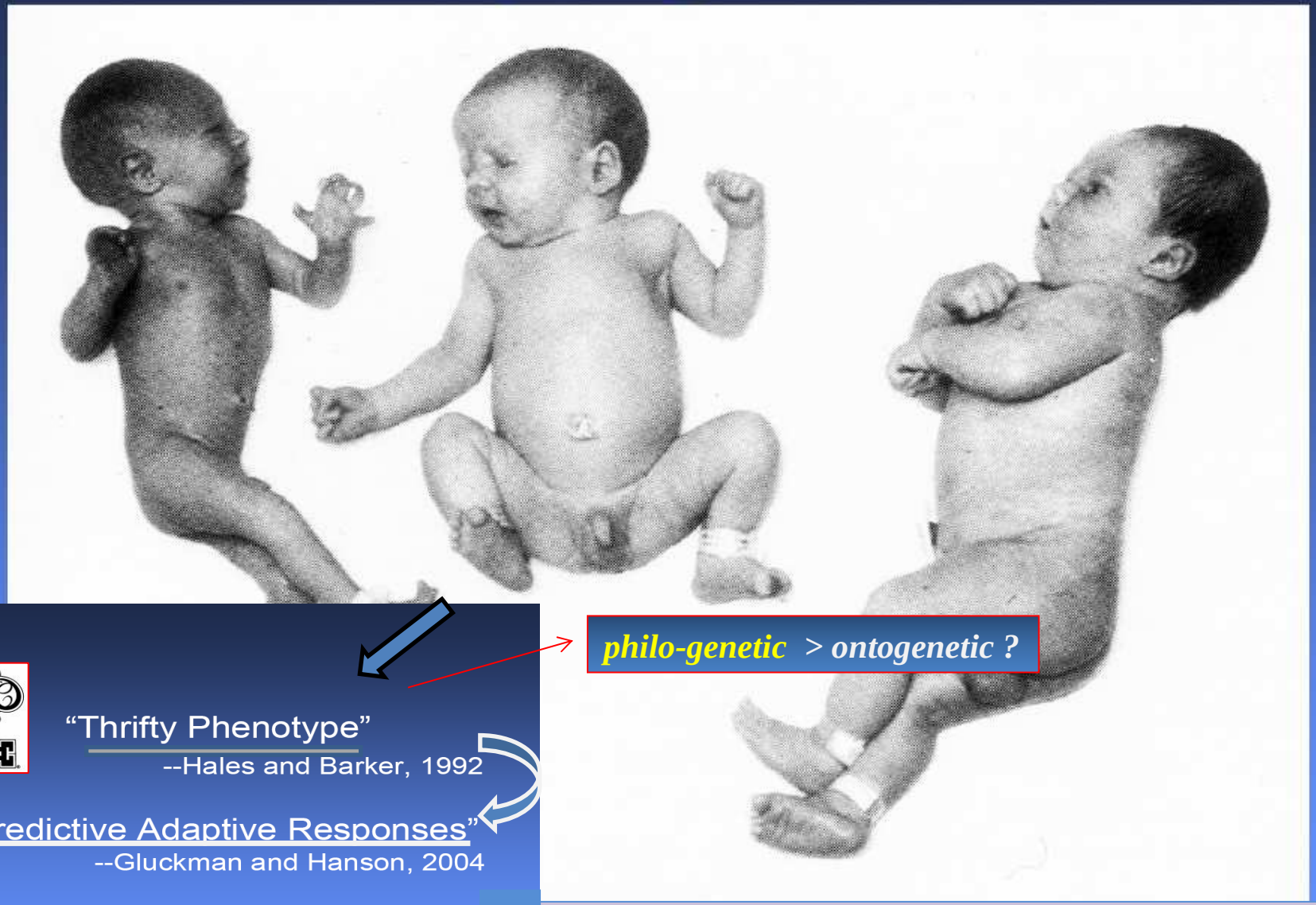
Developmental Programming



La ***drammatica/epocale*** trasformazione dell'**ambiente** e *quindi* del **microambiente** uterino può essere meglio valutata in termini **evolutivi**

Exposure of developing tissues or organs to an adverse stimulus or insult during critical periods of development that can permanently reprogram normal physiological responses in such a way as to give rise to disease later in life

Does Obesity Begin in the Womb?



philo-genetic > *ontogenetic ?*

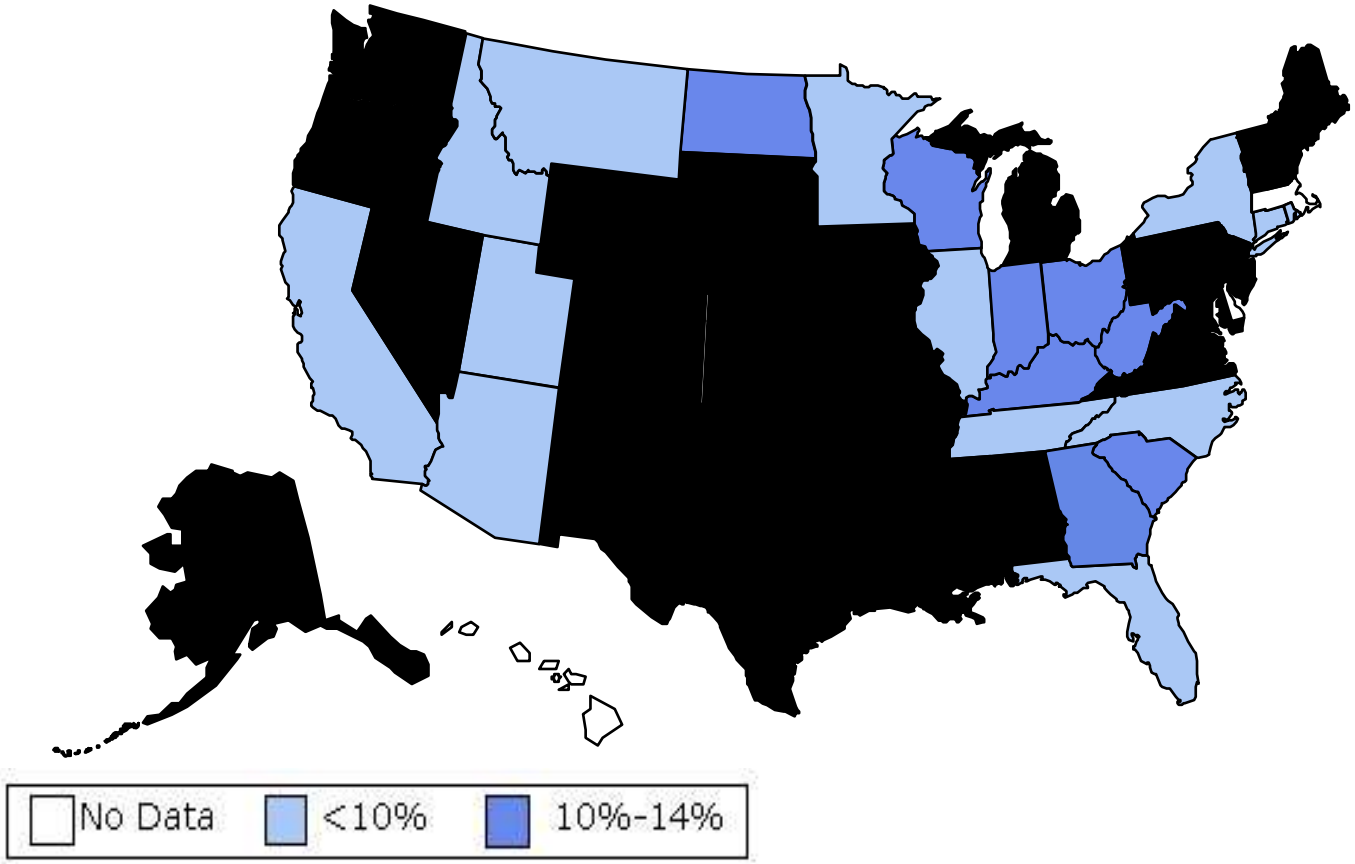
"Thrifty Phenotype"
--Hales and Barker, 1992

"Predictive Adaptive Responses"
--Gluckman and Hanson, 2004

\+ **Exposure during a critical period in development** may influence **later metabolic** functions **in adult life**

Obesity Trends* Among U.S. Adults 1985

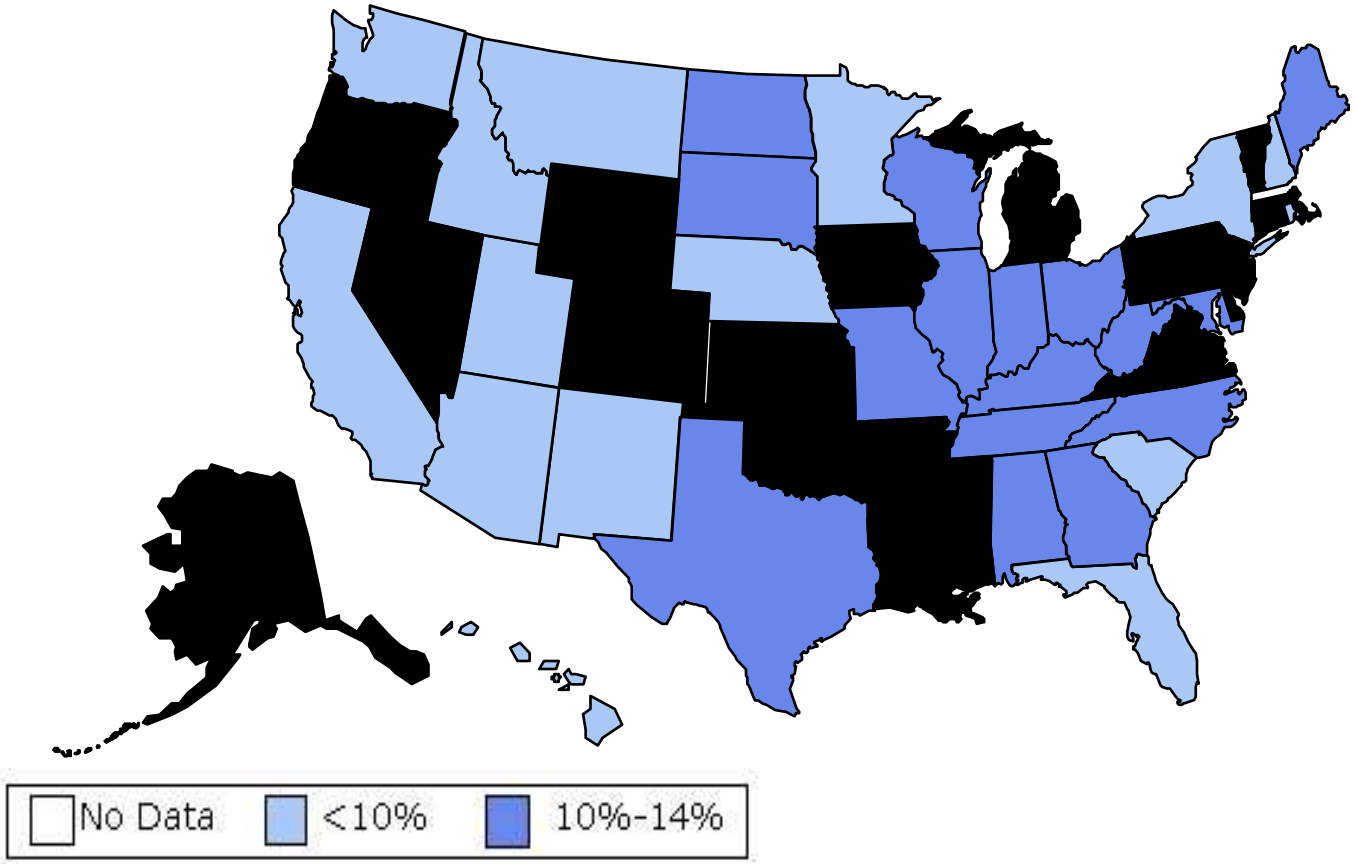
(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)



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

Obesity Trends* Among U.S. Adults 1987

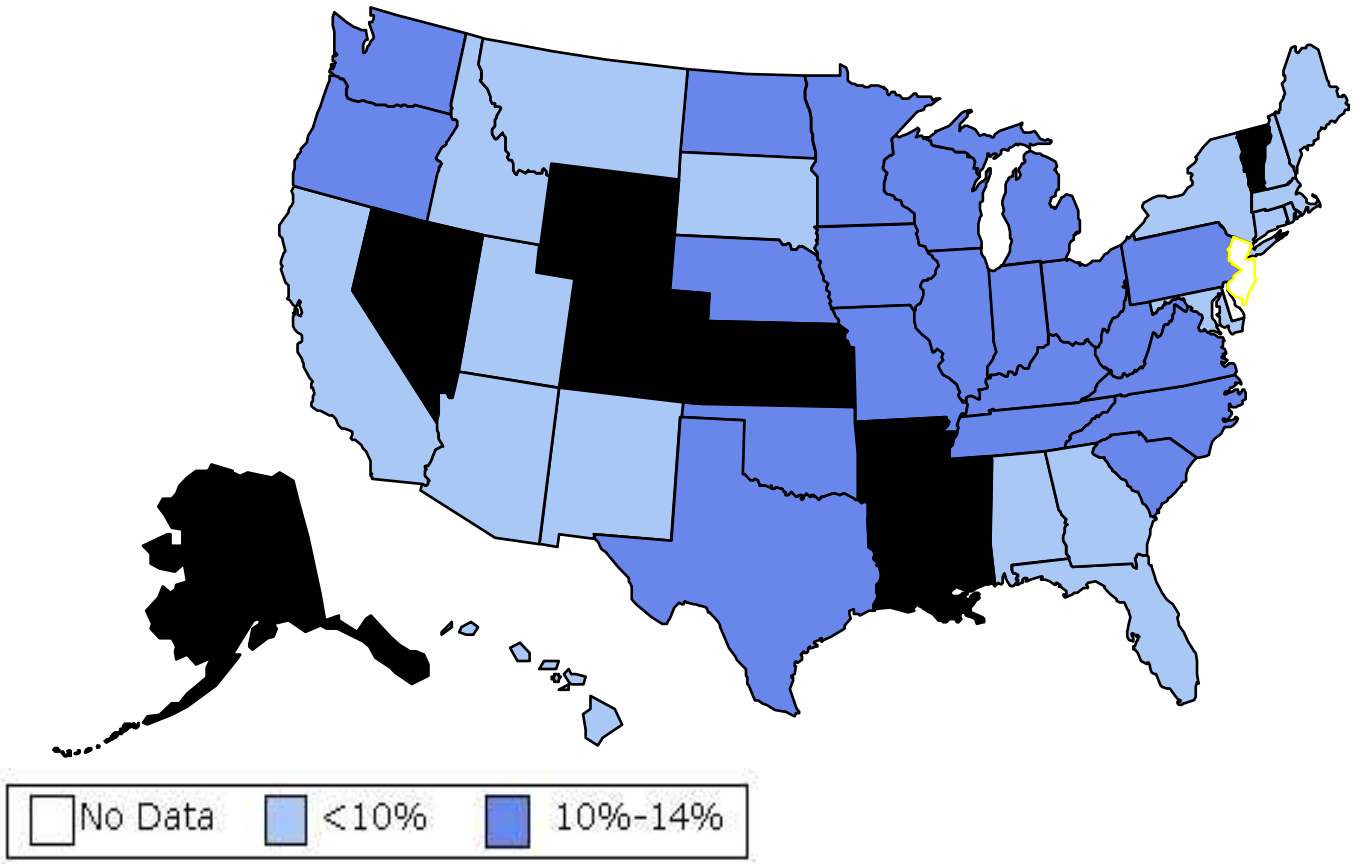
(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)



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

Obesity Trends* Among U.S. Adults

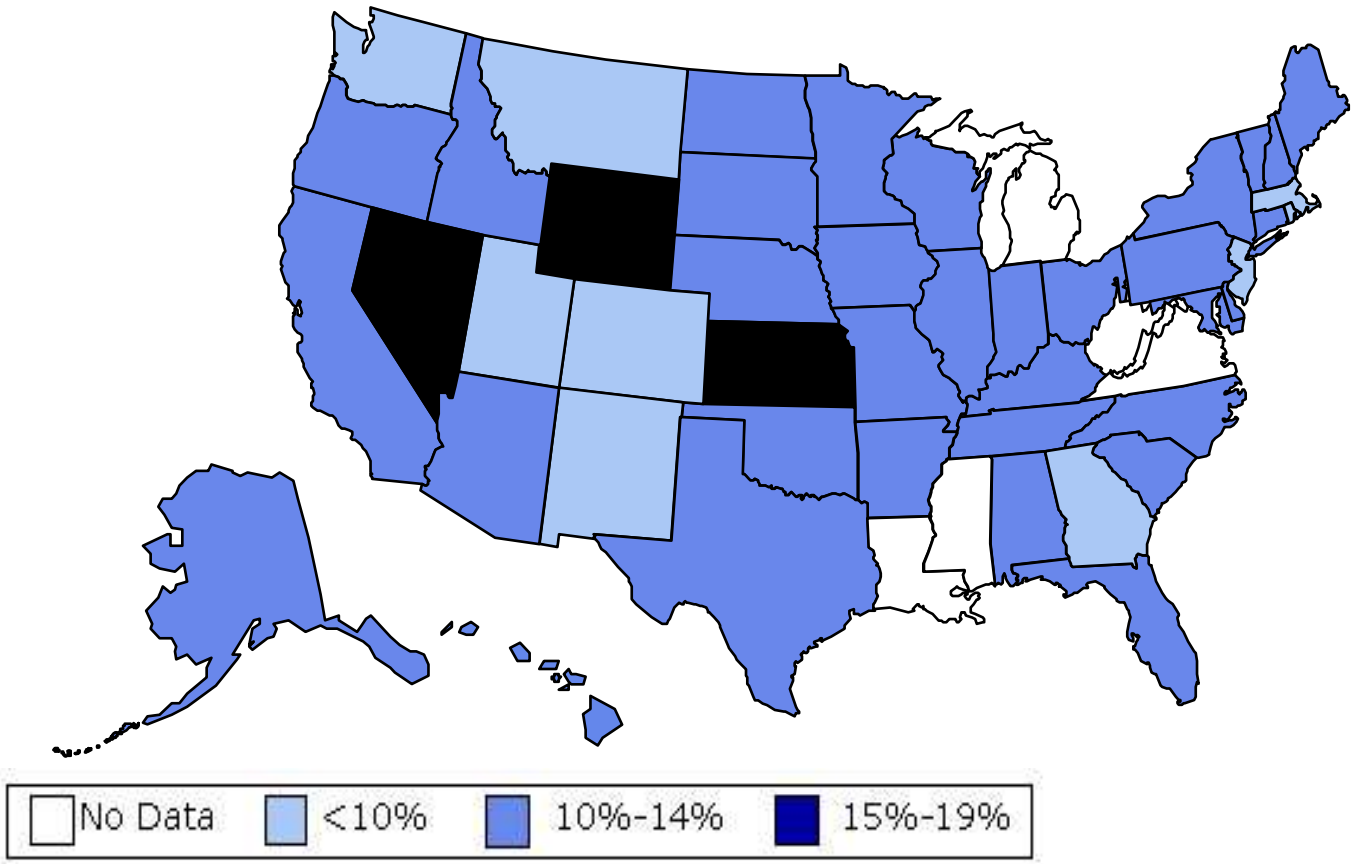
(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)



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

Obesity Trends* Among U.S. Adults

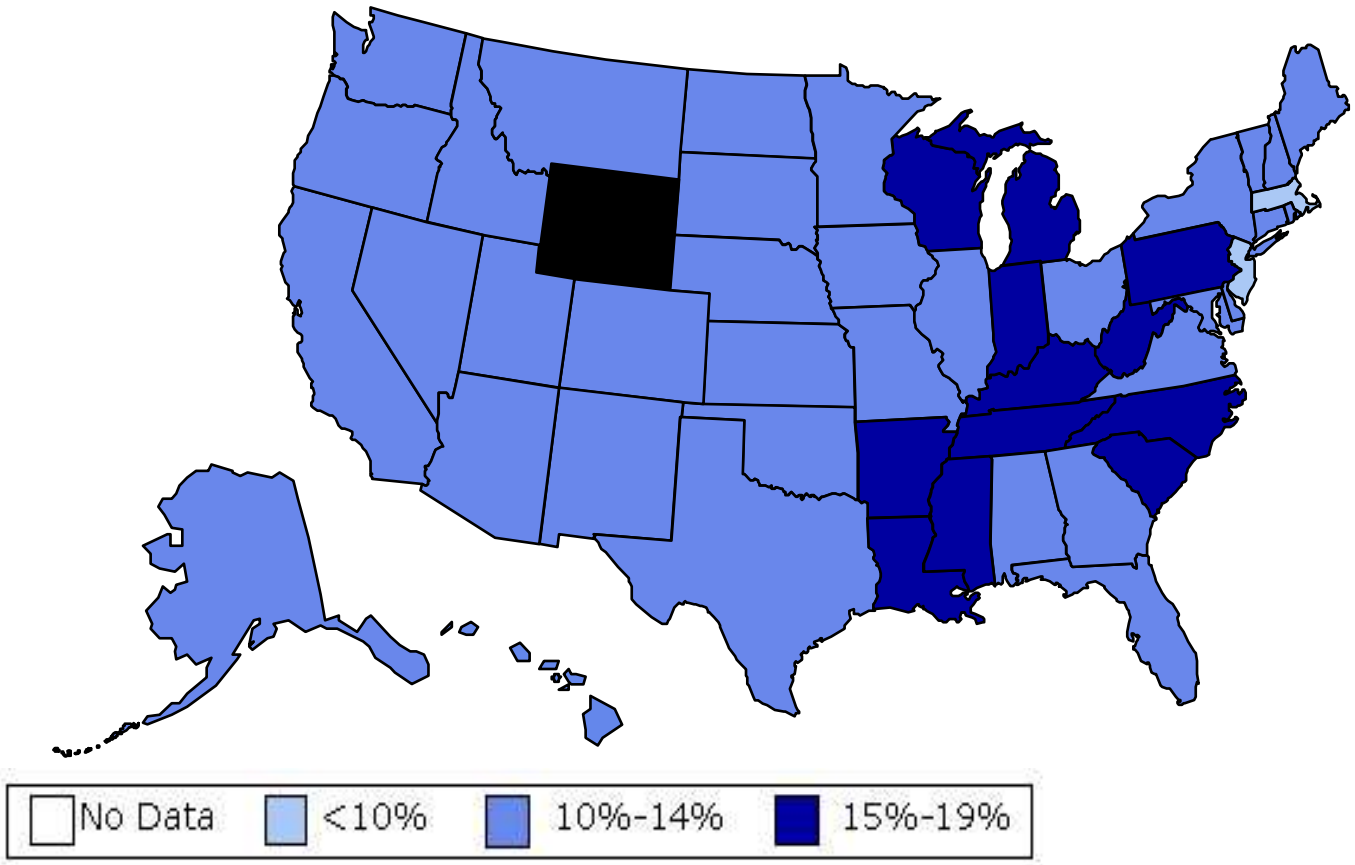
(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)



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

Obesity Trends* Among U.S. Adults

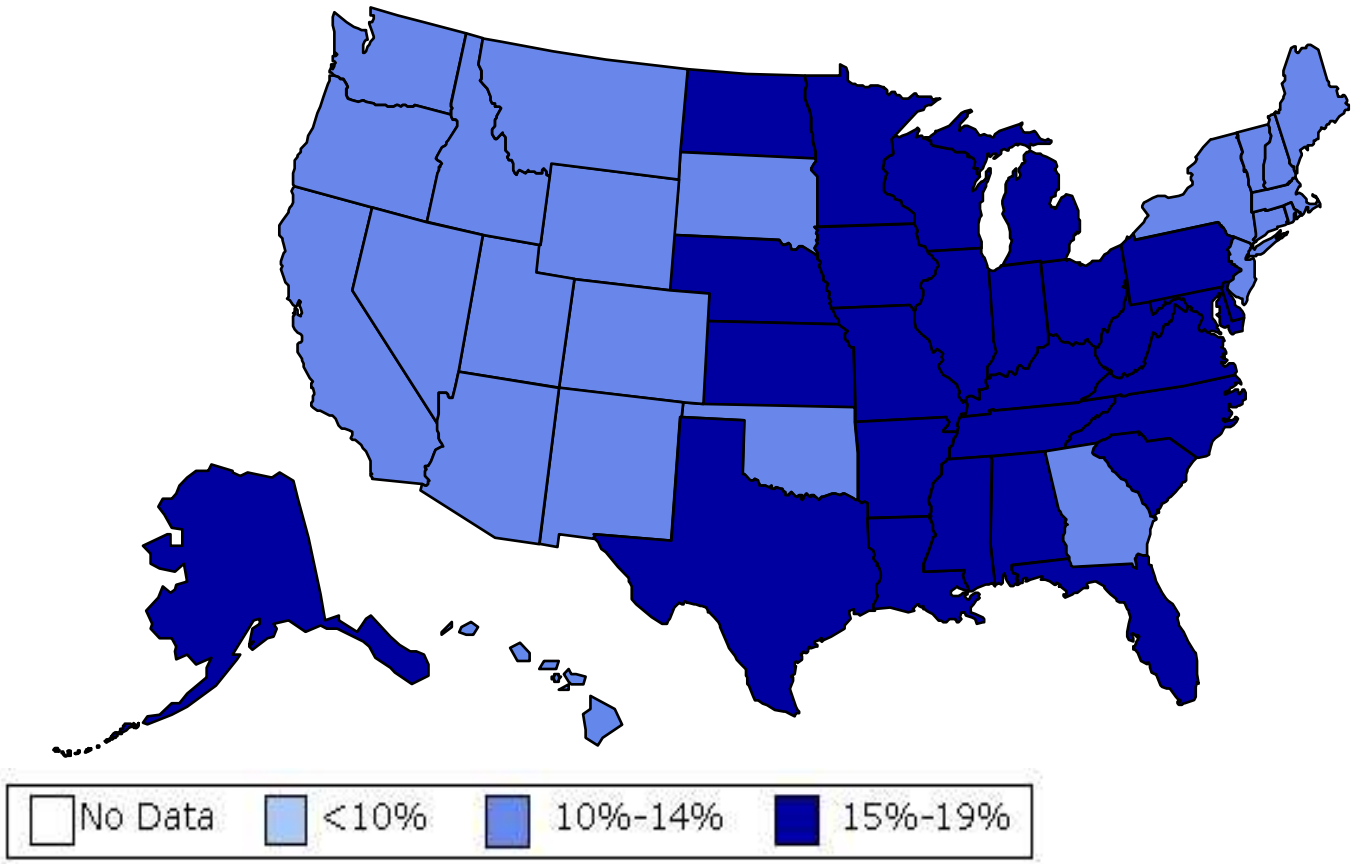
(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)



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

Obesity Trends* Among U.S. Adults

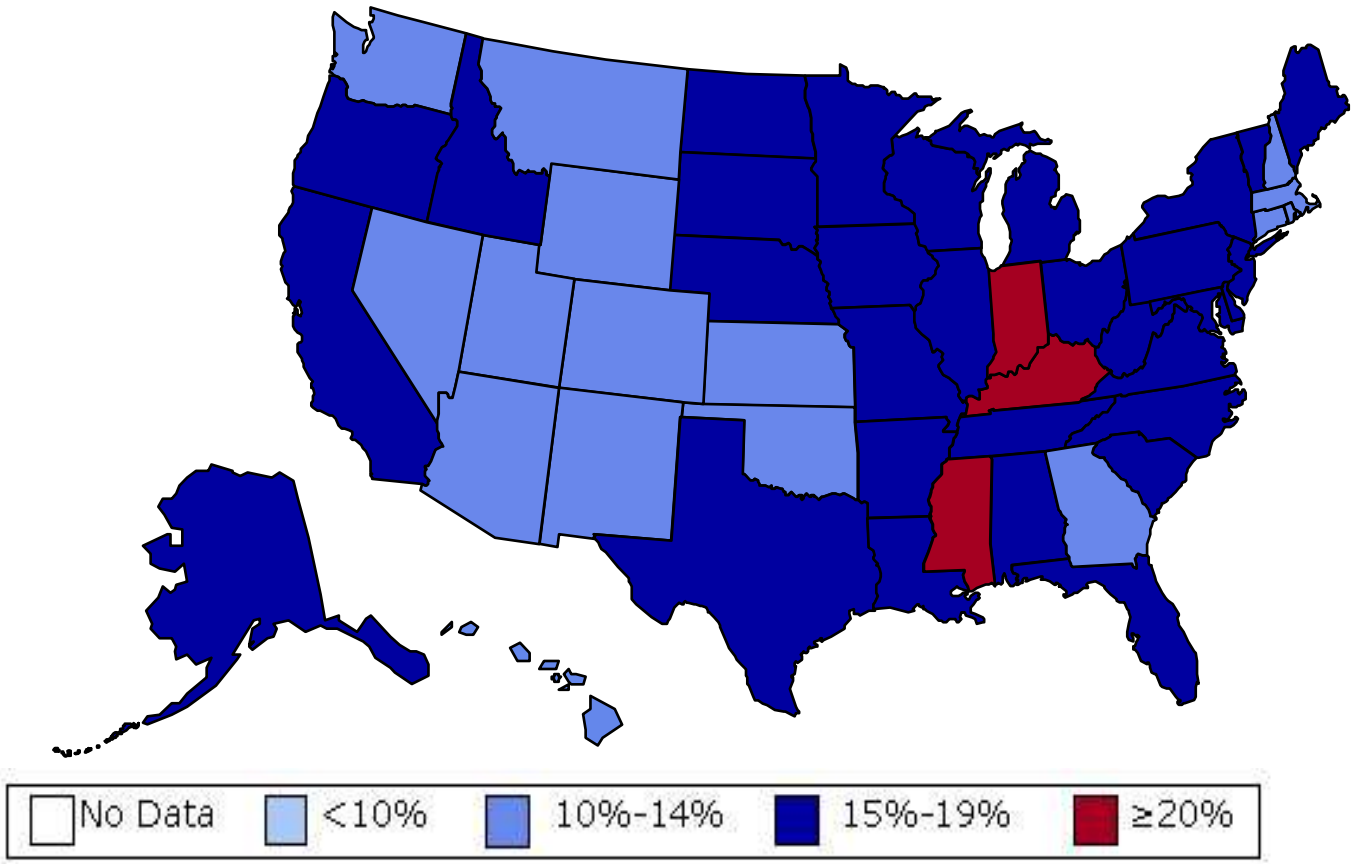
(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)



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

Obesity Trends* Among U.S. Adults 1997

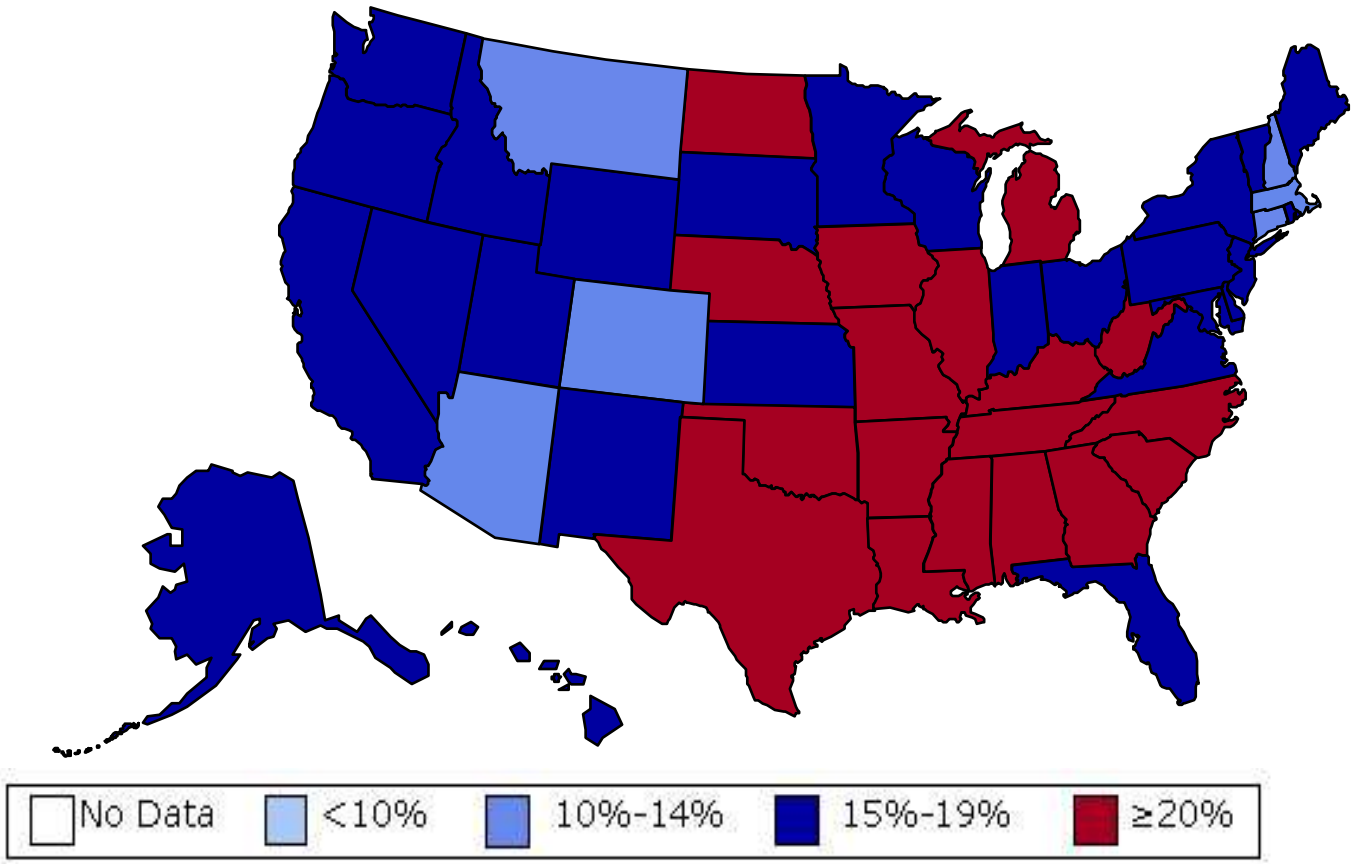
(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)



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

Obesity Trends* Among U.S. Adults 1999

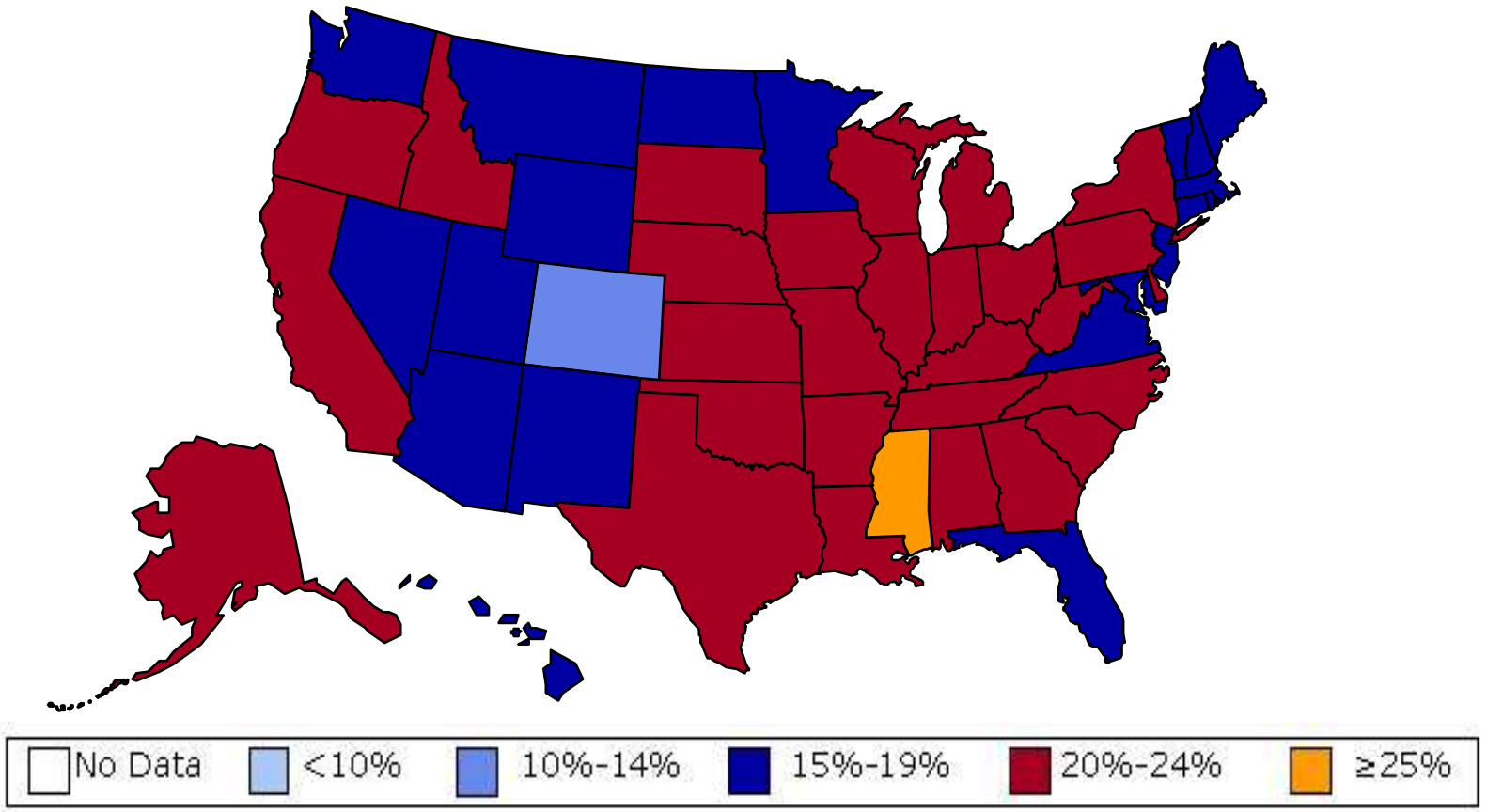
(*BMI ≥30, or ~ 30 lbs overweight for 5'4" woman)



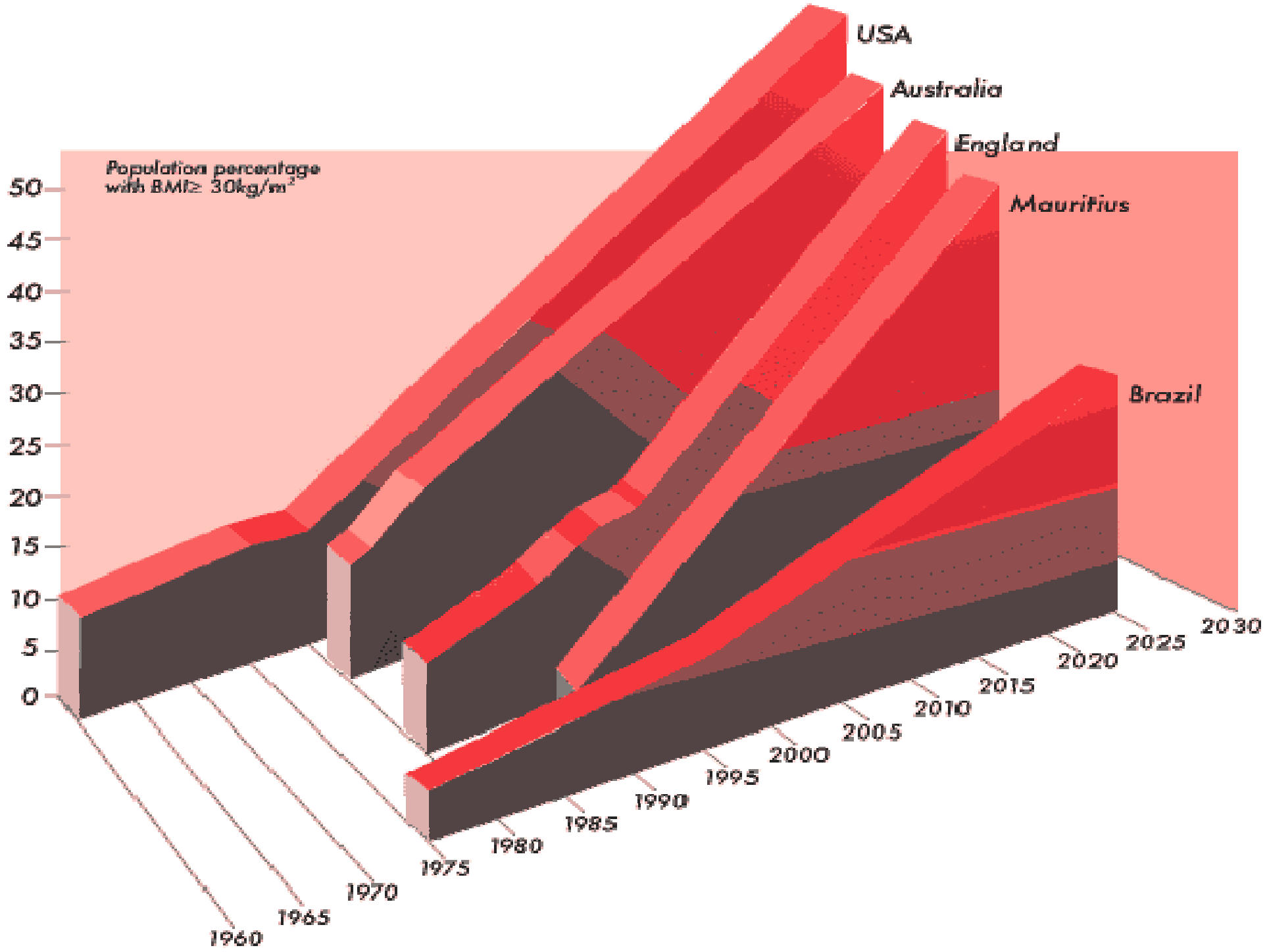
Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

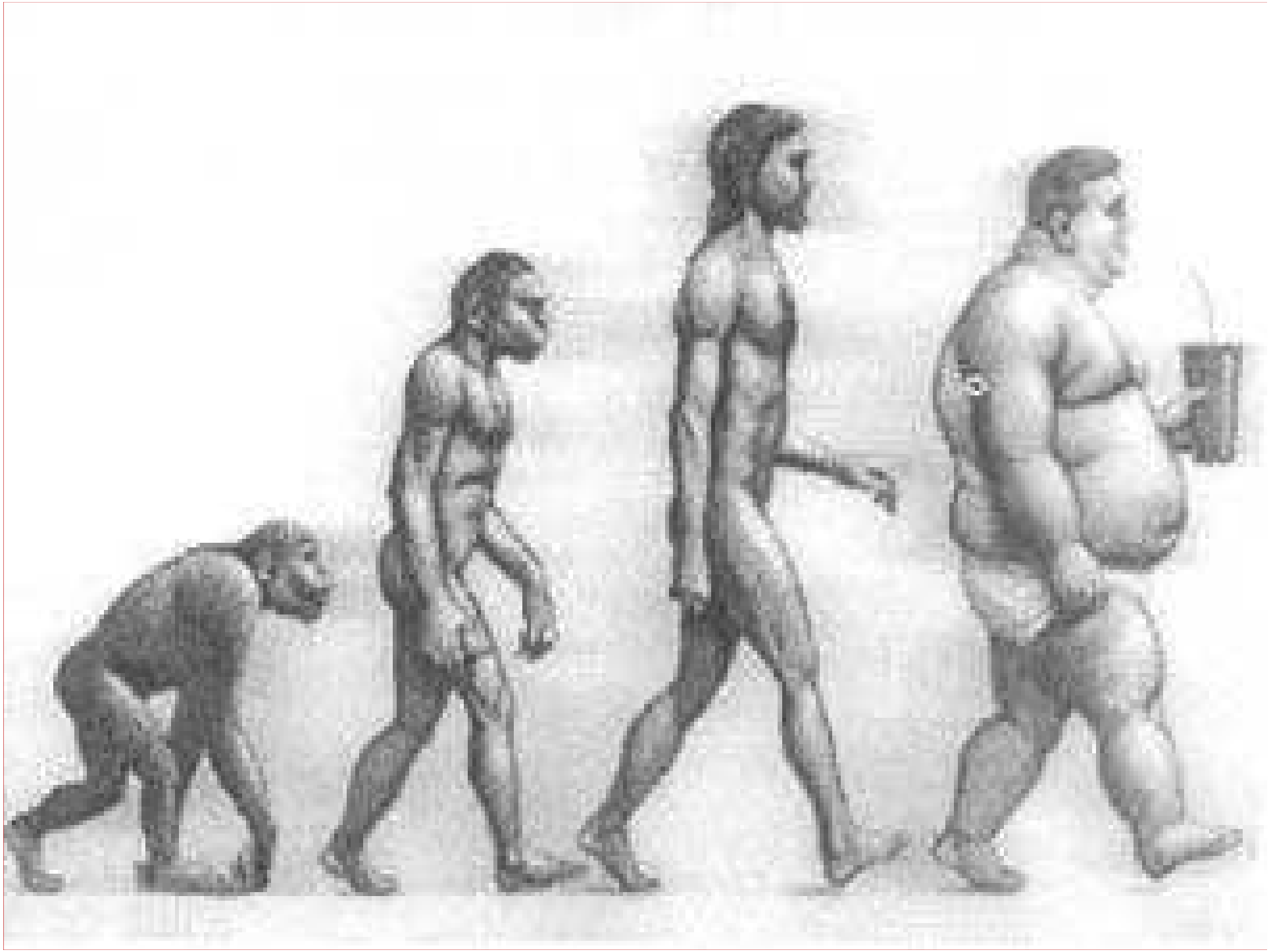
Obesity Trends* Among U.S. Adults 2001

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



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


USA
Australia
England
Mauritius
Brazil
Population percentage
with BMI≥ 30kg/m²
50
45
40
35
30
25
20
15
10
5
0
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
2020
2025
2030



TOXICOLOGICAL SCIENCES 76, 247–249 (2003)
DOI: 10.1093/toxsci/kfg255

TOXICOLOGICAL HIGHLIGHT

Endocrine Disruptors and the Obesity Epidemic

Jerrold J. Heindel

Cellular, Organs, and Systems Pathobiology Branch, Division of Extramural Research and Training, National Institute of Environmental Health Sciences, NIH, DHHS, POB 12233, Research Triangle Park, NC 27709

The major environmental influence on birth weight has been considered to be *in utero* nutrition. Therefore, maternal nutrition has been the focus of research into the fetal basis of diseases including obesity. However, nutrition is not the only environmental influence that may have an effect on adult diseases. There is increasing evidence that *in utero* exposure to environmental chemicals at environmentally relevant concentrations may alter developmental programming via alterations in gene expression or gene imprinting that do not result in either low birth weight or malformations but in functional deficits that do not become apparent until later in life where they surface as increased susceptibility to disease. With regard

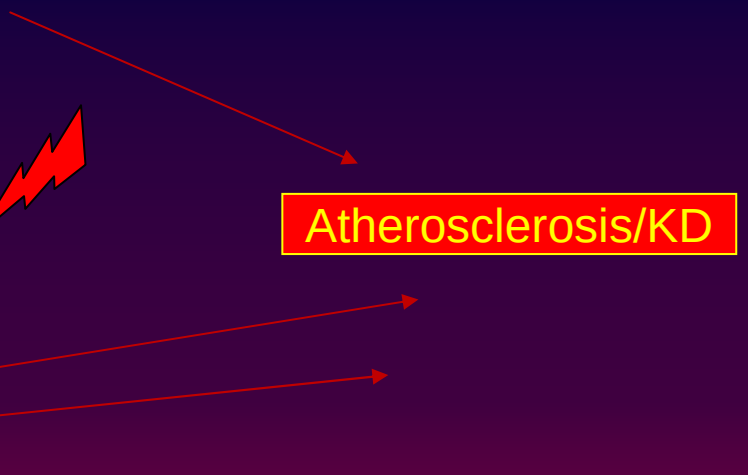
3

Systemic Flogosis

- Un ***terzo paradigma*** consiste in quella che può essere definita l'***ipotesi flogistica,*** che si fonda sul dato di fatto che **in tutte queste patologie è documentabile una componente flogistica cronica,** che avrebbe un ruolo **patogenetico chiave**.
- Tale paradigma è ovviamente valido nel campo delle ***patologie immunomediate***: tanto perciò che concerne le **allergie *sensu stricto*** (I tipo di G.C.), quanto per ciò che concerne le **patologie sistemiche** di II e III tipo …
- Bisogna però notare come più che la componente flogistica acuta assu rilievo, in questo ambito **la componente cronica, connessa al perdur dell'esposizione allo stimolo ambientale flogogeno/antigenico ed ai processi di riparazione del danno (in particolare del *remodeling* del tessuto danneggiato)**:
- discorso che vale non soltanto per le patologie immunomediate classiche (***asma allergico, immuno-artriti, immuno-vasculiti***... ivi compresa, in ambito pediatrico, la ***Kawasaki Disease***), ma anche per quella che è /'***endotelite-vasculite cronica-sistemica*** per antonomasia, l'***aterosclerosi***, la cui **origine infiammatoria** (prima e più che metabolico-degenerativa) è ormai ben documentata

Atherosclerosis: an *inflammatory vascular disease*.

Before the 1970s, the link between lipids and atherosclerosis had been well established. In the 1970s and 1980s, additional studies focused on growth factors and the proliferation of vascular smooth muscle cells (VSMCs). Since the 1990s, the role of inflammation has been considered and has now been confirmed by many clinical studies and experimental data (14, 24). Indeed, inflammation accompanies all the stages of atherosclerosis from initiation to athromatous neointima progression and to plaque disruption and complication formation. Inflammation is reported to be involved in endothelial cell injury and endothelial dysfunction, inflammatory cell recruitment, VSMC proliferation, and lipid accumulation. Therefore, atherosclerosis is actually an inflammatory vascular disease (14, 24). However, there is no inflammatory product-elicited neointimal model to support the causal role of inflammation in atherogenesis.



14. **Libby P.** Inflammation in atherosclerosis. *Nature* 420: 868–874, 2002.

24. **Ross R.** Atherosclerosis–an inflammatory disease. *N Engl J Med* 340: 115–126, 1999.

Getz GS. **Thematic review series: the immune system and atherogenesis. Bridging the innate and adaptive immune systems**. *J Lipid Res* 2005;46:619-622.

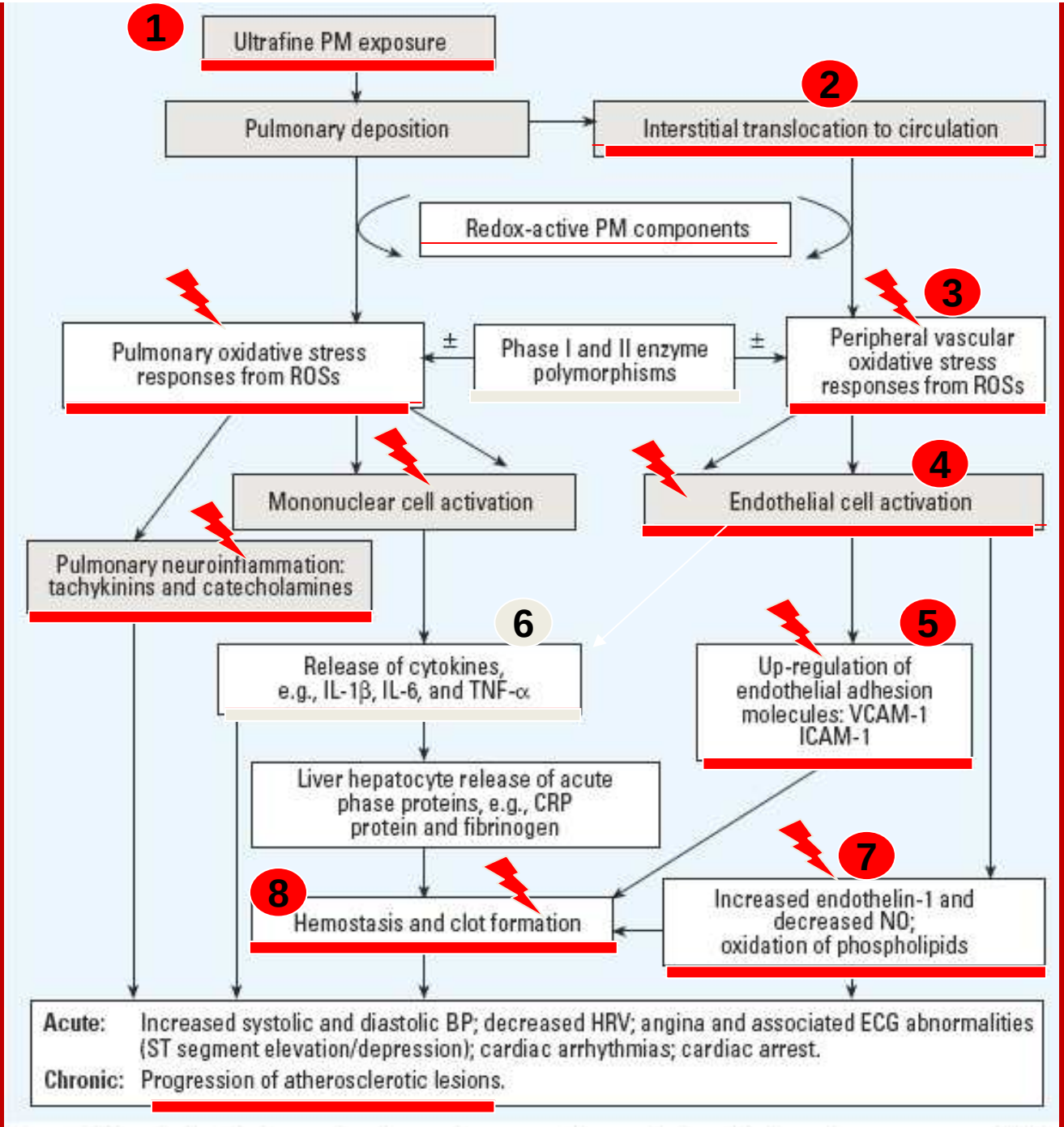


Figure 1. Hypothesized pathways leading to adverse cardiovascular health effects from exposure to UFPs.

Environmental Health Perspectives • VOLUME 114 | NUMBER 1 | January 2006

Inhalation of Ultrafine Particles Alters Blood Leukocyte Expression of Adhesion Molecules in Humans

Mark W. Frampton,[1,2] Judith C. Stewart,[1] Günter Oberdörster,[2] Paul E. Morrow,[2] David Chalupa,[1] Anthony P. Pietropaoli,[1] Lauren M. Frasier,[1] Donna M. Speers,[1] Christopher Cox,[3] Li-Shan Huang,[4] and Mark J. Utell[1,2]

[1]Department of Medicine, and [2]Department of Environmental Medicine, University of Rochester School of Medicine, Rochester, New York, USA; [3]Department of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA; [4]Department of Biostatistics, University of Rochester School of Medicine, Rochester, New York, USA

Ultrafine particles (UFPs; aerodynamic diameter < 100 nm) may contribute to the respiratory and cardiovascular morbidity and mortality associated with particulate air pollution. We tested the hypothesis that inhalation of carbon UFPs has vascular effects in healthy and asthmatic subjects, detectable as alterations in blood leukocyte expression of adhesion molecules. Healthy subjects inhaled filtered air and freshly generated elemental carbon particles (count median diameter ~ 25 nm, geometric standard deviation ~ 1.6), for 2 hr, in three separate protocols: 10 μg/m^3 at rest, 10 and 25 μg/m^3 with exercise, and 50 μg/m^3 with exercise. In a fourth protocol, subjects with asthma inhaled air and 10 μg/m^3 UFPs with exercise. Peripheral venous blood was obtained before and at intervals after exposure, and leukocyte expression of surface markers was quantitated using multiparameter flow cytometry. In healthy subjects, particle exposure with exercise reduced expression of adhesion molecules CD54 and CD18 on monocytes and CD18 and CD49d on granulocytes. There were also concentration-related reductions in blood monocytes, basophils, and eosinophils and increased lymphocyte expression of the activation marker CD25. In subjects with asthma, exposure with exercise to 10 μg/m^3 UFPs reduced expression of CD11b on monocytes and eosinophils and CD54 on granulocytes. Particle exposure also reduced the percentage of CD4$^+$ T cells, basophils, and eosinophils. Inhalation of elemental carbon UFPs alters peripheral blood leukocyte distribution and expression of adhesion molecules, in a pattern consistent with increased retention of leukocytes in the pulmonary vascular bed. *Key words:* blood leukocytes, human, monocytes, ultrafine particles. *Environ Health Perspect* 114:51–58 (2006). doi:10.1289/ehp.7962 available via *http://dx.doi.org/* [Online 20 September 2005]

There is ongoing controversy that all patients with Kawasaki disease, including those without any history of dilated coronary artery, may have the potential to develop premature atherosclerosis. Our findings support the need for long-term follow-up of these patients using various diagnostic

We found that the remodeling of the coronary arterial lesion seen in Kawasaki disease was different from that observed in atherosclerosis [,21)]

Based on animal studies, three processes of formation of atherosclerotic lesions were identified[22)]: (1) the proliferation of smooth muscle cells, macrophages and lymphocytes; (2) the formation of extracellular matrix by smooth muscle cells; and (3) the accumulation of lipid. In Kawasaki disease, there was no accumulation of lipid or macrophages.

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⇔

21. Saksela O, Rifkin DB. Release of basic fibroblast growth factor-heparanate complexes from endothelial cells by plasminogen activator-mediated proteolytic activity. J Cell Biol 1990; 110: 767-75.

22. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993; 362: 801-9.

KD versus Atherosclerosis

3B

- Ma il **paradigma flogistico** è utilizzabile anche
- per ciò che concerne le principali **malattie metaboliche** oggi in rapido incremento, a cominciare dall'***obesità***, il **tessuto adiposo** essendo ben più che un semplice tessuto di riserva, un vero e proprio **tessuto/organo con importanti funzioni endocrino-metaboliche** (con produzione di un'ampia gamma di molecole specifiche, dotate di attività ormonale) ed **immunitarie** (non solo in quanto gli ***adipociti*** sarebbero per molti versi equiparabili ai ***macrofagi***, ma anche per la notevole presenza di macrofagi attivati nel **tessuto adiposo infiammato degli obesi**)
- per varie patologie direttamente connesse all'obesità stessa e a disordini del metabolismo glicidico e lipidico (***sindrome metabolica***, ***diabete II***);
- per le principali **patologie neuro-degenerative croniche** (in particolare per ***Alzheimer Disease, Parkinson Disease, Amiotrophic Lateral Sclerosis***);
- per numerose ***neoplasie*** (anche per ciò che concerne **il ruolo predisponente e direttamente onco-patogenetico delle flogosi croniche** locali e sistemiche nell'ambito delle degenerazioni tessutali di tipo metaplastico e neoplastico

Obesity is associated with macrophage accumulation in adipose tissue

Stuart P. Weisberg,[1] Daniel McCann,[1] Manisha Desai,[2]

J. Clin. Invest. 112:1796–1808 (2003).

Review

Distinct Role of Macrophages in Different Tumor Microenvironments

Claire E. Lewis[1] and Jeffrey W. Pollard[2]

[1]Academic Unit of Pathology, Division of Genomic Medicine, University of Sheffield Medical School, Sheffield, United Kingdom and [2]Center for the Study of Reproductive Biology and Women's Health, Departments of Developmental and Molecular Biology and Obstetrics & Gynecology and Women's Health, Albert Einstein College of Medicine, Bronx, New York

(Cancer Res 2006; 66(2): 605-12)

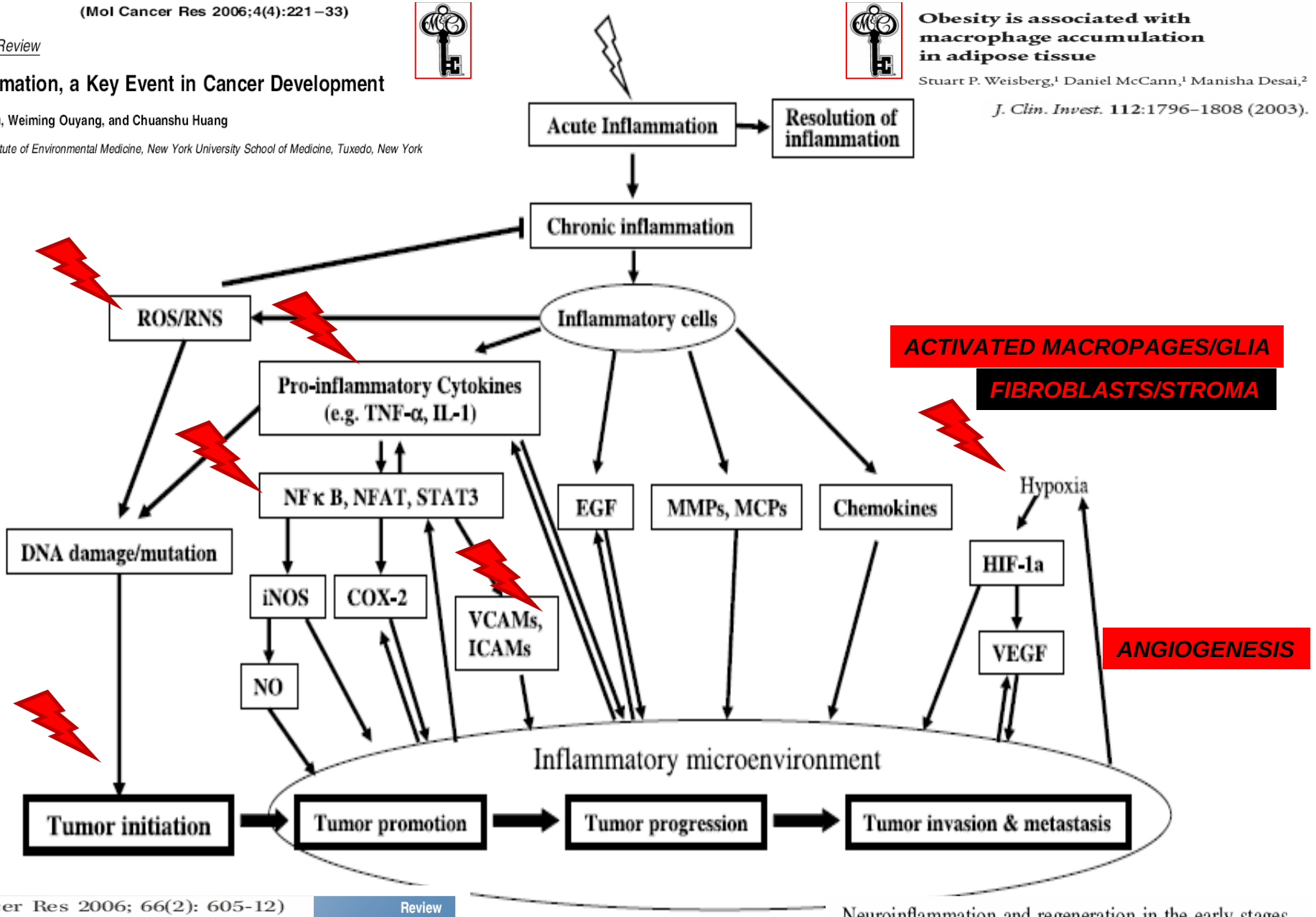
(Mol Cancer Res 2006;4(4):221–33)

Subject Review

Inflammation, a Key Event in Cancer Development

Haitian Lu, Weiming Ouyang, and Chuanshu Huang

Nelson Institute of Environmental Medicine, New York University School of Medicine, Tuxedo, New York



Obesity is associated with macrophage accumulation in adipose tissue

Stuart P. Weisberg,[1] Daniel McCann,[1] Manisha Desai,[2]

J. Clin. Invest. 112:1796–1808 (2003).

ACTIVATED MACROPAGES/GLIA

FIBROBLASTS/STROMA

ANGIOGENESIS

(Cancer Res 2006; 66(2): 605-12) Review

Distinct Role of Macrophages in Different Tumor Microenvironments

Claire E. Lewis[1] and Jeffrey W. Pollard[2]

[1]Academic Unit of Pathology, Division of Genomic Medicine, University of Sheffield Medical School, Sheffield, United Kingdom and [2]Center for the Study of Reproductive Biology and Women's Health, Departments of Developmental and Molecular Biology and Obstetrics & Gynecology and Women's Health, Albert Einstein College of Medicine, Bronx, New York

Neuroinflammation and regeneration in the early stages of Alzheimer's disease pathology

J.J.M. Hoozemans[a,b,*], R. Veerhuis[d], J.M. Rozemuller[a], P. Eikelenboom[c,d]

Int. J. Devl Neuroscience 24 (2006) 157–165

Infection, inflammation, height, and longevity

Eileen M. Crimmins* and Caleb E. Finch

Andrus Gerontology Center, College of Letters, Arts, and Sciences, University of Southern California, Los Angeles, CA 90089-0191

Edited by Kenneth W. Wachter, University of California, Berkeley, CA, and approved November 15, 2005 (received for review February 21, 2005)

Using historical data from cohorts born before the 20th century in four northern European countries, we show that increasing longevity and declining mortality in the elderly occurred among the same birth cohorts that experienced a reduction in mortality at younger ages. Concurrently, these cohorts also experienced increasing adult height. We hypothesize that both the decline in old-age mortality and the increase in height were promoted by the reduced burden of infections and inflammation. Thus, early growth and cardiovascular diseases of old age may share infectious and inflammatory causes rooted in the external environment.

aging | vascular disease | mortality | historical cohorts

498–503 | PNAS | January 10, 2006 | vol. 103 | no. 2

transition from **pre-industrialized *** to **industrialized ** society**

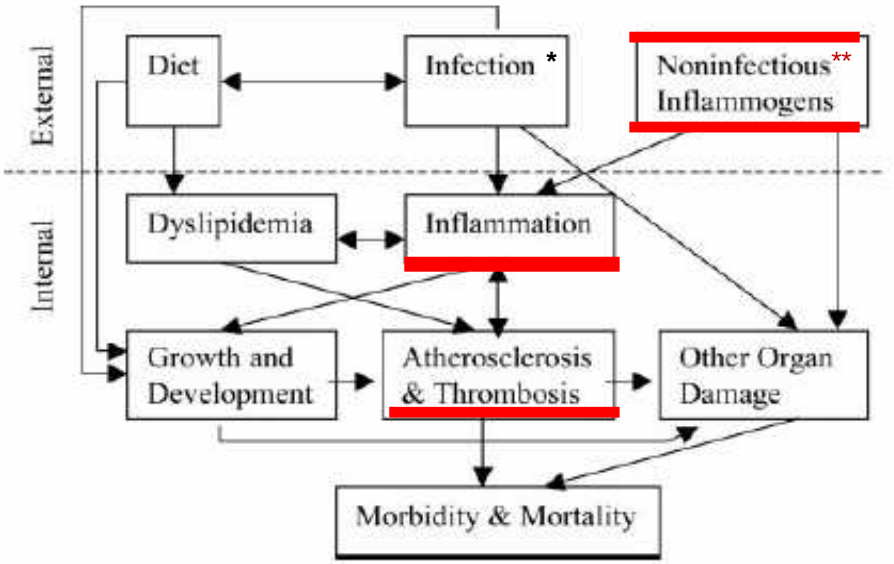
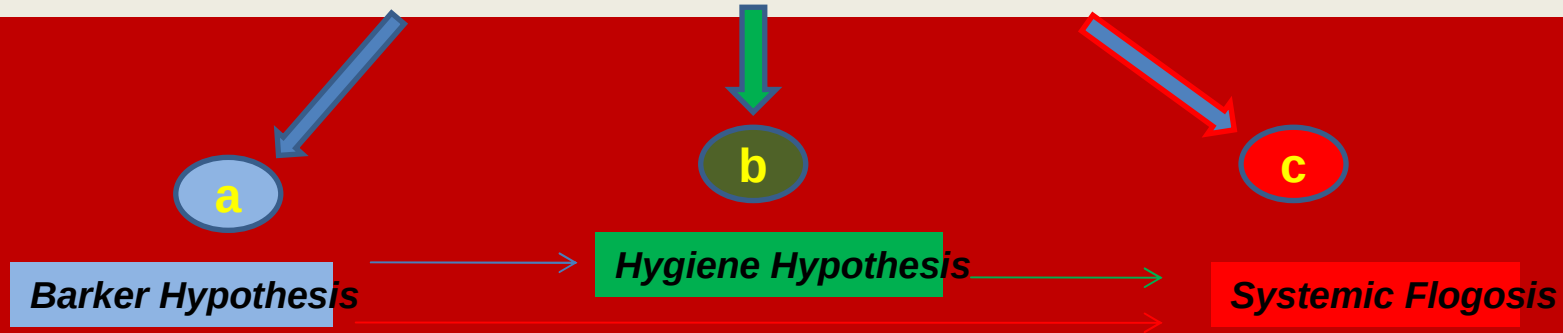


Fig. 1. Model linking infectious exposure at earlier ages and external environment to inflammation, height, organ damage, morbidity, and mortality at older ages. Barker (10) and Fogel (11) emphasize dietary influences on growth/development as a central mechanism.

Possiamo a questo punto mettere in rilievo alcuni aspetti chiave concernenti i 3 suddetti **PARADIGMI PATOGENETICI**



Prima di tutto possiamo notare come i tre paradigmi siano **complementari**
(il minimo comune denominatore essendo, in tutti i casi, la **repentina trasformazione ambientale** che ha **disorientato i sistemi biologici)**
e in un certo senso **sequenziali:**

b

Hygiene Hypothesis

- In particolare per quanto concerne l'***ipotesi igienica,*** che propone come principale meccanismo patogenetico un alterazione dell'equilibrio del sistema immunocompetente, **legata a un'imperfetta sequenza di sviluppo** dello stesso
- il **principale momento critico** **cadrebbe nel** **periodo perinatale o immediatamente post-natale** allorché si dovrebbe costituire , essenzialmente in relazione al *set* microbico materno, **l'ecosistema intestinale del neonato più idoneo a garantire il corretto sviluppo del suo sistema immunitario** (in particolare per ciò che concerne l'equilibrio tra le componenti basilari dell'***immunità adattativa***).
- **L'alterazione del sistema microbico vaginale** della madre e/o della **flora tipica dei principali alimenti** (a cominciare ovviamente dal **latte**) determinerebbe nel neonato **un'alterazione dell'ecosistema microbico** e, quindi

a

Barker Hypothesis

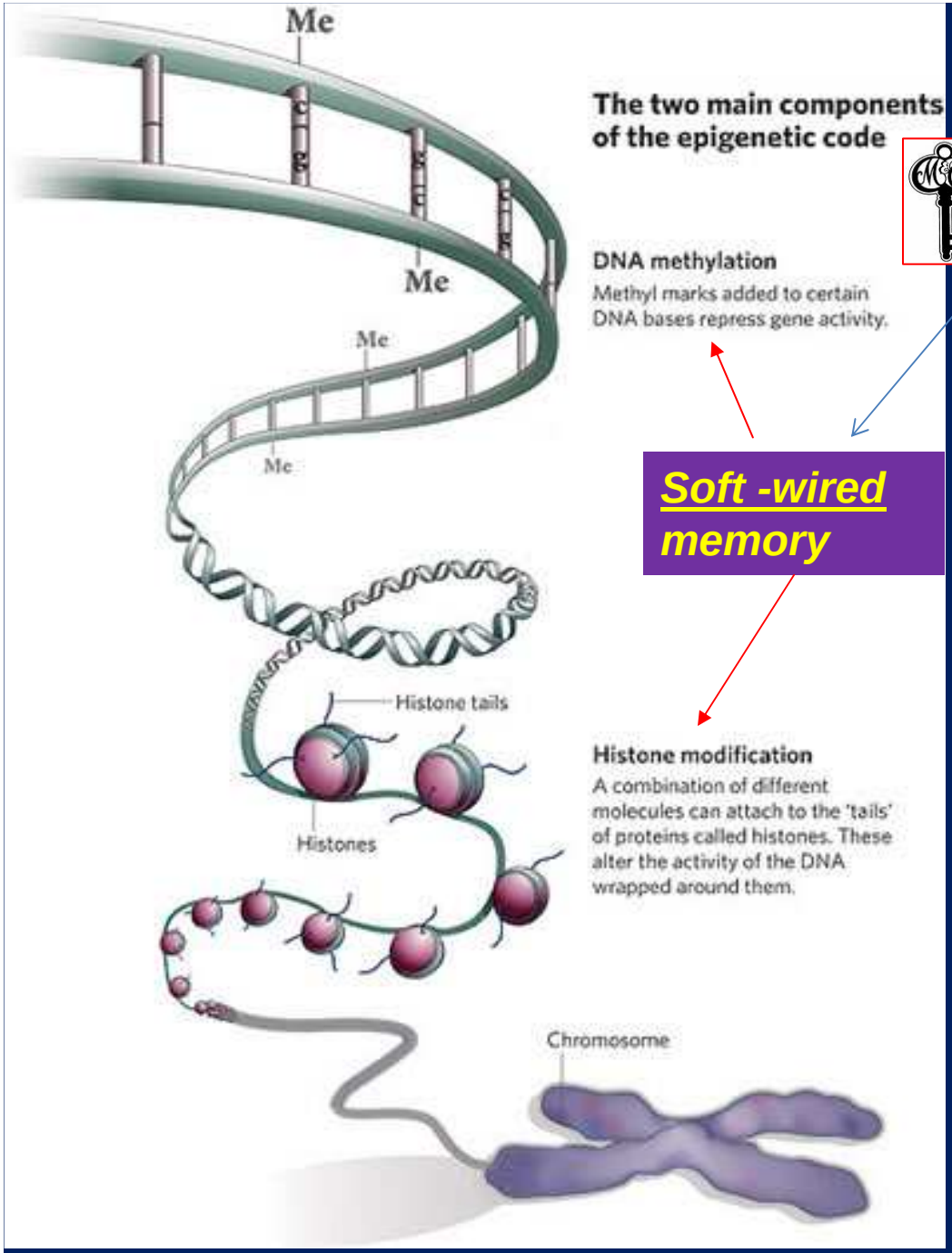
Per quanto concerne l'***ipotesi Barker*** l'origine dei problemi viene **retrodatata e collocata nei primi mesi dello sviluppo embrio-fetale:** in questo caso infatti le alterazioni del macro-ambiente si ripercuoterebbero sul **micro-ambiente uterino** e, quindi, sul feto determinando essenzialmente

un'alterazione del programma epigenetico, essenzialmente a carico delle cellule destinate a costituire i tessuti e gli organi che dovranno regolare l'omeostasi metabolico-energetica dell'organismo stesso e i suoi rapporti con il mondo esterno (in particolare con ciò che è classicamente definibile come *non self*), cioè i **sistemi neuro-endocrino-metabolico** ed **immunitario**.

- Le **alterazioni del *programming fetale*** sarebbero almeno in parte adattative (interessante è in tal senso l'ipotesi attinente al cosiddetto ***epigenoma/fenotipo metabolico risparmiatore*** che, adottato dal feto che abbia dovuto affrontare situazioni carenziali **si rivela inadatto a regolare il metabolismo dello stesso individuo in età adulta**, nelle situazioni di **eccesso calorico e nutrizionale in genere**, tipiche delle "società avanzate").
- Ma appare sempre più probabile che tali alterazioni siano da mettere anche in relazione ad una **condizione di *stress* materno e quindi fetale**: sia esso uno ***stress* psicologico** ed **endocrino-mediato**, sia esso uno ***stress* chimico-fisico** **trattamento ambientale** che, paradossalmente

Hales CN, Barker DJ **The thrifty phenotype hypothesis** British Medical Bulletin 2001; 65; 5-20

Szyf, M. **The Dynamic Epigenome and its Implications in Toxicology**



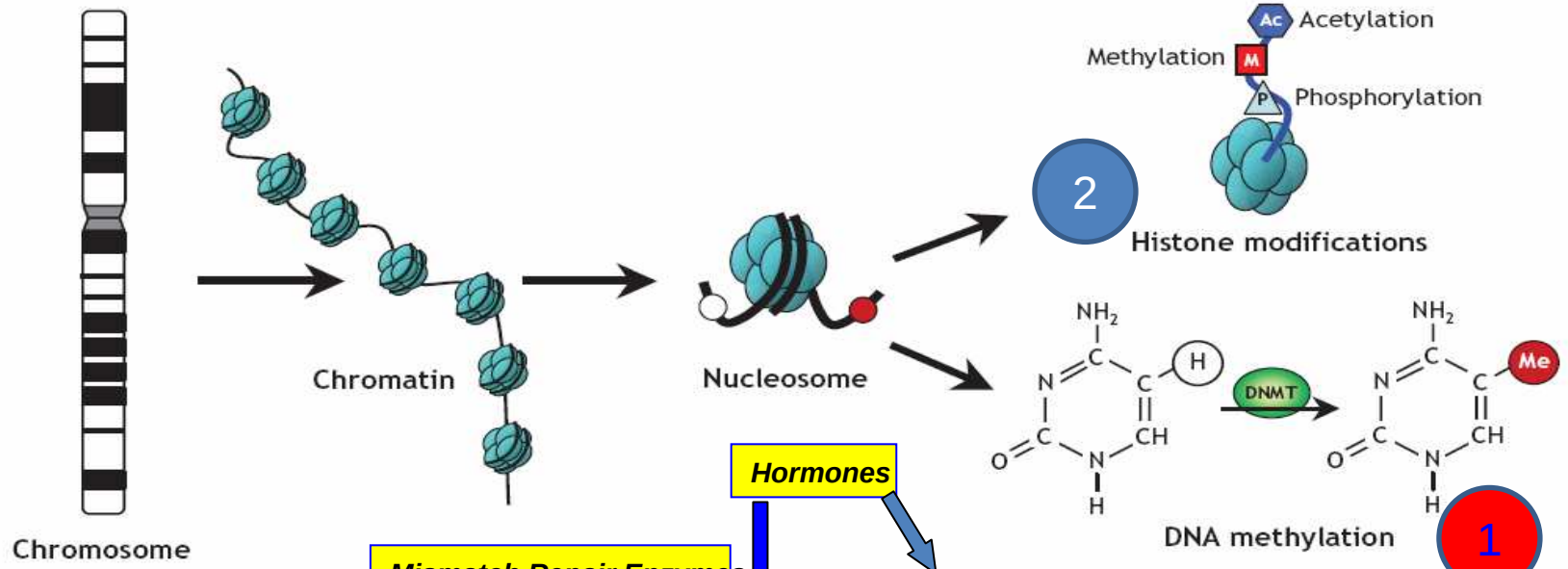
http://www.nature.com/news/2006/060508/images/441143a-i2.0.jpg

- L'**ambiente** agisce più direttamente sull'**epigenoma** (assetto cromatinico-*hystone code*, metilazione DNA, RNA minori..)
- e attraverso questo sul **genoma**
- Possiamo anche dire che **l'evoluzione** del **fenotipo individuale anche patologico (!)** è determinato dall'**epigenoma** più che dal **genoma**

Brena RM, Costello JF. ***Genome-epigenome interactions in cancer.*** *Hum Mol Genet*. 2007 Apr 15;16(R1):R96-R105

Controlling active and inactive states of embryonic and somatic cells 1

Gene- and tissue-specific epigenetic patterns 2



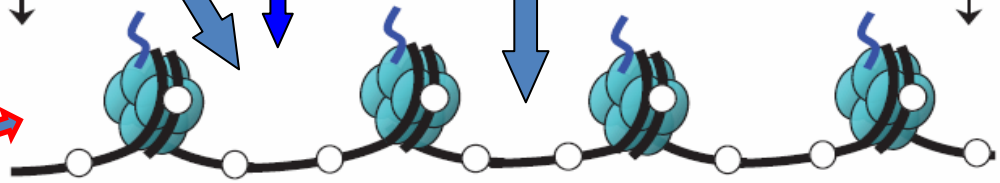
Hormones

Mismatch Repair Enzymes

Trascription Factors

Correct organization of chromatin 3

Gene "switched on"
- Active (open) chromatin
- Unmethylated cytosines (white circles)
- Acetylated histones



X chromosome inactivation 5

Gene "switched off"
- Silent (condensed) chromatin
- Methylated cytosines (red circles)
- Deacetylated histones

Genomic imprinting 6

Silencing repetitive elements 4

Epigenetic modifications : a molecular environmental effect

Nature

Genetics

Critical determinants of the epigenome

Nurture

Environment

Acute enviroemental events

Daily (low intensity) enviromental events

Genetic Mutations etc.

Epi-Mutations

CHANGING EPIGENOME

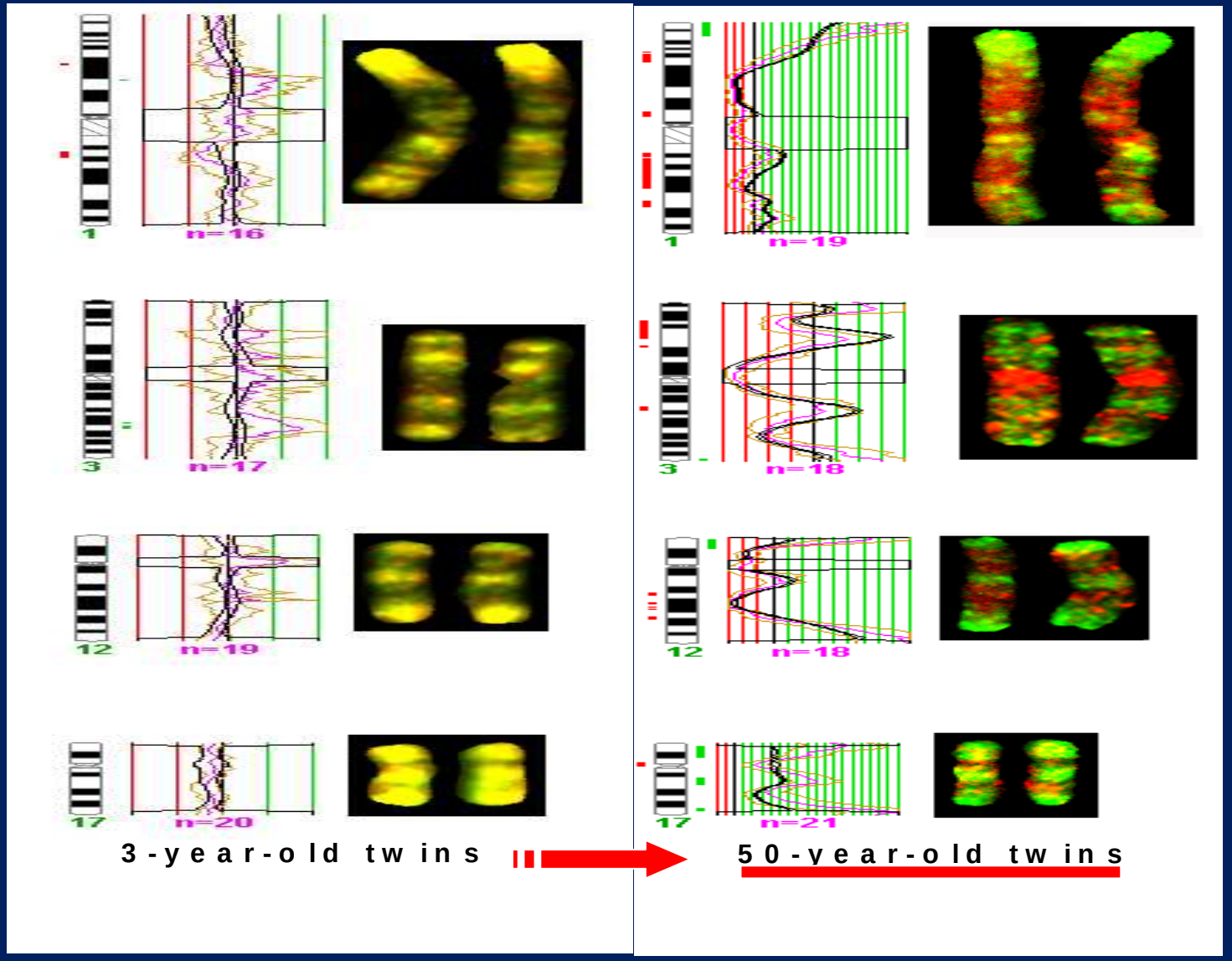
Celiac Disease

Why this disease is concordant in only **60**% to **70**% of **identical twin**

*And **Alzheimer Disease ?***

Instituto de Salud Carlos III

Epigenetic differences in homozygotic twins



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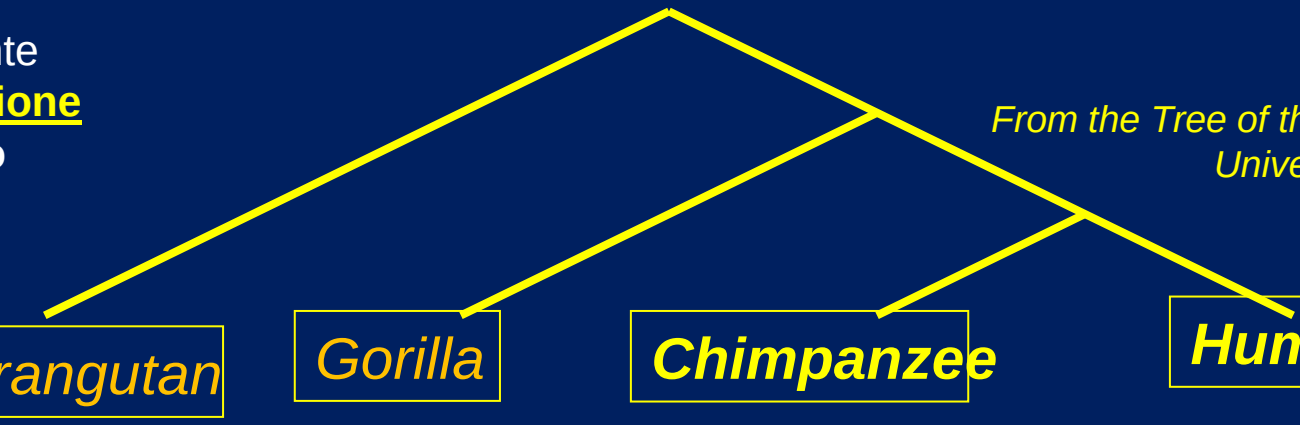
Fraga et al., PNAS. 2005.

Il **genoma dello scimpanzé è per il 98.77% identico** a quello umano.
In media, un **gene codificante una proteina** in un uomo differisce dal suo **ortologo** nello scimpanzé per **due sole sostituzioni aminoacidiche**
..quasi **un terzo dei geni umani** hanno esattamente **la stessa traduzione proteica dei loro ortologhi** nello scimpanzé

..piuttosto ***stabili*** da **milioni di anni** sul piano genetico e fenotipico...

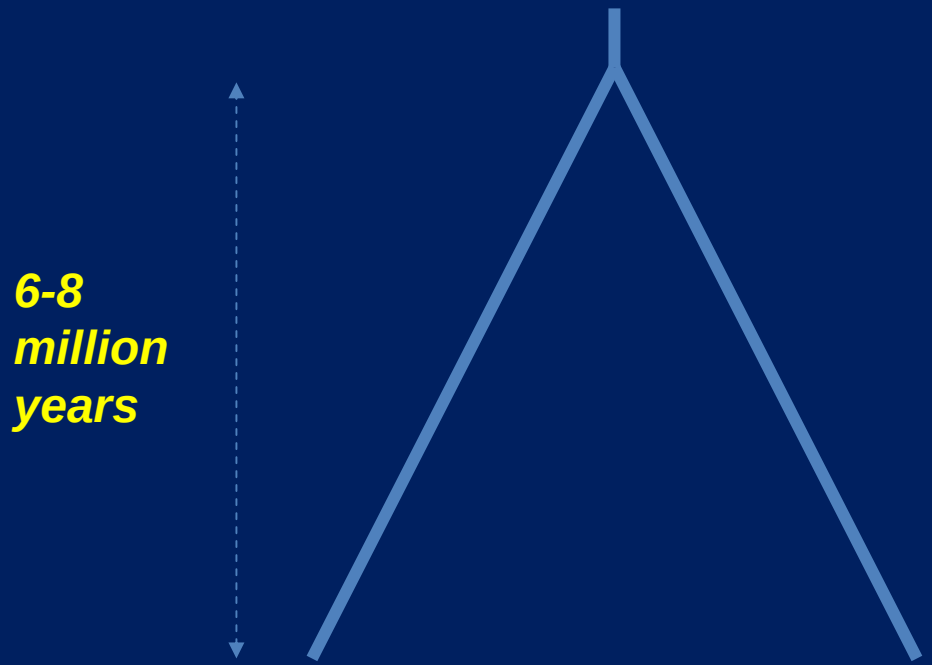
Species ***phylogeny***



From the Tree of the Life Website, University of Arizona

Sanger Institute

Chimpanzee-human divergence



6-8 million years

Chimpanzees

Humans

Hominids or hominins

***Soft Wired*-memory**

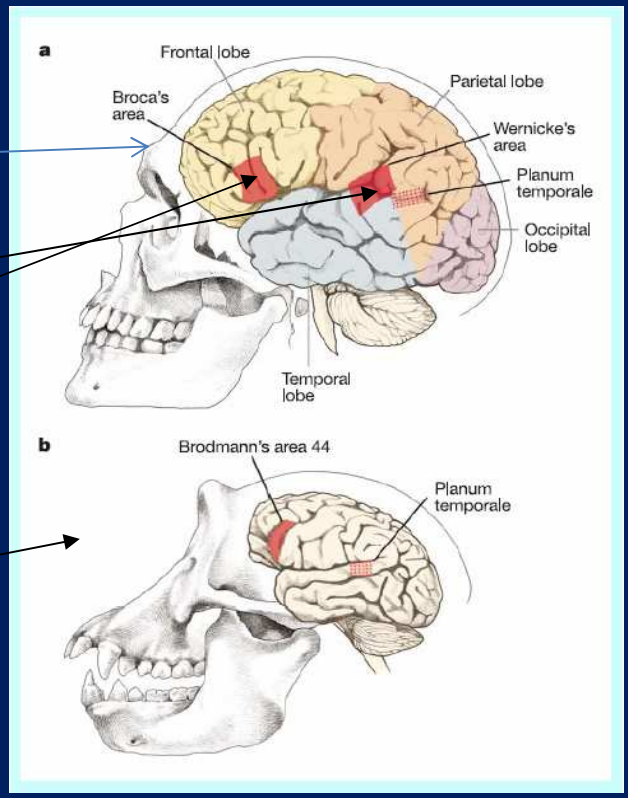
epigenomica

Brain: a *rapidly evolving organ*

Phenotypic differences between humans and ***other*** apes

Selected traits that distinguish humans from other apes[5–7]

Body shape and thorax
Cranial properties (brain case and face)
Relative brain size
Relative limb length
Long ontogeny and lifespan
Small canine teeth
Skull balanced upright on vertebral column
Reduced hair cover
Elongated thumb and shortened fingers
Dimensions of the pelvis
Presence of a chin
S-shaped spine
Language
Advanced tool making
Brain topology



Carroll (2003) *Nature* **422**, 849-857

EPIGENETIC MECHANISMS IN MEMORY FORMATION

Jonathan M. Levenson and J. David Sweatt

NATURE REVIEWS | NEUROSCIENCE
FEBRUARY 2005 | VOLUME 6

.. **Neurobiologists** have only recently begun to investigate the possible **roles of epigenetic mechanisms in behaviour, physiology and neuropathology**. …Strikingly, the relevant data from the few extant neurobiology-related studies have already indicated a theme — **epigenetic mechanisms probably have an important role in synaptic plasticity** and **memory formation.**

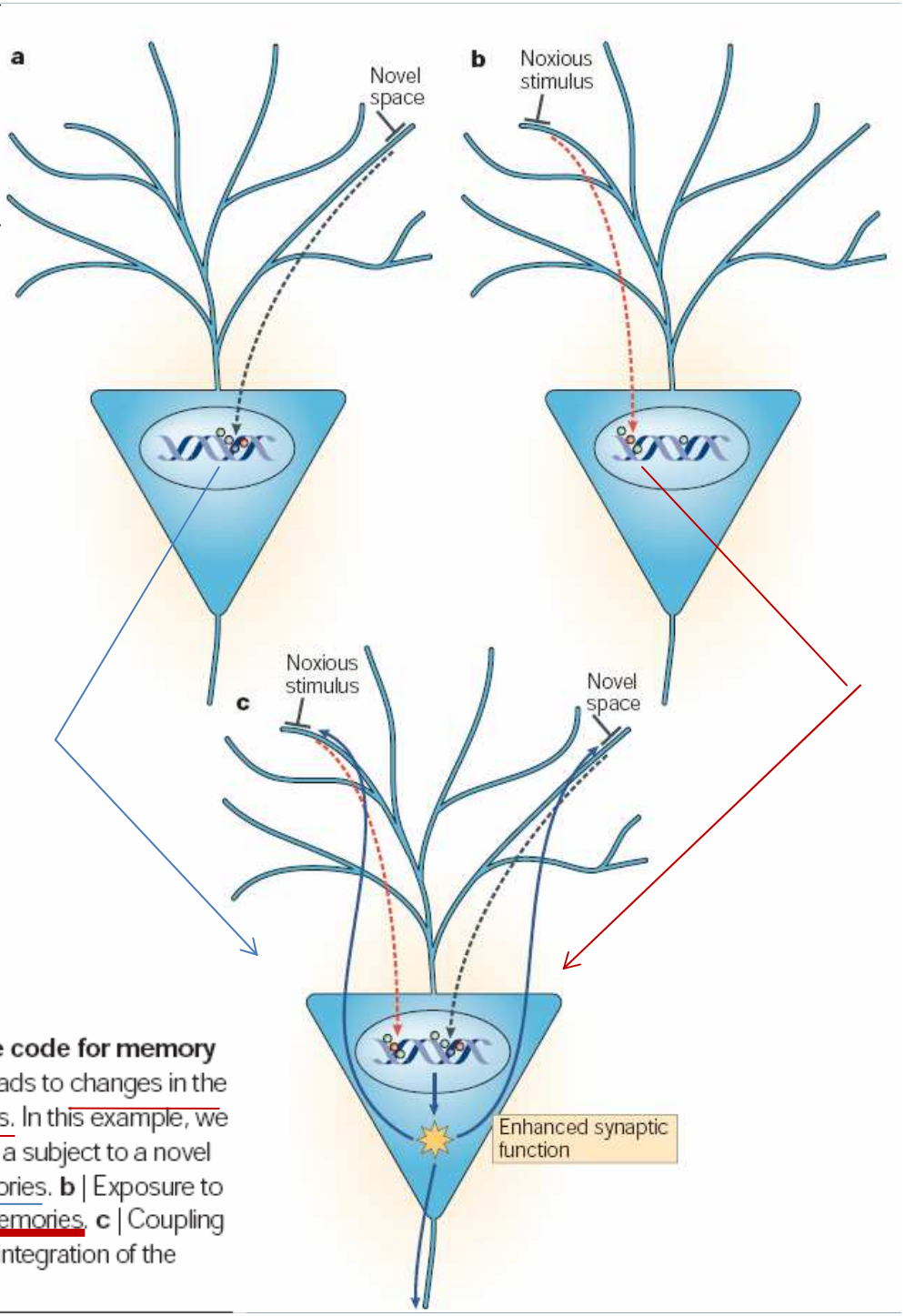


Figure 4 | **Model for epigenetics in contextual fear memory — a histone code for memory formation?** Exposure of a test subject to various environmental conditions leads to changes in the epigenetic profile of the genome in neurons that reside in relevant brain regions. In this example, we focus on pyramidal neurons in area CA1 of the hippocampus. **a** | Exposure of a subject to a novel environment leads to epigenetic changes and formation of novel spatial memories. **b** | Exposure to a noxious stimulus leads to epigenetic changes and formation of novel fear memories. **c** | Coupling the presentation of the novel environment with the noxious stimulus results in integration of the epigenetic responses, and formation of specific contextual fear memories.

TOXICOLOGICAL SCIENCES **80**, 218–224 (2004)
DOI: 10.1093/toxsci/kfh164
Advance Access publication May 12, 2004

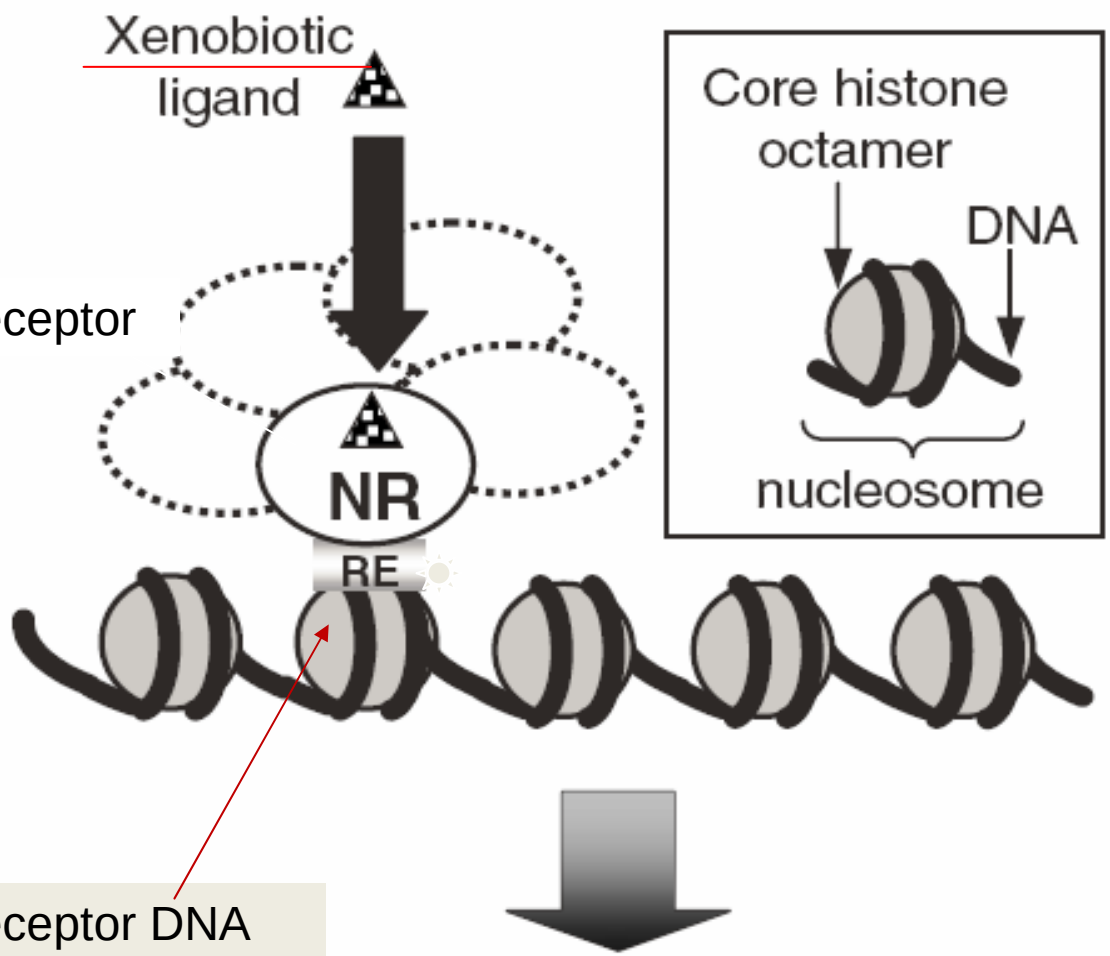
The Role of Chromatin in Molecular Mechanisms of Toxicity

Jonathan G. Moggs[1] and George Orphanides

Syngenta CTL, Cheshire SK10 4TJ, United Kingdom

Eukaryotic cells store their genetic information in the form of a highly organized nucleoprotein complex termed chromatin. The high degree of compaction of DNA within chromatin places severe constraints on proteins that require access to the DNA template to facilitate gene transcription, DNA replication, and DNA repair. As a consequence, eukaryotic cells have developed sophisticated mechanisms to allow chromatin to be rapidly decompacted locally for access by DNA-binding proteins. Once thought to play only a structural role, it now appears that chromatin plays a key regulatory role by marshalling access to the DNA template. We have reviewed the role played by chromatin in the cellular response to physiological and toxicological stimuli and described how changes in chromatin structure may in the future be used as markers of toxicity. We also review the evidence that chromatin itself is the direct target of certain toxicants and that toxicant-induced perturbations in chromatin structure may precipitate adverse effects.

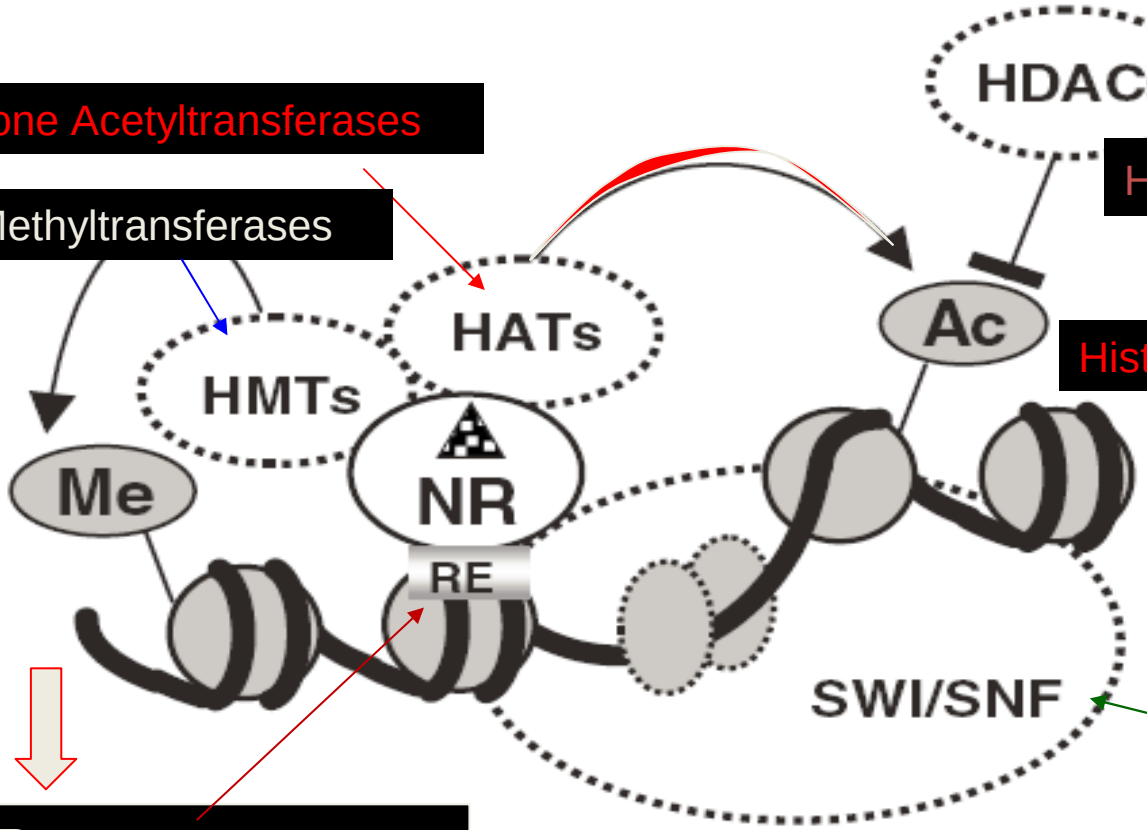
Binding of ligand to nuclear receptor, cofactor recruitment, binding to gene promoter.



Nuclear Receptor

Nuclear Receptor DNA Response Element

Modification of chromatin structure by histone modifying and nucleosome remodelling proteins



Histone Acetyltransferases

Histone Methyltransferases

Histone Deacetylases

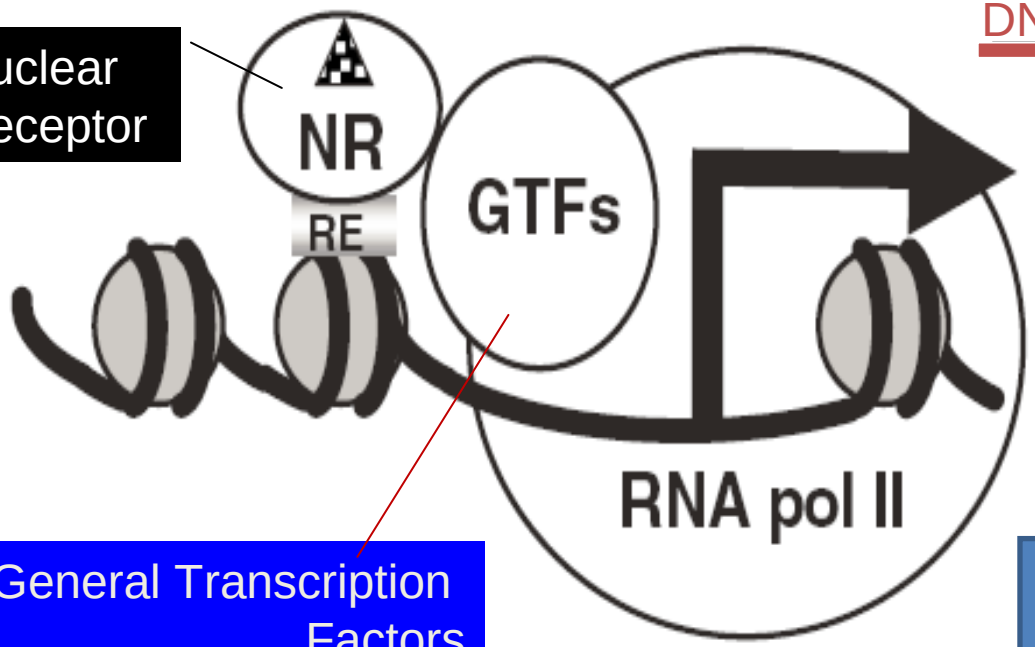
Histone Lysine Acetylation

Nuclear Receptor
DNA Response Element

ATP-dependent Nucleosome
Remodeling Enzymes

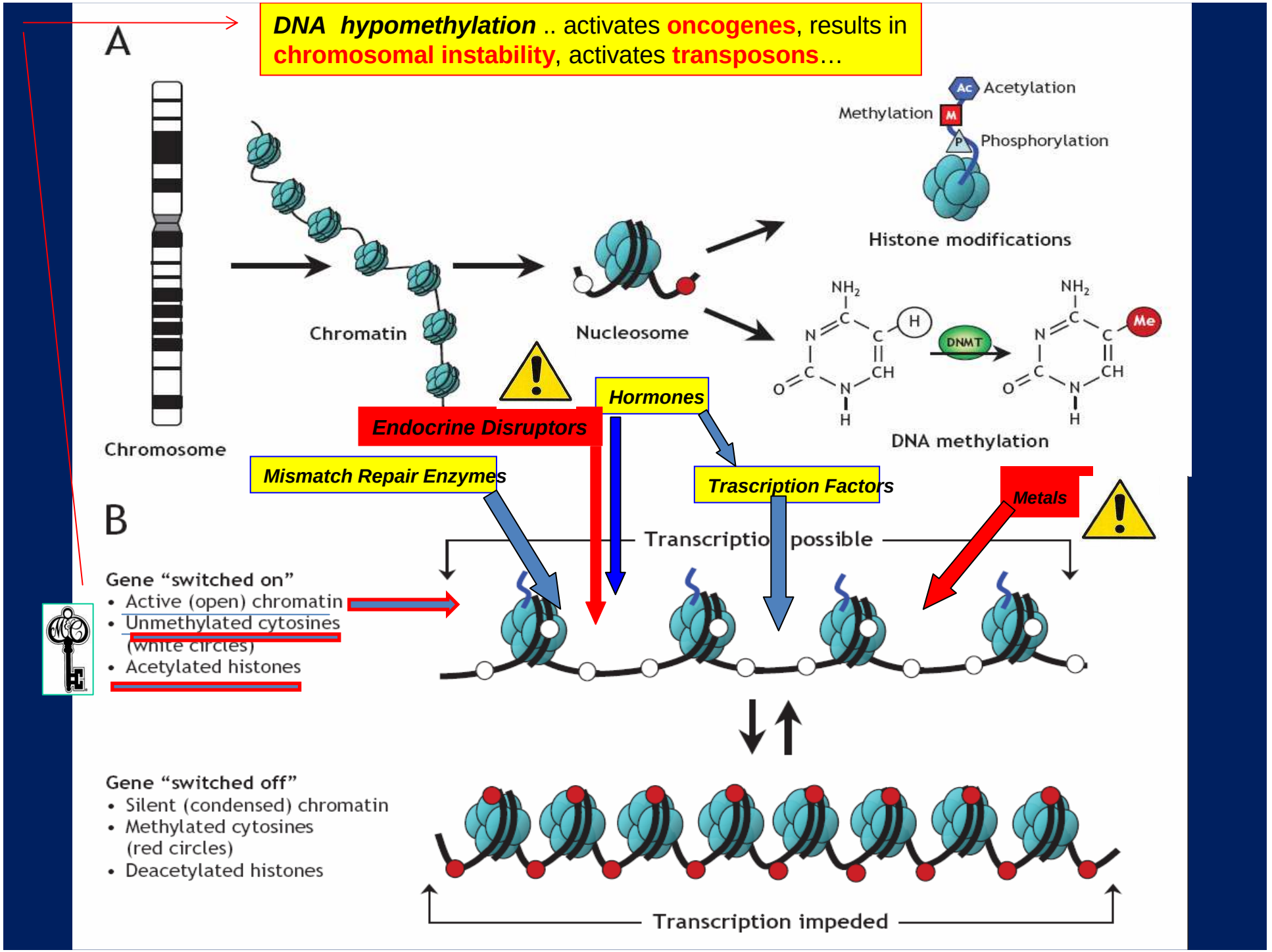
Increased in DNA accessibility of gene, binding of RNA polymerase II and gene transcription

DNA Repair



What would be the consequences of direct chemical perturbation of chromatin structure? In addition to their role in regulating gene expression and DNA repair, chromatin modifications play an important part in the transmission of epigenetic information, epigenetics being the study of heritable alterations in gene expression that occur in the absence of changes in genome sequence (Wolffe and Matzke, 1999). Thus, the perturbation of chromatin structure by toxicants may lead to long-term and possibly transgenerational changes in epigenetic programming.

Una condizone di ***instabilità genomica*** **(ipometilazione diffusa, iper-metilazione delle sequenze *promoter* di geni onco-soppressori, specifiche combinazioni del "*codice istonico*")** è di frequente riscontro nelle ***lesioni (pre)-neoplastiche***

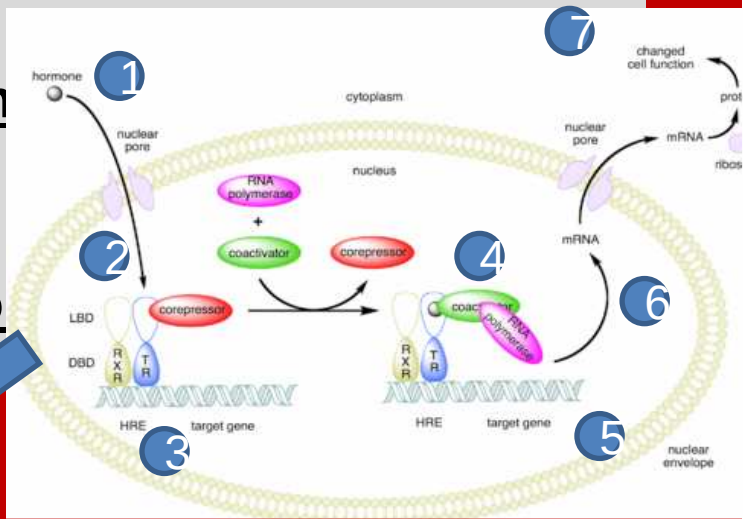

A
DNA hypomethylation .. activates oncogenes, results in chromosomal instability, activates transposons…
Acetylation
Methylation
Phosphorylation
Histone modifications
Chromosome
Chromatin
Nucleosome
DNA methylation
DNMT
Endocrine Disruptors
Hormones
Mismatch Repair Enzymes
Trascription Factors
Metals
B
Transcriptio possible
Gene "switched on"
• Active (open) chromatin
• Unmethylated cytosines (white circles)
• Acetylated histones
Gene "switched off"
• Silent (condensed) chromatin
• Methylated cytosines (red circles)
• Deacetylated histones
Transcription impeded

Bisogna sottolineare come l'ormai ben documentata interferenza tra ***metalli e/o interferenti endocrini*** e **Dna** non rappresenti l'eccezione,
ma la **regola…** nel senso che le modalità di **"*lettura*"** e **"*induzione dell'espressione genica"*** da parte delle **molecole-segnale specifiche**
sono sempre le stesse (e note ormai da tempo)..

- ***sia*** che si tratti di ***processi fisiologici***,

1 ***sia*** che si tratti di ***meccanismi tossicologici e potenzialmente patogenetici***, secondo lo schema:
2 **Ormoni/UV/ Endocrine Disruptors →**
3 **recettori nucleari/fattori di trascrizione →**
4 legame al **Dna (*sequenze specifiche*)→**
5 riarrangiamento**(*epi*)genomico/cod. iston**
6 riarrangiamento genomico →
7 **trascrizione** (*proteine/Rna minori*) →

- **differe ziazione/proliferazione/secrezio → *citoc ine/ormoni/enzimi…***



Parte II

The Environmental Toxic Burden
and **the fetal origins of adult diseases**

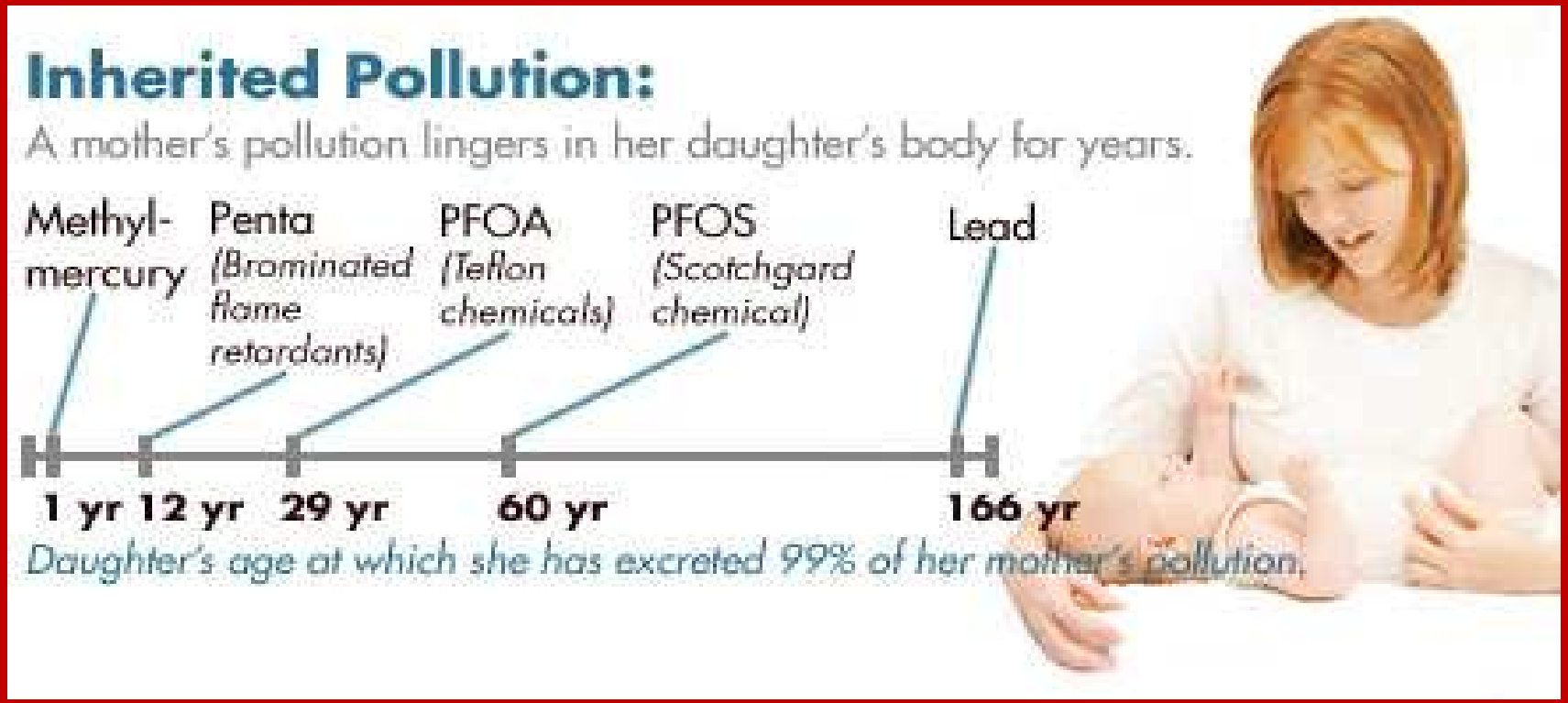
The gift our mothers never wanted to give us

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

A CHEMICAL FALL OUT

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

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



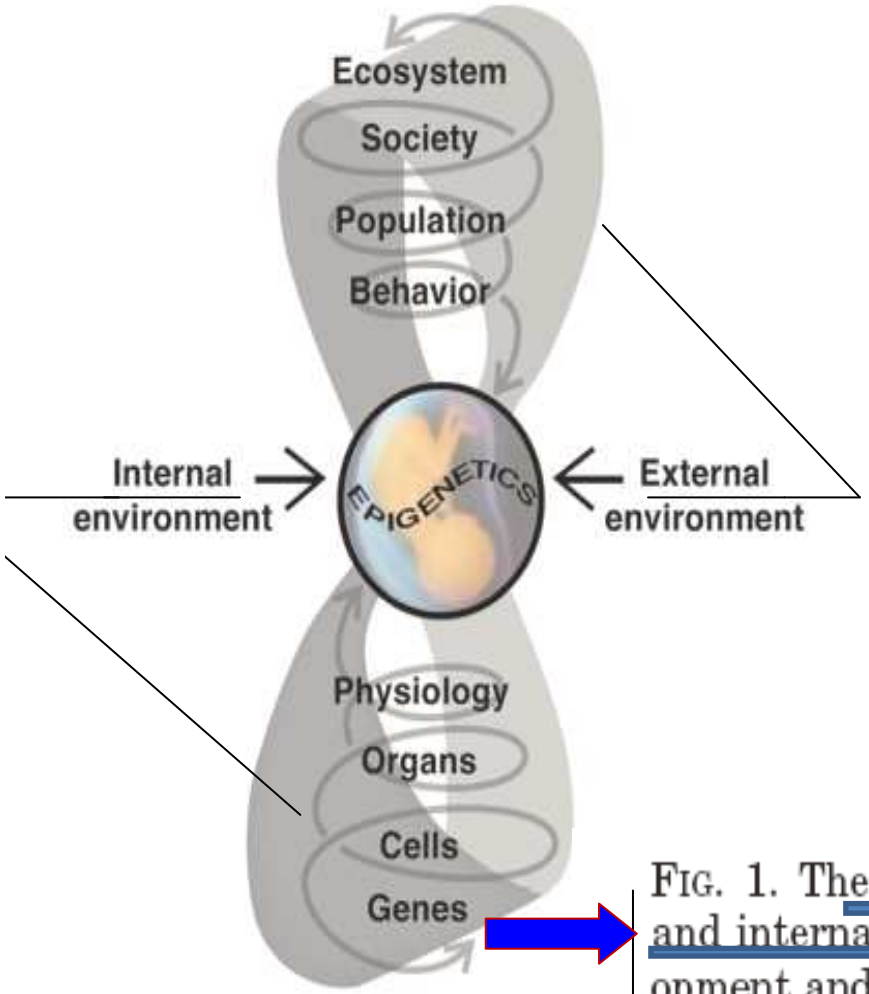
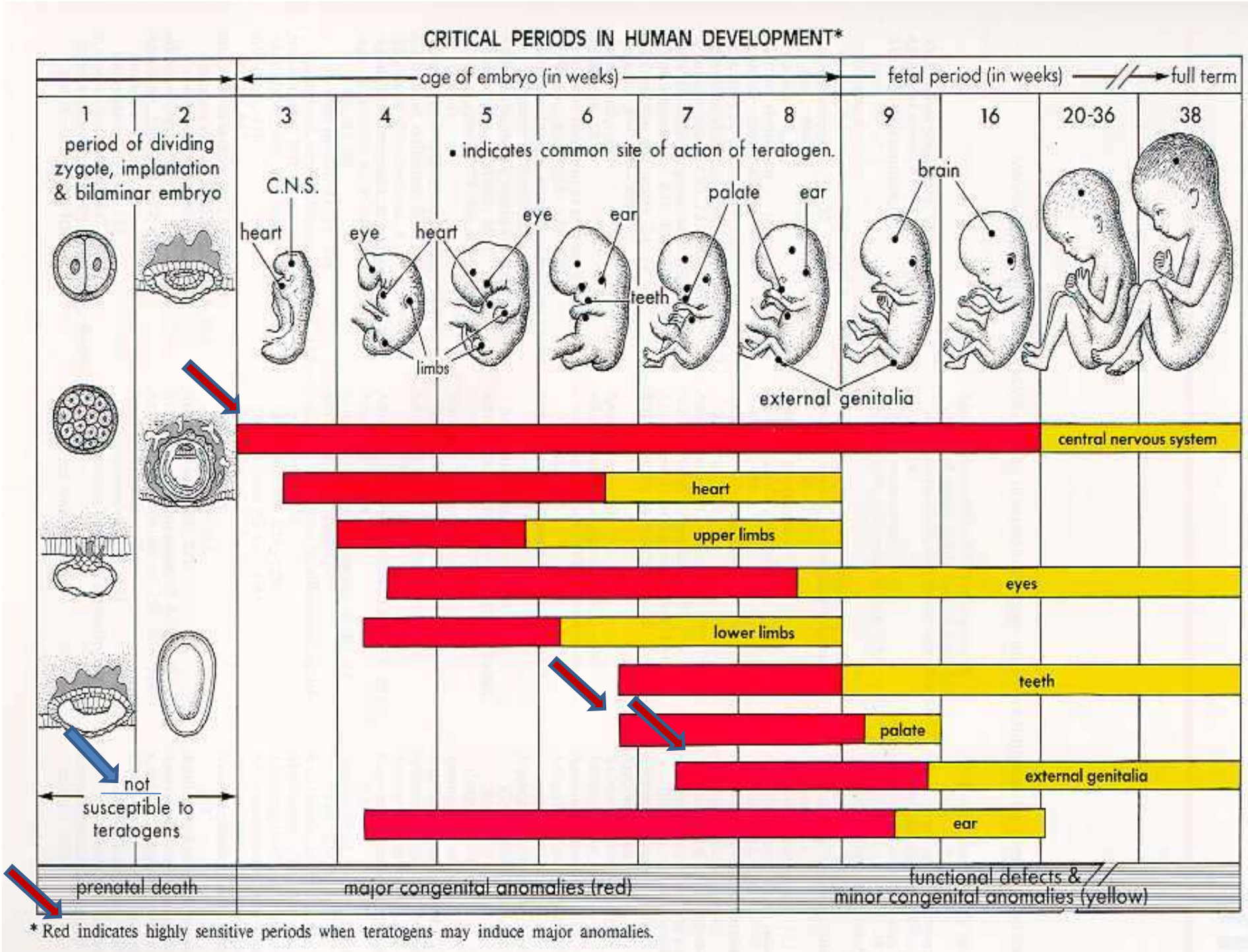


FIG. 1. The fetus is particularly vulnerable to changes in the external and internal environments, which interact to influence fetal development and have both immediate and life-long consequences. Such environmentally induced changes can occur at all levels of biological organization, from the molecular 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.



* Red indicates highly sensitive periods when teratogens may induce major anomalies.

Endocrinology 147(6) (Supplement):S43–S49

doi: 10.1210/en.2005-1058

Epigenetic Transgenerational Actions of Endocrine Disruptors

Matthew D. Anway and Michael K. Skinner

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

Epigenetics is defined as the molecular phenomena that regulate gene expression without alterations to the DNA sequence (1). The most studied epigenetic modification is DNA methylation of CpG nucleotides that are essential for mammalian development (2–5). DNA methylation of CpG sites is used by mammals to regulate transcription of genes, alter chromosomal positioning, influence X-chromosome inactivation, control imprinted genes, and repress parasitic DNAs (1, 5–9). Alterations in the DNA methylation state can lead to multiple disease states including cancers (10, 11), Rett syndrome, and Prader-Willi/An-

the true risk:
transgenerational
amplification

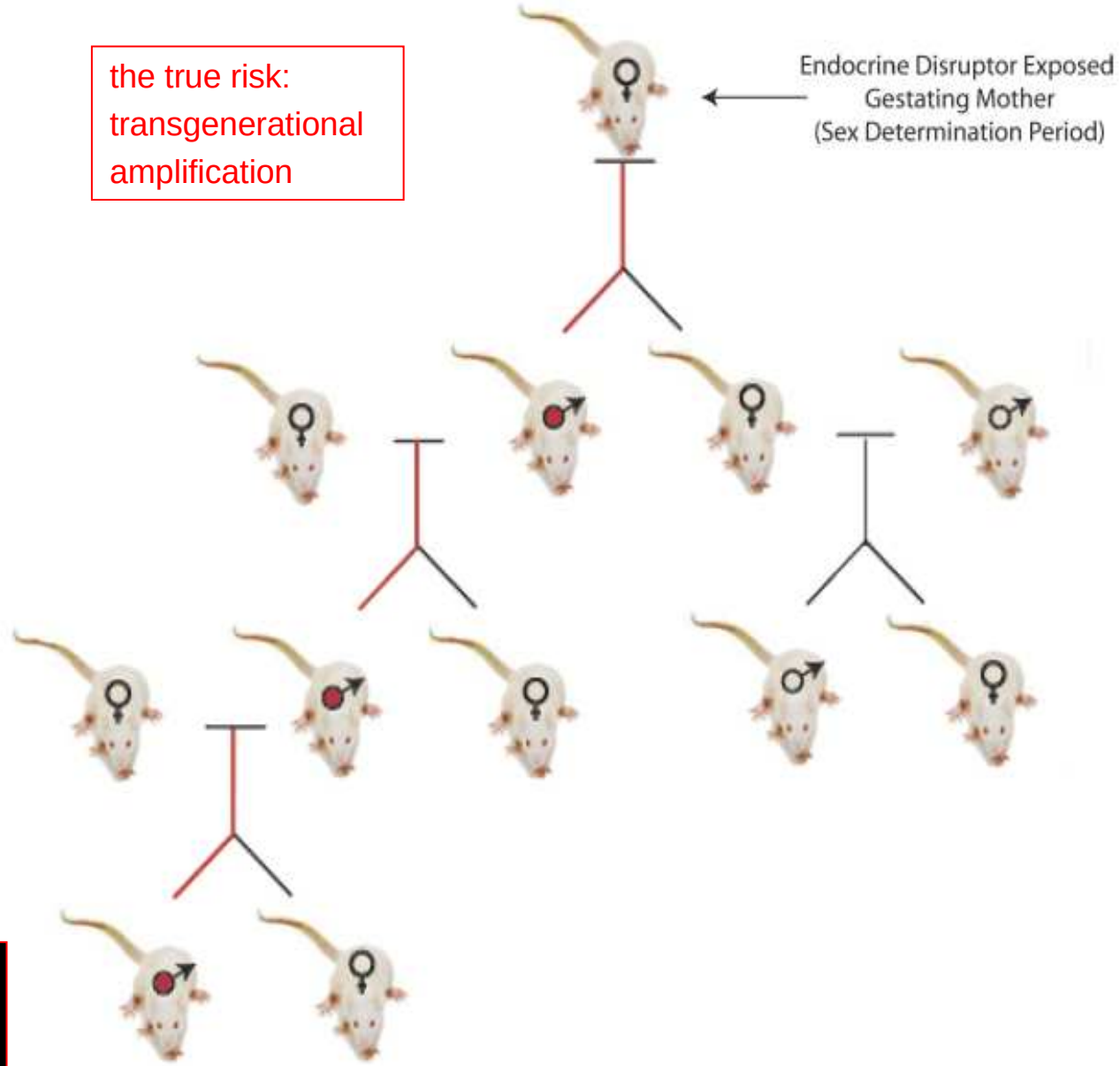


FIG. 1. Epigenetic transgenerational actions of endocrine disruptors through the male germ line.

Trasmissione ed
amplificazione
transgenerazionale
del danno

- I dati del ***Centro nascite di Augusta*** dimostrano un **aumento progressivo del numero dei nati con difetti congeniti**:

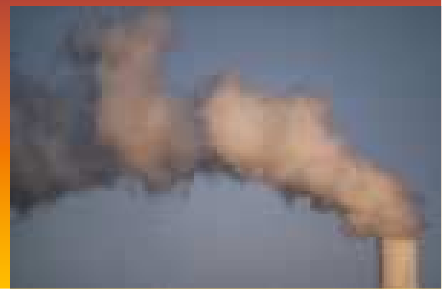
  si passa dall' 1,5% dell''80

  a una media del 3% dei primi anni '90,

  a una media del **3,5%** del '96-'97-'98

- fino ad **un picco del 5,6% del 2000.**

Trasmissione ed amplificazione transgenerazionale del danno



C

Systemic Flogosis

- Per quanto concerne infine quello che abbiamo assunto come **terzo modello patogenetico**

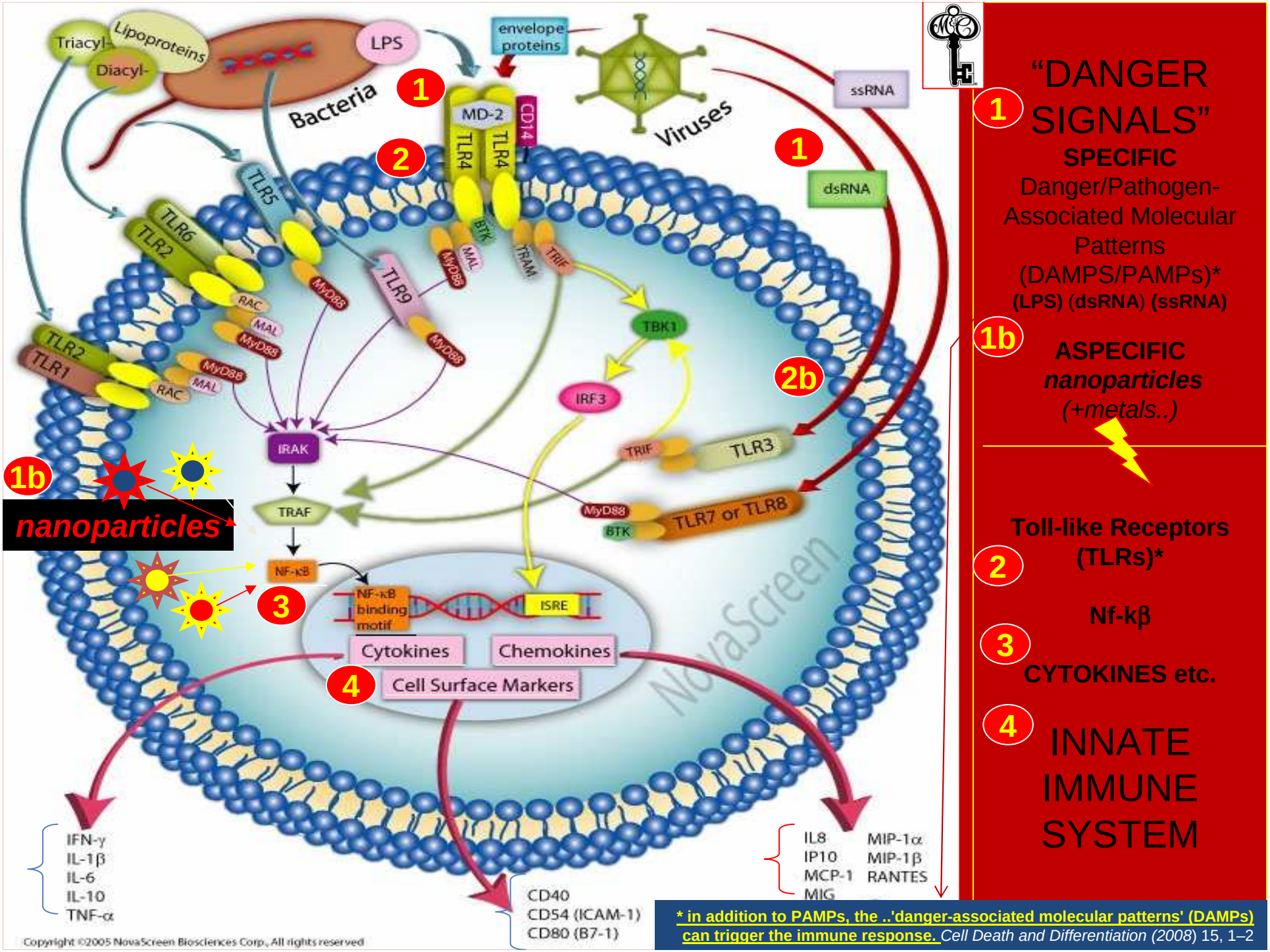
si tratta di un **meccanismo essenzialmente reattivo a condizioni ambientali alterate che possono intervenire in tutte le fasi** della vita dell'organismo
(ed è noto che la gran parte dei tessuti e organi degli organismi complessi reagiscono in modo simile a fattori di ordine **chimico-fisico o biologico** che potrebbero interferire negativamente sul loro assetto/equilibrio)

- Ancora **più ampio ed inclusivo** del paradigma, essenzialmente immunologico, ***self/non self***,

che resta valido per ciò che concerne le relazioni tra organismi (*id est* tra molecole complesse di natura essenzialmente proteica, portatrici dell'individualità biologica) é

- il **paradigma molecolare della reattività a segnali di pericolo/*stress***, secondo cui le cellule componenti vari tessuti dell'organismo reagirebbero **a segnali chimico-fisici di *stress/pericolo*** attivando alcune ***pathways* biochimiche** diffuse e comuni a molte forme viventi ("*conservate*" nell'ambito dell'evoluzione) ed essenzialmente finalizzate a indurre l'espressione di proteine dotate di ***funzioni enzimatiche/riparative*** (come le ***proteine dello stress*** che collaborano a ristabilire un corretto *folding* proteico o gli enzimi ***di riparazione del Dna***) e reattive in senso lato (come ***citochine***, ***chemochine***, ***fattori di regolazione della proliferazione e/o della m***

Matzinger P (1994) **Tolerance, danger, and the extended family**. Annu Rev Immunol 12: 991–1045.



"DANGER SIGNALS"

1 **SPECIFIC** Danger/Pathogen-Associated Molecular Patterns (DAMPS/PAMPs)* **(LPS) (dsRNA) (ssRNA)**

1b **ASPECIFIC** ***nanoparticles*** *(+metals..)*

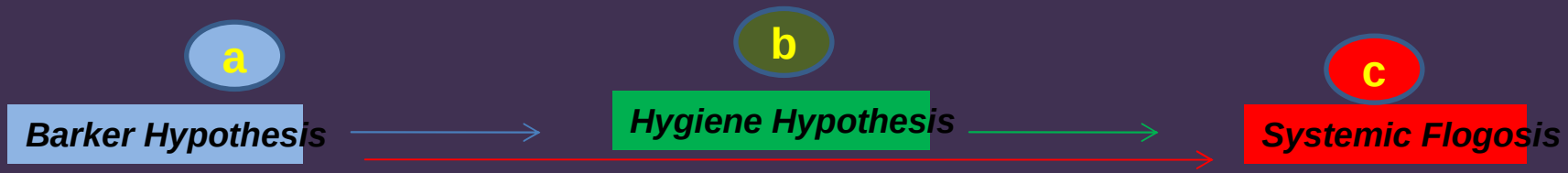
Toll-like Receptors (TLRs)*

2 **Nf-kβ**

3 **CYTOKINES etc.**

4 INNATE IMMUNE SYSTEM

*** in addition to PAMPs, the ..'danger-associated molecular patterns' (DAMPs) can trigger the immune response.** *Cell Death and Differentiation (2008)* 15, 1–2



- Un secondo punto chiave, per quanto concerne **i tre paradigmi,** consiste nel fatto che essi sono in grado di offrire una **spiegazione sensata, e già in larga misura documentata in ambito sperimentale/tossicologico ed epidemiologico**, circa l'incremento di quelle **patologie croniche (flogistico-degenerative e neoplastiche)**
che, come detto, caratterizza la **rivoluzione epidemica del XX secolo**
- **collegandole tra l'altro alla repentina trasformazione dell'ambiente** e, in particolare,
alla **trasformazione degli ecosistemi microbici** (*ipotesi igienica*); alla ***pressione* chimico-fisica** sull'**epigenoma** (*Barker Hypothesis*); alle modifiche in ultima analisi **epi-genetiche** conseguenti a condizioni di **stress chimico-fisico tissutale e cellulare protratto** (*paradigma flogisistico*).

E' importante sottolineare, insomma, come se il primo paradigma concerne essenzialmente
il **mutato *challenge* biologico** a cui sono esposti gli organismi nel mondo da noi trasformato e il secondo la sempre maggiore **pressione sull'epigenoma fetale di un ambiente**
chimico-fisico in continua trasformazione, il terzo paradigma rappresenti una sort di ***fattore complementare*** che contribuisce alla realizzazione di quanto i due meccanismi precedenti hanno preparato (e non mancano gli studi che dimostrano come alcuni "inquinanti" chimico-fisici sempre più diffusi – in particolare ***metalli***

VOLUME 115 | NUMBER 9 | September 2007 • Environmental Health Perspectives

Review

Environmental Exposures and Gene Regulation in Disease Etiology

Thea M. Edwards[1,2] *and John Peterson Myers*[2]

[1]Department of Zoology, University of Florida, Gainesville, Florida, USA; [2]Environmental Health Sciences, Charlottesville, Virginia, USA

DATA SYNTHESIS: Pharmaceuticals, pesticides, air pollutants, industrial chemicals, heavy metals, hormones, nutrition, and behavior can change gene expression through a broad array of gene regulatory mechanisms. Mechanisms include regulation of gene translocation, histone modifications, DNA methylation, DNA repair, transcription, RNA stability, alternative RNA splicing, protein degradation, gene copy number, and transposon activation. Furthermore, chemically induced changes in gene regulation are associated with serious and complex human diseases, including cancer, diabetes and obesity, infertility, respiratory diseases, allergies, and neurodegenerative disorders such as Parkinson and Alzheimer diseases. One of the best-studied areas of gene regulation is epigenetics, especially DNA methylation. Our examples of environmentally induced changes in DNA methylation are presented in the context of early development, when methylation patterns are initially laid down. This approach highlights the potential role for altered DNA methylation in fetal origins of adult disease and inheritance of acquired genetic change.

1

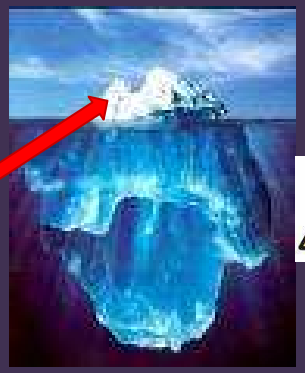
2

3

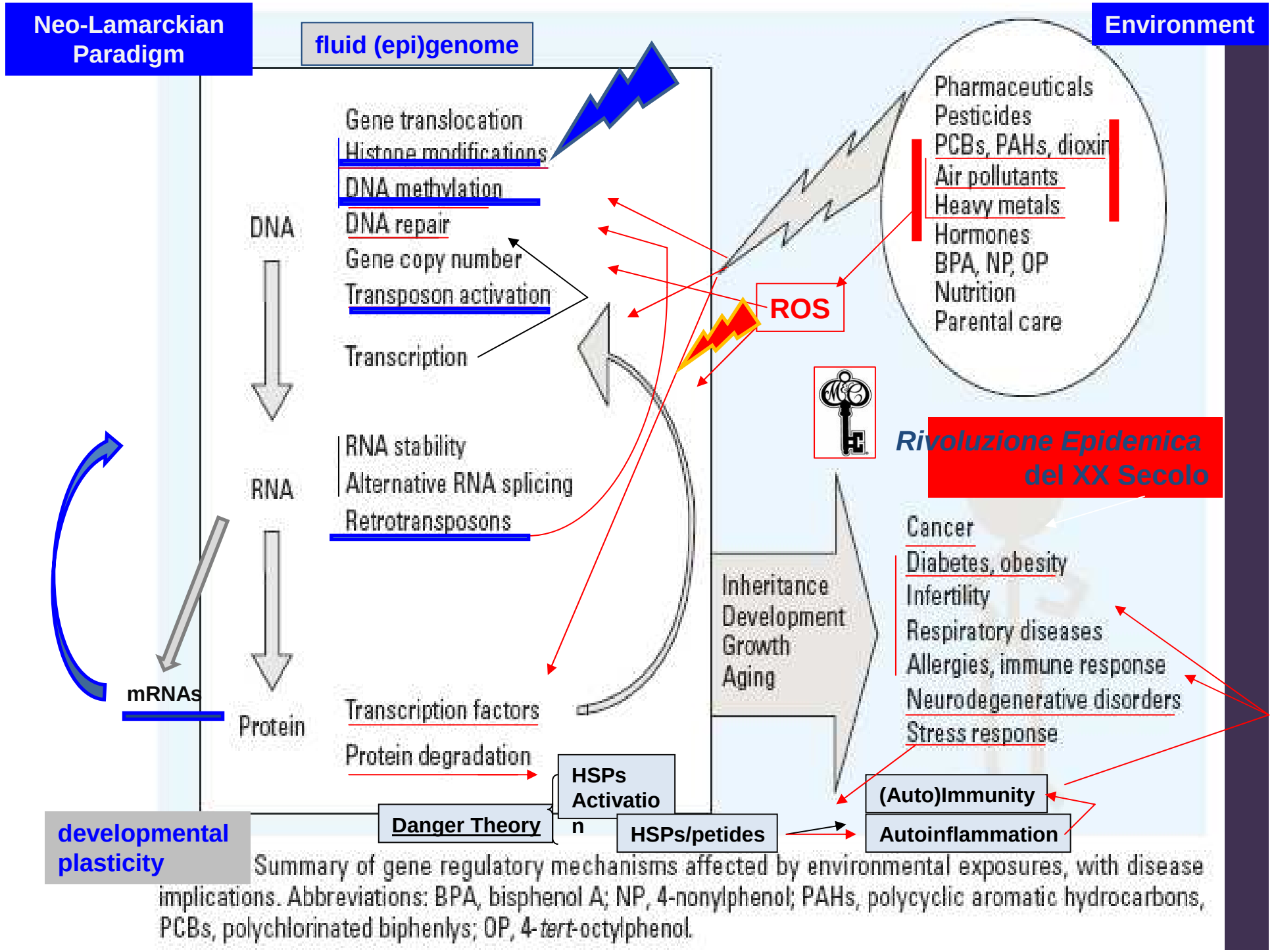
++ epigenetic patterns

Over the last 20 years, endocrine disruption research has shown how chemicals in our environment can profoundly affect development, growth, maturation, and reproduction by mimicking hormones or interacting with hormone receptors. One important mechanism of endocrine disruption is altered gene expression, mediated by inappropriate activation or deactivation of receptors that act as transcription factors.

Yet, receptor-mediated changes in gene expression are just the tip of the iceberg.



The purpose of this review is to identify points of gene expression regulation, occurring along the process described by the central dogma (DNA → RNA → protein), that have been shown to be affected by environmental factors, particularly contaminants (Figure 1). We have drawn on research that shows a strong connection between environmentally induced changes in gene regulatory mechanisms and disease etiology (Figure 1).



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

- Già sulle basi di quanto detto fin qui dovrebbe essere evidente come **le attuali modalità di valutazione del rischio** siano **del tutto insufficienti**
  a valutare le conseguenze per i singoli individui, per le collettività,
  per la specie e per l'intera biosfera di un inquinamento sempre più ubiquitario e pervasivo connesso alla **continua immissione in ambiente**
  e catena alimentare di sostanze tossiche
- e che la suddetta **Rivoluzione epidemica del XX secolo**, se interpretata come il portato di una **troppo repentina trasformazione ambientale** e della diffusione capillare di **migliaia di molecole di sintesi in grado di interferire con gli assetti epi-genomici programmatici fetali**, è di per se stessa [illegible] significativo e sintomatico di uno ***stress (epi)-genomico e bio-evolutivo*** che coinvolge l'intera specie (e l'intera biosfera).

XENO-BIOTICI

PARTE II: gli effetti..

Low and Very Low Birth Weight in Infants Conceived with Use of Assisted Reproductive Technology

N ENGL J MED 356;4 WWW.NEJM.ORG JANUARY 25, 2007

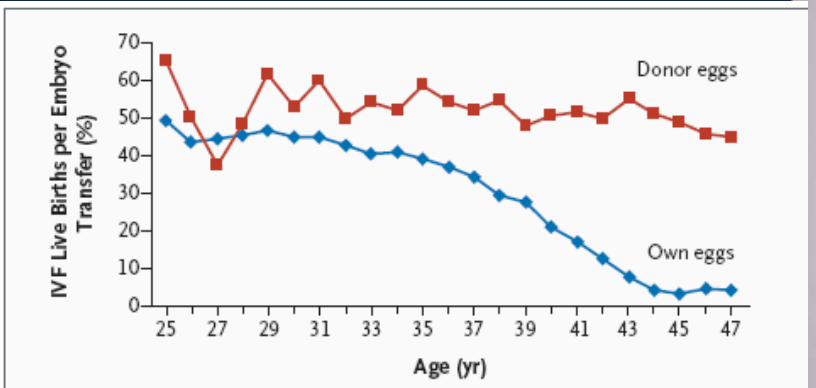
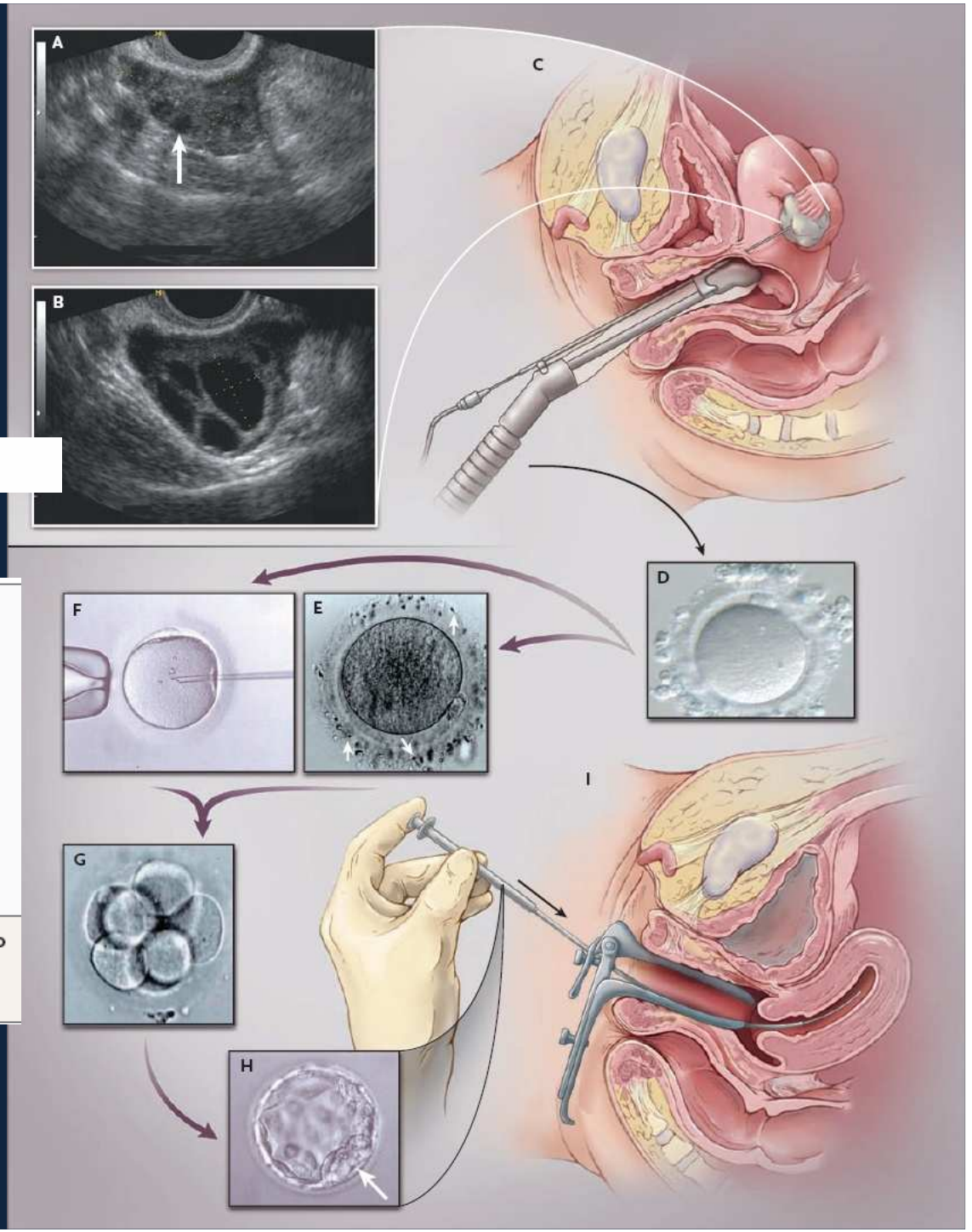


Figure 2. Effect of a Woman's Age on the Rate of Live Births per IVF Embryo Transfer.

Data are for the United States in 2003.[8]



cent confidence interval, 2.4 to 2.7). The use of assisted reproductive technology was associated with an increased rate of multiple gestations; however, its use was not associated with a further increase in the risk of low birth weight in multiple births. Among twins, the ratio of the rate of low birth weight after the use of assisted reproductive technology to the rate in the general population was 1.0 (95 percent confidence interval, 1.0 to 1.1). Infants conceived with assisted reproductive technology accounted for 0.6 percent of all infants born to mothers who were 20 years of age or older in 1997, but for 3.5 percent of low-birth-weight and 4.3 percent of very-low-birth-weight infants.

Conclusions The use of assisted reproductive technology accounts for a disproportionate number of low-birth-weight and very-low-birth-weight infants in the United States, in part because of absolute increases in multiple gestations and in part because of higher rates of low birth weight among singleton infants conceived with this technology. (N Engl J Med 2002;346:731-7.)

ART

SGA

Epigenetic perturbations early in life

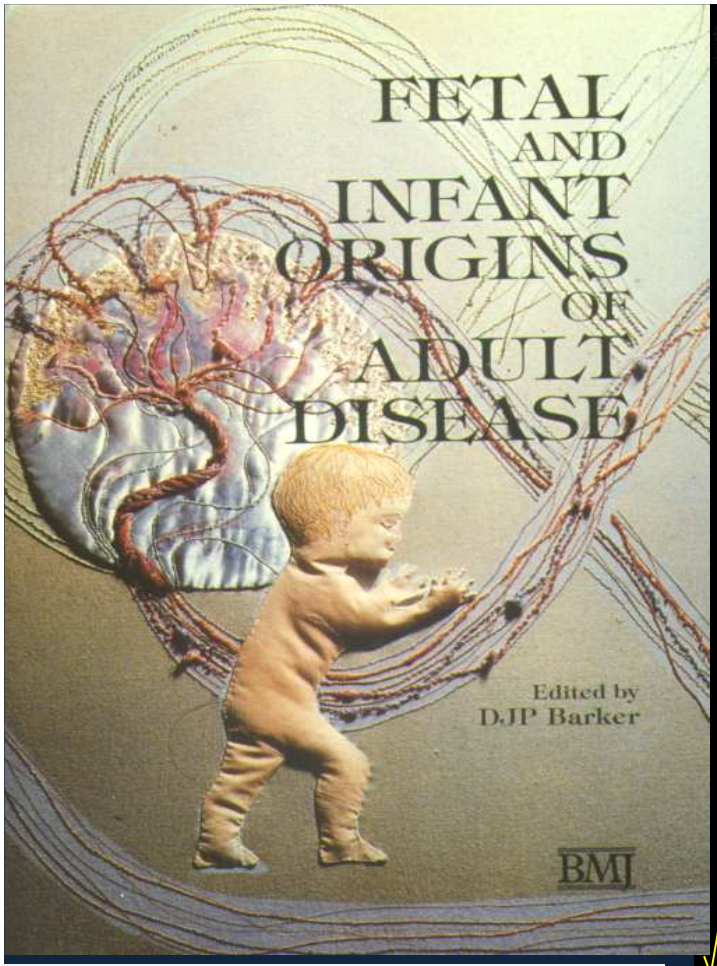
Assisted reproductive technology

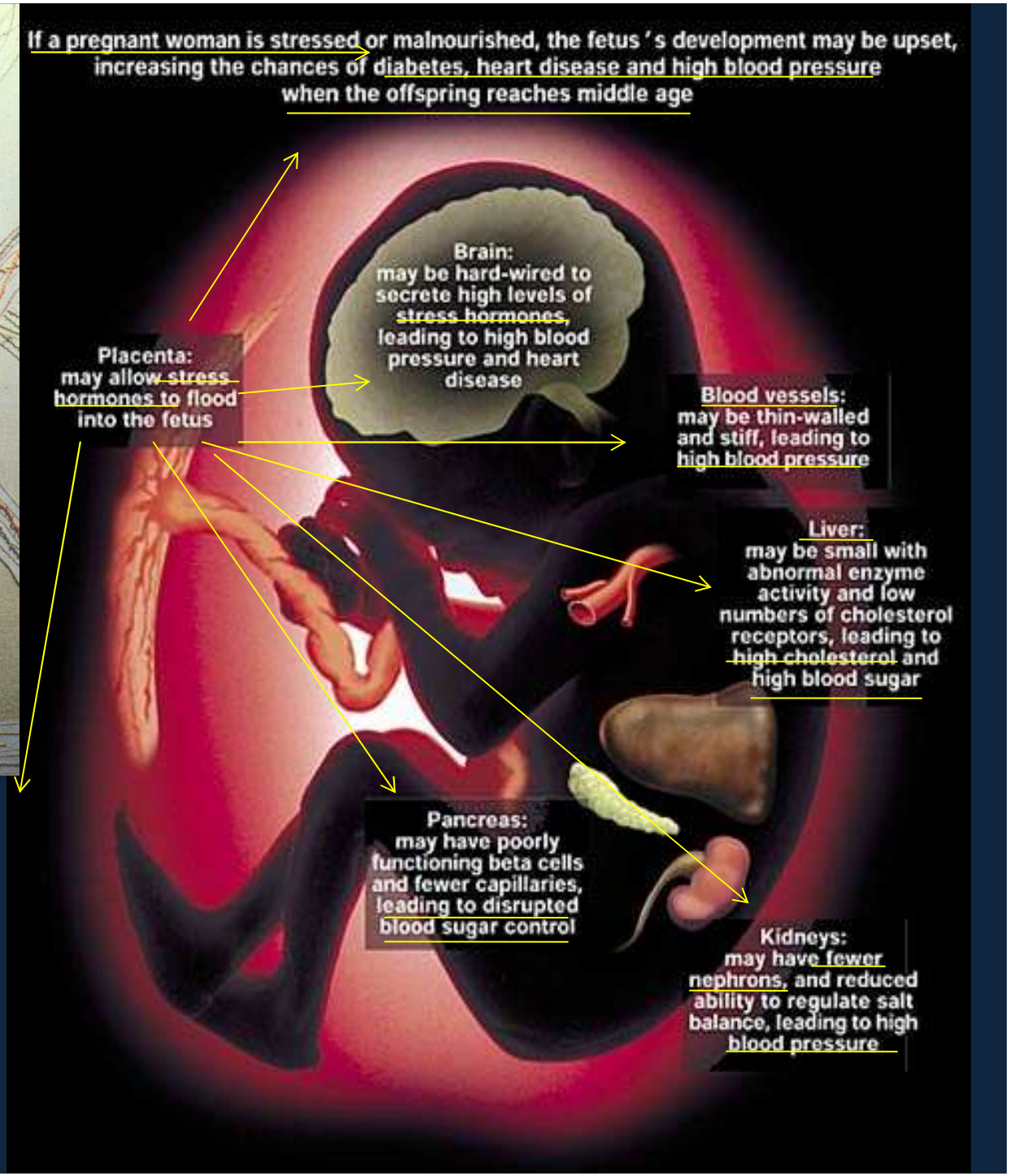
Epigenetic mechanisms regulate DNA accessibility throughout a person's lifetime. Immediately following fertilization, the paternal genome undergoes rapid DNA demethylation and histone modifications.[27] The maternal genome is demethylated gradually, and eventually a new wave of embryonic methylation is initiated that establishes the blueprint for the tissues of the developing embryo. As a result, each cell has its own epigenetic pattern that must be carefully maintained to regulate proper gene expression. Perturbations in these carefully arranged patterns of DNA methylation and histone modifications can lead to congenital disorders and multisystem pediatric syndromes or predispose people to acquired disease states such as sporadic cancers and neurodegenerative disorders (Box 1).

Recent evidence suggests that the manipulation of embryos for the purposes of assisted reproduction or cloning may impose inherent risks to normal development. For example, assisted reproductive technologies (ARTs) have been linked to an increased risk of intrauterine growth retardation (odds ratio [OR] 1.59, 95% confidence interval [CI] 1.20–2.11), premature birth (< 33 weeks' gestation, OR 2.99, 95% CI 1.54–5.80; < 37 weeks' gestation, OR 1.93, 95% CI 1.36–2.74), low birth weight (< 1500 g, OR 3.78, 95% CI 2.20–5.75) and prenatal death (OR 2.40, 95% CI 1.59–3.63

CMAJ · JANUARY 31, 2006 · 174(3) | 341

Epigenetics and human disease





Glucocorticoids act at **cellular** and **molecular**
levels to alter cell function by changing the
expression of receptors, enzymes,
ion channels and transporters.
They also alter various **growth factors,**
cytoarchitectural proteins, binding proteins
and components of the intracellular
signalling pathways.
Glucocorticoids **act, directly, on genes**

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

In particolare è l'incremento delle **neoplasie infantili** il vero SEGNALE D'ALLARME.. Perché le neoplasie infantili non possono essere "archiviate" come il portato di un **accumulo parafisiologico (legato all'aumento dell'età media) di lesioni ossidative a carico del DNA**.. Perché, ancora una volta, sono il segno di una possibile **amplificazione transgenerazionale del danno**

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Environmental Research 105 (2007) 414–429
Environmental Research
www.elsevier.com/locate/envres

Review

The multitude and diversity of environmental carcinogens

D. Belpomme[a,b,*], P. Irigaray[b], L. Hardell[c], R. Clapp[d], L. Montagnier[e], S. Epstein[f], A.J. Sasco[g]

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[b]*Cancer Research Center, Association for Research and Treatments Against Cancer (ARTAC), F-75015 Paris, France*
[c]*Department of Oncology, University Hospital, Orebro, Sweden Department of Natural Sciences, Orebro University, Orebro, Sweden*
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[e]*World Foundation for AIDS Research and Prevention, UNESCO, F-75008 Paris, France*
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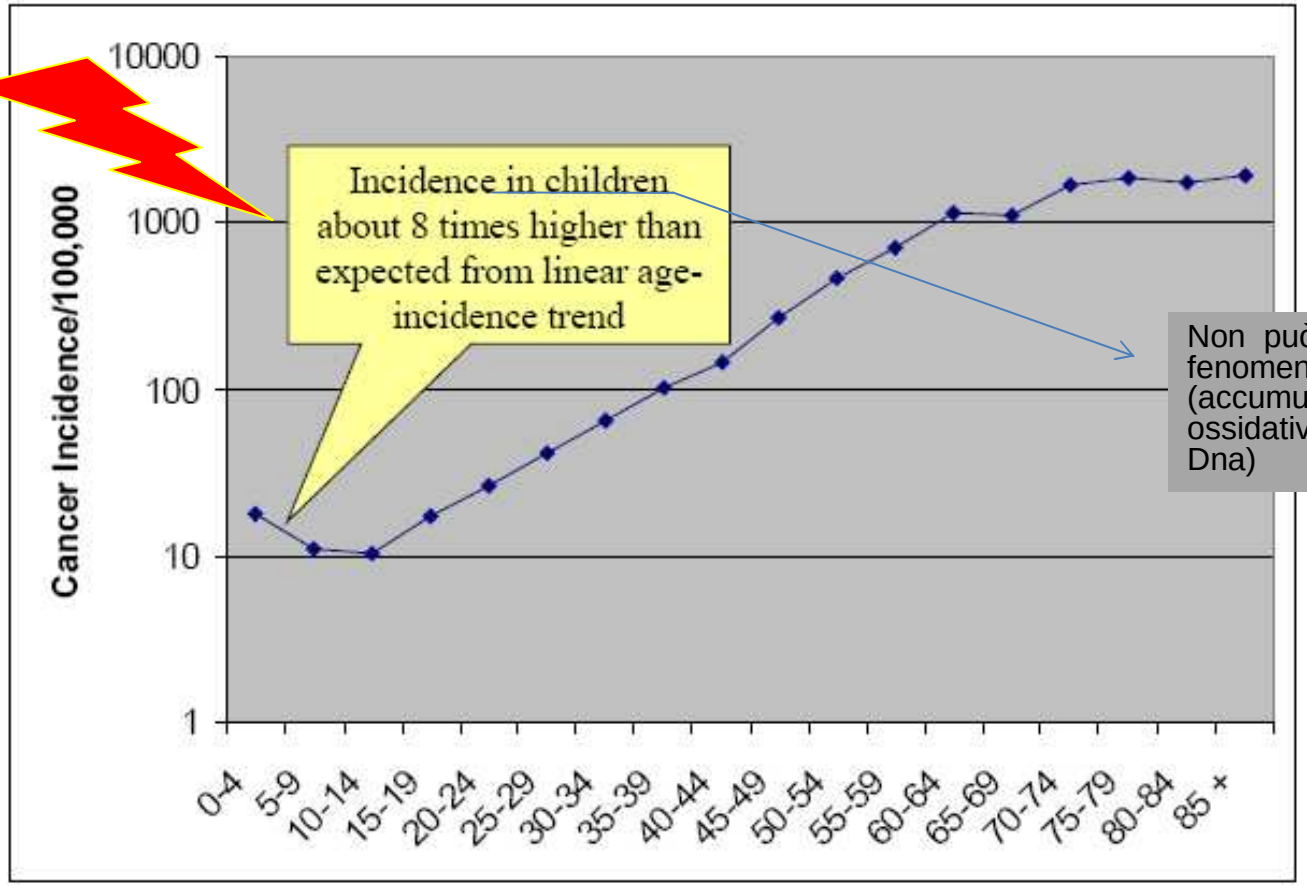
Received 4 January 2007; received in revised form 25 June 2007; accepted 5 July 2007
Available online 9 August 2007

We have recently proposed that lifestyle-related factors, screening and aging cannot fully account for the present overall growing incidence of cancer. In order to propose the concept that in addition to lifestyle related factors, exogenous environmental factors may play a more important role in carcinogenesis than it is expected, and may therefore account for the growing incidence of cancer, we overview herein environmental factors, rated as certainly or potentially carcinogenic by the International Agency for Research on Cancer (IARC).

We thus analyze the carcinogenic effect of microorganisms (including viruses), radiations (including radioactivity, UV and pulsed electromagnetic fields) and xenochemicals. Chemicals related to environmental pollution appear to be of critical importance, since they

Cancer Incidence by Age



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

Austria, 2003

Childhood Leukaemia

- Overall only about 10-20% of childhood ALL can be attributed to environmental risk factors
- Considering potential combined effects as suggested by similar pathways of some identified risk factors the attributable fraction may be somewhat higher
- One key element seems to be error-prone NHEJ during double-strand break repair

Cancer in Childhood

Prenatal origin of certain childhood leukaemias

- There is evidence that at least one stage of the malignant process is already present at time of birth
  - twin studies of acute lymphocytic leukaemia
  - umbilical cord samples
- Higher turn-over rate of stem cells increases the likelihood of further genetic events

Oil combustion and childhood cancers

E G Knox

J. Epidemiol. Community Health 2005;59;755-760
doi:10.1136/jech.2004.031674

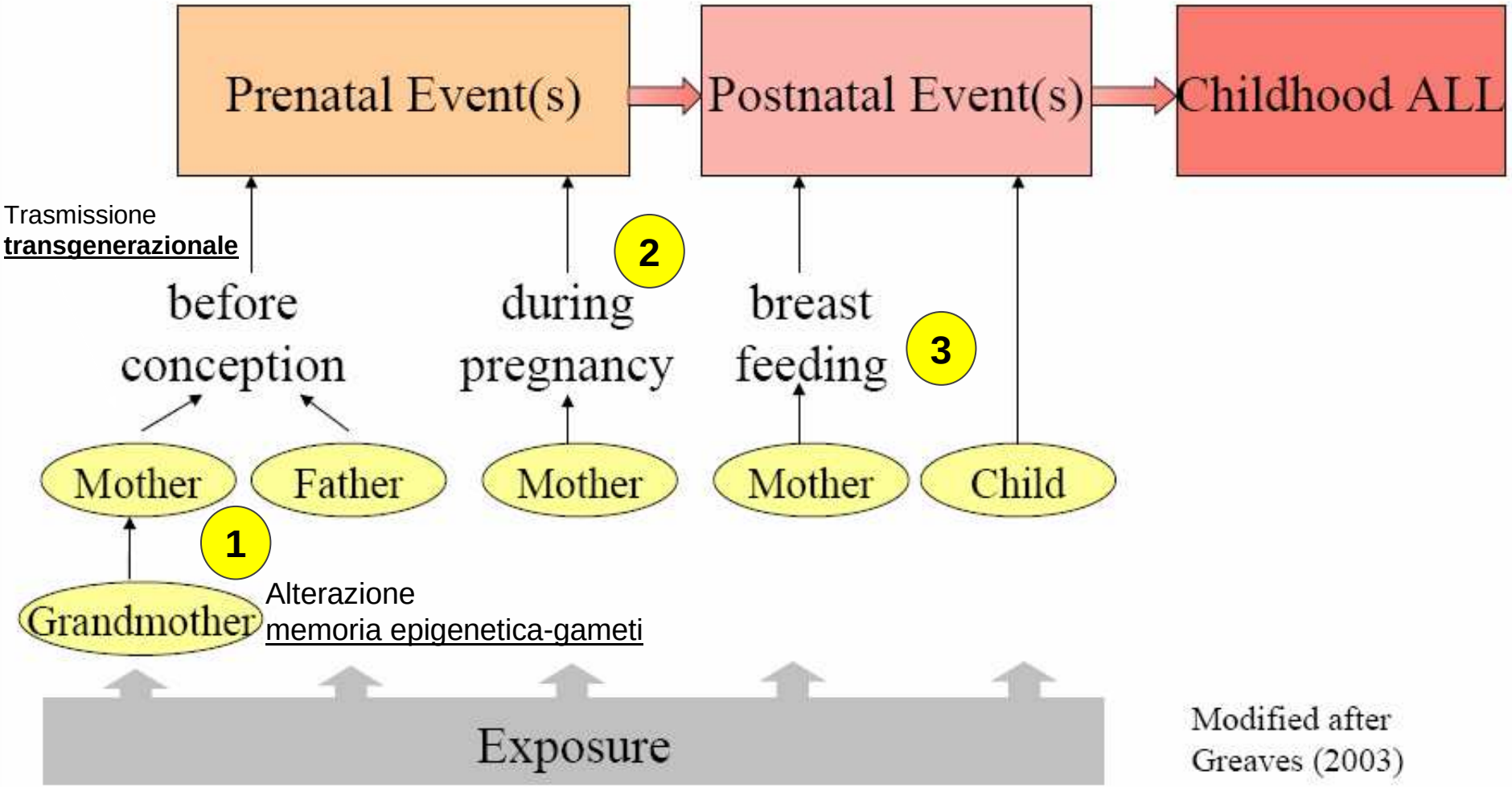
Study objectives: To identify specific toxic atmospheric emissions and their industrial sources in Great Britain. To link them with each other and with the birth addresses of children dying from cancer. To identify specific causal agents and sources.

Design: Birth and death addresses of children dying from cancer were linked to emissions hotspots for specific chemicals: and to related source installations. Among those who moved house, distances from each address to the nearest hazard were compared. Relative excesses of close-to-hazard birth addresses showed high prenatal or early postnatal risks. Relative risks for individual and for combined exposures were measured.

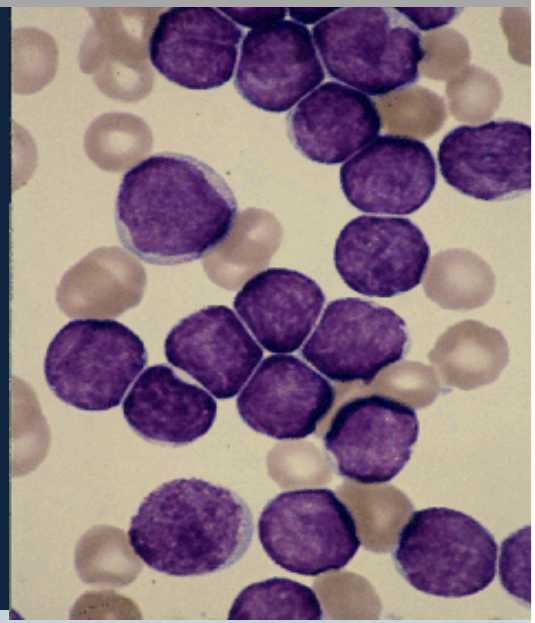
Main results: There were excess relative risks (RR) within 0.3 km of hotspots for carbon monoxide, PM10 particles, nitrogen oxides, 1,3-butadiene, benzene, dioxins, benzo(a)pyrene, and volatiles; and within 1.0 km of bus stations, hospitals, heavy transport centres, railways, and oil installations. Some excesses were attributable to mutual confounding, but 1,3-butadiene and carbon monoxide, mainly derived from engine exhausts, were powerful independent predictors. They were strongly reinforced when associated with bus stations, hospitals, railways, oil installations, and industrial transport centres; RR = 12.6 for joint <0.5 km exposure to bus stations and 1,3-butadiene.

Conclusions: Childhood cancers are strongly determined by prenatal or early postnatal exposures to oil based combustion gases, especially from engine exhausts. 1,3-butadiene, a known carcinogen, may be directly causal.

Model of Childhood ALL



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) *L.Tomatis*



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

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

COMMENTARY

Transgeneration transmission of carcinogenic risk

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

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

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

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

AACR Meeting Abstracts Online

PEDIATRIC CANCER BIOLOGY AND MOLECULAR ONCOLOGY: POSTER PRESENTATIONS:

Katherine La Fiura, Dawn Bielawski, Norberto Posecion, Enrique Ostrea, Larry Matherly, Jeffrey Taub, and Yubin Ge

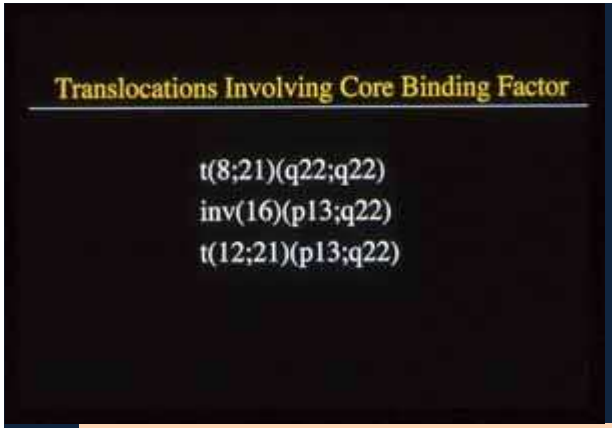
Prenatal pesticide exposure and the generation of leukemia-associated t(8;21)

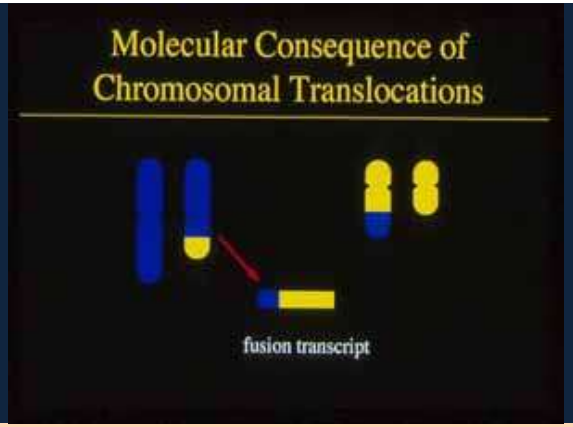
AACR Meeting Abstracts, Apr 2007; 2007: 1794.

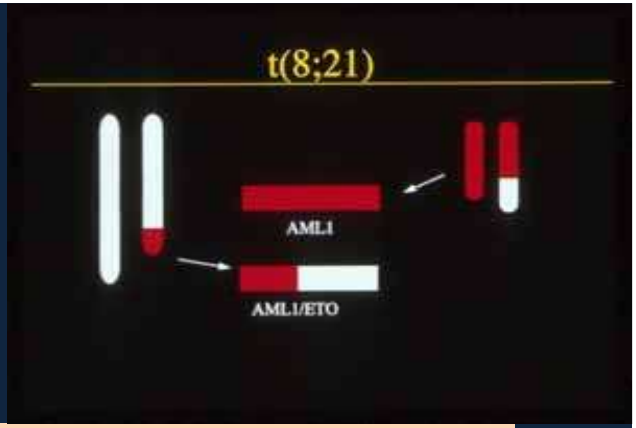
1 **t(8;21)(q22;q22)** is a balanced translocation between chromosomes 8 and 21, resulting in the fusion of the 5' end of the **AML1** gene normally located on chromosome 21q22 with the 3' end of the **ETO** gene on chromosome 8q22. t(8;21) **is one of the most common cytogenetic abnormalities in childhood acute myeloid leukemia (AML),** present in ~12% of cases and has been considered a favorable prognostic factor in some studies. We previously reported a wide range of AML1-ETO (**A1E**) transcript levels in primary t(8;21) AMLs and identified numerous *in-frame* and *out-of-frame* AML1b-ETO **(A1bE)** and AML1c-ETO (**A1cE**) transcript forms, **likely resulting from *alternate splicing*, *internal deletions*, and/or *breakpoint region insertions* involving both the AML1 and ETO regions.** ….

2
- t(8;21) leukemic clones were detected retrospectively in dried blood spots in children with AML, confirming **an *in utero* origin for childhood leukemia cases and suggesting that *in utero* exposures may initiate a multi-step process of leukemogenesis**.

3
- In one study, **occupational exposure to benzene was associated with a higher frequency (up to 15-fold) of detecting A1E fusion transcripts** resulting from t(8;21) in blood samples compared to a lower-exposed group. This suggests **that environmental exposures may lead to the generation of t(8;21) transcripts.**







- In the present study using **umbilical cord blood samples obtained from infants whose prenatal exposure to the pesticide, *propoxur***, was determined by meconium analysis, we showed that

4 **(i) incidence of t(8;21) in the exposed group is 2-fold higher** than that in the unexposed group; and

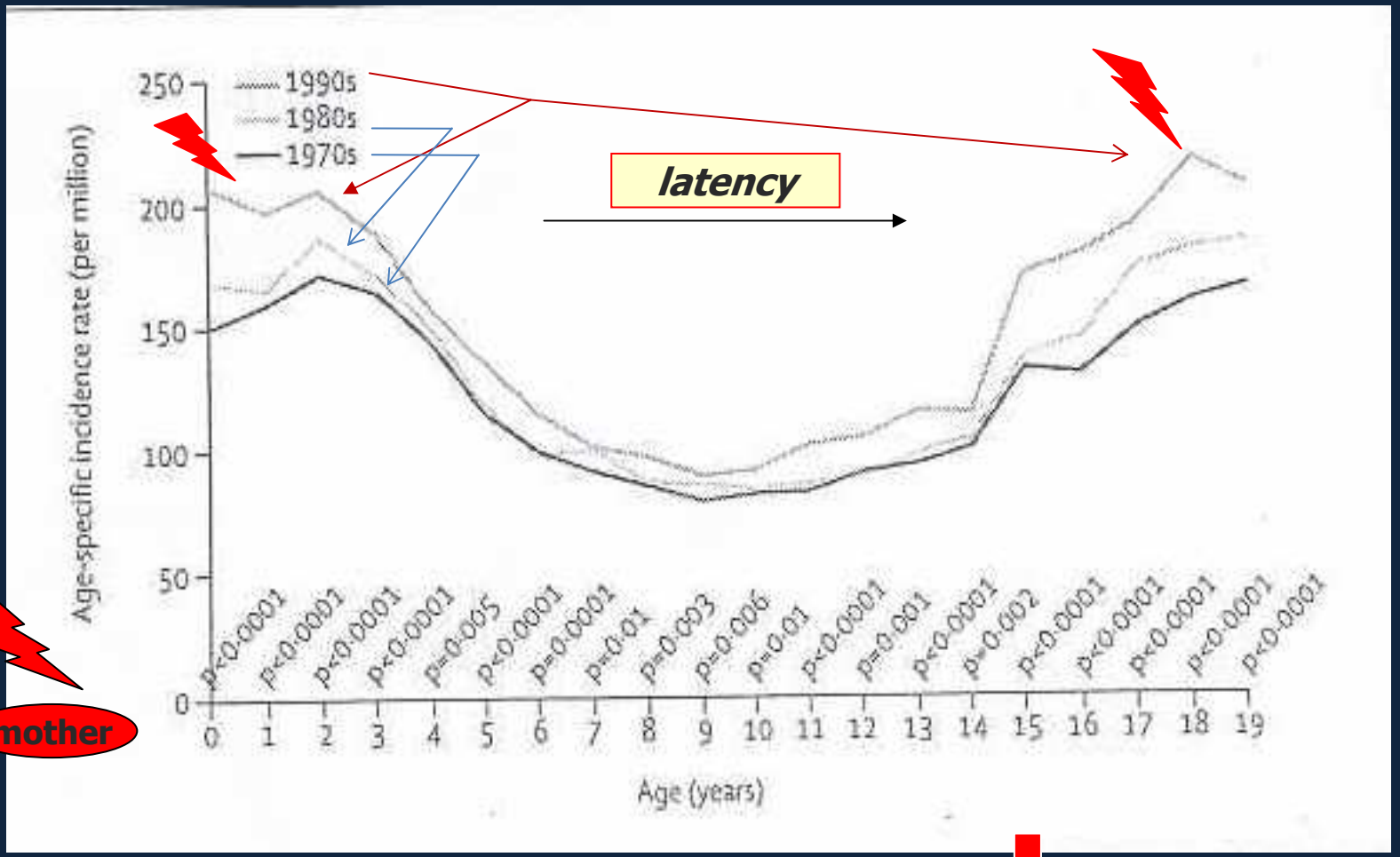
(ii) the **levels for AML1-ETO fusion transcripts resulting from t(8;21)** positively correlated with ***propoxur*** concentrations in meconium. These results further **confirm the prenatal origin of t(8;21) and establish a significant correlation between prenatal pesticide exposures** and the generation of t(8;21).

5 **(iii) novel *in-frame* and *out-of-frame* A1E fusion transcript forms** previously identified in primary t(8;21) AML samples were detected in the t(8;21) positive cord blood samples.

6 In co-transfection experiments, **the different A1E proteins showed various effects on AML1b transactivation of GM-CSF**.

- Our results further establish the remarkable heterogeneity in A1E fusion transcripts in t(8;21) myeloblasts and suggest that **synthesis of alternate A1E transcript and protein forms can significantly impact the regulation of AML1 responsive genes**. Further, they indicate the previously reported **novel A1E fusion transcripts can arise *in utero* and may play an important role in AML leukemogenesis**.

INCIDENZA DI **NEOPLASIE NELL'INFANZIA E NELL'ADOLESCENZA** IN EUROPA (anni 1970-1999)



mother

(Lancet, Dic. 2004)

EUROPEAN JOURNAL OF CANCER 42 (2006) 1961–1971

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Time trends of cancer incidence in European children (1978–1997): Report from the Automated Childhood Cancer Information System project

Peter Kaatsch[a,*], Eva Steliarova-Foucher[b], Emanuele Crocetti[c], Corrado Magnani[d], Claudia Spix[a], Paola Zambon[e]

[a]German Childhood Cancer Registry (GCCR), Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University of Mainz, 55101 Mainz, Germany

[b]Descriptive Epidemiology Group, International Agency for Research on Cancer (IARC), Lyon, France

[c]Tuscany Cancer Registry, Firenze, Italy

[d]Childhood Cancer Registry of Piedmont, CPO-Piemonte, CERMS and University of East Piedmont, Novara, Italy

[e]Veneto Cancer Registry University of Padua, IOV, Italy

Within the framework of the Automated Childhood Cancer Information System (ACCIS), time trend analyses for childhood cancer were performed using data from 33 population-based cancer registries in 15 European countries for the period 1978–1997. The overall incidence rate based on 77,111 cases has increased significantly ($P < 0.0001$), with an average annual percentage change (AAPC) of 1.1%. The rising trend was observed in all five geographical regions and in the majority of the disease groups (in order of AAPC): soft tissue sarcomas (1.8%), brain tumours, tumours of the sympathetic nervous system, germ-cell tumours, carcinomas, lymphomas, renal tumours, and leukaemias (0.6%). No change was seen in incidence of bone tumours, hepatic tumours and retinoblastoma. The increased incidence can only partly be explained by changes in diagnostic methods and by registration artefacts. The patterns and magnitude of these increases suggest that other factors, e.g. changes in lifestyle and in exposure to a variety of agents, have contributed to the increase in childhood cancer in the recent decades.

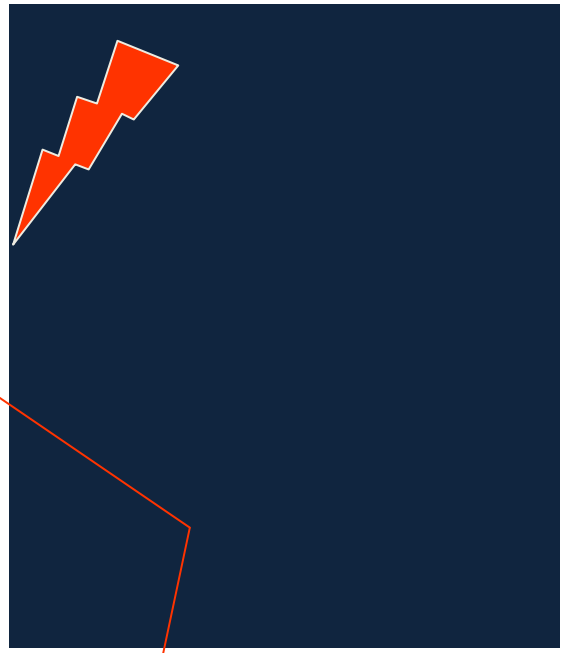

Table 4 – Average annual percent of change (AAPC) and result of trend test for childhood cancer (age 0–14 years) in Europe by age groups and sex for total cancer and main diagnostic groups (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.0001$) (1978–1997) (Source: ACCIS)

	AAPC for diagnostic groups												AAPC for total (%)
	Leu (%)	Ly (%)	CNS (%)	Symp (%)	Ret (%)	Ren (%)	Hep (%)	Bone (%)	Soft (%)	Germ (%)	Ca (%)	Oth (%)	
Age 0	0.6	−1.6	2.4***	2.2***	0.9	1.9*	1.5	−7.4	1.3	3.9***	−0.4	3.2	2.1***
Age 1–4 years	0.7***	0.6	1.8***	1.7***	0.4	0.8*	1.2	−0.5	1.9**	−0.1	0.6	−0.2	1.1***
Age 5–9 years	0.5*	0.7	1.6***	0.1	−0.6	0.5	−1.8	−1.2	1.3*	0.90	−0.9	1.0	0.8***
Age 10–14 years	0.5*	1.3***	1.7***	1.9	−6.0	0.5	0.3	0.2	2.6**	2.5***	2.2***	1.7	1.3***
Male	0.7***	0.5*	1.5***	1.5***	0.3	0.4	0.9	−0.3	1.7**	1.2*	1.2	0.2	0.9***
Female	0.6**	1.7***	2.0***	2.0***	0.7	1.3**	0.6	−0.2	2.0**	2.0***	1.3*	2.0	1.4***

Leu, leukaemias; Ly, lymphomas; CNS, CNS tumours; Symp, tumours of the sympathic nervous system; Ret, retinoblastoma; Ren, renal tumours; Hep, hepatic tumours; Bone, malignant bone tumours; Soft, soft tissue sarcomas; Germ, germ-cell tumours; Ca, carcinomas; Oth, other and unspecified malignant neoplasms.

EUROPEAN JOURNAL OF CANCER 42 (2006) 2136–2149

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Childhood soft tissue sarcomas incidence and survival in European children (1978–1997): Report from the Automated Childhood Cancer Information System project

Guido Pastore[a,b,*], *Rafael Peris-Bonet*[c], *Modesto Carli*[d], *Carmen Martínez-García*[e], *José Sánchez de Toledo*[f], *Eva Steliarova-Foucher*[g]

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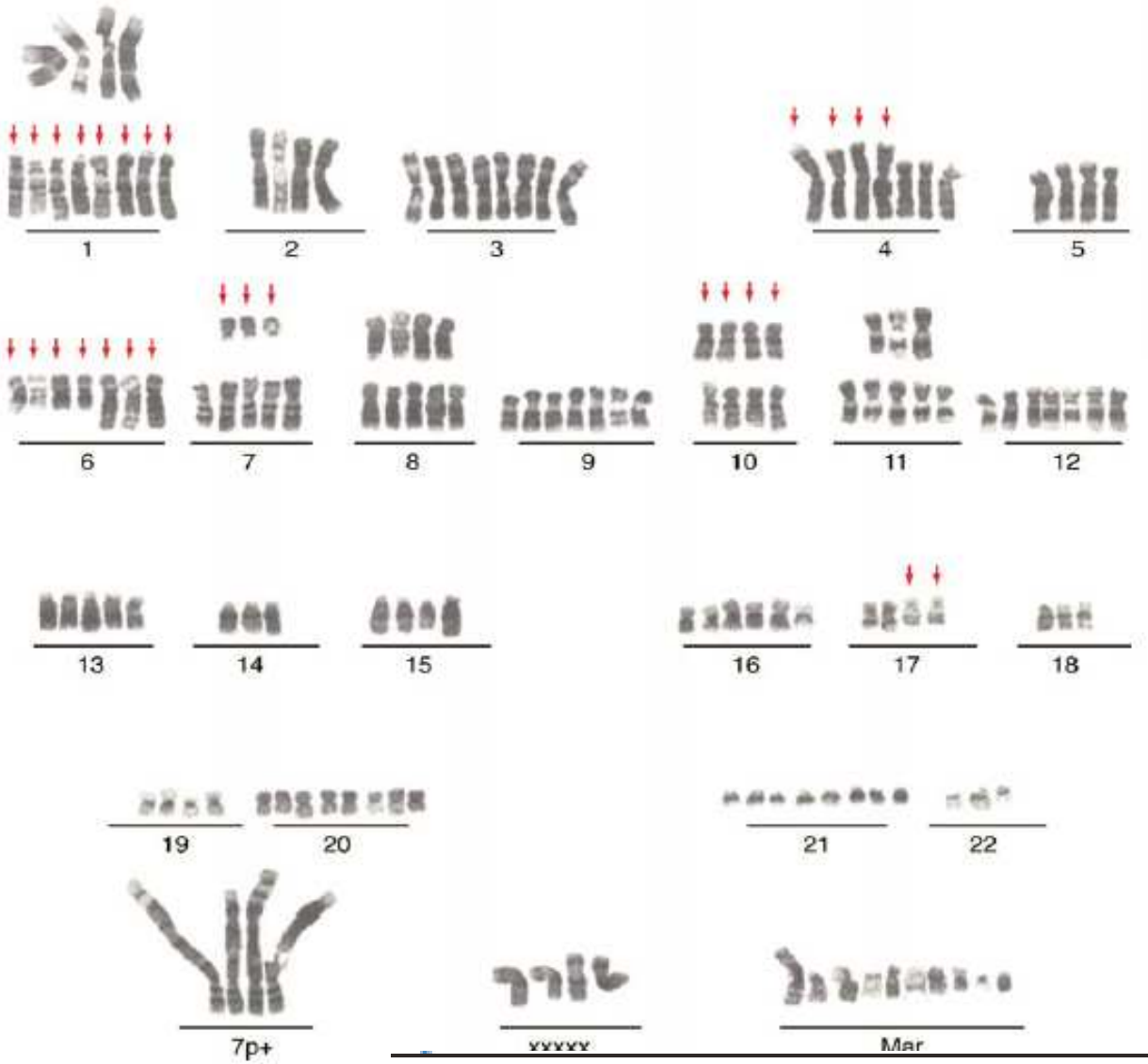
[b]Division of Pediatrics, Department of Medical Sciences, University of Piemonte Orientale, Novara, Italy
[c]National Childhood Cancer Registry, Spain (RNTI-SEOP) and Instituto López Piñero (CSIC-Universitat de València), Valencia, Spain
[d]Department of Paediatrics, Oncology/Haematology Division, University of Padova, Italy
[e]Granada Cancer Registry, Andalusian School of Public Health, Granada, Spain
[f]Paediatric Oncology and Haematology Unit, Hospital Infantil Vall d'Hebron, Barcelona, Spain
[g]Descriptive Epidemiology Group, International Agency for Research on Cancer, Lyon, France

Genetics of Soft Tissue Tumors

Matt van de Rijn[1] and Jonathan A. Fletcher[2]

[1]Department of Pathology, Stanford University Medical Center, Stanford, California 94305; email: mrijn@stanford.edu

[2]Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts 02115; email: jfletcher@partners.org



Karyotype of a low-grade leiomyosarcoma, showing a highly aneuploid cell with complex chromosomal aberrations. Red arrows indicate clonal chromosome rearrangements that were present in all cells analyzed from this tumor. "Mar" is an abbreviation for marker, which indicates an abnormal chromosome of uncertain origin. Chromosome rearrangements not designated by arrows (e.g., the bizarre chromosome 7 rearrangements at *lower left*) were not present in all of the tumor cells and reflect the genetic heterogeneity of this tumor.

EUROPEAN JOURNAL OF CANCER 42 (2006) 2050–2063

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Non-Hodgkin's lymphoma incidence and survival in European children and adolescents (1978–1997): Report from the Automated Childhood Cancer Information System project

M. Isabel Izarzugaza[a,*], *Eva Steliarova-Foucher*[b], *M. Carmen Martos*[c], *Snezana Zivkovic*[d]

[a]*Basque Country Health Department, Registro de Cáncer, Donostia-San Sebastian, 1. 01010 Vitoria-Gasteiz, Spain*
[b]*International Agency for Research on Cancer, 150 Cours Albert Thomas, Lyon, Cedex 08, France*
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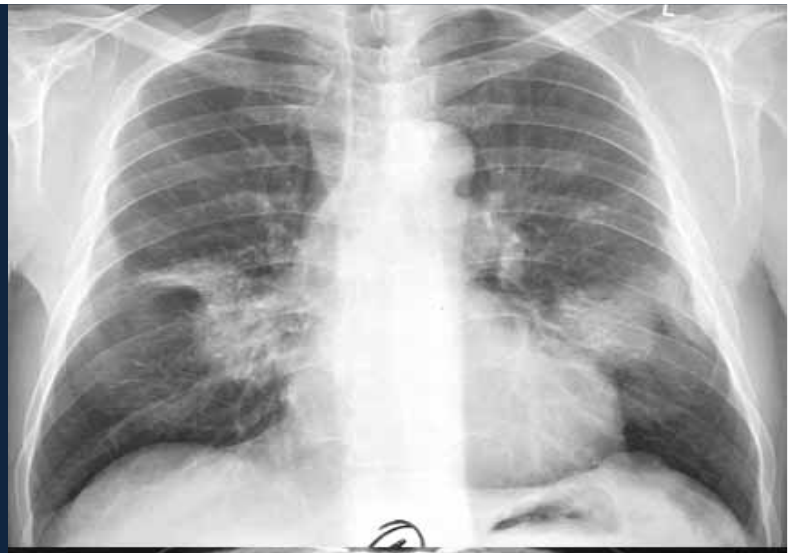
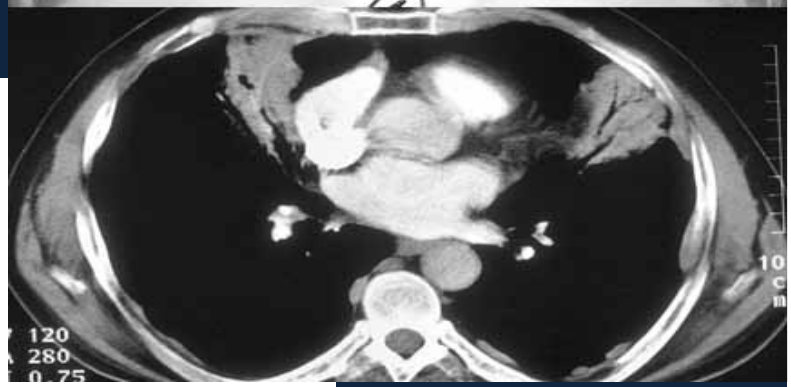
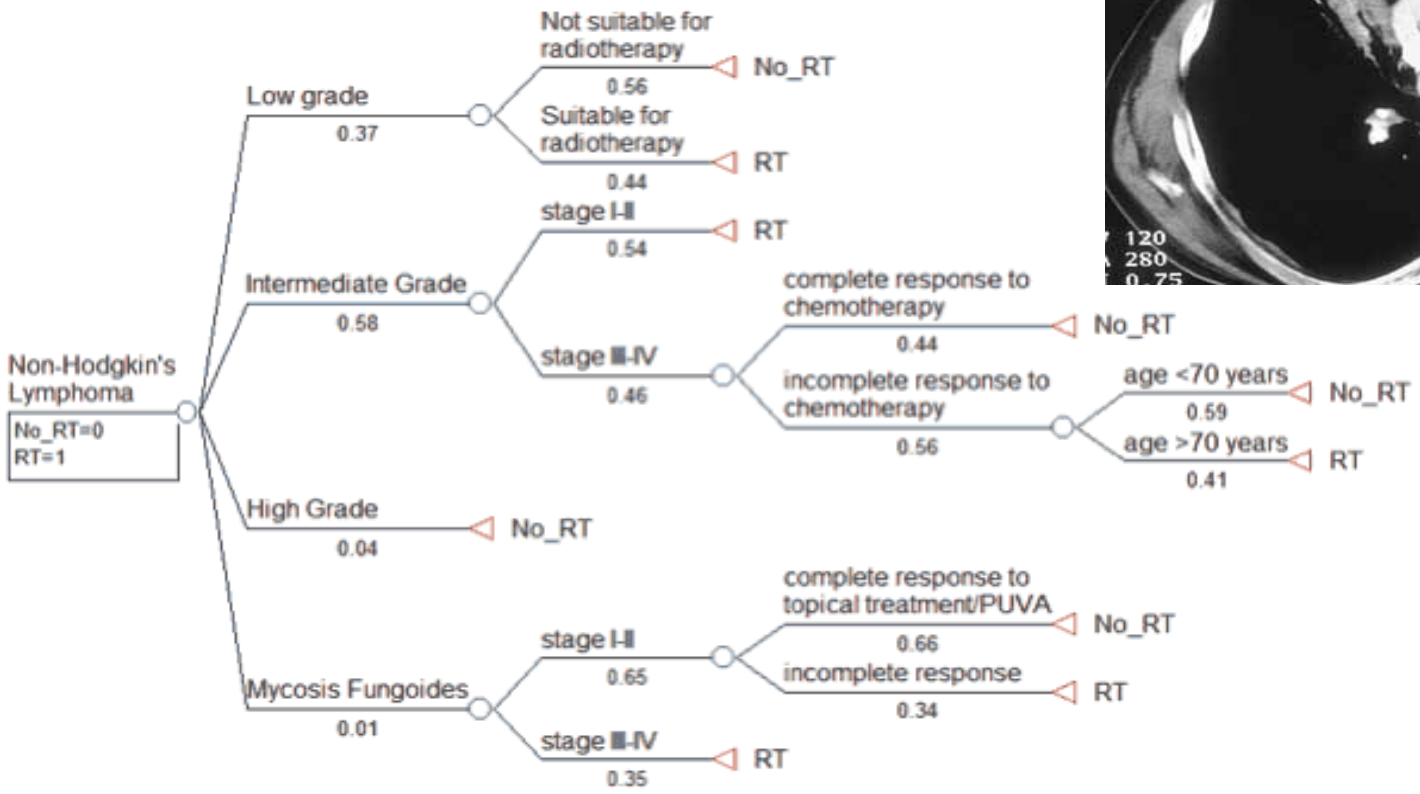
[d]*Institute of Public Health of Serbia, Center for Prevention and Control of Non-Communicable Diseases, Childhood Cancer Registry for Central Serbia, 5, Dr Subotica Street, 11000 Belgrade, Serbia & Montenegro*

A B S T R A C T

Non-Hodgkin's lymphomas (NHLs) constitute a large and heterogeneous group of malignant tumours. This paper describes and interprets geographical patterns (1988–1997) and time trends (1978–1997) of NHL incidence and survival in European children and adolescents. All 7702 lymphomas that were not Hodgkin's, were extracted from the Automated Childhood Cancer Information System (ACCIS) database and included in different analyses. In children under 15 years of age and for the period 1988–1997, the overall NHL age-adjusted incidence rate was 9.4 per million and has been increasing over 20 years by 0.9% per year on average ($P = 0.002$). In adolescents aged 15–19 years, the age-specific incidence rate was 15.9 per million, increasing annually by 1.7% ($P = 0.007$). Five-year survival of children diagnosed in 1988–1997 was 77%, ranging from 58% in the East to 83% in the West. A substantial increase in survival was observed in all European regions. Systematic monitoring and evaluation of childhood and adolescent data on NHL will contribute to further improvement in public health policy for the young population of Europe.




120
280


Non-Hodgkin's Lymphoma
No_RT=0
RT=1
Low grade
0.37
Not suitable for radiotherapy
0.56
No_RT
Suitable for radiotherapy
0.44
RT
Intermediate Grade
0.58
stage I-II
0.54
RT
stage III-IV
0.46
complete response to chemotherapy
0.44
No_RT
incomplete response to chemotherapy
0.56
age <70 years
0.59
No_RT
age >70 years
0.41
RT
High Grade
0.04
No_RT
Mycosis Fungoides
0.01
stage I-II
0.65
complete response to topical treatment/PUVA
0.66
No_RT
incomplete response
0.34
RT
stage III-IV
0.35
RT

EUROPEAN JOURNAL OF CANCER 42 (2006) 2064–2080

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Childhood central nervous system tumours – incidence and survival in Europe (1978–1997): Report from Automated Childhood Cancer Information System project

Rafael Peris-Bonet[a,*], *Carmen Martínez-García*[b], *Brigitte Lacour*[c], *Svetlana Petrovich*[d,e], *Begoña Giner-Ripoll*[a], *Aurora Navajas*[f], *Eva Steliarova-Foucher*[g]

[a]National Childhood Cancer Registry, Spain (RNTI-SEOP) and Instituto López Piñero (CSIC-Universitat de València), Faculty of Medicine, Avd. Blasco Ibáñez, 15, 46010-Valencia, Spain

[b]Granada Cancer Registry, Andalusian School of Public Health, Granada, Spain

[c]French National Registry of Childhood Solid Tumours, Faculty of Medicine, Vandoeuvre, France

[d]Belorussian Childhood Cancer Subregistry, National Scientific and Practical Center of Childrens Oncology and Haematology, Minsk, Belarus

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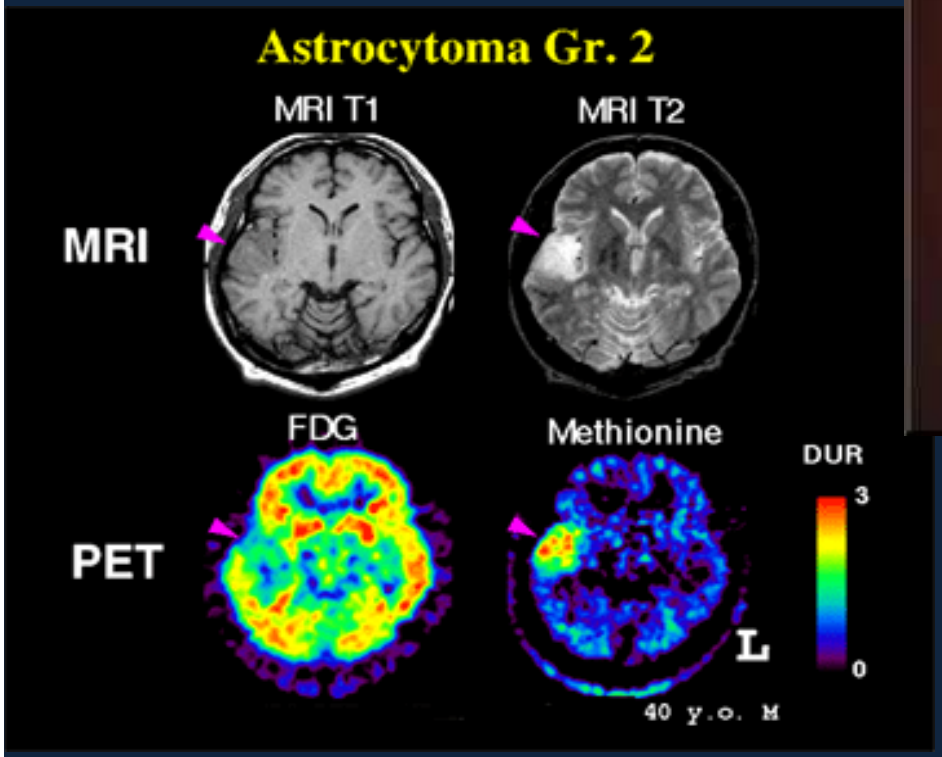
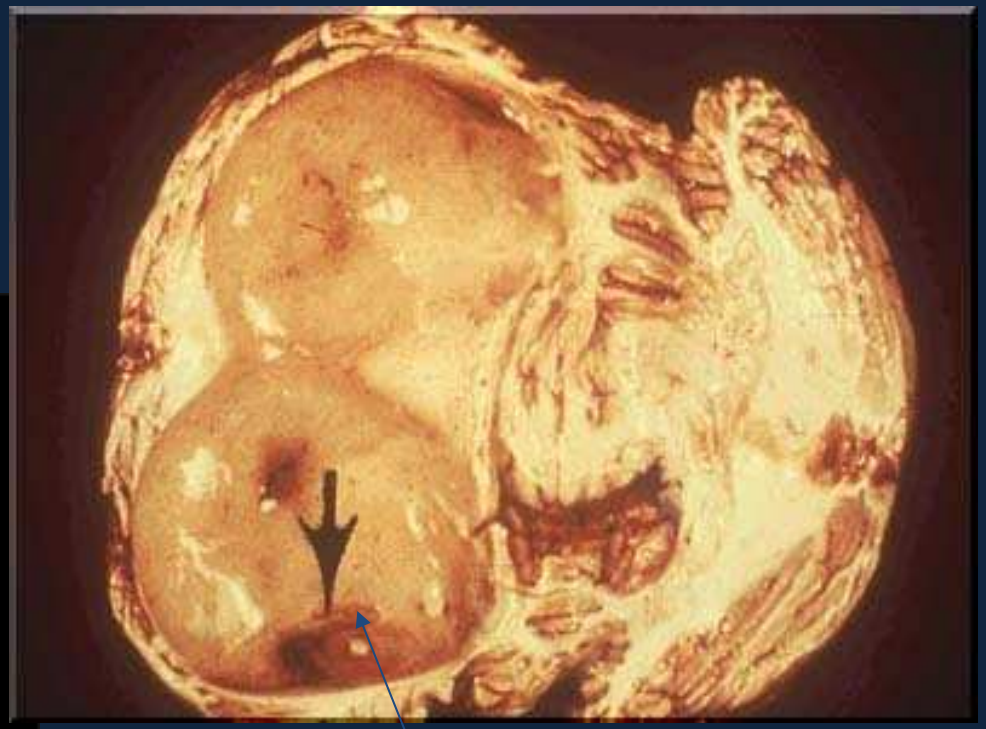
[f]Paediatric Oncology Unit, Hospital de Cruces, Bilbao, Spain

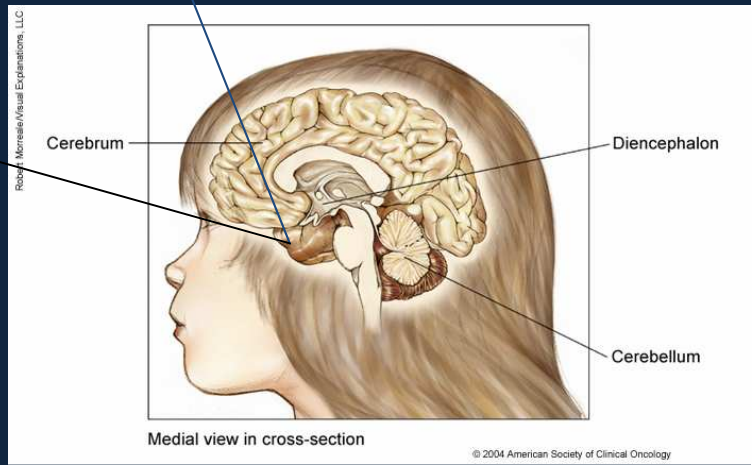
[g]Descriptive Epidemiology Group, International Agency for Research on Cancer, Lyon, France

ABSTRACT

This paper describes the incidence and survival of childhood central nervous system (CNS) tumours in Europe for the period 1978–1997. A total of 19,531 cases, aged 0–14 years, from the ACCIS database were analysed by five regions: the British Isles, East, North, South, and West. Overall age-standardised incidence rate (ASR) of CNS tumours in Europe (1988–1997) was 29.9 per million, with the highest rates in the North. Astrocytoma (ASR = 11.8), primitive neuroectodermal tumours (PNET) (ASR = 6.5) and ependymoma (ASR = 3.4) were the most frequent types. Incidence increased significantly during 1978–1997, on average by 1.7% per year. Diagnostic methods may partially explain incidence rates and trends, although a role of variations in risk factors cannot be excluded. Overall 5-year survival was 64% and varied between 72% in the North and 53% in the East. PNET had the poorest prognosis (49%) and astrocytoma the best (75%). Survival has improved by 29% since late 1970s. The positive trends were seen in all regions, although the interregional differences persisted, as a reflection of the different healthcare systems.

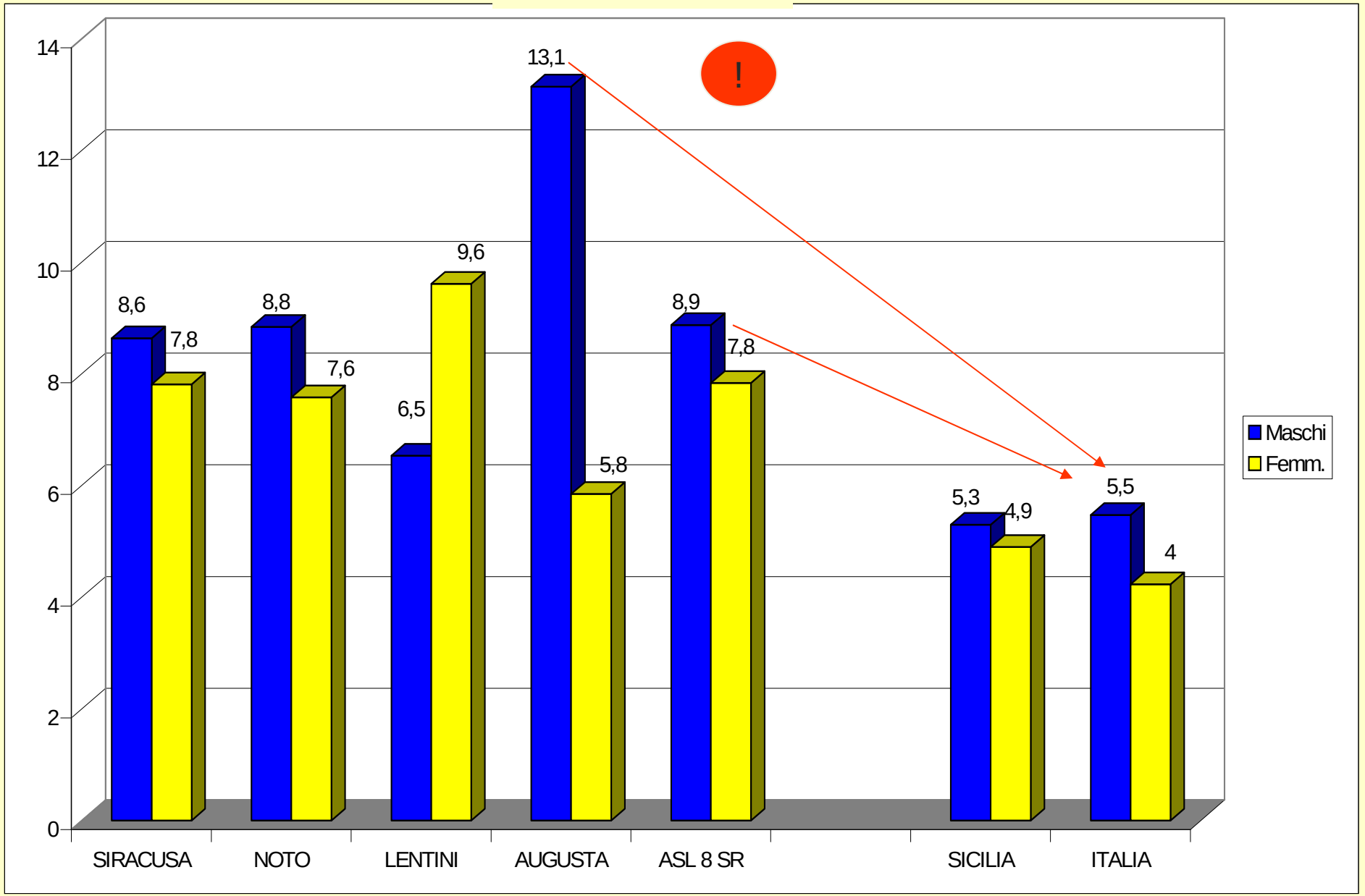

Astrocytoma Gr. 2
MRI T1
MRI T2
MRI
FDG
Methionine
PET
DUR
3
0
L
40 y.o. M




Robert Morreale/Visual Explanations, LLC
Cerebrum
Diencephalon
Cerebellum
Medial view in cross-section
© 2004 American Society of Clinical Oncology

DISTRETTI A CONFRONTO (TASSI STANDARDIZZATI ANNUI PER 100.000 ABITANTI) *1995-2002*

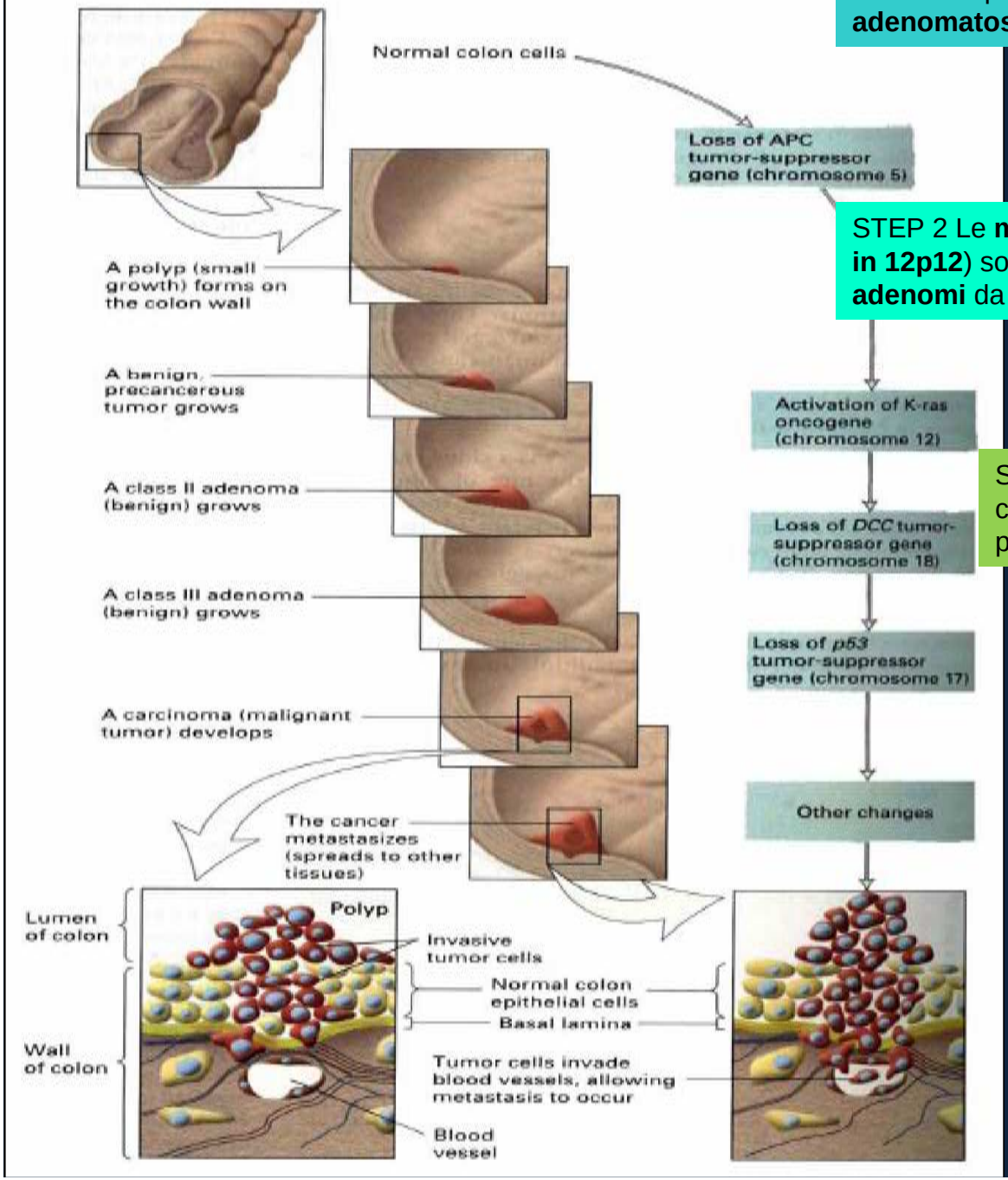
Tumori Encefalo



Darwinian Evolution Through Random Mutation

STEP 1 La **delezione** o la **mutazione** del **gene APC** in **5q21** è sufficiente perché il colon venga tappezzato di **polipi adenomatosi**; Il **DNA** diventa **ipometilato ⇒nuove mutazioni**

1



STEP 2 Le **mutazioni** di K-RAS (**K-RAS1 in 6p12-11 e K-RAS2 in 12p12**) sono spesso coinvolte nella progressione degli **adenomi** da precoci a **intermedi**.

STEP 3 Il presunto **gene soppressore** dei tumori coinvolto è **DCC** ("Deleted in Colon Cancer" → perdita di eterozigosi in **18q21.3**).

1

STEP 4 mutazioni **gene oncosoppressore p53** (localizzato in 17p12-13)**.**

STEP 5 MutazionI del **gene NM23-H1 (17q22)** rendono il CA altamente invasivo/metastatico..

 Basic & Clinical Pharmacology & Toxicology, **102**, 125–133

MiniReview

Does Breast Cancer Start in the Womb?

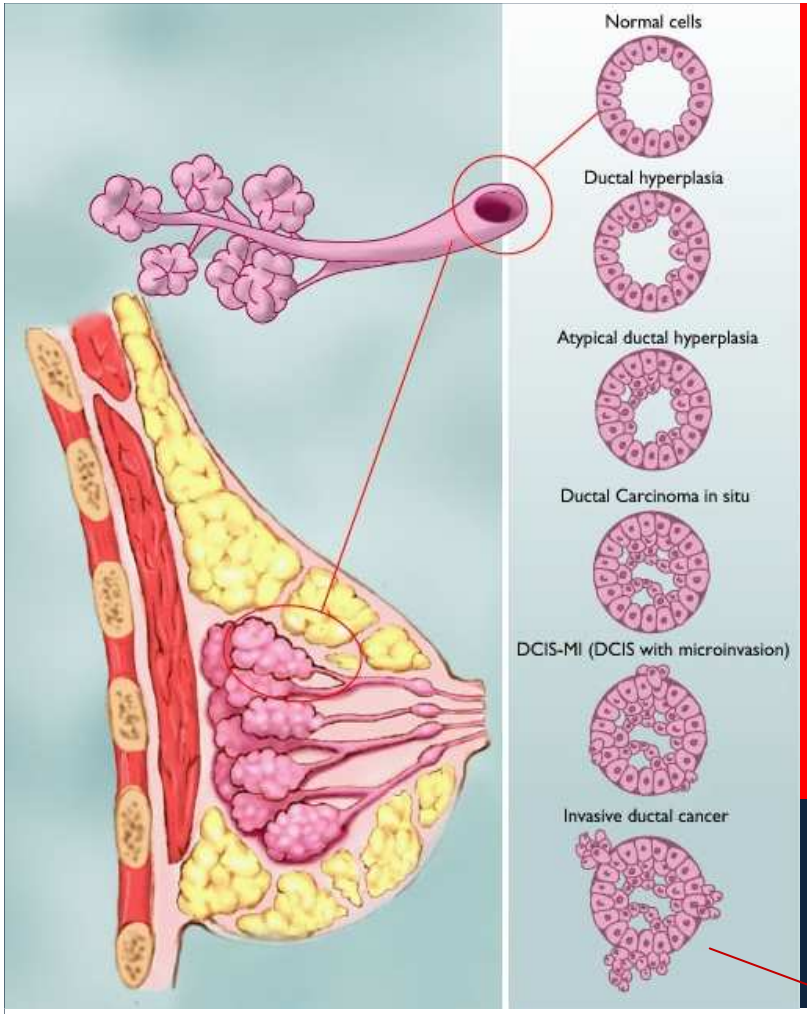
Ana M. Soto, Laura N. Vandenberg, Maricel V. Maffini and Carlos Sonnenschein

Department of Anatomy and Cellular Biology, Tufts University School of Medicine, Boston, MA, USA

(Received June 28, 2007; Accepted September 7, 2007)

Abstract: Perturbations in the foetal environment predispose individuals to diseases that become apparent in adulthood. These findings prompted researchers to hypothesize that foetal exposure to environmental oestrogens may play a role in the increased incidence of breast cancer observed in European and US populations over the last 50 years. There is widespread human exposure to bisphenol A, an oestrogenic compound that leaches from dental materials and consumer products. In CD-1 mice, perinatal exposure to environmentally relevant bisphenol A levels induced alterations of the mammary gland architecture. Bisphenol A increased the number of terminal end buds at puberty and terminal ends at 6 months of age and increased ductal lateral branching at 4 months of age. Exposed mice also showed an enhanced sensitivity to oestradiol when ovariectomized prior to puberty. All these parameters are associated in human beings with an increased risk for developing breast cancer. To assess whether bisphenol A induces mammary gland neoplasia, we chose a rat model because it more closely mimics the human disease than mouse models. Examination of the mammary glands of Wistar/Furth rats during early adulthood revealed that gestational exposure to bisphenol A induced the development of pre-neoplastic lesions and carcinoma *in situ* in the absence of any additional treatment aimed at increasing tumour development. Emerging epidemiological data reveal an increased incidence of breast cancer in women exposed to diethylstilboestrol during gestation. Hence, both animal experiments and epidemiological data strengthen the hypothesis that foetal exposure to xenooestrogens may be an underlying cause of the increased incidence of breast cancer observed over the last 50 years.

BC Genetics



BRCA1
BRCA2

↓

CHEK2

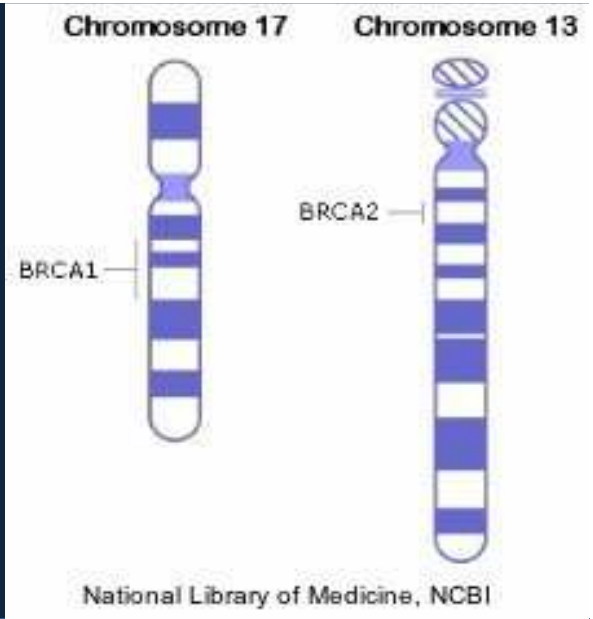
↓

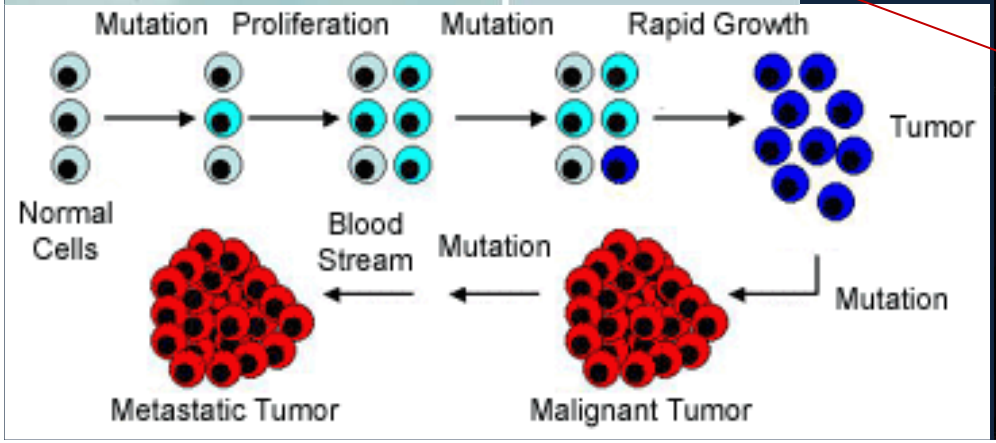
HMMR

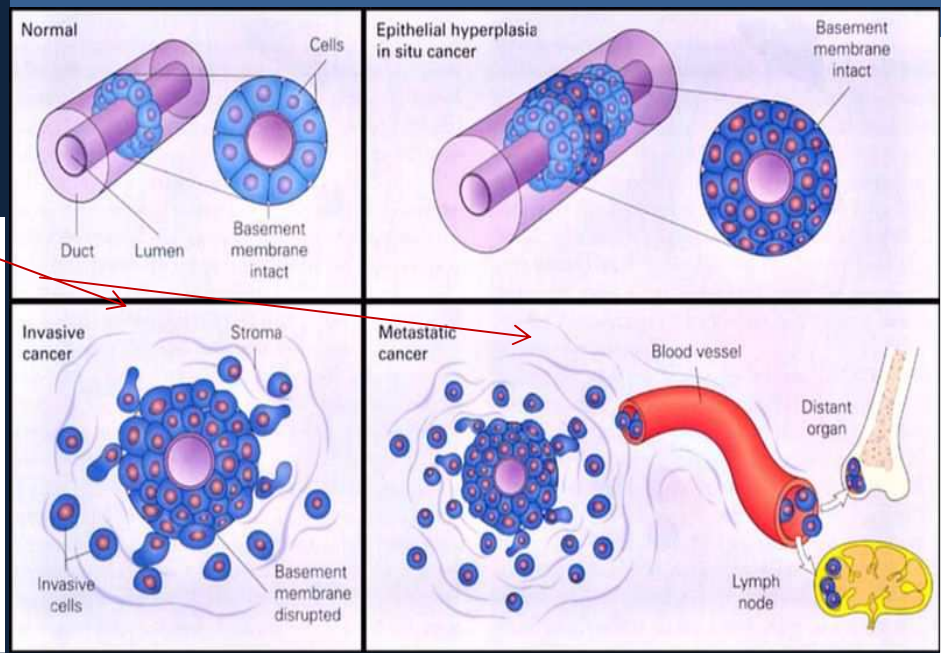
↓

TP53

Somatic **mutations** that can lead to breast cancer have been experimentally linked to estrogen exposure







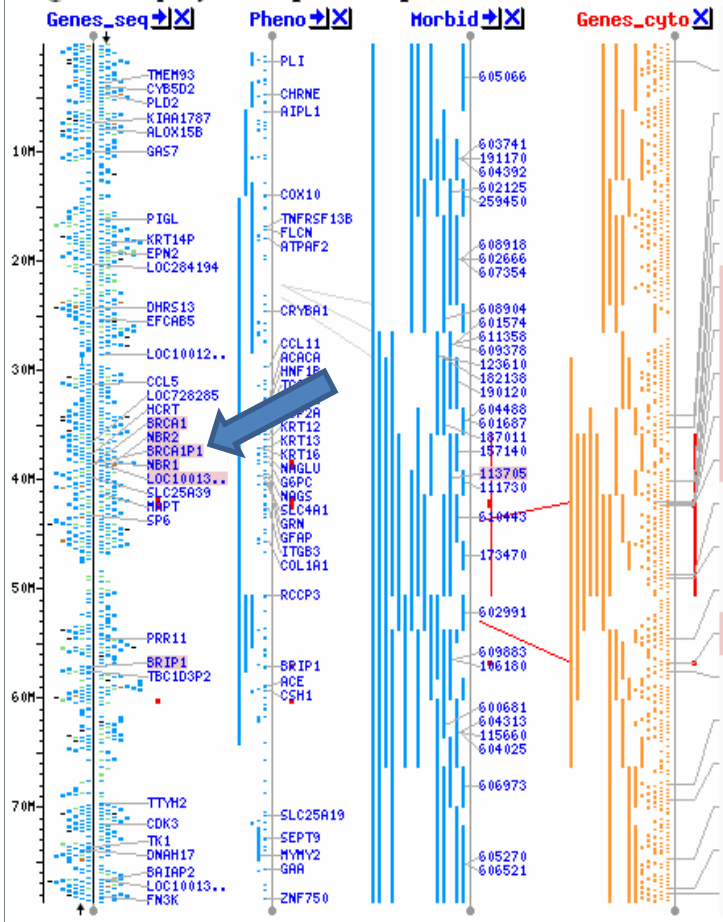
Homo sapiens (human) Build 36.3 (Current) BLAST The Human Genome

Chromosome: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 [17] 18 19 20 21 22 X Y MT

Query: BRCA1 [clear]

Master Map: Genes On Cytogenetic Summary of Maps Maps & Options

Region Displayed: **17pter-17qter**



Symbol	Links	Cyto	Description
MRPL14P1		17p13.3	mitochondrial ribosomal protein L14 pseudogen
CCT6B	OMIM pr hm sts	17q12	chaperonin containing TCP1, subunit 6B (zeta 2
LOC284100	pr hm	17q12	hypothetical protein LOC284100
KRTAP4-1	pr hm	17q12-q21	keratin associated protein 4-1
LOC728318	pr hm	17q21.2	similar to keratin associated protein 9.2
BRCA1	OMIM pr hm sts	17q21	breast cancer 1, early onset
NBR2	pr sts	17q21	neighbor of BRCA1 gene 2
BRCA1P1		17q21	BRCA1 pseudogene 1
NBR1	OMIM pr hm sts	17q21.31	neighbor of BRCA1 gene 1
LOC100133166		17q21.31	similar to neighbor of BRCA1 gene 1
ITGA3	OMIM pr hm sts	17q21.33	integrin, alpha 3 (antigen CD49C, alpha 3 subun
XYLT2	OMIM pr hm sts	17q21.3-q22	xylosyltransferase II
LOC51136	pr sts	17q23.1	PTD016 protein
BRIP1	OMIM pr hm sts	17q22-q24	BRCA1 interacting protein C-terminal helicase
LOC100130106		17q23.2	hypothetical LOC100130106
C17orf77	pr sts	17q25.1	chromosome 17 open reading frame 77
ACOX1	OMIM pr hm sts	17q25.1	acyl-Coenzyme A oxidase 1, palmitoyl
CBX4	OMIM pr hm sts	17q25.3	chromobox homolog 4 (Pc class homolog, Dros
RFNG	OMIM pr hm sts	17q25	RFNG O-fucosylpeptide 3-beta-N-acetylglucos
TRNAM-CAU		1q21.3	transfer RNA methionine (anticodon CAU)

BRCA1

- Tumor suppressor gene on chromosome 17
- Autosomal dominant transmission
- Protein has role in genomic stability
- ~500 different mutations reported

Breast Cancer Information Core

ASCO

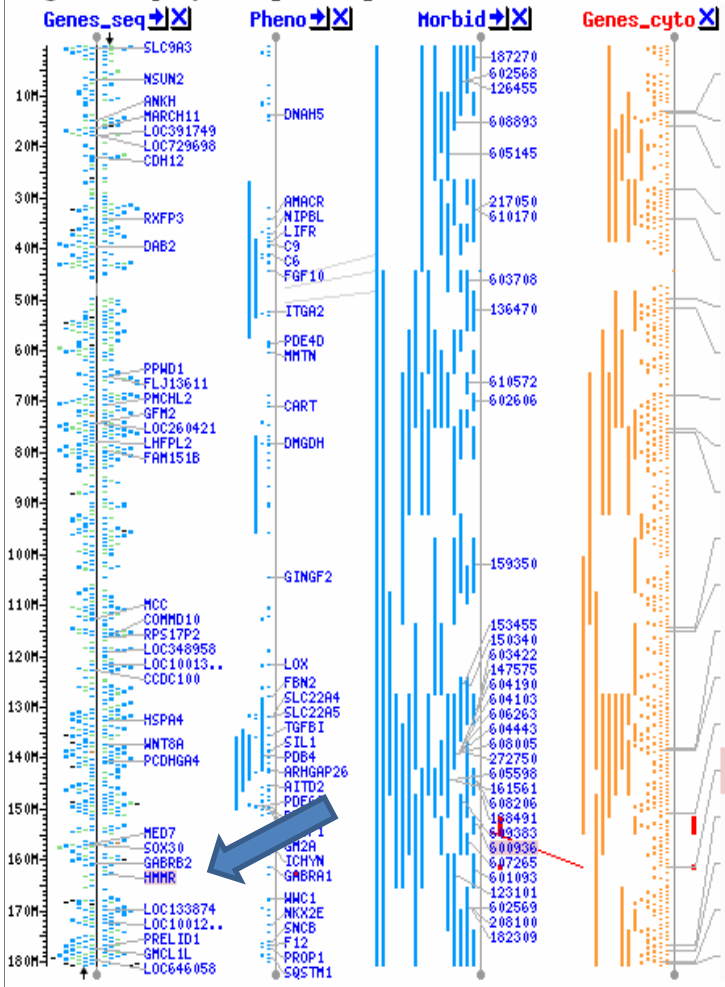
Homo sapiens (human) Build 36.3 (Current) BLAST The Human Genome

Chromosome: 1 2 3 4 [5] 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X Y MT

Query: HMMR [clear]

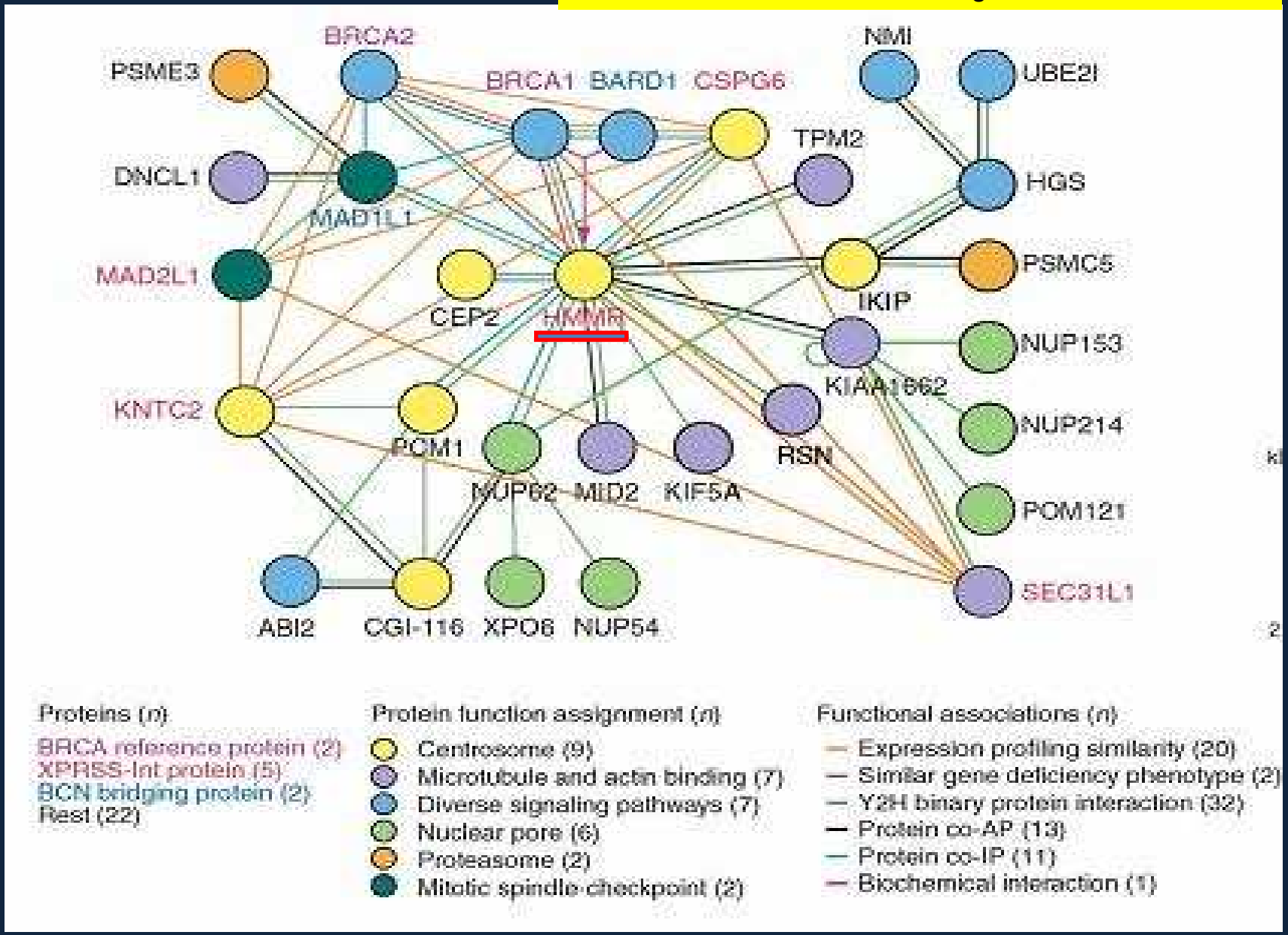
Master Map: Genes On Cytogenetic Summary of Maps Maps & Options

Region Displayed: **5pter-5qter**



Symbol	Links	Cyto	Description
LOC391738		5p15.2	similar to 60S ribosomal protein L29 (Cell sur
TRIO	OMIM pr hm sts	5p15.1-p14	triple functional domain (PTPRF interacting)
LOC729703	pr hm	5p15.1	similar to Transcription initiation factor TFIID
CDH6	OMIM pr hm sts	5p15.1-p14	cadherin 6, type 2, K-cadherin (fetal kidney)
OFD1P1		5p13	OFD1 pseudogene 1
PELO	OMIM pr hm sts	5q11.2	pelota homolog (Drosophila)
LOC100130990		5q11.2	hypothetical LOC100130990
MARVELD2	OMIM pr hm sts	5q13.2	MARVEL domain containing 2
LOC100129287		5q14.1	hypothetical LOC100129287
ACTBP2	sts	5q14.1	actin, beta pseudogene 2
LOC644146		5q23.1	similar to ribosomal protein S14
LOC728342	pr	5q23.1	hypothetical protein LOC728342
SLC35A4	pr hm sts	5q31.3	solute carrier family 35, member A4
PCDHAC1	OMIM pr hm sts	5q31	protocadherin alpha subfamily C, 1
G3BP1	OMIM pr hm sts	5q33.1	GTPase activating protein (SH3 domain) bindi
HMMR	OMIM pr hm sts	5q33.2-qter	hyaluronan-mediated motility receptor (RHAM
ZNF454	pr hm	5q35.3	zinc finger protein 454
LOC441120	pr	5q35.3	similar to LOC285679 protein
BTNL8	pr hm	5q35.3	butyrophilin-like 8
FOXO1B		5q35.2-q35.3	forkhead box O1B pseudogene

… HMMR gene, encoding a centrosome subunit, interacts with the well-known breast cancer gene BRCA1 ...



Cancer Cell
Previews

Cancer Cell *11*, February 2007 ©2007 Elsevier Inc.

Ten Genes for Inherited Breast Cancer

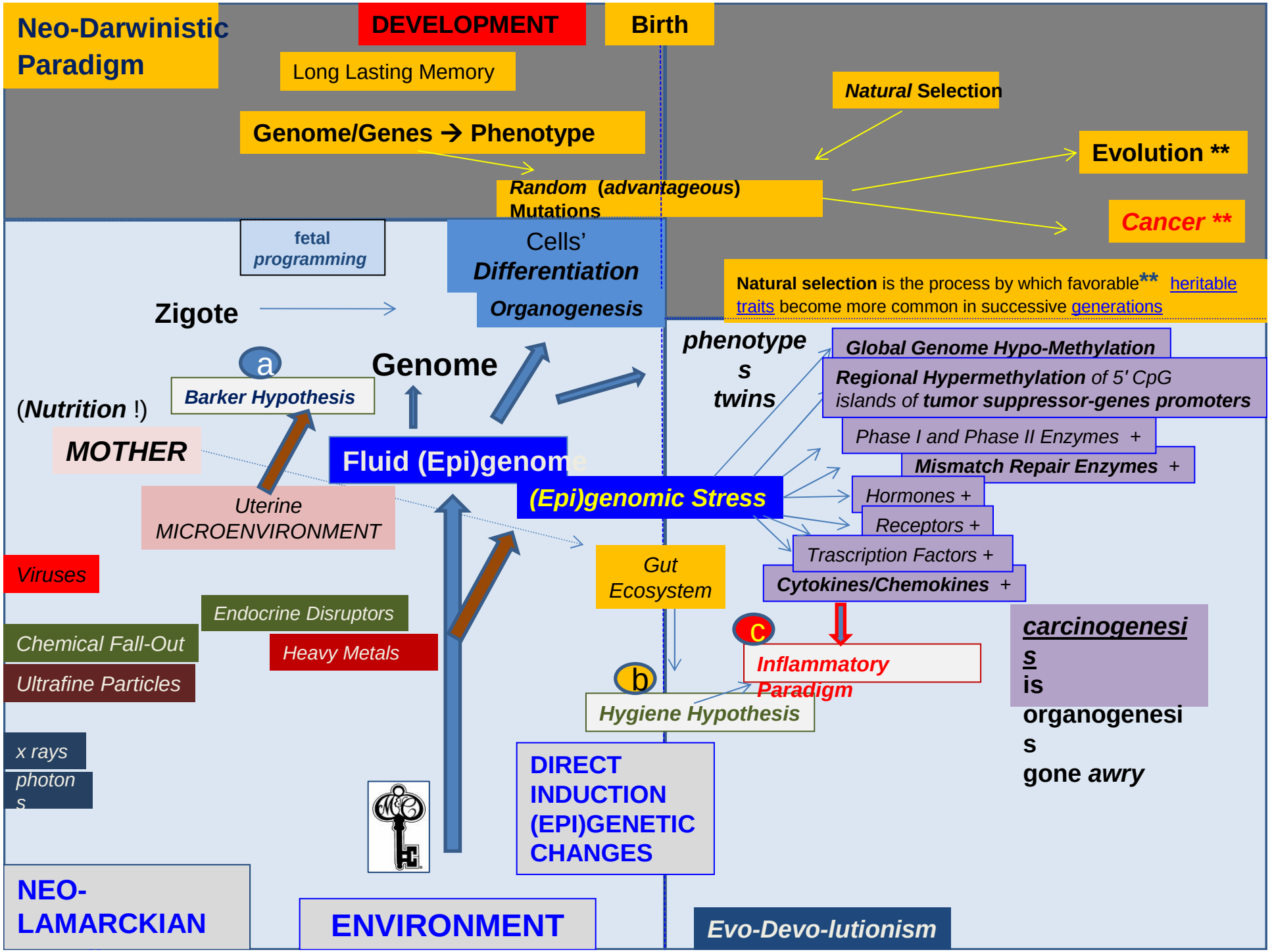
Tom Walsh[1] and Mary-Claire King[1,*]
[1]Departments of Medicine and Genome Sciences, University of Washington, Seattle, Washington 98195, USA
*Correspondence: mcking@u.washington.edu, twalsh@u.washington.edu
DOI 10.1016/j.ccr.2007.01.010

Inherited breast cancer is associated with germline mutations in ten different genes in pathways critical to genomic integrity. *BRCA1* and *BRCA2* mutations confer very high risks of breast and ovarian cancer. *p53* and *PTEN* mutations lead to very high breast cancer risks associated with rare cancer syndromes. Mutations in *CHEK2*, *ATM*, *NBS1*, *RAD50*, *BRIP1*, and *PALB2* are associated with doubling of breast cancer risks. In addition, biallelic mutations in *BRCA2*, *BRIP1*, and *PALB2* cause Fanconi anemia. The convergence of these genes in a shared role reveals underlying biology of these illnesses and suggests still other breast cancer genes.

There are many deleterious mutations, and each mutation is individually rare. That is, for none of these genes (individually or in combination) does increased risk of breast cancer result from additive effects of multiple common alleles, each of small influence.

Inherited breast cancer is highly genetically heterogeneous with respect to both loci and alleles involved. All evidence to date is that the model that best reflects this heterogeneity is not a "common disease-common allele" model, but instead a "common disease-multiple rare alleles" model.

The ten known genes for inherited breast cancer function in a pathway whose role is to preserve genomic integrity. Roughly 50% of familial breast cancer remains unresolved by any of these genes. Clearly other genes in this pathway are worthy of in-depth genomic analysis in unresolved families.


Neo-Darwinistic Paradigm
DEVELOPMENT
Birth
Long Lasting Memory
Genome/Genes → Phenotype
Natural Selection
Evolution **
Random (advantageous) Mutations
Cancer **
fetal programming
Cells' Differentiation
Organogenesis
Natural selection is the process by which favorable** heritable traits become more common in successive generations
Zigote
a
Genome
Barker Hypothesis
(Nutrition !)
MOTHER
Fluid (Epi)genome
(Epi)genomic Stress
Uterine MICROENVIRONMENT
phenotypes twins
Global Genome Hypo-Methylation
Regional Hypermethylation of 5' CpG islands of tumor suppressor-genes promoters
Phase I and Phase II Enzymes +
Mismatch Repair Enzymes +
Hormones +
Receptors +
Trascription Factors +
Cytokines/Chemokines +
Gut Ecosystem
Viruses
Endocrine Disruptors
Chemical Fall-Out
Heavy Metals
Ultrafine Particles
c
Inflammatory Paradigm
b
Hygiene Hypothesis
carcinogenesis is organogenesis gone awry
x rays
photons
DIRECT INDUCTION (EPI)GENETIC CHANGES
NEO-LAMARCKIAN
ENVIRONMENT
Evo-Devo-lutionism

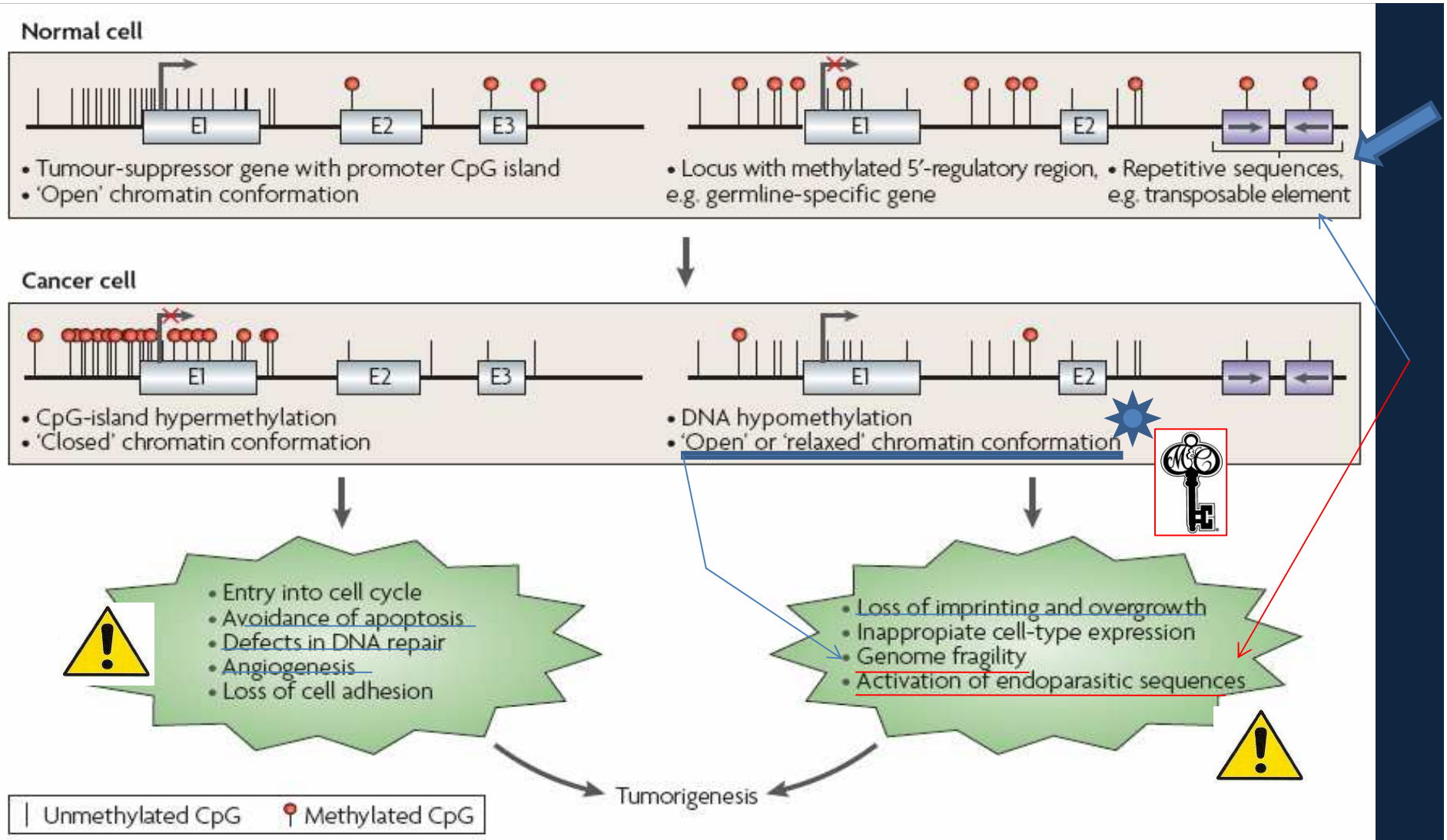


Figure 1 | **Altered DNA-methylation patterns in tumorigenesis.** The hypermethylation of CpG islands of tumour-suppressor genes is a common alteration in cancer cells, and leads to the transcriptional inactivation of these genes and the loss of their normal cellular functions. This contributes to many of the hallmarks of cancer cells. At the same time, the genome of the cancer cell undergoes global hypomethylation at repetitive sequences, and tissue-specific and imprinted genes can also show loss of DNA methylation. In some cases, this hypomethylation is known to contribute to cancer cell phenotypes, causing changes such as loss of imprinting, and might also contribute to the genomic instability that characterizes tumours. E, exon.

long range epigenetic silencing (LRES).

Human Molecular Genetics, 2007, Vol. 16, Review Issue 1 **R88–R95**
doi:10.1093/hmg/ddm051

Action at a distance: epigenetic silencing of large chromosomal regions in carcinogenesis

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Received February 15, 2007; Revised and Accepted February 28, 2007

Despite the completion of the Human Genome Project, we are still far from understanding the molecular events underlying epigenetic change in cancer. Cancer is a disease of the DNA with both genetic and epigenetic changes contributing to changes in gene expression. Epigenetics involves the interplay between DNA methylation, histone modifications and expression of non-coding RNAs in the regulation of gene transcription. We now know that tumour suppressor genes, with CpG island-associated promoters, are commonly hypermethylated and silenced in cancer, but we do not understood what triggers this process or when it occurs during carcinogenesis. Epigenetic gene silencing has always been envisaged as a local event silencing discrete genes, but recent data now indicates that large regions of chromosomes can be co-coordinately suppressed; a process termed long range epigenetic silencing (LRES). LRES can span megabases of DNA and involves broad heterochromatin formation accompanied by hypermethylation of clusters of contiguous CpG islands within the region. It is not clear if LRES is initiated by one critical gene target that spreads and conscripts innocent bystanders, analogous to large genetic deletions or if coordinate silencing of multiple genes is important in carcinogenesis? Over the next decade with the exciting new genomic approaches to epigenome analysis and the initiation of a Human Epigenome Project, we will understand more about the interplay between DNA methylation and chromatin modifications and the expression of non-coding RNAs, promising a new range of molecular diagnostic cancer markers and molecular targets for cancer epigenetic therapy.

PERSPECTIVE

Science Signaling
AAAS

GENE SILENCING

Silent Assassin: Oncogenic Ras Directs Epigenetic Inactivation of Target Genes

Xiaodong Cheng

Published 1 April 2008

Oncogenic transformation is associated with genetic changes and epigenetic alterations. A study now shows that oncogenic Ras uses a complex and elaborate epigenetic silencing program to specifically repress the expression of multiple unrelated cancer-suppressing genes through a common pathway. These results suggest that cancer-related epigenetic modifications may arise through a specific and instructive mechanism and that genetic changes and epigenetic alterations are intimately connected and contribute to tumorigenesis cooperatively.

Silent Assassin: Oncogenic Ras Directs Epigenetic Inactivation of Target Genes
Xiaodong Cheng (1 April 2008)
Science Signaling **1** (13), pe14. [DOI: 10.1126/stke.113pe14]

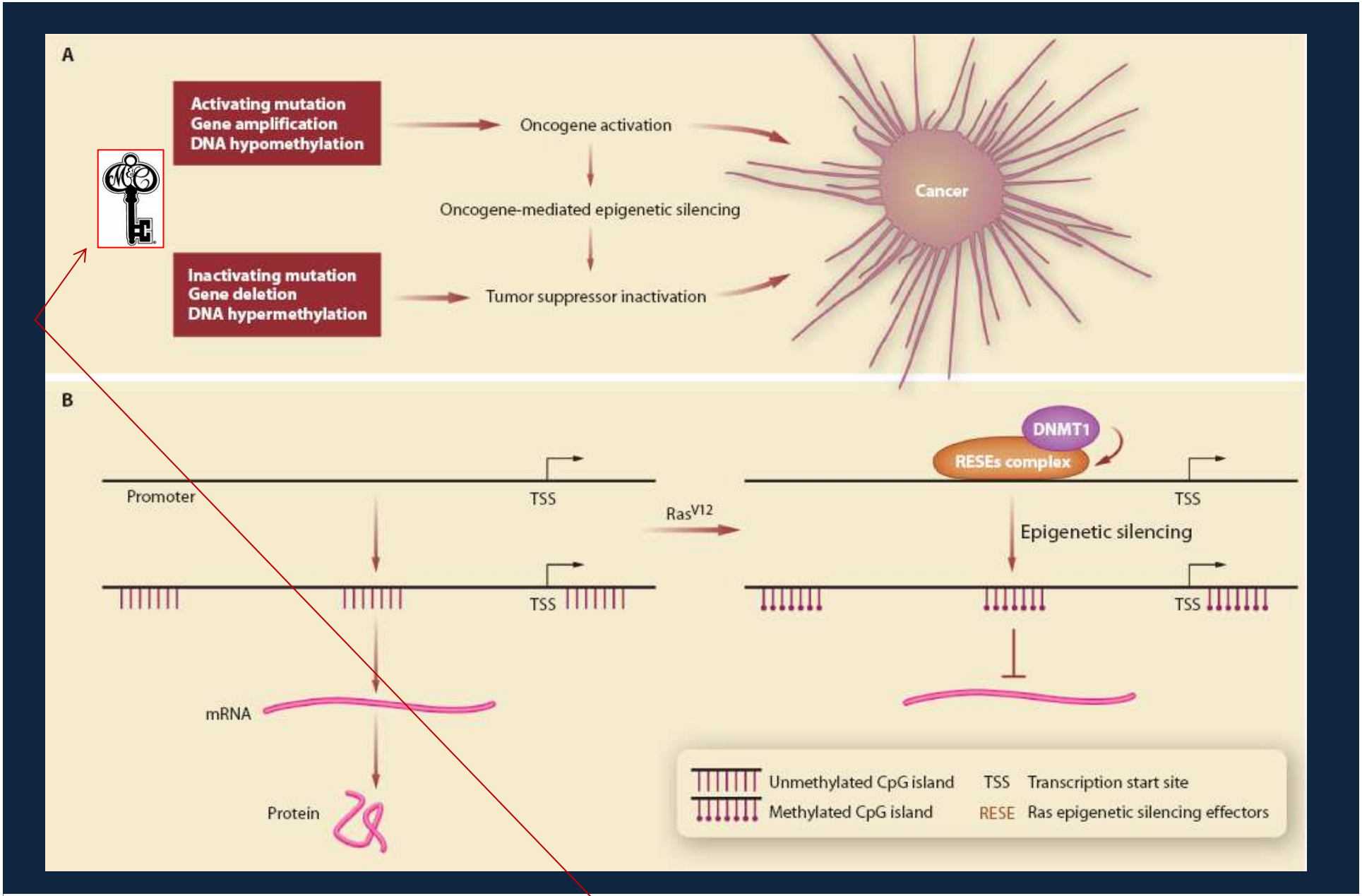


Fig. 1. Mechanism of oncogenic transformation. (**A**) Cooperation between genetic changes and epigenetic alterations leads to the activation of oncogenes and the inactivation of tumor suppressors, which results in tumorigenesis. (**B**) Activation of oncogenic Ras (Ras^{V12}) directs a specific epigenetic silencing program during tumorigenesis by recruiting epigenetic modification enzymes, such as DNMT1, and hypermethylating specific promoters of cancer-related genes.

- **Fetal origins of breast cancer.**

Hilakivi-Clarke L, **de Assis S**.
Georgetown University, Washington DC 20057, USA. Clarkel@georgetown.edu

Trends Endocrinol Metab. **2006** Nov;17(9):340-8.

Susceptibility to breast cancer might be pre-determined in utero.

Alterations in the fetal hormonal environment, caused by either maternal diet or exposure to environmental factors with endocrine activities, can modify the epigenome, and these modifications

are inherited in somatic daughter cells and maintained throughout life.

These epigenetic modifications might lead to changes in mammary gland development, such as increased vulnerability of epithelial targets for malignant transformation.

According to this hypothesis, on post-pubertal exposure to an initiating factor, such as a carcinogen, high levels of hormones and radiation, the **mammary epithelial targets, perhaps stem cells, in terminal end buds/terminal ductal lobular units would be at an increased risk of malignant transformation**.

The increased susceptibility for cancer initiation might result from ***high levels of cell proliferation,***

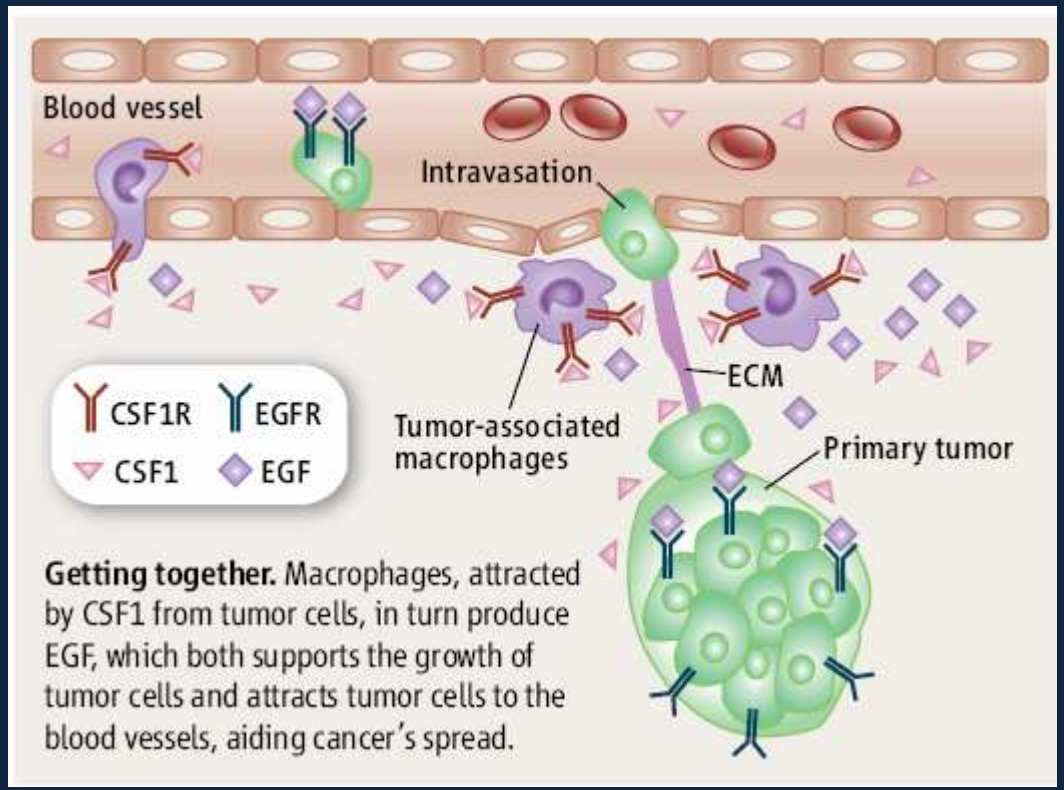
reduced apoptosis and/or ***altered stromal regulation.***

Thus, maternal diet and environmental exposure might increase the risk of breast cancer by inducing permanent epigenetic changes in the fetus that alter the susceptibility to factors that can initiate breast cancer. Identifying the epigenetically altered target genes and their ligands might lead to strategies to prevent this disease in some women.

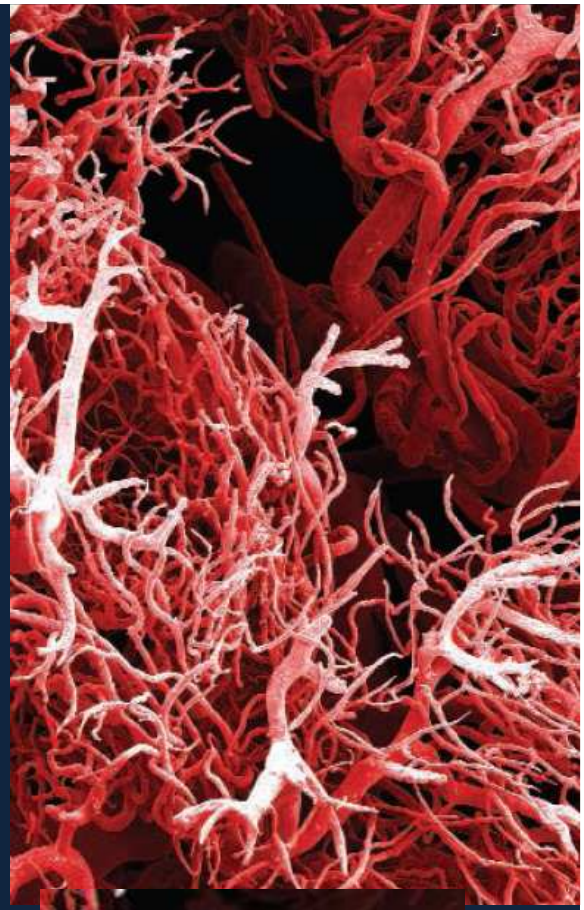
All in the Stroma: Cancer's Cosa Nostra

After focusing for decades on what happens within tumor cells to make them go wrong, biologists are turning to the tumor environment and finding a network of coconspirators

4 APRIL 2008 VOL 320 **SCIENCE** www.sciencemag.org



Getting together. Macrophages, attracted by CSF1 from tumor cells, in turn produce EGF, which both supports the growth of tumor cells and attracts tumor cells to the blood vessels, aiding cancer's spread.



Support system. Promoting new blood vessel growth is one of many ways that tumor cells can make the microenvironment more hospitable to cancer.

The **Somatic Mutation Theory** of **Carcinogenesis**

For most of the 20th century, the dominant stance regarding cancer was the somatic mutation theory [1]. The premises of this theory are: (i) cancer is derived from a single somatic cell that has accumulated multiple DNA mutations, (ii) the default state in metazoan cells is proliferative quiescence, and (iii) cancer is a disease of cell proliferation caused by mutations in genes that control the cell cycle.

1 Hahn WC, Weinberg RA. Modelling the molecular circuitry of cancer. Nat Rev Cancer 2002;**2**:331–42.

The dominant view in developmental biology at the end of the 20th century was that **development is the unravelling of a genetic programme** where the **environment plays virtually no relevant role**. Two main factors contributed to the **dominance of the genetic programme view.** One was the advent of **developmental mechanics, which concentrated on the inner workings of the embryo** rather than on the ecological determination of phenotype. Another was the **dominance of a genocentric view originating from the molecular biology revolution**.

The ***environment*** is again accepted as a **main player in phenotype determination.**

The **Tissue Organization Field Theory (TOFT)** of **Carcinogenesis**

In contrast to the somatic mutation theory, the TOFT postulates that: (i) carcinogenesis represents a problem of tissue organization, (ii) proliferation is the default state of all cells, and (iii) carcinogenesis is a reversible phenomenon [2]. Carcinogens, as well as teratogens, would disrupt the normal dynamic interaction of neighbouring cells and tissues during early development and throughout adulthood [3]. According to this theory, carcinogenesis is comparable to organogenesis gone awry.

2 Sonnenschein, C, Soto, AM. The Society of Cells: Cancer and Control of Cell Proliferation. Springer Verlag, New York, 1999.

3 Maffini MV, Soto AM, Calabro JM, Ucci AA, Sonnenschein C. The stroma as a crucial target in rat mammary gland carcinogenesis. J Cell Sci 2004;**117**:1495–502.

A number of factors can influence the DNA methylation levels of a cell without requiring a change in genomic DNA sequence.

- *Aging:* With **aging** in certain tissues there is a general **tendency for the genome to become hypomethylated** whereas **certain CpG islands become hypermethylated, a situation reminiscent of that found in many cancer cells**. Whether this age-dependent change in DNA methylation is linked to the increased cancer incidence in later life remains to be determined.

Richardson B. **Impact of aging on DNA methylation.** Ageing Res. Rev. (2003) **2**:245-261.

!!!

Rodenhiser D, Mann M. **Epigenetics and human disease: translating basic biology into clinical applications.** C.M.A.J. (2006) **174**:341-348.

!!!

- ***Diet***: **Nutrition supplies the methyl groups for DNA (and histone) methylation via the folate and methionine pathways**. Importantly, **mammals cannot synthesise folate or methionine** and so a diet low in these compounds leads to alterations in DNA methylation. These changes have been associated with ***cancer***.
- ***Environment***: Agents such as **arsenic** and **cadmium** can have profound effects on DNA methylation.
  Arsenic causes **hypomethylation of the *ras* gene** whereas **cadmium induces global hypomethylation by inactivating *DNMT1***

Takiguchi M, Achanzar WE, Qu W, Li G, Waalkes MP. **Effects of cadmium on DNA-(Cytosine-5) methyltransferase activity and DNA methylation status during cadmium-induced cellular transformation.** Exp. Cell Res. (2003) **286**:355-365.

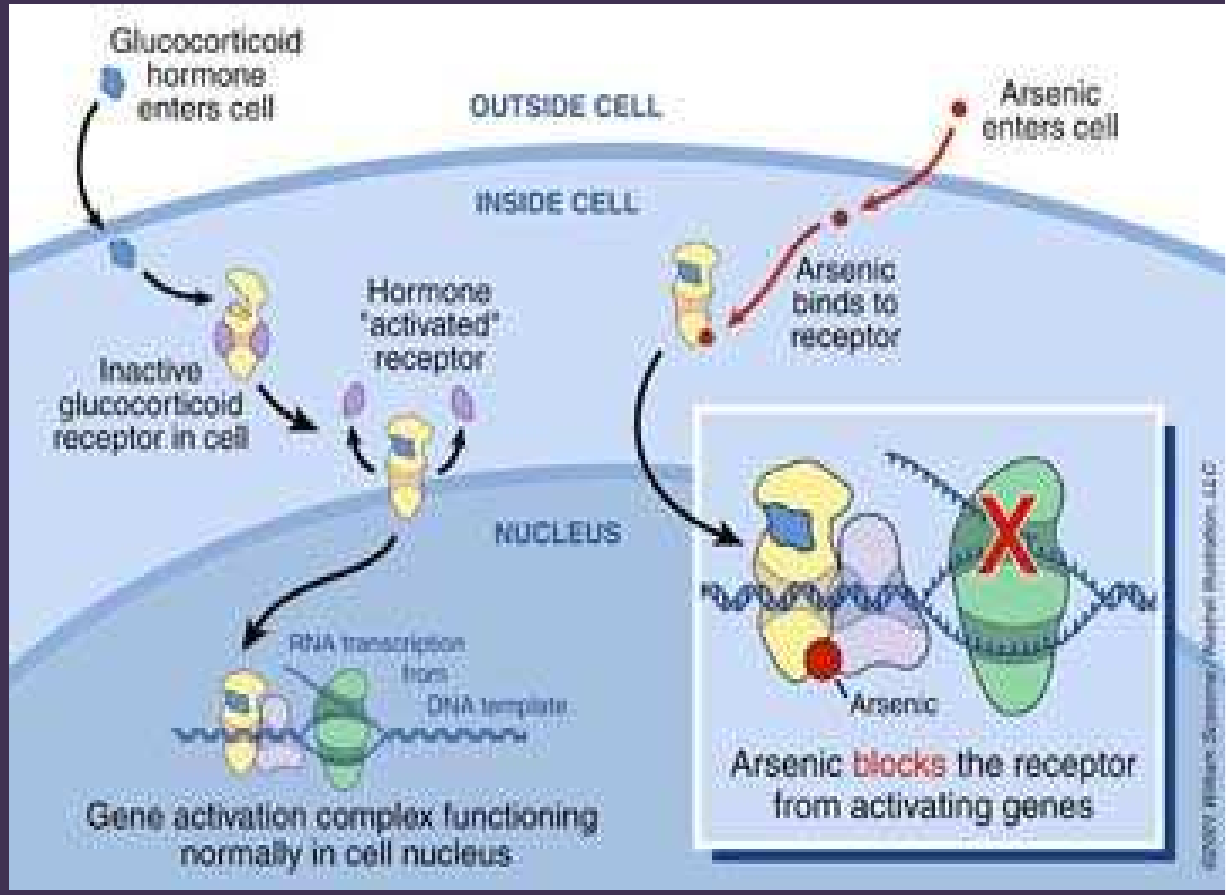
Okoji RS, Yu RC, Maronpot RR, Froines JR. **Sodium arsenite administration via drinking water increases genome-wide and Ha-ras DNA hypomethylation in methyl-deficient C57BL/6J mice.** Carcinogenesis (2002) **23**:777-785.

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



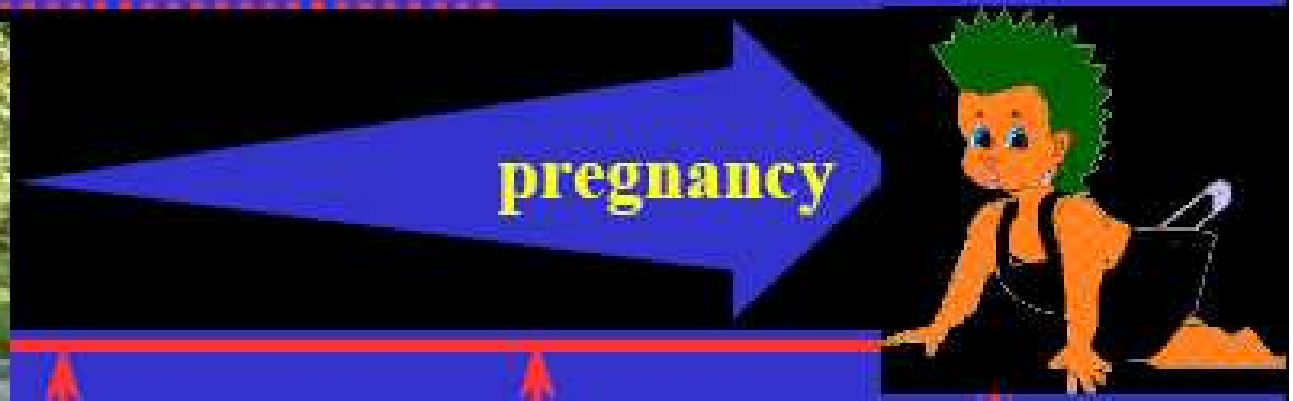
Kaltreider *et al*. 2002

3

Note al PARADIGMA 3
Systemic Flogosis

Exposure → Health outcome

Prental Exposure to FP



B C D

Interviews on prental nutrition

Wieslaw Jedrychowski*, Elzbieta Flak*, Elzbieta Mroz*, Agnieszka Pac*, Ryszard Jacek*, Elzbieta Sochacka-Tatara *, John Spengler**, Virginia Rauh*** and Frederica Perera***

Prenatal exposure to fine particles and respiratory symptoms in early childhood, modulating effects of fish consumption in pregnancy. Krakow Epidemiologic Study

*/ Chair of Epidemiology and Preventive Medicine, Coll. Med. Jagiellonian University, Krakow, Poland
**/ Department of Environmental Health, School of Public Health, Harvard University, Boston, USA
***/ Columbia Center for Children's Environmental Health, Mailman School Public Health, Columbia University, New York, NY, USA

Conclusions:

1. the results of our study suggested that prenatal exposure to $PM_{2.5}$ had an effect on the occurrence of respiratory inflammatory symptoms during early infancy and that this effect was independent of postnatal indoor air quality (environmental tobacco smoke and/or molds in the households)

- **Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential effect modification by nutrition.**
- **Kannan S**, **Misra DP**, **Dvonch JT**, **Krishnakumar A**.
- Department of Environmental Health Sciences, Human Nutrition Program, University of Michigan, Ann Arboe, Michigan 48109-2029, USA. kannans@umich.edu
- Environ Health Perspect. **2006** Nov;114(11):1636-42
- OBJECTIVES: The specific objectives are threefold: to describe the biologically plausible mechanistic pathways by which **exposure to particulate matter (PM) may lead to the adverse perinatal outcomes of low birth weight (LBW), intrauterine growth retardation (IUGR), and preterm delivery (PTD);** review the evidence showing that **nutrition affects the biologic pathways**;
and explain the **mechanisms by which nutrition may modify the impact of PM exposure on perinatal outcomes**.
METHODS: We propose an **interdisciplinary conceptual framework that brings together maternal and infant nutrition, air pollution exposure assessment, and cardiopulmonary and perinatal epidemiology.** Five possible albeit not exclusive biologic mechanisms have been put forth in the emerging environmental sciences literature and provide corollaries for the proposed framework. CONCLUSIONS: Protecting the environmental health of mothers and infants remains a top global priority. The existing literature indicates that **the effects of PM on LBW, PTD, and IUGR may manifest through the cardiovascular mechanisms of oxidative stress, inflammation, coagulation, endothelial function, and hemodynamic responses**. PM exposure studies relating mechanistic pathways to perinatal outcomes should consider the likelihood that **biologic responses and adverse birth outcomes may be derived from both PM and non-PM sources (e.g., nutrition).** In the concluding section, we present strategies for empirically testing the proposed model and developing future research efforts.

VOLUME 114 | NUMBER 9 | September 2006 • Environmental Health Perspectives

Research | Children's Health

Lung Radiology and Pulmonary Function of Children Chronically Exposed to Air Pollution

Lilian Calderón-Garcidueñas,[1,2] Antonieta Mora-Tiscareño,[1] Lynn A. Fordham,[3] Charles J. Chung,[4] Gildardo Valencia-Salazar,[5] Silvia Flores-Gómez,[1] Anna C. Solt,[1,6] Alberto Gomez-del Campo,[7] Ricardo Jardón-Torres,[8] Carlos Henríquez-Roldán,[9] Milan J. Hazucha,[10] and William Reed[10]

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We analyzed the chest radiographs (CXRs) of 249 clinically healthy children, 230 from southwest Mexico City and 19 from Tlaxcala. In contrast to children from Tlaxcala, children from southwest Mexico City were chronically exposed to ozone levels exceeding the U.S. National Ambient Air Quality Standards for an average of 4.7 hr/day and to concentrations of particulate matter (PM) with aerodynamic diameters ≤ 2.5 μm ($PM_{2.5}$) above the annual standard. CXRs of Mexico City children demonstrated bilateral hyperinflation (151 of 230) and increased linear markings (121 of 230). Hyperinflation and interstitial markings were significantly more common in Mexico City children ($p < 0.0002$ and 0.00006 respectively). Mexico City boys had a higher probability of developing interstitial markings with age ($p = 0.004$). Computed tomography (CT) scans were obtained in 25 selected Mexico City children with abnormal CXRs. Mild bronchial wall thickening was seen in 10 of 25, prominent central airways in 4 of 25, air trapping in 8 of 21, and pulmonary nodules in 2 of 21. Only 7.8% of Mexico City children had abnormal lung function tests based on predicted values. These findings are consistent with bronchiolar, peribronchiolar, and/or alveolar duct inflammation, possibly caused by ozone, PM, and lipopolysaccharide exposure. The epidemiologic implications of these findings are important for children residing in polluted environments, because bronchiolar disease could lead to chronic pulmonary disease later in life. *Key words:* air pollutants, chest X rays, children, high-resolution CT, hyperinflation, Mexico, ozone, particulate matter, small-airway disease, spirometry. *Environ Health Perspect* 114:1432–1437 (2006). doi:10.1289/ehp.8377 available via *http://dx.doi.org/* [Online 20 April 2006]

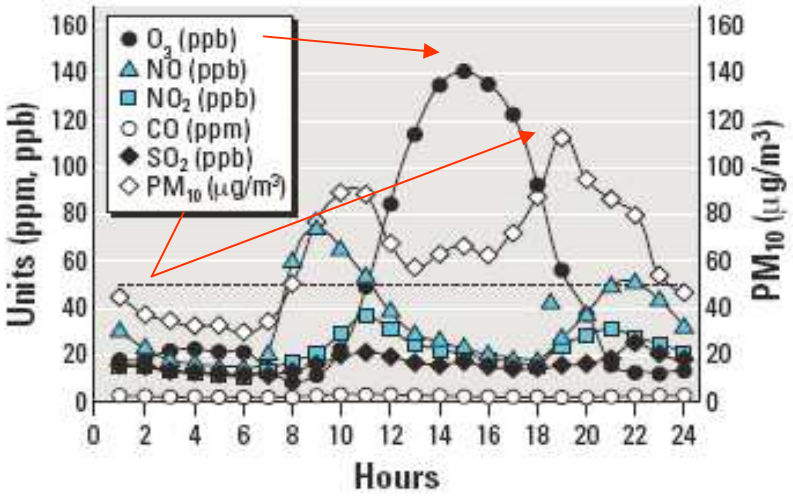

Figure 1. The typical 24-hr pattern of key air pollutants in southwest metropolitan Mexico City averaged over 31 days for the month of January 1999. Left scale: O_3, nitric oxide, NO_2, carbon monoxide, sulfur dioxide; right scale: PM_{10}. The horizontal dashed line at 50 µg/m³ represents the current 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.

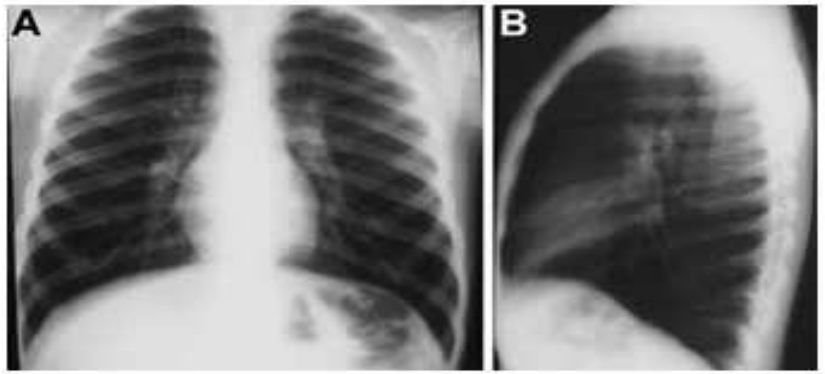

Figure 2. Eleven-year-old boy with frontal (*A*) and lateral (*B*) CXRs that demonstrate hyperinflation. The lateral film shows an increase in the anterior clear space, increased anterior–posterior diameter, and flattening of the hemidiaphragms.

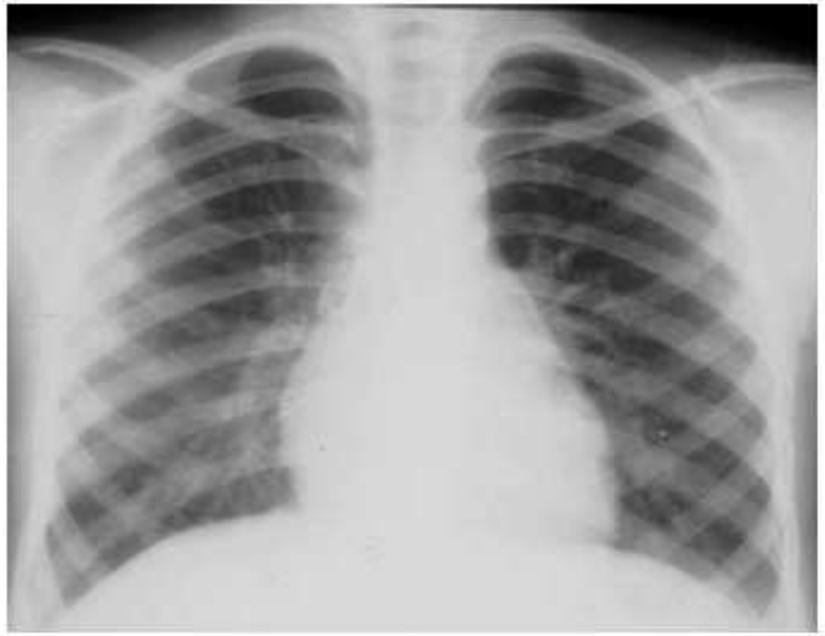

Figure 3. Ten-year-old boy with a frontal CXR that demonstrates subtle increased linear markings.

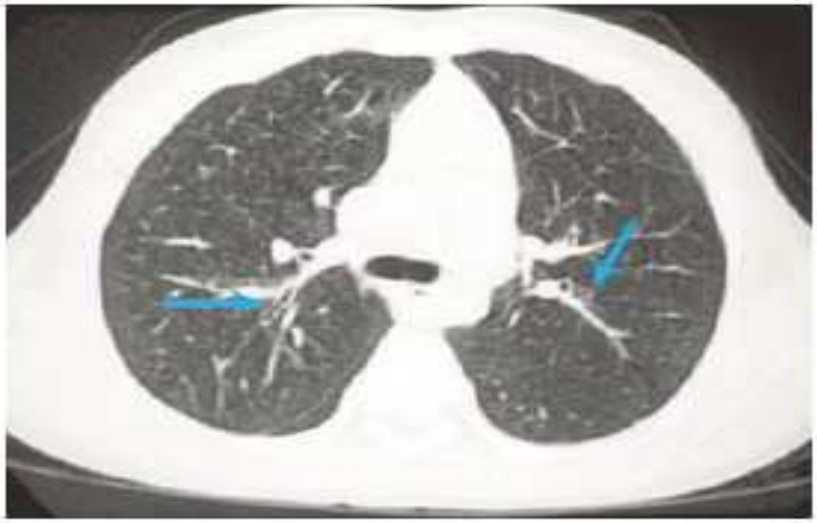

Figure 4. Inspiratory chest CT demonstrating mild peribronchial thickening (left arrow) and minimal airway dilatation (right arrow) in an 11-year-old boy.

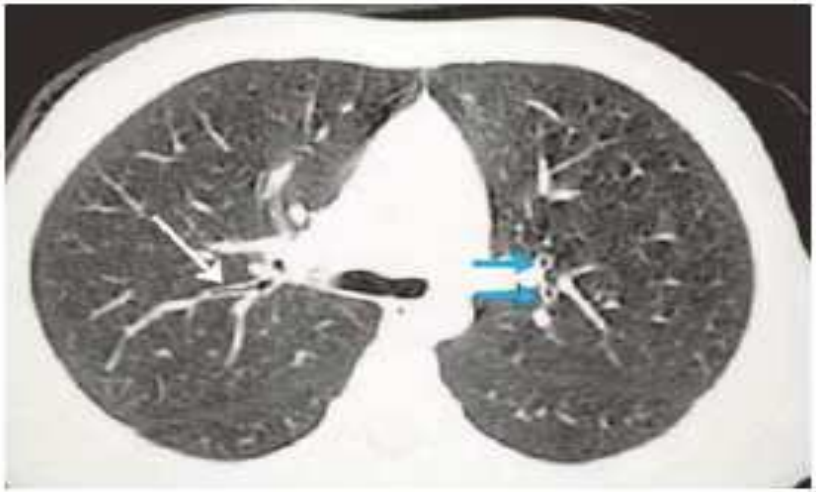

Figure 5. High-resolution axial CT of a 10-year-old boy demonstrating mildly dilated central airways (blue arrows) and mild peribronchial thickening (white arrow).

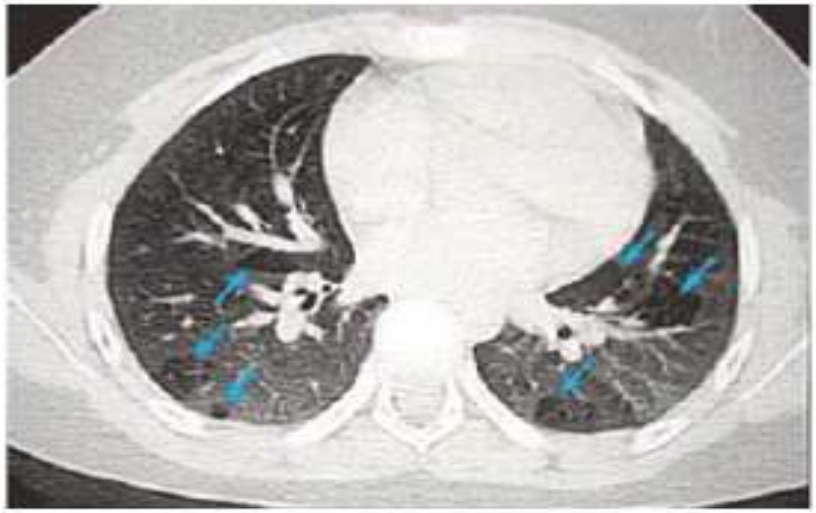

Figure 6. High-resolution expiratory CT of a 9-year-old boy demonstrating air trapping at the level of the secondary pulmonary lobule (arrows).

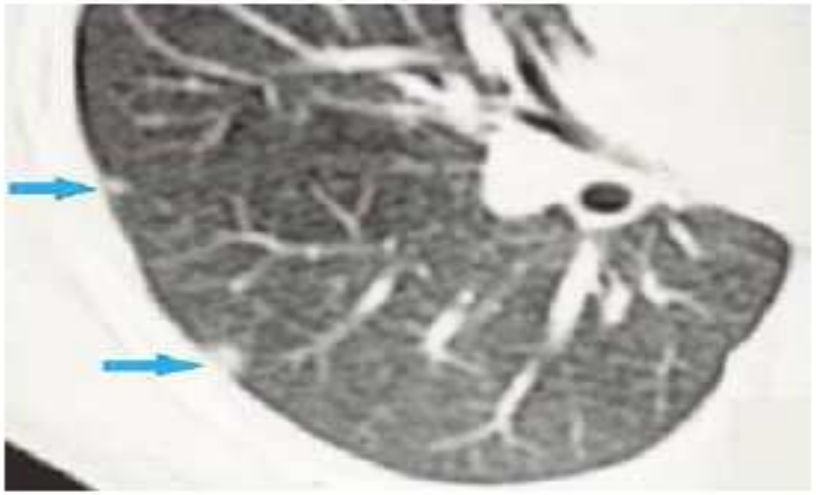

Figure 7. High-resolution CT of a 12-year-old demonstrating subpleural pulmonary nodules (arrows).

Particelle carboniose in macrofagi delle vie aeree di bambini in buona salute

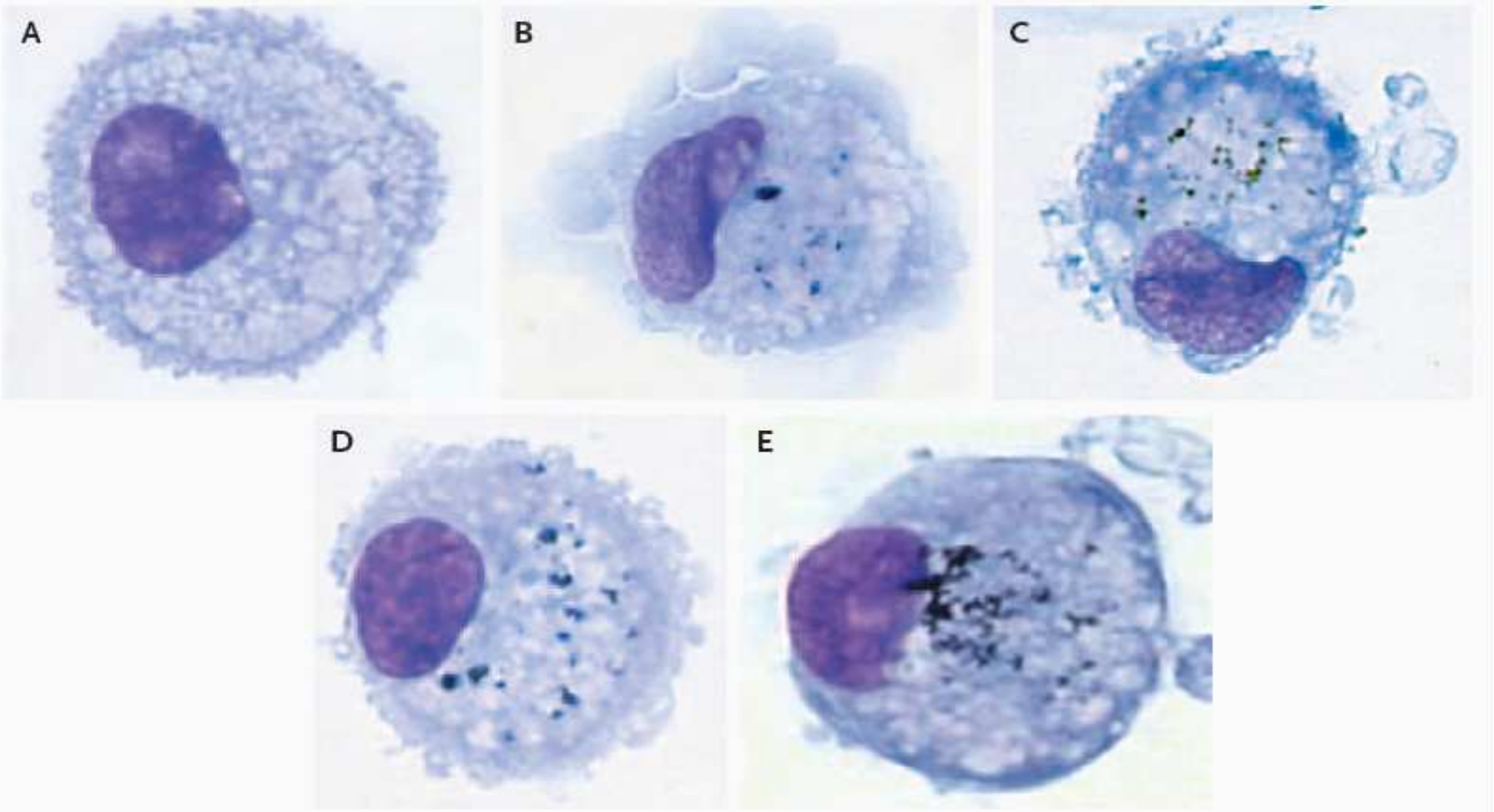

Figure 1. Representative Images of Carbon in Airway Macrophages from Healthy Children.

Panel A shows a macrophage with no carbon. Increasing levels of carbon are shown in Panels B through E. Airway macrophages were obtained from sputum, stained with Diff-Quik, and viewed with an oil-immersion lens. For each child, the area occupied by carbon in 100 randomly selected airway macrophages was determined by means of image analysis, and the median area (in square microns) per cell was calculated.

- **Prenatal exposures to persistent and non-persistent organic compounds and effects on immune system development.**
- Hertz-Picciotto I, Park HY, Dostal M, Kocan A, Trnovec T, Sram R.
- Center for Children's Environmental Health and Department of Public Health Sciences, University of California, Davis, CA 95616, USA. ihp@ucdavis.edu
  Basic Clin Pharmacol Toxicol. **2008** Feb;102(2):146-54.
- **Immune system development, particularly in the prenatal period, has far-reaching consequences for health during early childhood, as well as throughout life**.
- **Environmental disturbance of the complex balances of Th1 and Th2 response mechanisms can alter that normal development. Dysregulation of this process or an aberrant trajectory or timing of events can result in atopy, asthma, a compromised ability to ward off infection, or other auto-immune disease.**
- **A wide range of chemical, physical and biological agents appear to be capable of disrupting immune development**. This MiniReview briefly reviews developmental milestones of the immune system in the prenatal period and early life, and then presents examples of environmentally induced alterations in immune markers.

The first example involves a birth cohort study linked to an extensive programme of air pollution monitoring; the analysis shows **prenatal ambient polycyclic aromatic hydrocarbons (PAH) and fine particle (PM2.5) exposures** to be **associated with altered lymphocyte immunophenotypic distributions in cord blood and possible changes in cord serum immunoglobulin E levels**.

- The second example is a study of **prenatal-polychlorinated biphenyl (PCB) exposures and the foetal development of the thymus,** the organ responsible for lymphocyte maturation. Mothers with higher serum concentrations of PCBs gave birth to neonates having smaller indices of thymus size.
- Finally, this report underscores the **tight connection between development of the immune system and that of the central nervous system, and the plausibility that disruption of critical events in immune development may play a role in neurobehavioural disorders.**

Environmental Health Perspectives • VOLUME 114 | NUMBER 8 | August 2006

Effect of Prenatal Exposure to Airborne Polycyclic Aromatic Hydrocarbons on Neurodevelopment in the First 3 Years of Life among Inner-City Children

Frederica P. Perera,[1] Virginia Rauh,[1] Robin M. Whyatt,[1] Wei-Yann Tsai,[1,2] Deliang Tang,[1] Diurka Diaz,[1] Lori Hoepner,[1] Dana Barr,[3] Yi-Hsuan Tu,[1] David Camann,[4] and Patrick Kinney[1]

[1]Columbia Center for Children's Environmental Health, Mailman School of Public Health, Columbia University, New York, New York, USA; [2]Department of Statistics, National Cheng Kung University, Taiwan, Republic of China; [3]Centers for Disease Control and Prevention, National Center for Environmental Health, Division of Laboratory Sciences, Atlanta, Georgia, USA; [4]Department of Analytical and Environmental Chemistry, Southwest Research Institute, San Antonio, Texas, USA

The impact of environmental toxicants on children's health is increasingly recognized as significant (Faustman 2000; Greater Boston Physicians for Social Responsibility 2000; Landrigan et al. 1999; Perera et al. 2002). Human and experimental studies indicate that the fetus and infant are more sensitive than adults to diverse environmental toxicants, including lead, mercury, environmental tobacco smoke (ETS), polycyclic aromatic hydrocarbons (PAHs), and pesticides (National Research Council 1993; Neri et al. 2006; Perera et al. 2005b; Whyatt and Perera 1995; World Health Organization 1986).

Although urban air pollution crosses geographic and socioeconomic boundaries, these same populations are likely to be more heavily exposed to indoor and outdoor air pollution and pesticides (Breysse et al. 2005; Olden and Poje 1995; Perera et al. 2002). As reported previously, the present study cohort has had substantial although variable exposure to multiple contaminants during pregnancy, with 100% of subjects having exposure to PAHs and pesticides in the air during pregnancy and 40% reporting ETS exposure (Perera et al. 2003; Rauh et al. 2004; Whyatt et al. 2002).

To our knowledge, there have been no prior human studies of the effect of prenatal exposure to airborne PAHs on child development. However, prenatal exposure to ETS has been associated with reduced fetal growth and cognitive functioning (Martinez et al. 1994; Rauh et al. 2004; Schuster and Ludwig 1994; Sexton et al. 1990; Windham et al. 1999; Yolton et al. 2005). Associations have been observed between prenatal exposure to the pesticide chlorpyrifos (CPF) and neurodevelopmental outcomes in experimental systems (Aldridge et al. 2005). Lead and mercury are known developmental toxicants affecting fetal development (Agency for Toxic Substances and Disease Registry 1999; Canfield et al. 2003; Grandjean et al. 1997; Lanphear et al. 2000).

Conclusion

This study provides evidence that environmental PAHs at levels recently encountered in the air of New York City may adversely affect cognitive development of children. The results require confirmation but are of potential concern because compromised mental performance in the preschool years is an important precursor of subsequent educational performance deficits. PAHs are widespread in urban environments worldwide largely as a result of fossil fuel combustion. Fortunately, airborne PAH concentrations can be reduced through currently available pollution controls, greater energy efficiency, and the use of alternative energy sources (Wong et al. 2004).

AACR Meeting Abstracts Online

EPIDEMIOLOGY 5: BIOMARKERS OF HUMAN EXPOSURE TO CARCINOGENS

Kirsti A. Bocskay, Dorothy P. Warburton, Manuela A. Orjuela, Xinhua Liu, and Frederica P. Perera

Chromosomal aberrations induced by prenatal polycyclic aromatic hydrocarbon exposure

AACR Meeting Abstracts, Mar 2004; 2004: 454.

- Molecular and traditional epidemiology studies have indicated a possible **relationship between *in utero* environmental exposures and increased risk for childhood cancers, especially acute leukemias.** In order to more clearly define this association, chromosomal aberrations, a biomarker of cancer risk, were measured in a subset of newborns from the Columbia Center for Children's Environmental Health (CCCEH) Prospective Cohort Study.. Linear regression demonstrated a significant positive association of PAHs, as measured by personal air monitoring during the third trimester, with stable aberration frequencies .. There were no significant associations between prenatal PAHs and unstable aberrations, which are less relevant to carcinogenesis ($p>0.1$).
- These results demonstrate **an association between prenatal exposure to environmental levels of PAHs and chromosomal aberrations in cord blood, raising concern about a potentially increased risk of cancer** in this cohort

AACR Meeting Abstracts Online

SYMPOSIUM: PRENATAL EXPOSURE AND CHILDHOOD CANCER:

Frederica P. Perera, Manuela A. Orjuela, Kirsti A. Bocskay, Deliang Tang, Robin M. Whyatt, Mel Greaves, Anthony Ford, and Dorothy P. Warburton

Prenatal exposures and childhood cancer.

AACR Meeting Abstracts, Apr 2006; 2006: 1356 - 1357

1 Many lines of evidence suggest a role for ***in utero*** **environmental exposures in childhood cancer, especially in childhood acute lymphocytic leukemia (ALL).** For example, the chromosomal rearrangement **t(12;21)**, commonly seen in childhood ALL, is detectable in the neonatal blood spots (Guthrie cards) of the cases. Although data are conflicting, there is epidemiologic evidence that **maternal exposure in pregnancy to pesticides, vehicle exhaust emissions, benzene, environmental tobacco smoke (ETS)** as well as **polymorphisms in children's genes that metabolize these xenobiotics (e.g., CYP1A1, GST-M1, -T1, -P1)** are associated with **childhood ALL (3;5)(4;8)**.

2 **Despite the estimated 10-fold lower PAH dose to the fetus based on laboratory animal experiments, the adduct levels in the newborns were similar to or higher than in the mothers.** This finding suggests that **the fetus may be 10-fold more susceptible to DNA damage than the mother and that in utero exposure to PAHs may disproportionately increase carcinogenic risk.**

Heightened fetal susceptibility could result from higher rate of cell proliferation and differentiation, greater absorption or retention of xenobiotics, and/or less efficient detoxification, DNA repair, or apoptotic mechanisms

Common fragile sites are specific regions in the human genome that are particularly prone to genomic instability under conditions of replicative stress. Recent data suggest that these sites depend on the checkpoint kinase ATR to maintain their stability.

Current Biology, Vol. 13, R231–R233, March 18, 2003,

3

Preliminary analysis has shown that **the number of aberrations observed per painted chromosome in this study population was not proportional to DNA content, suggesting that certain chromosomes may be more susceptible to breakage by certain chemical agents** .

These results show an association between prenatal exposure to airborne carcinogenic PAHs and chromosomal aberrations in cord blood, suggesting that **such prenatal exposures have the potential to cause the type of cytogenetic damage that has been related to increased cancer risk in other populations.** We are now analyzing chromosomal aberrations in larger numbers of newborns and children from the cohort. In addition, we are exploring **mediation of the effect of environmental exposures on fetal chromosomal aberrations by fetal and maternal genotypes (e.g., GST-M1, -P1, -T1, CYP1A1, PON1).** In addition to documenting the overall level of chromosomal damage in relation to *in utero* exposures, **we are evaluating specific changes known to be directly pre-leukemogenic.** The **TEL-AML1 fusion product appears to be a necessary but not sufficient step for the development of childhood ALL (4;6)**. The origin of these initial chromosomal translocations is not known but **appears to be linked to prenatal exposures**. We are currently analyzing cord blood samples from our cohort for TEL-AML1 in order to evaluate their possible relationship with prenatal exposures.

4

These studies suggest that **there is substantial transplacental exposure to carcinogens in the urban environment, that procarcinogenic genetic damage in the form of adducts and chromosomal aberrations results from prenatal exposures, and that the fetus is more susceptible to DNA damage than the mother**. Further studies are ongoing to determine the persistence of chromosomal aberrations through early childhood and the relationship between prenatal exposures and specific pre-leukemogenic rearrangements in cord blood samples. Such molecular epidemiologic data can help inform us of the full range of carcinogenic risk from environmental exposures and thus contribute to the development of policies that will protect the young.

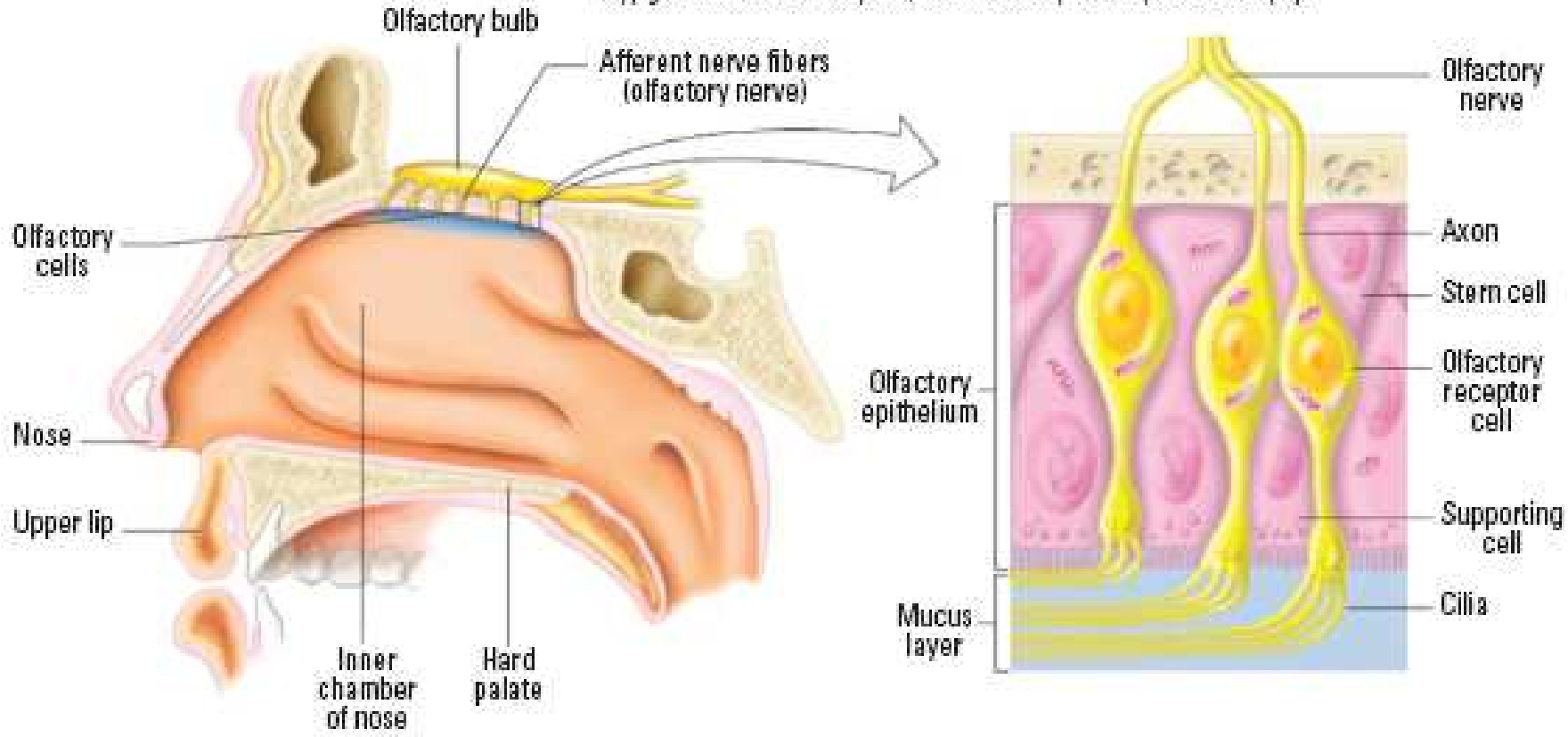

Figure 12. Close proximity of olfactory mucosa to olfactory bulb of the CNS. Inhaled NSP[s], especially below 10 nm, deposit efficiently on the olfactory mucosa by diffusion, similar to airborne "smell" molecules which deposit in this area of olfactory dendritic cilia. Subsequent uptake and translocation of solid NSP[s] along axons of the olfactory nerve has been demonstrated in non-human primates and rodents. Surface chemistry of the particles may influence their neuronal translocation. Copyright © the McGraw-Hill Companies, Inc. Reproduced from Widmaier et al. (2004) with permission from McGraw-Hill.

Particle and Fibre Toxicology

BioMed Central

Review

Open Access

Translocation and potential neurological effects of fine and ultrafine particles a critical update

Annette Peters*[1,2], Bellina Veronesi[3], Lilian Calderón-Garcidueñas[4,5], Peter Gehr[6], Lung Chi Chen[7], Marianne Geiser[6], William Reed[8], Barbara Rothen-Rutishauser[6], Samuel Schürch[6,9] and Holger Schulz[2,10]

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Accepted: 08 September 2006

This article is available from: http://www.particleandfibretoxicology.com/content/3/1/13

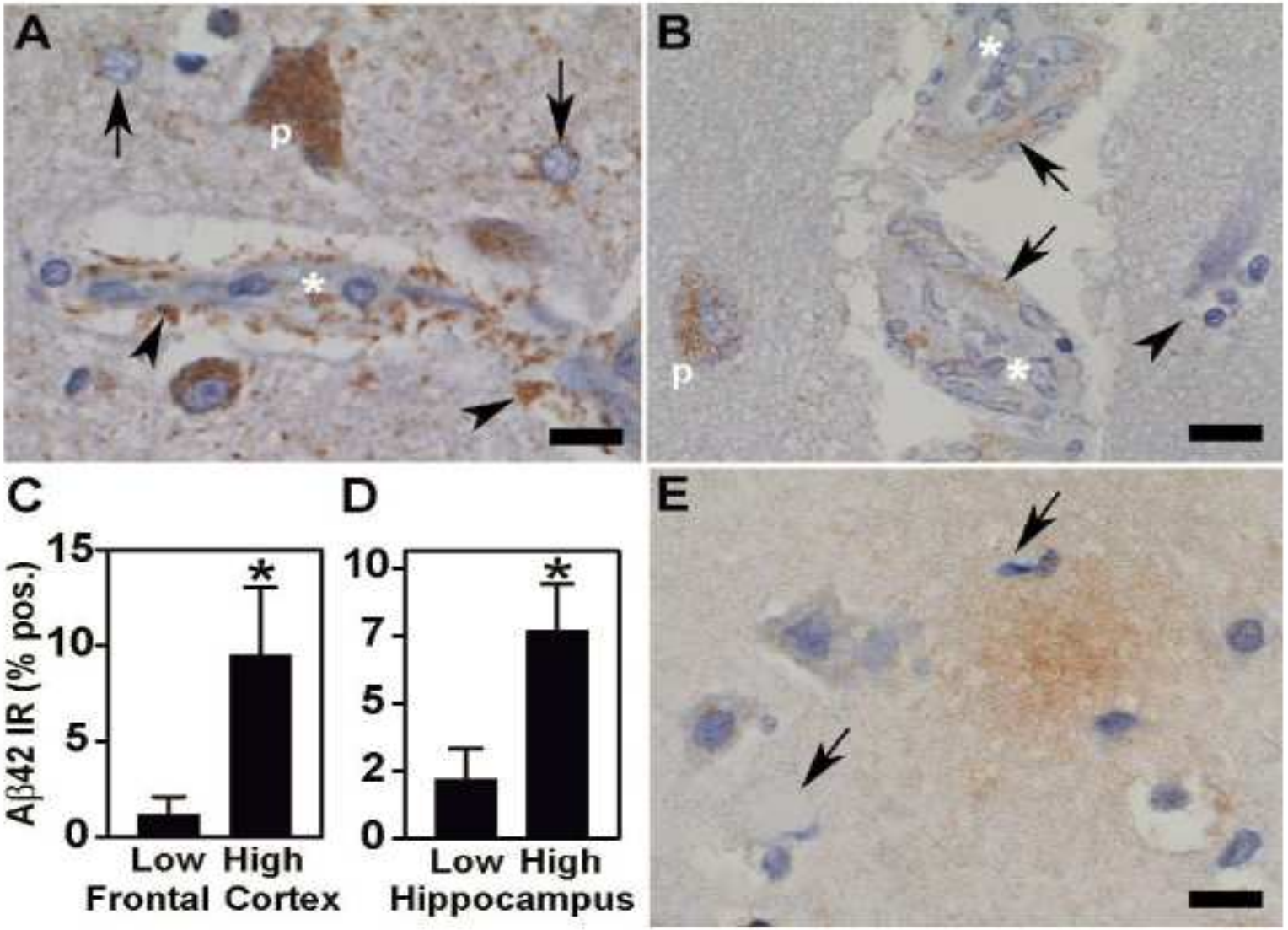


Figure 3

Aβ42 accumulation in frontal cortex and hippocampus. Aβ42 was localized in sections of paraffin-embedded tissues by IHC. (A) Aβ42 IHC stained pyramidal neurons (p), astrocytes (arrows) and astrocytic processes (arrowheads) around blood vessels (*). (B) In addition to accumulation in pyramidal neurons (p) Aβ42 was deposited in smooth muscle cells (arrows) in cortical arterioles (*). A dead neuron surrounded by glial cells is indicated (arrowhead). (C and D) Quantitative image analysis of Aβ42 IHC showed a significant increase in Aβ42 immunoreactivity (Aβ42 IR) in both frontal cortex (C, * $p = 0.04$) and hippocampus (D, * $p = 0.001$) in the high exposure group. (E) Aβ42 IHC of frontal cortex from a 38 year old subject from Mexico City showing diffuse plaque-like staining with surrounding reactive astrocytes (arrows). Scale = 20 μm.

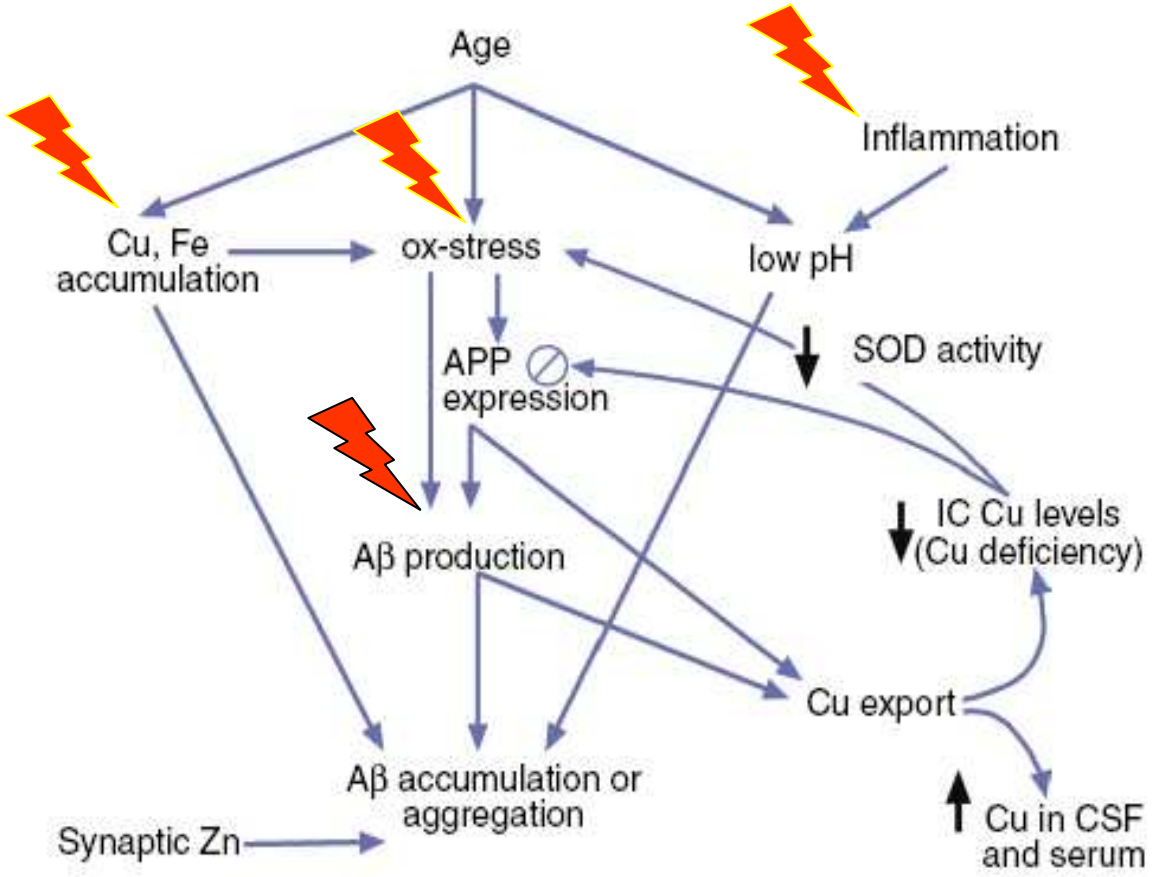
Int. J. Exp ath. (2005), 86, 147– 59

REVIEW

Metals and amyloid-β in Alzheimer's disease

Christa J. Maynard*†, Ashley I. Bush*†‡§, Colin L. Masters*†, Roberto Cappai*† and Qiao-Xin Li*†

*Department of Pathology, The University of Melbourne, Parkville, Victoria. Australia. †The Mental Health Research Institute of Victoria, Parkville, Victoria, Australia, ‡Laboratory for Oxidation Biology, C Hospital, Charlestown, MA, USA, and §Department of Psychiatry, Harvard Charlestown, MA, USA



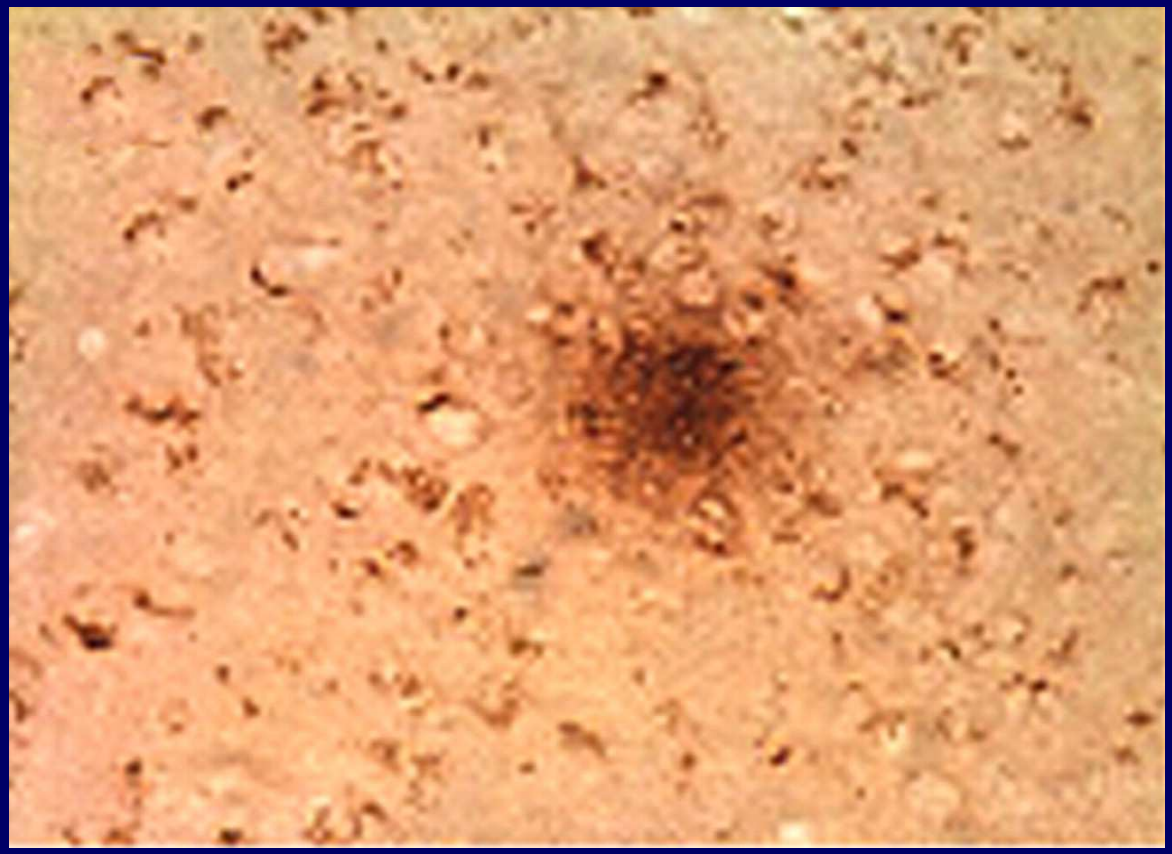
Oxidative stress and other metabolic stresses may promote *Ab production*
by jointly *upregulating amyloid precursor protein (APP) expression*

Developmental (Embrio-Fetal) Origin of AD.

Alzheimer Disease in primates exposed to lead as infants

Environmental Trigger

Early life exposures



J. Neurosci. 2008;28:i

SOCIETY FOR NEUROSCIENCE The Journal of Neuroscience

Alzheimer's disease (AD)-like pathology in aged monkeys after infantile exposure to environmental metal lead (Pb): evidence for a developmental origin and environmental link for AD.

J Neurosci. **2008** Jan 2;28(1):3-9.

Wu J, **Basha MR**, **Brock B**, **Cox DP**, **Cardozo-Pelaez F**, **McPherson CA**, **Harry J**, **Rice DC**, **Maloney B**, **Chen D**, **Lahiri DK**, **Zawia NH**.

Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, Rhode Island 02881, USA.

The sporadic nature of Alzheimer's disease (AD) argues for an environmental link that may drive AD pathogenesis; however, the triggering factors and the period of their action are unknown.

Recent studies in rodents have shown that **exposure to lead (Pb) during brain development predetermined the expression and regulation of the amyloid precursor protein (APP) and its amyloidogenic beta-amyloid (Abeta) product in old age**.

Here, we report that the **expression of AD-related genes [APP, BACE1** (beta-site APP cleaving
enzyme 1)] as well as their **transcriptional regulator (Sp1) were elevated in aged (23-year-old) monkeys exposed to Pb as infants.**

Furthermore, **developmental exposure to Pb altered the levels**, characteristics, and **intracellular distribution of A-beta staining** and **amyloid plaques in the frontal association cortex**.

These latent effects were accompanied by a **decrease in DNA methyltransferase activity and higher levels of oxidative damage to DNA, indicating that epigenetic imprinting in early life influenced the expression of AD-related genes and promoted DNA damage and pathogenesis**.

These data suggest that **AD pathogenesis is influenced by early life exposures** and argue for both an **environmental trigger** and a **developmental origin of AD**.

Environmental risk factors and the developmental basis for Alzheimer's disease.

Zawia NH, Basha MR.
Neurotoxicology and Epigenomics Lab, Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston 02881, USA. nzawia@uri.edu

Rev Neurosci. **2005;16(4)**:325-37

Alzheimer's disease (AD) is a progressive neurodegenerative disorder whose clinical manifestations appear in old age. **The hallmark pathological features of AD (amyloid plaques and associated proteins) are present in normal aging individuals, suggesting that AD may result from the acceleration of normal age-related processes in the brain**.

The sporadic nature of most AD cases strongly argues for an environmental link that may drive AD pathogenesis; however, it is unclear when this environmental stress may occur. Therefore it is important to **identify an environmental trigger(s)** and to **pinpoint the period** during which such factors pose the greatest risk.

Recently, we reported that **developmental exposure of rats to the xenobiotic metal lead (Pb)** resulted in **a delayed overexpression (20 months later) of the amyloid precursor protein (APP)** and its **amyloidogenic Aβ product**.

Similarly, **aged monkeys exposed to Pb as infants** also responded in the same way.

These data suggest that **environmental influences occurring during brain development predetermine the expression and regulation of APP later in life**, potentially influencing the course of ***amyloidogenesis***, and argue for both an **environmental trigger** and a **developmental origin of AD**. In this review, we present evidence for the **developmental basis of neurodegeneration** and discuss mechanisms that may explain how perturbations during development can have long-term or delayed consequences in the aging brain.

TRENDS IN CAUSES OF DEATH FROM 1979 TO 1998, USA

CAUSE	1998 PERCENT	CHANGE FROM 1979
• Alzheimer's Disease*	< 1 %	+1,200 %
Septicemia	< 1 %	+91 %
• Chronic Obstr. Lung	5 %	+46 %
• Diabetes mellitus	3 %	+39 %
• Hypertension	< 1 %	+26 %
• Pneumonia/influenza	4 %	+18 %
• Nephritis	< 1 %	+2 %
• Cancer	23 %	-6 %?

*The figures for Alzheimer's Disease may be misleading, because consciousness of Alzheimer's Disease has increased so much in that period that physicians may be increasingly likely to list it as a cause of death.

A Silent Pandemic

Industrial Chemicals Are Impairing The Brain Development of Children Worldwide

For immediate release: Tuesday, November 7, 2006

Fetal and early childhood exposures to industrial chemicals in the environment can damage the developing brain and can lead to neurodevelopmental disorders (NDDs) autism, attention deficit disorder (ADHD), and mental retardation.

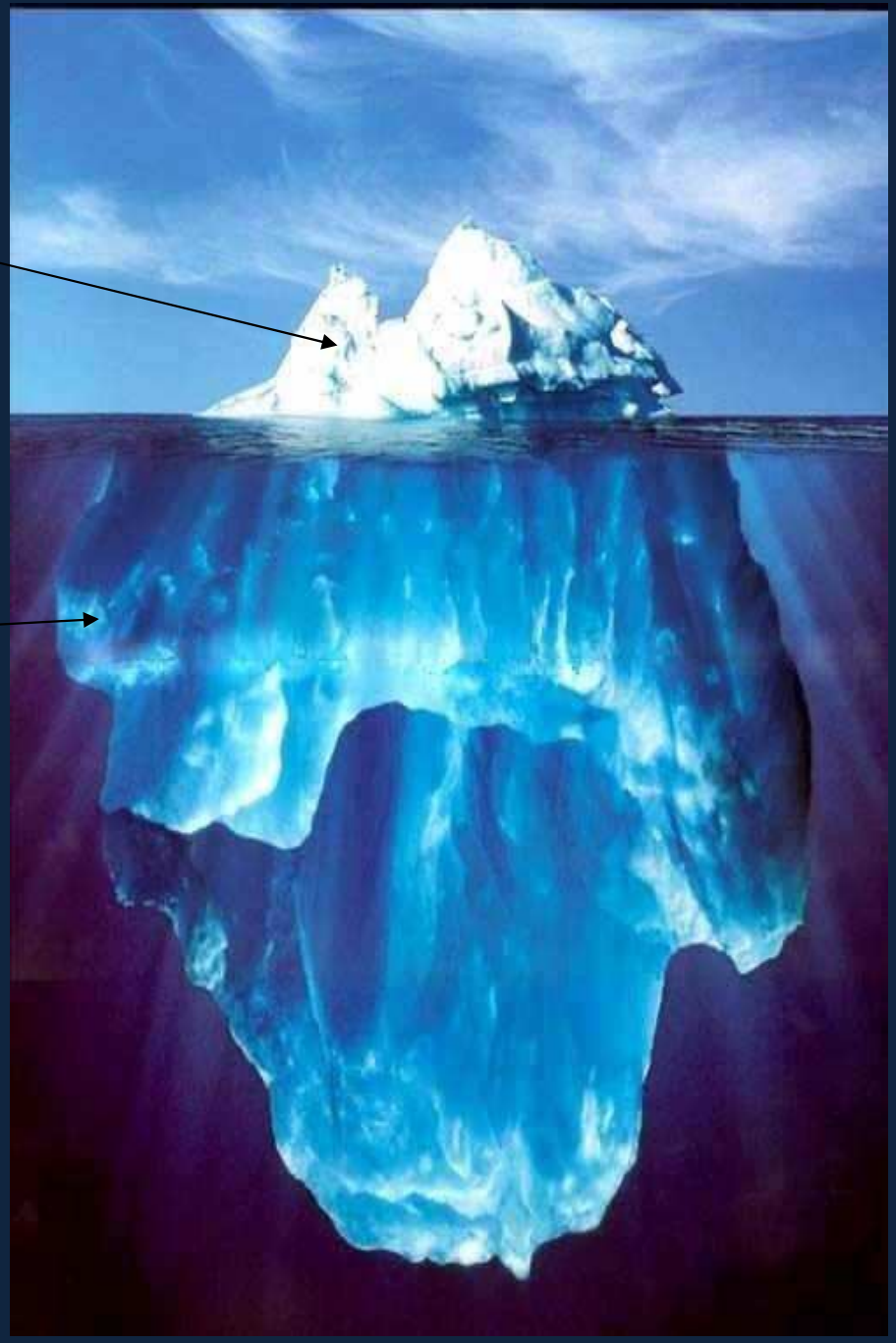
Developmental neurotoxicity of industrial chemicals.

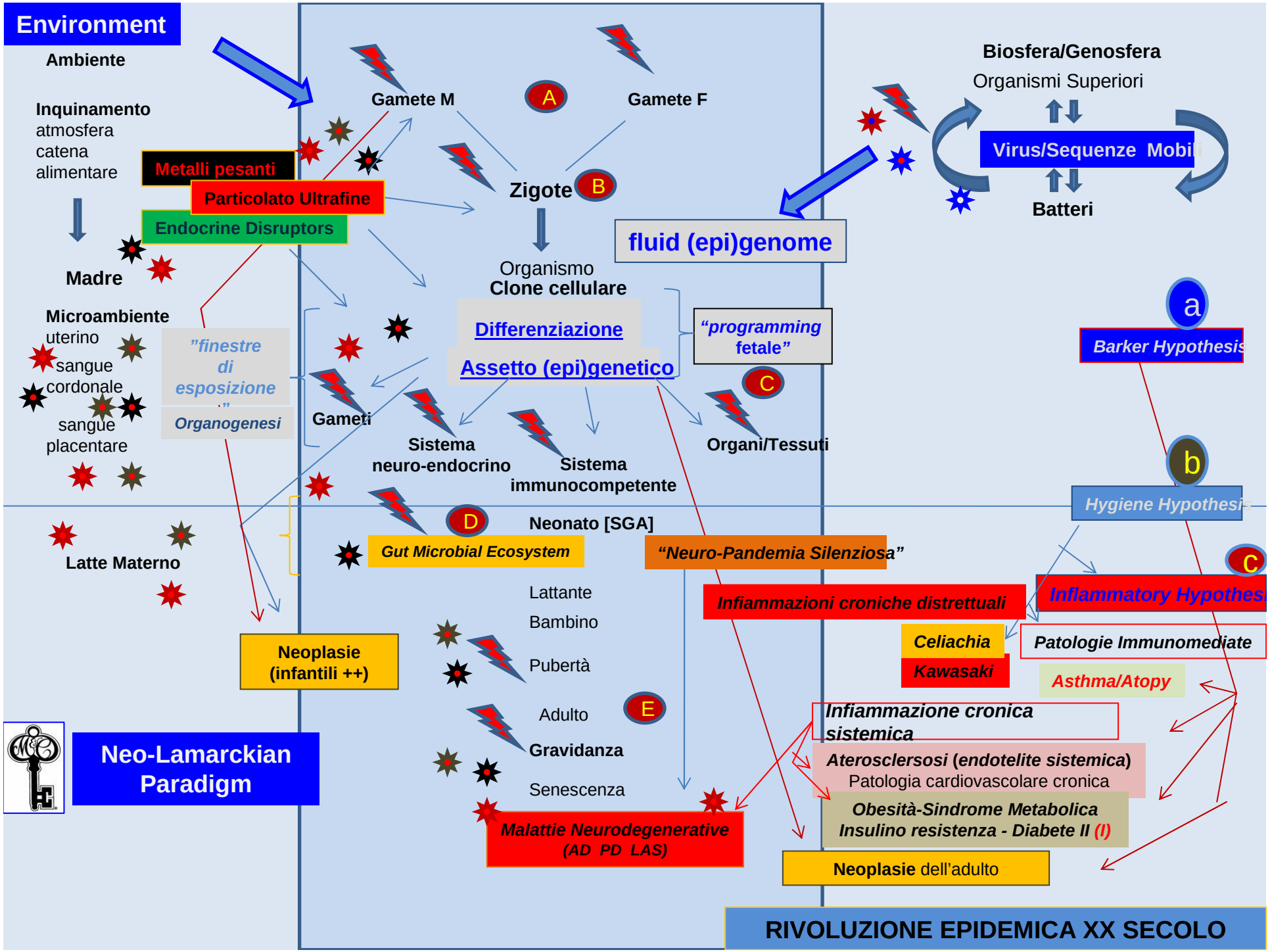
- **Grandjean P**, **Landrigan PJ**.
- Institute of Public Health, University of Southern Denmark, Odense, Denmark. pgrand@hsph.harvard.edu
- *Lancet*. 2006 Dec 16;368(9553):2167-78
- **Neurodevelopmental disorders such as autism, attention deficit disorder, mental retardation, and cerebral palsy are 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.

Patologie **cronico-degenerative** dell'adulto

Modifiche **epi-genomiche** fetali (***programming***

Amplificazione transgenerazionale del danno




Environment
Ambiente
Inquinamento
atmosfera
catena
alimentare
Metalli pesanti
Particolato Ultrafine
Endocrine Disruptors
Madre
Microambiente
uterino
sangue
cordonale
sangue
placentare
Latte Materno
"finestre
di
esposizione
"
Organogenesi
Gamete M
A
Gamete F
Zigote
B
Organismo
Clone cellulare
Differenziazione
Assetto (epi)genetico
Gameti
Sistema
neuro-endocrino
Sistema
immunocompetente
Organi/Tessuti
C
"programming
fetale"
D
Neonato [SGA]
Gut Microbial Ecosystem
Lattante
Bambino
Pubertà
Adulto
E
Gravidanza
Senescenza
Neoplasie
(infantili ++)
Malattie Neurodegenerative
(AD PD LAS)
fluid (epi)genome
Biosfera/Genosfera
Organismi Superiori
Virus/Sequenze Mobili
Batteri
"Neuro-Pandemia Silenziosa"
Infiammazioni croniche distrettuali
Neoplasie dell'adulto
a
Barker Hypothesis
b
Hygiene Hypothesis
c
Inflammatory Hypothesis
Celiachia
Kawasaki
Patologie Immunomediate
Asthma/Atopy
Infiammazione cronica
sistemica
Aterosclersosi (endotelite sistemica)
Patologia cardiovascolare cronica
Obesità-Sindrome Metabolica
Insulino resistenza - Diabete II (I)
Neo-Lamarckian
Paradigm
RIVOLUZIONE EPIDEMICA XX SECOLO

"Everything should be made as simple as possible, but not simpler."

Albert Einstein

God is **subtle** but not malicious

God does **not** play dice

È la celebre affermazione che suggella l'acceso dibattito tra Einstein e i sostenitori di una certa interpretazione della fisica quantistica…

I believe in Spinoza's God who reveals himself in the orderly harmony of what exists