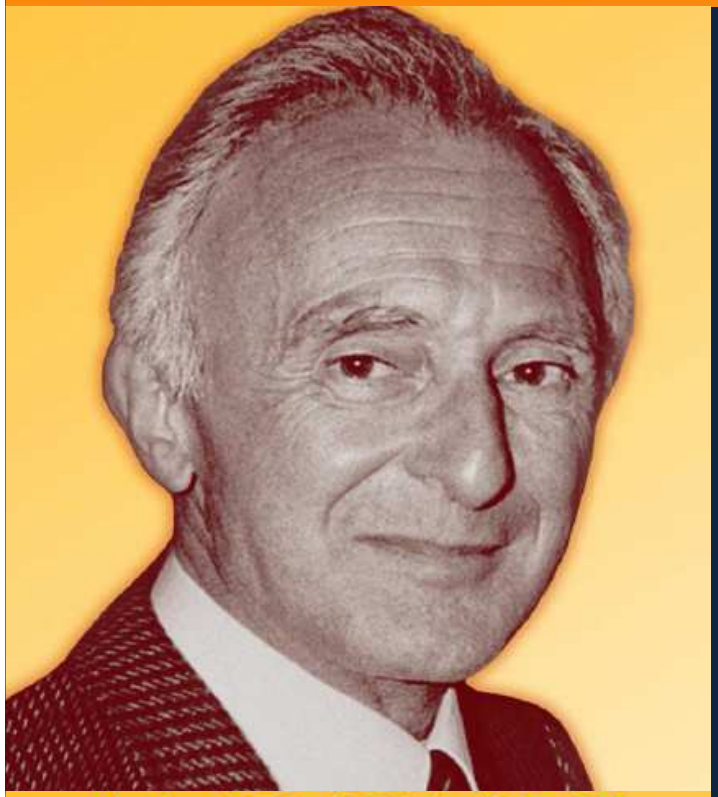
ASP Cosenza - P.O. di Castrovillari

U.O. DI MEDICINA INTERNA (Direttore: F. Laghi)



AMBIENTE è SALUTE

in memoria di Lorenzo Tomatis

La Rivoluzione Epidemica

Del XXI Secolo

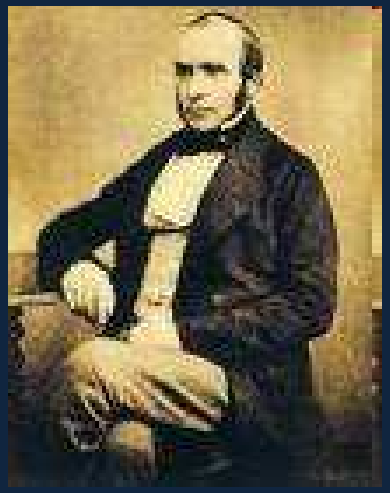
Ernesto Burgio
Comitato Scientifico
ISDE Italia

I Congresso Regionale Calabrese Associazione Medici per l'Ambiente ISDE – Italia

22 / 23 maggio 2009 - Castrovillari (CS) – Protoconvento

Epidemiology

"Distribution and determinants of disease frequency in human populations"



John Snow (15 March 1813 – 16 June 1858) was a British physician and a leader in the adoption of anesthesia and hygiene. He is considered to be one of the **fathers of epidemiology**, because of his work in **tracing the source of a cholera outbreak in Soho, England, in 1854.**

Faina Linkov, PhD; Research Assistant Professor of Medicine and Epidemiology; University of Pittsburgh Cancer Institute

Business Bias:

How Epidemiologic Studies May Underestimate or Fail to Detect Increased Risks of Cancer and Other Diseases

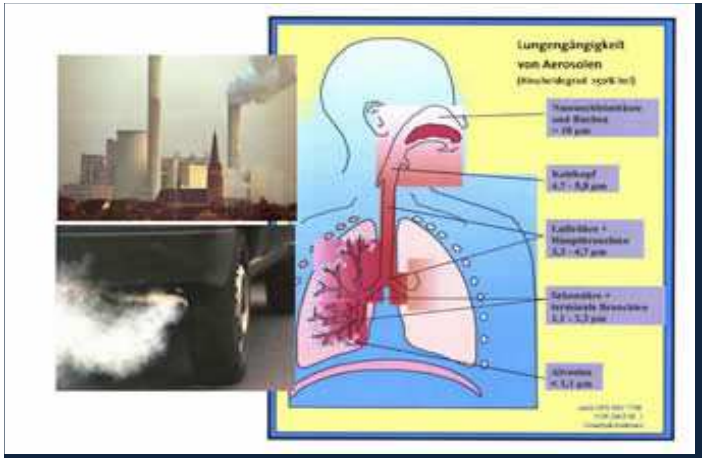
VALERIO GENNARO, MD, LORENZO TOMATIS, MD

In spite of claiming primary prevention as their aim, studies of potential occupational and environmental health hazards that are funded either directly or indirectly by industry are likely to have negative results. The authors present three common scenarios in which faulty design of epidemiologic studies skews results, and list 15 study design flaws that lead to results that are dangerously misleading with regard to both the evaluation and the improvement of public health. *Key words*: epidemiology; industry influence; study design; public health.

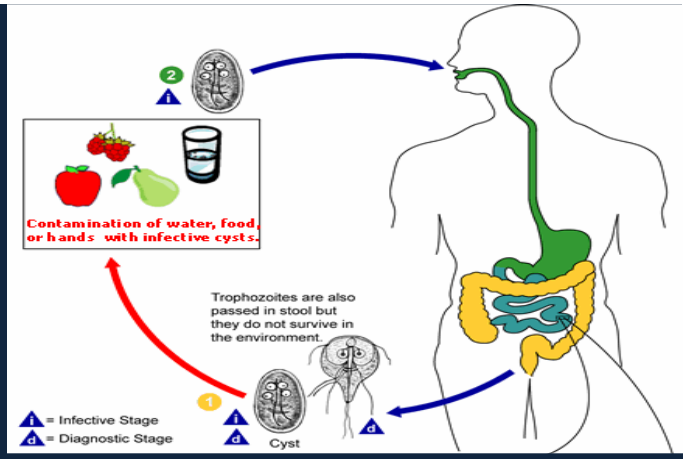
workers (vs unexposed). This may, of course, occur because there is no exposure at all, but in other instances the real cause of the negative results—that is, the absence of an association between exposure and adverse health effects—may reside in the epidemiologic study design.

We present three scenarios, examples of which have been observed in recent studies, in which real risks of disease are underestimated. In addition, we put forth 15 points, some of which are borrowed from a nearly [illegible] that are both critical and dan- [illegible] with regard to both the evaluation [illegible]t of public health. As reanalyses [illegible]re not available, we cannot, how- [illegible]t evaluation or simulation of spe-

…a list of 15 points oriented to show the reason why we cannot take for granted that the studied population is in good health even if the scientific documentation has given some indications about it..



1



A

- 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**)…

B

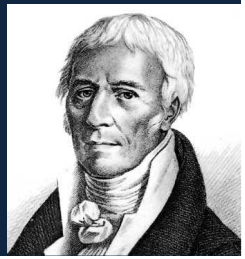
- **trascurando** quello che è il **contesto più generale**: una **drammatica e rapidamente progressiva trasformazione dell'ambiente fisico-chimico, degli ecosistemi biologici (in particolare micro-biologici) delle catene alimentari e dei singoli organismi** (in tutte le loro componenti e a tutti i livelli: sistemico, organico, tissutale, cellulare, **molecolare**) prodotta dall'uomo in pochi decenni …

A Generalmente ci si limita a valutare il **rischio legato a singole fonti di inquinamento confrontando popolazioni più o meno direttamente esposte**,

B e trascurando il fatto che **oggi l'inquinamento è un fenomeno ubiquitario e capillare e che l'esposizione** agli **agenti epi-genotossici** (fisici, (bio)chimici, biologici..) più pericolosi concerne, e in misura sempre più rilevante, **l'intera popolazione umana, le generazioni future,** l'**intera eco/biosfera**.

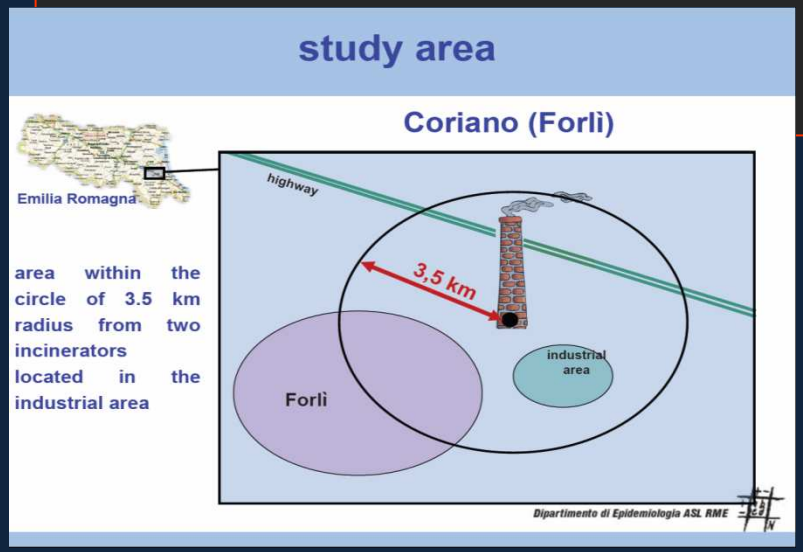
… a causa del **bio-accumulo/biomagnificazione degli *xeno-biotici***
in **ambiente, catena alimentare** e **tessuti degli organismi complessi**
e della **possibile trasmissione transgenerazionale delle modifiche epigenetiche**

CHEMICAL BURDEN-Carico Chimico Globale

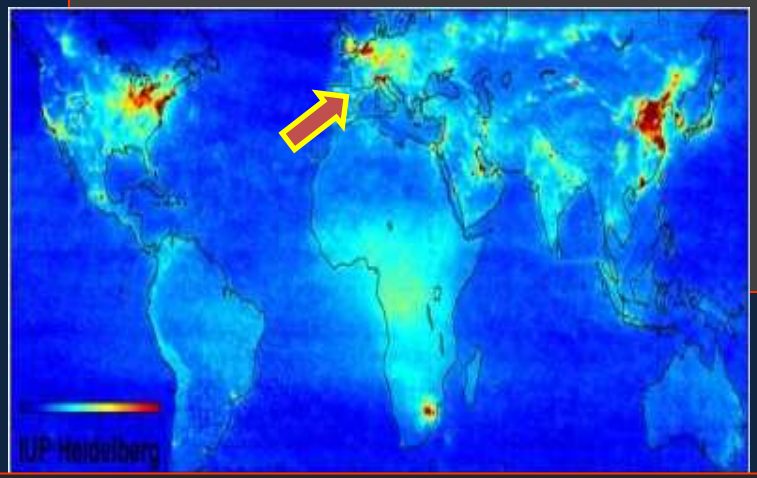


(in genere vengono paragonate **due popolazioni)**

- **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)



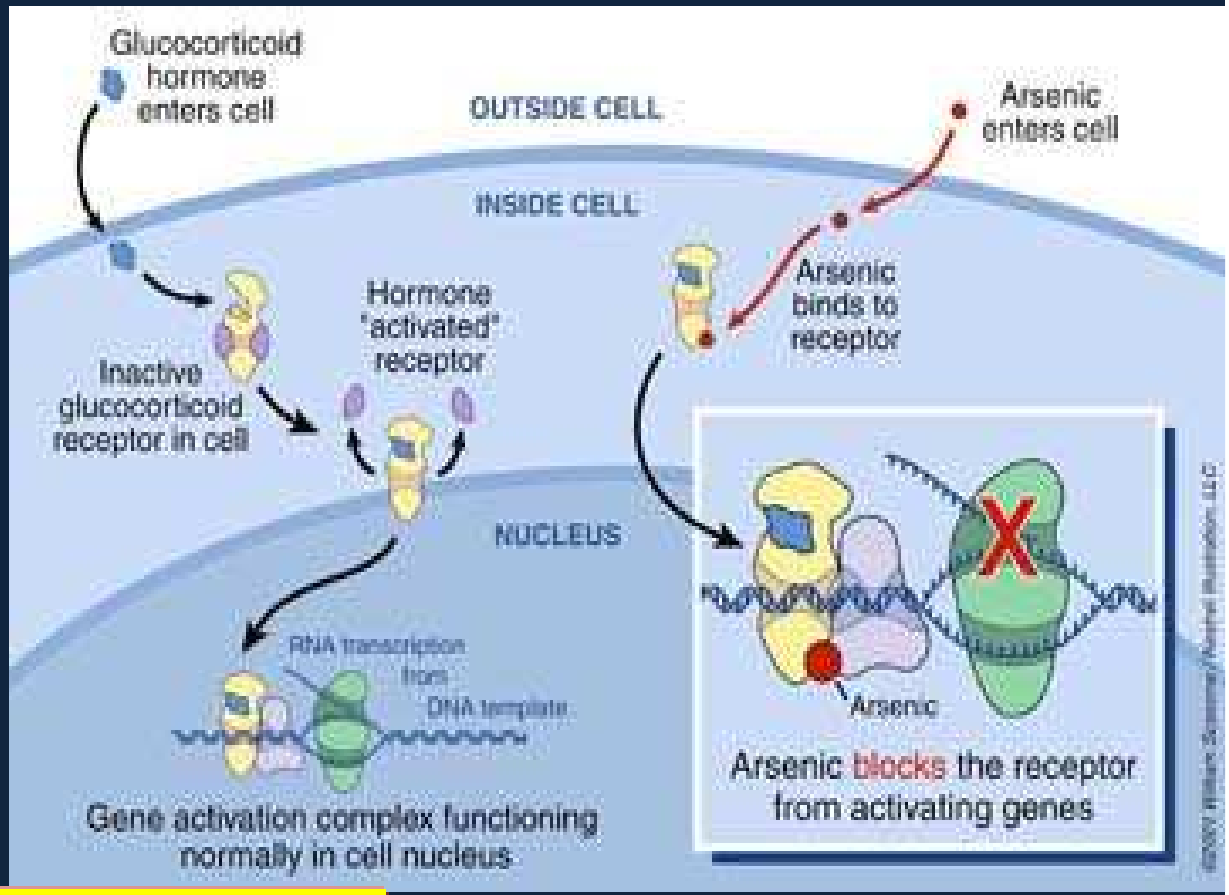
Né il discorso cambia di molto se si paragonano
l'incidenza locale di una o più patologie (prevalentemente ***neoplastiche***)..
e le **cosiddette patologie attese**, che sono a loro volta il frutto
di una **esposizione massiccia e progressiva agli stessi inquinanti**
(e la cui incidenza aumenta nel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

Everyday levels matter

At high levels… arsenic kills people

At <u>moderately low levels</u>… it causes a range of diseases

<u>At truly low levels …</u>
<u>it interferes with gene activation</u>



Kaltreider *et al.* 2002

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

- .. ma **soprattutto trascurando** il fatto che non solo le **patologie neoplastiche**, ma **tutte le patologie cronico-degenerative (cardio-vascolari, immuno-mediate/immuno-flogistiche, neuro-endocrine, neuro-degenerative)** hanno presentato, nel corso dell'ultimo secolo, un ***trend* costante di incremento** da taluni ricercatori messo in relazione con la **opposta e simme riduzione delle patologie acute da cause esogene (infettive e parassitarie)**, che per milioni di anni hanno contribuito alla organizzazione e stabilizzazione del nostro stesso **sistema immunocompetente**, ma che bisognerebbe mettere anche in relazione

Hygiene Hypothesis

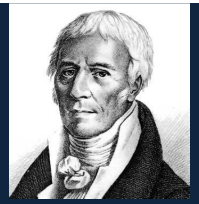
- con la **diffusione in ambiente di agenti esogeni (bio)chimico-fisici artificiali non co-evoluti** con gli organismi stessi **e potenzialmente in grado di interferire con tutti i sistemi bio-molecolari di regolazione cellulare e tessutale** e, soprattutto,
  - con l'assetto (epi)genetico delle cellule staminali negli organismi adulti e
  - con il *programming fetale* (cioè con le modifiche, almeno in certa misura reattive/adattative e programmatiche, dell'assetto epi-genetico dei vari tessuti nel corso dell'ontogenesi)

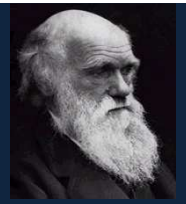
Barker Hypothesis

xeno-biotics

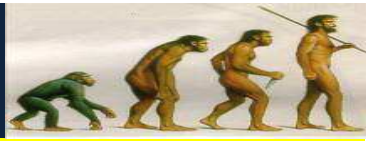
"Ambiente"

Milioni di anni





Evo



Challenge "naturale"

I processi *filo-genetici* durano milioni di anni

1

Agenti Fisici

Adattamento

Co-evoluzione

Tolleranza

Sistemi Neuro-endocrino Immunocompetente

>100mila molecole "*nuove*" non portato di una di co-evoluzione

Fall-Out Chimico

2

Self

(Epi)-genoma

Fetal Programming

Danger Signals

MHC

Antigeni

Non self

Genoma

virus

HERVs

Onco-géni

(*Retro-viruses*)

3

Agenti Biologici

(Retro)Trasposons)

V-onc

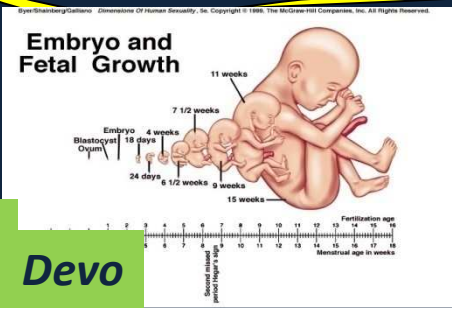
C-onc

Genosfera

IXX-XX SECOLO

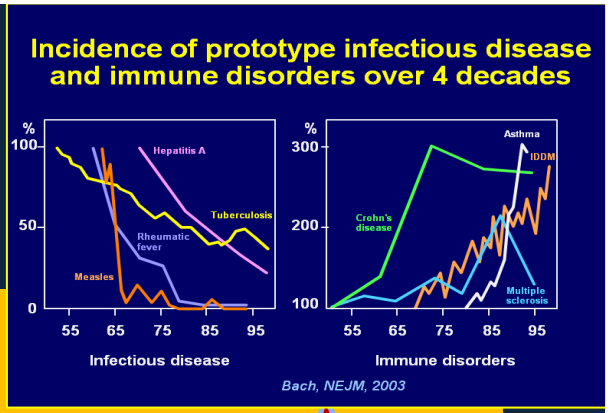
Drammatica Trasformazione Ambientale e Climatica

Biosfera



Lo sviluppo *onto-genetico* *dura 9 mesi → una vita*

Devo



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

1. *Barker Hypothesis*
2. *Hygiene Hypothesis*
3. *Systemic-chronic (low grade) Inflammation*

- Back to the NEO-LAMARCKIAN PARADIGM

ENVIRONMENT → Epigenetic Changes
→ Fetal Programming

Fluid (Epi)genome

A scientific challenge

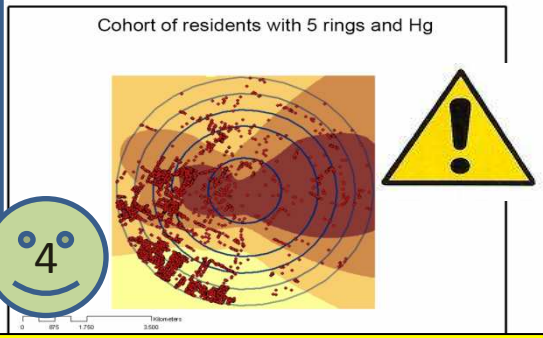
Limiti **tossicologia tradizionale**:
Dose-risposta → Tossicità acuta-diretta
Esposizione collettiva a minime dosi quotidiane – sinergie – bioaccumulo e biomagnificazione * – EDCs e Barker Hypothesis ** – Trasmissione Transgenerazionale *** …

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.

Limiti epidemiologia tradizionale:
Confronto (difficile) tra popolazioni esposte
Esposizione collettiva e ubiquitaria a minime dosi quotidiane
bioaccumulo e biomagnificazione* Barker Hypothesis *
Trasmissione Transgenerazionale*

Environmental Health Sciences



**** ** *** Effetti dilazionati** (di decenni) **e progressivi***

SOLUZIONE: Calcolo Emissioni** e **Carico Chimico Globale

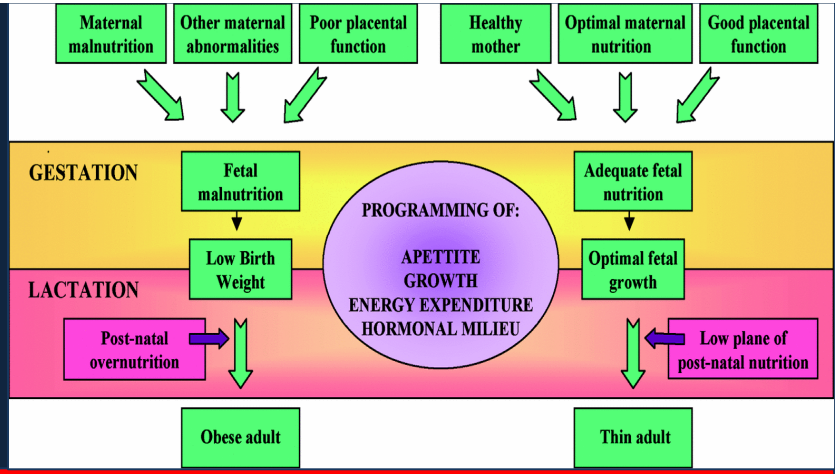
Four key scientific discoveries

-Some contaminants can alter gene behavior at **extremely low doses.**

-Adult diseases and sensitivity to subsequent exposures can be **programmed during development.**

-High dose experiments don't predict those **low dose impacts.**

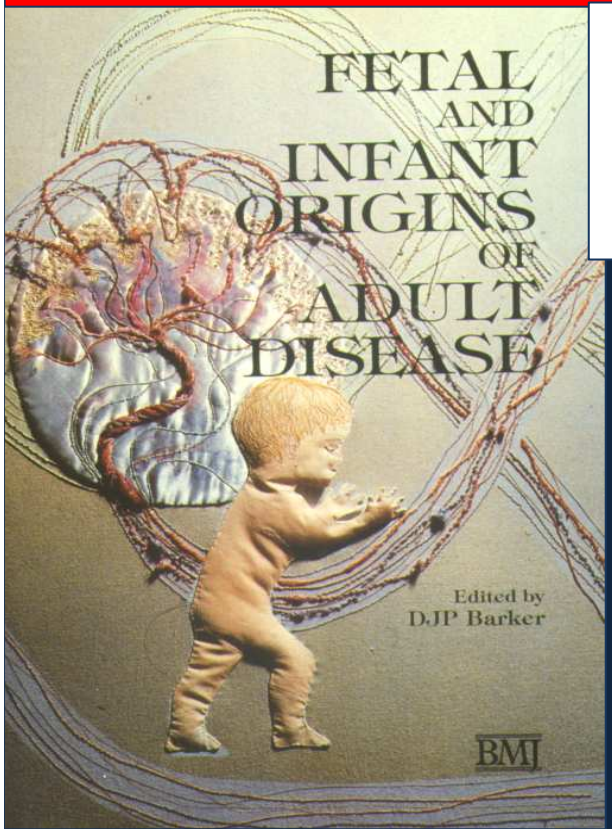
- Mixtures are ubiquitous; they alter impacts, sometimes **unpredictably**



ISDE Directing Board Meeting

ENVIRONMENT AND HEALTH
April 18 to 20 – 2008
International Conference

The Environmental Toxic Burden and the fetal origins of adult diseases



doctors for the environment

Ernesto Burgio (ISDE Italy)

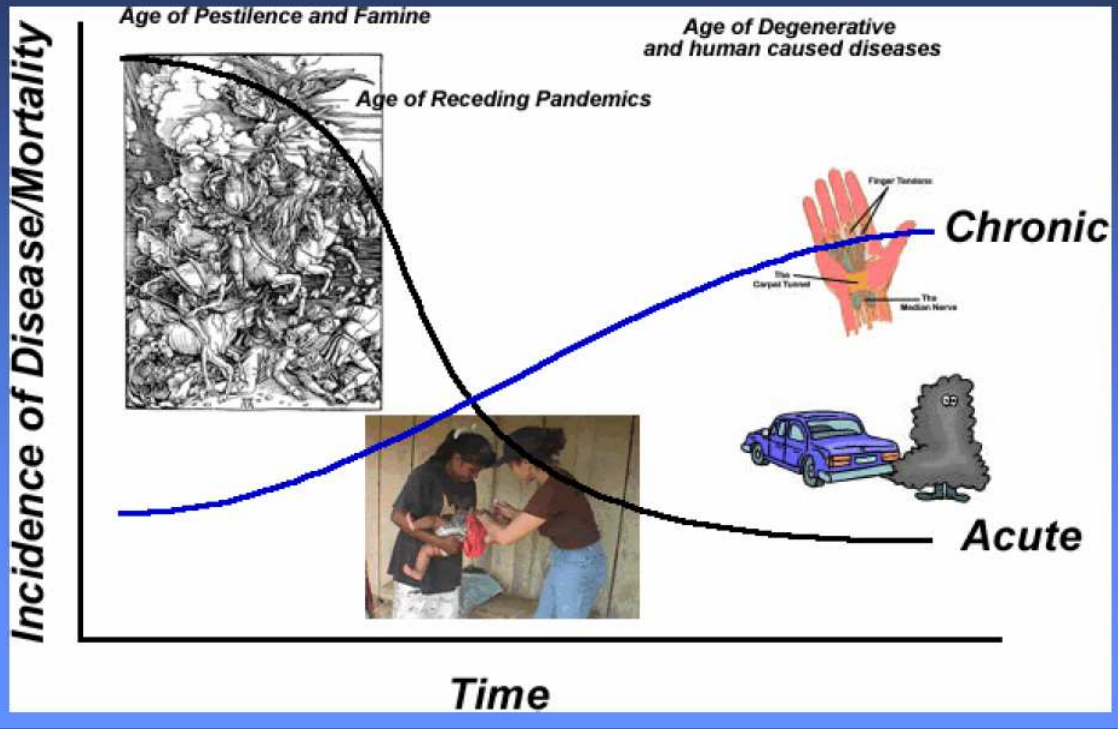
ENCYCLOPÆDIA Britannica

Epidemiologic transition

- The epidemiologic transition is that process by which the pattern of mortality and disease is transformed
- from **one of high mortality among infants and children and episodic famine and epidemic affecting all age groups**
- **to one of degenerative and man-made diseases affecting principally the elderly.**

Stages of ***Epidemiological Transition***

- **Age of Pestilence and Famine**
- Age of **Receding Pandemics**
- Age of **Degenerative and Man-made diseases**



OXFORD JOURNALS CONTACT US MY BASKET MY ACCOUNT

Journal of
Tropical Pediatrics

ABOUT THIS JOURNAL CONTACT THIS JOURNAL SUBSCRIPTIONS CURRENT ISSUE ARCHIVE SEARCH

Oxford Journals › Medicine › Journal of Tropical Pediatrics › Volume 29, Number 6 › Pp. 305-316

Journal of Tropical Pediatrics 1983 29(6):305-316; doi:10.1093/tropej/29.6.305

The Epidemiologic Transition Theory. A Preliminary Update

Abdel R. Omran

The Epidemiologic Transition: A Theory of the Epidemiology of Population Change

ABDEL R. OMRAN

The Milbank Quarterly, Volume 83, Issue 4 **(p 731-757)**

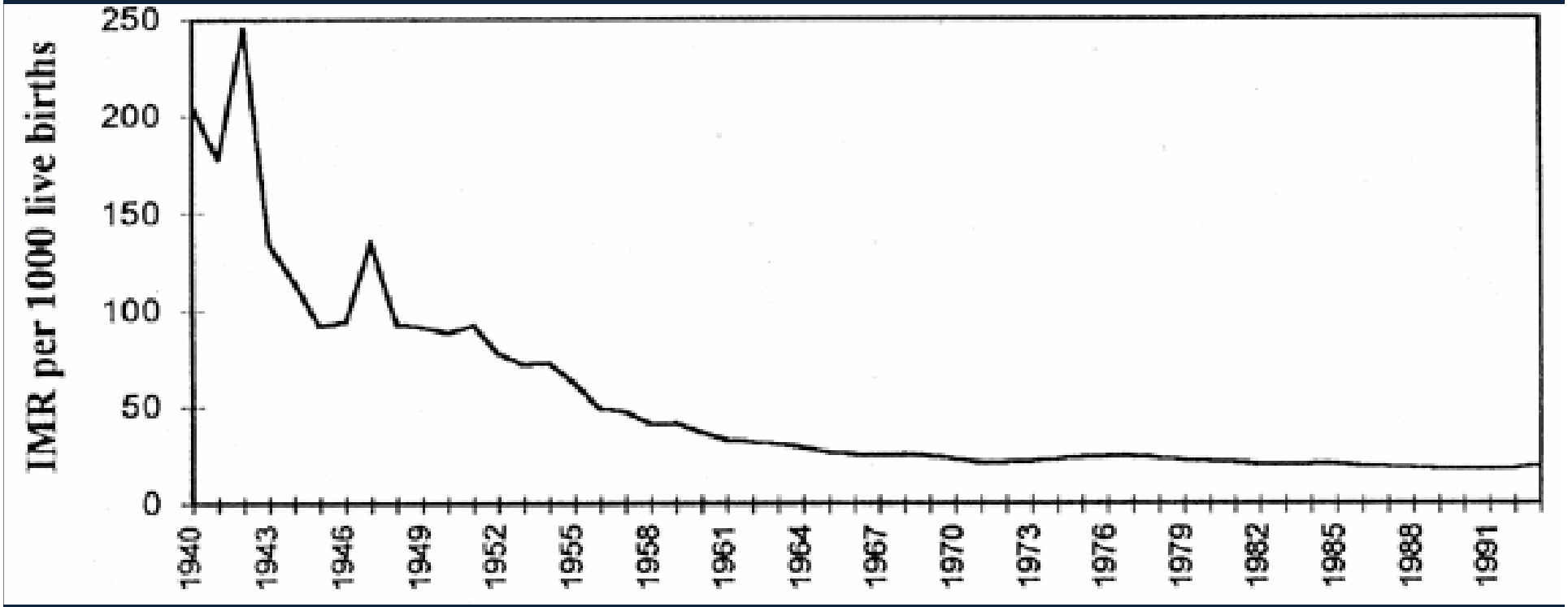
Focus of the Theory of Epidemiologic Transition

Conceptually, the theory of epidemiologic transition focuses on the complex change in patterns of health and disease *and* on the interactions between these patterns and their demographic, economic and sociologic determinants and consequences. An epidemiologic transition has paralleled the demographic and technologic transitions in the now developed countries of the world and is still underway in less-developed societies. Ample evidence may be cited to document this transition in which degenerative and man-made diseases displace pandemics of infection as the primary causes of morbidity and mortality.

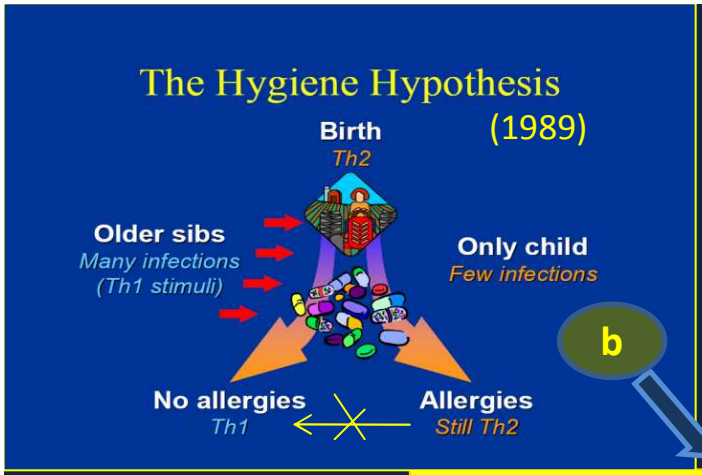
Ample evidence may be cited to document this **transition** in which **degenerative** and **man-made diseases displace pandemics of infection** as the primary causes of morbidity and mortality.

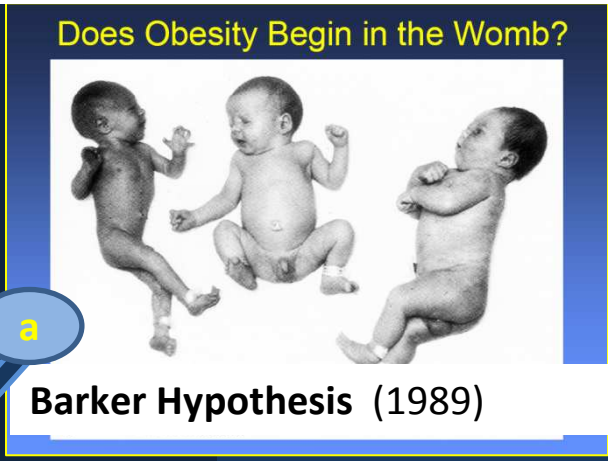
Infant Mortality Rate

Russia: 1940-1993



One of the major points of **Omran's theory** is that infant mortality is the basic driving force for increases and decreases of life expectancy





a

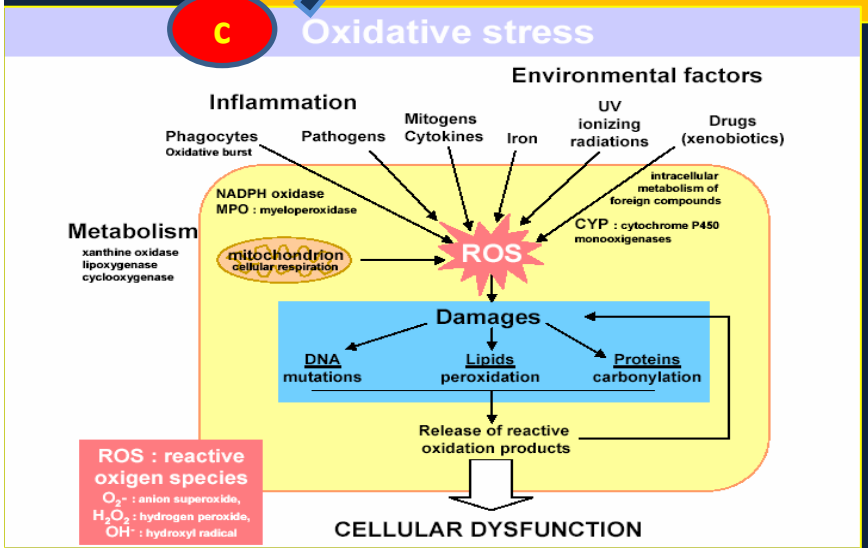
b

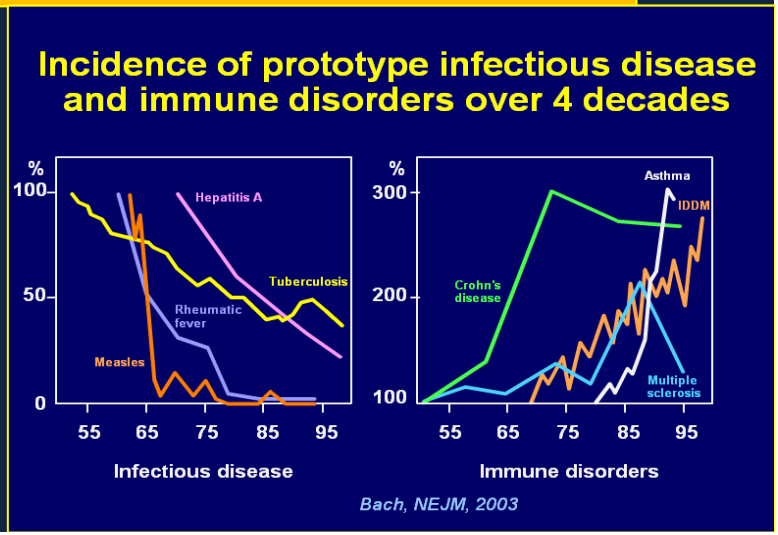
La **Rivoluzione Epidemica** del **XX Secolo**

Insulino-resistance
Diabetes
Cardiovascular Diseases

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

c





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

1

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

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

Hygiene Hypothesis

- 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 ***mal. autoimmuni***, ***sclerosi multipla*** …
- 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*** siano:
- *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)
- *dall'altro* le (connesse) alterazioni nello sviluppo e nell'azione dello stesso sistema immuncompetente (ritardo dello *switch* ***TH2-TH1***, **difetti nei meccanismi di *tolleranza*** ecc..)

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

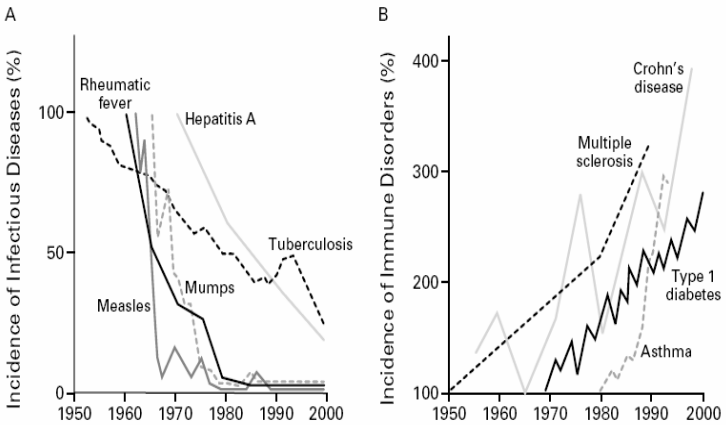


Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

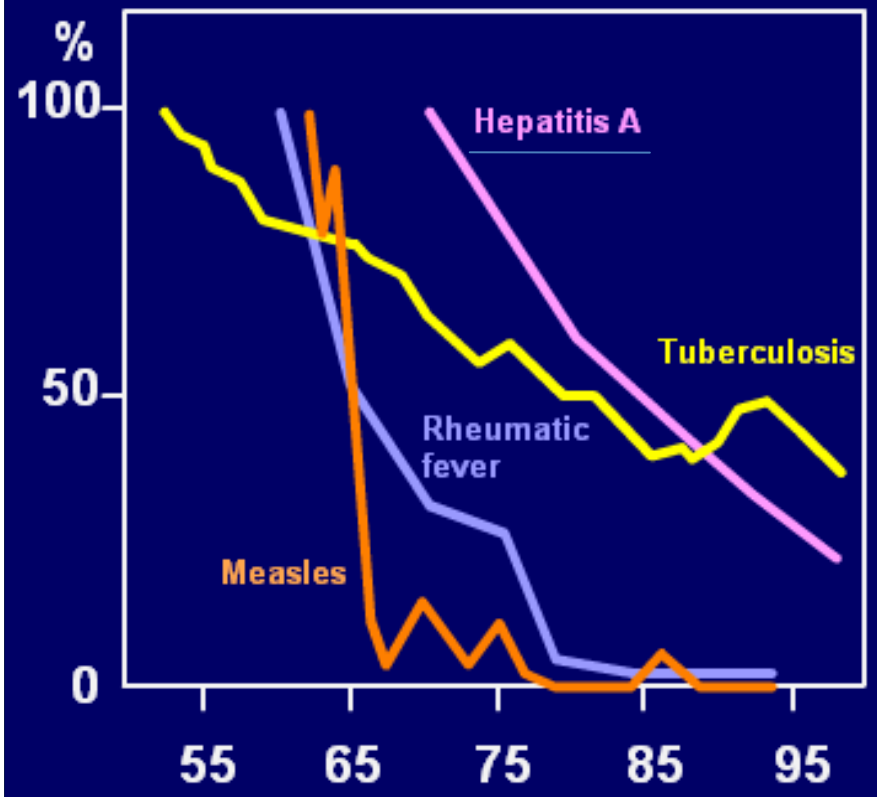
In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Joussemet et al.[12] In Panel B, data on immune disorders are derived from Swarbrick et al.,[10] Dubois et al.,[13] Tuomilehto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

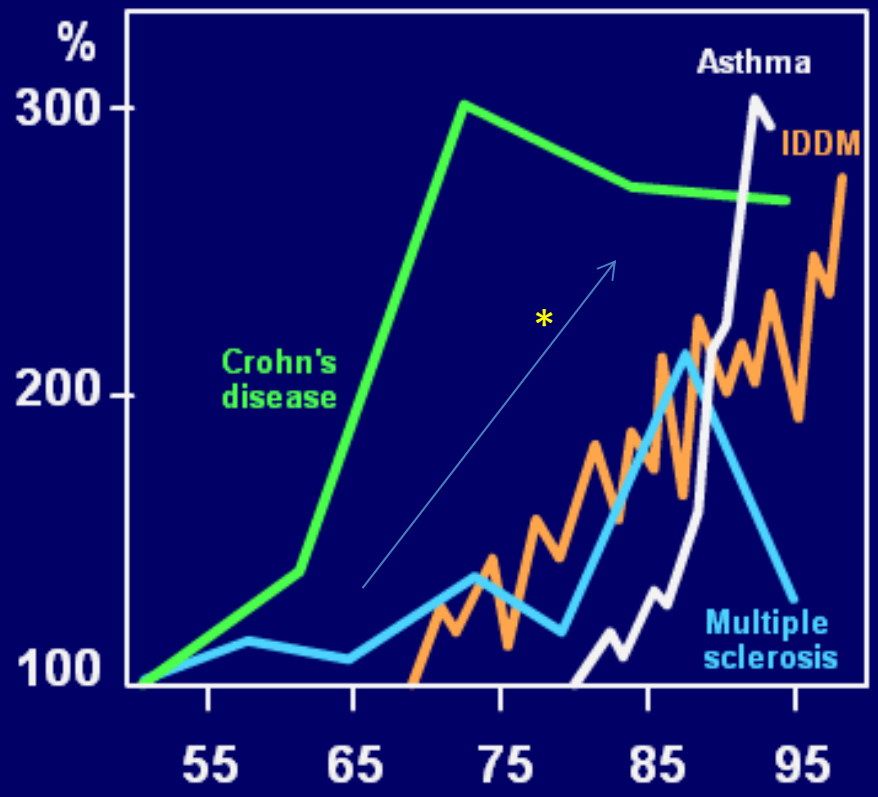
INFECTIOUS agents can induce autoimmune diseases in several experimental settings, some of which have clinical counterparts. A variety of mechanisms have been invoked to explain these observations, including molecular mimicry and an increase in the immunogenicity of autoantigens caused by inflammation 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



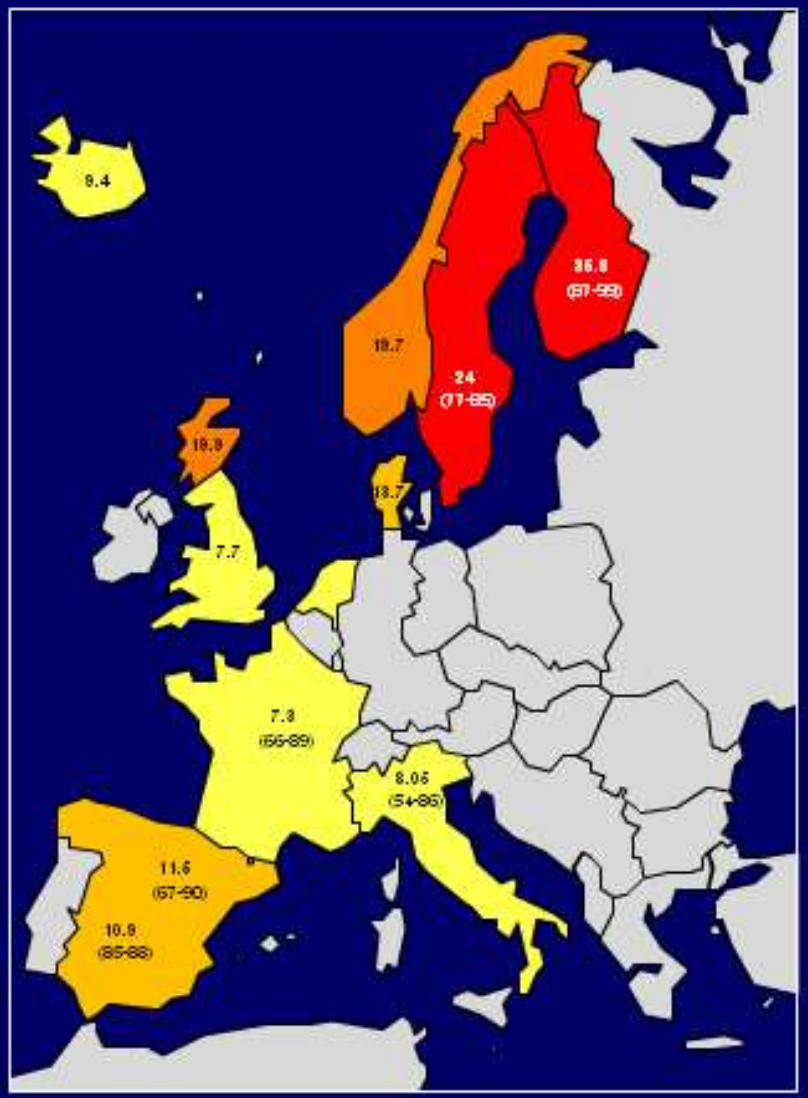


Bach, NEJM, 2003

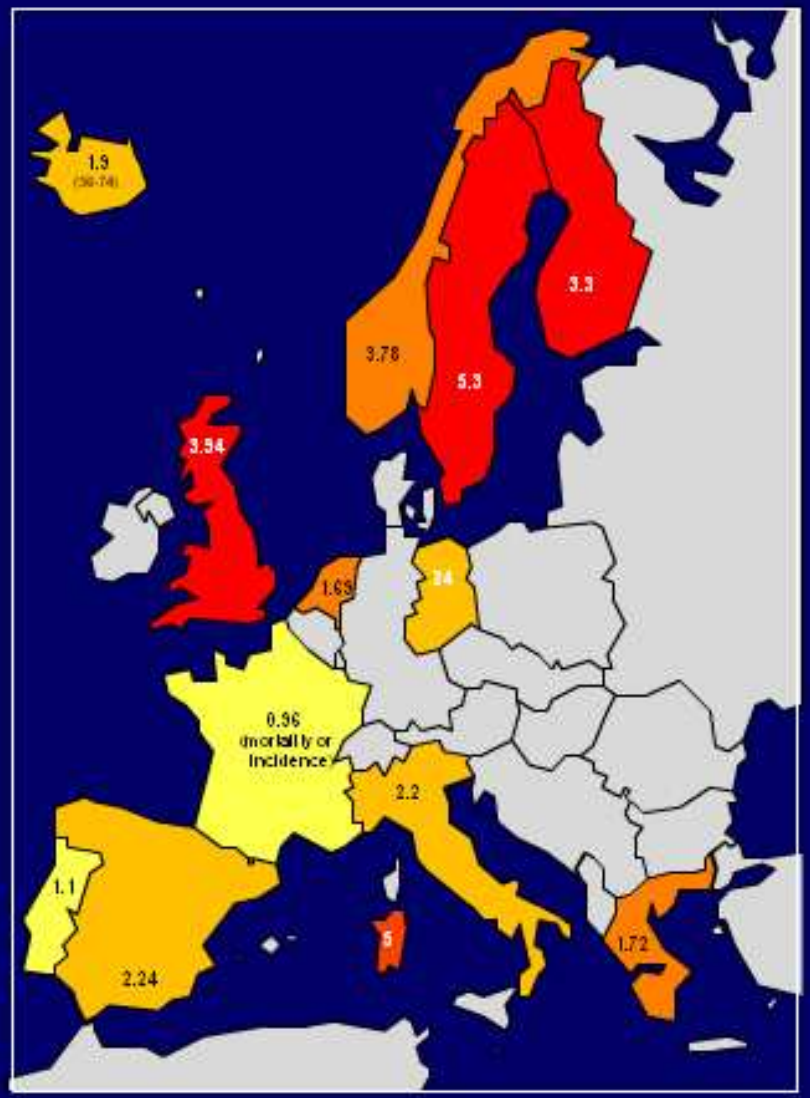
* Hepatitis B -C

!

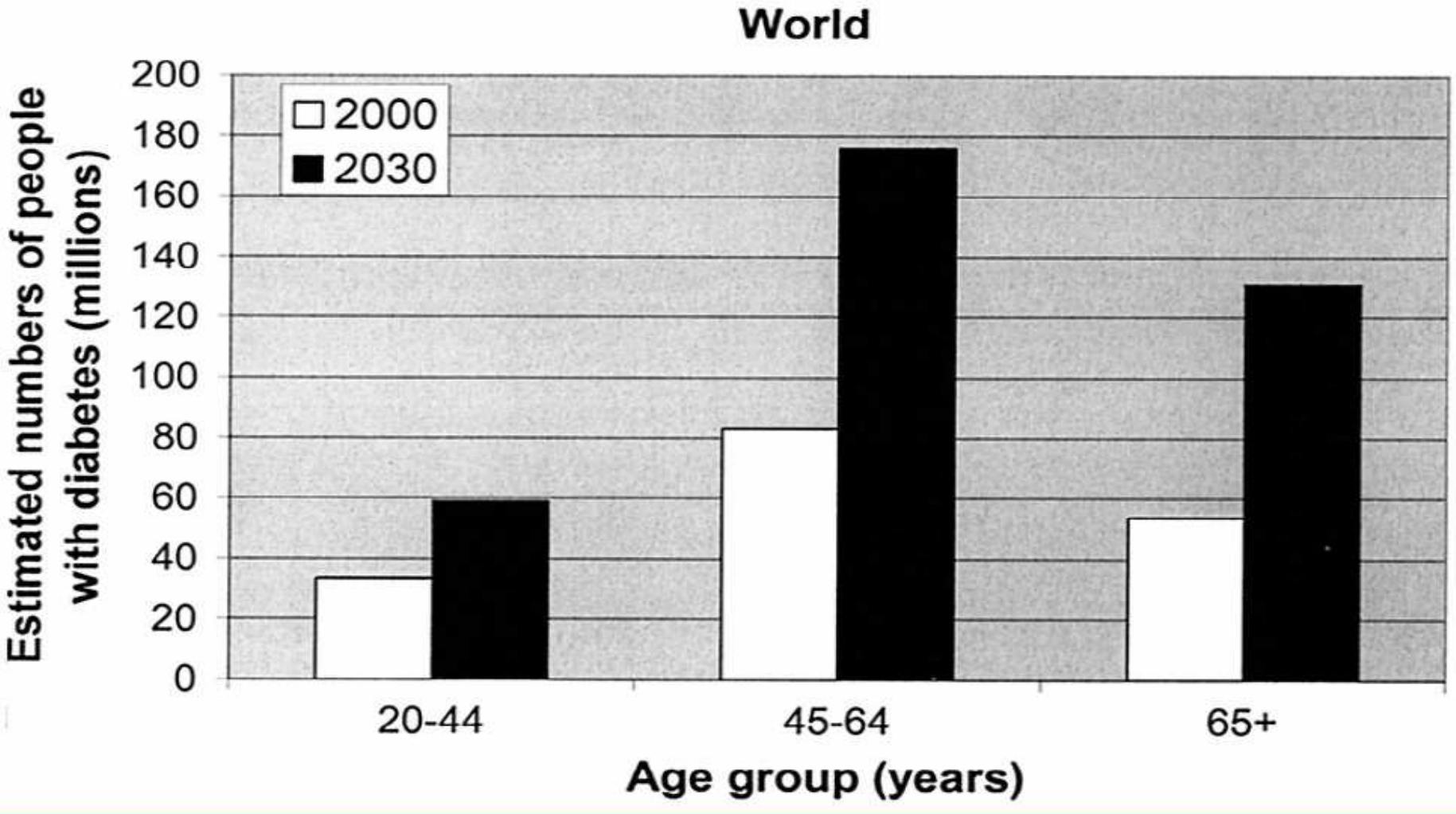
Incidence of IDDM
(per 100,000)



Incidence of multiple sclerosis
(per 100,000)



Diabetes Increasing Rapidly Worldwide

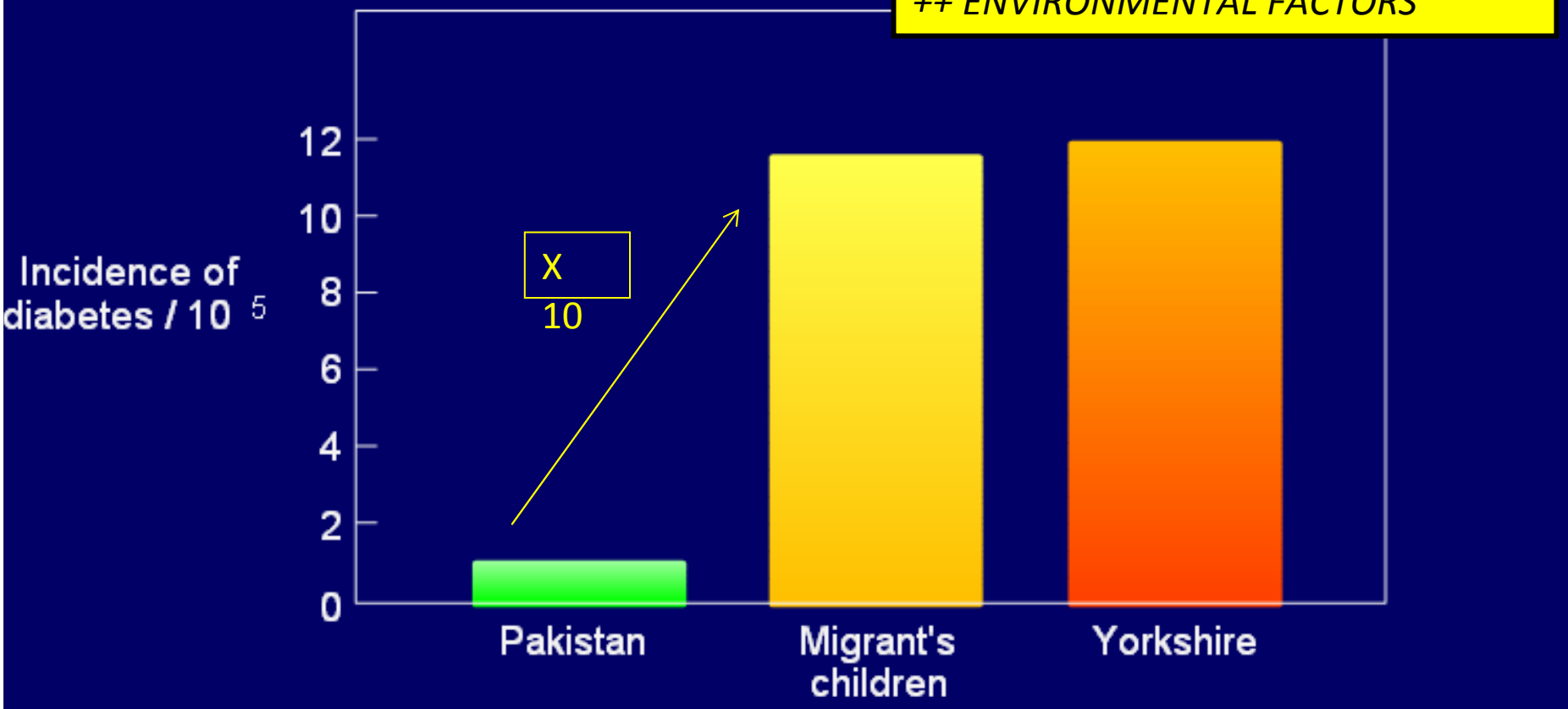


Wild S et al. Diabetes Care 2004; 27:1047

TIPE I DIABETES

IDDM incidence in children of migrants from Pakistan to Yorkshire

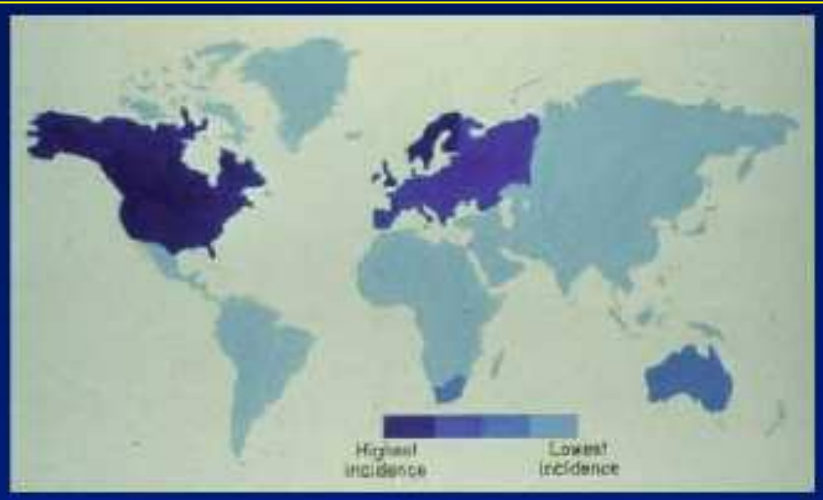
++ ENVIRONMENTAL FACTORS

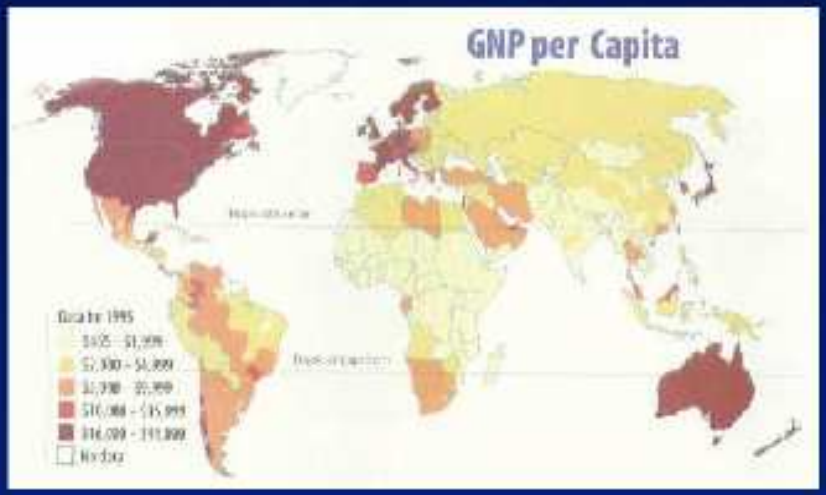


Staines A. (1997) and Bodansky H.J. (1992)

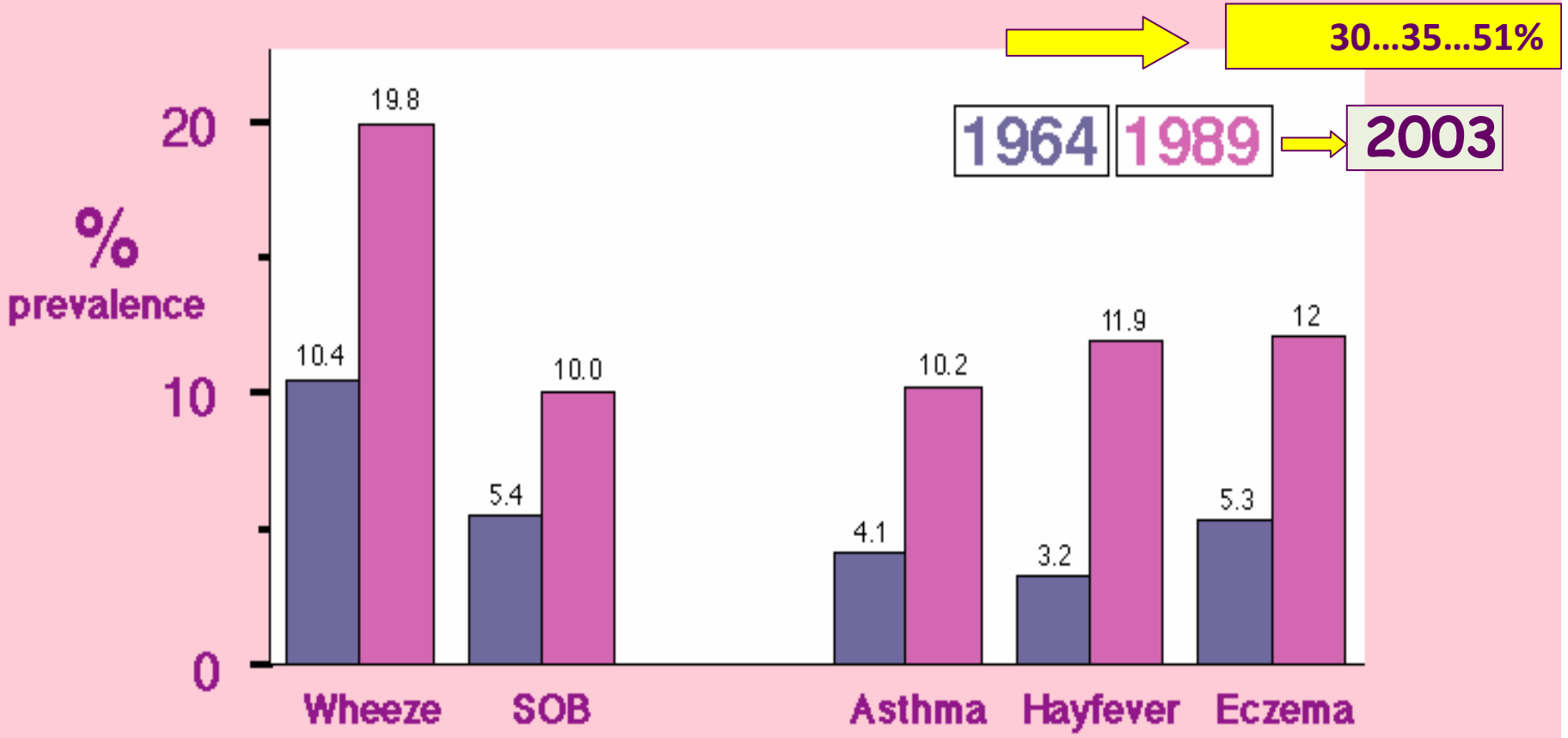
IBD & Industrialization and urbanization

INFLAMMATORY BOWEL DISEASES





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

Pulmonary Perspective

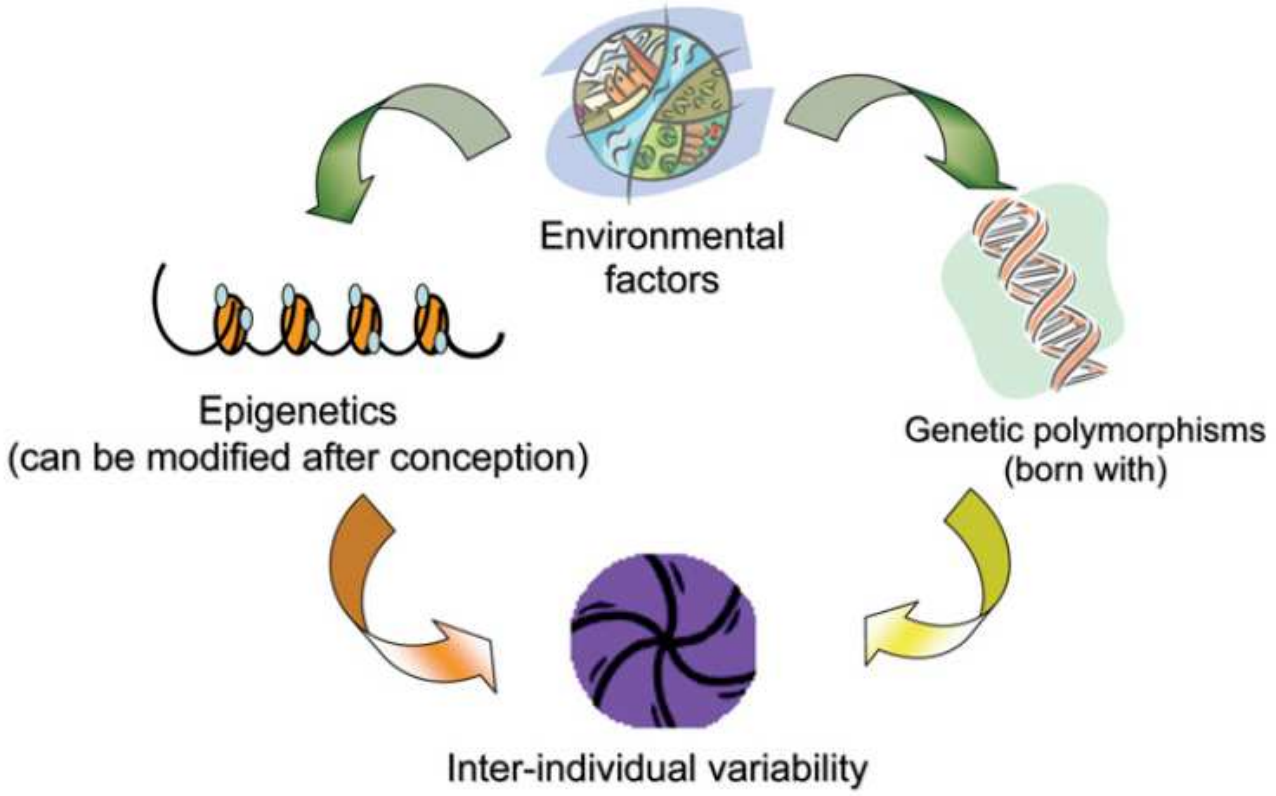
Environmental Epigenetics and Asthma

Current Concepts and Call for Studies

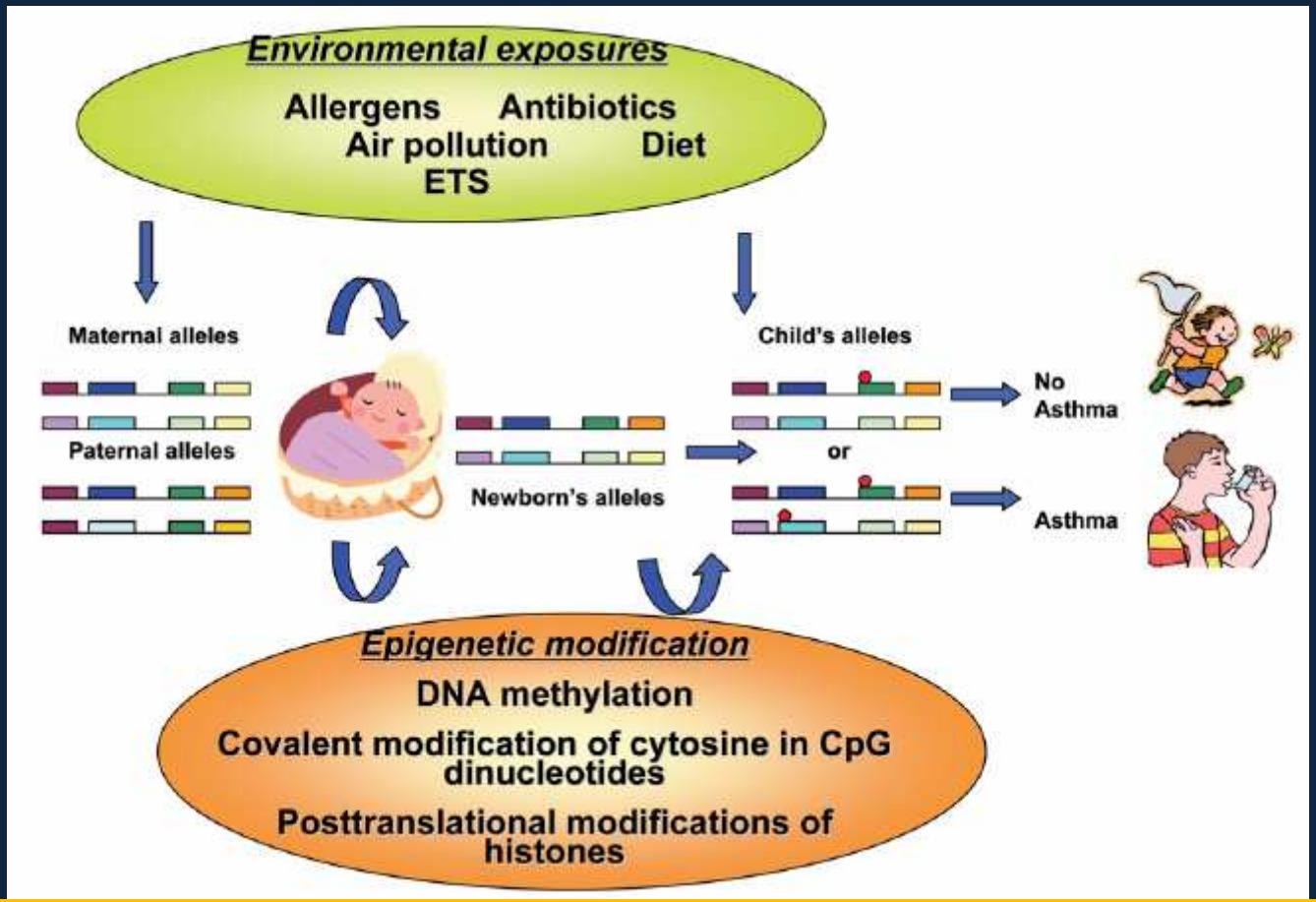
Rachel L. Miller[1] and Shuk-mei Ho[2]

[1]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York; and [2]Department of Environmental Health and Cancer Center, College of Medicine, University of Cincinnati, Cincinnati, Ohio

The traditional view that interindividual risk for asthma, like other complex diseases, is determined solely by interactions between genetic polymorphisms and environmental exposures needs to be reconciled with **new findings suggesting that epigenetic mechanisms also may contribute**



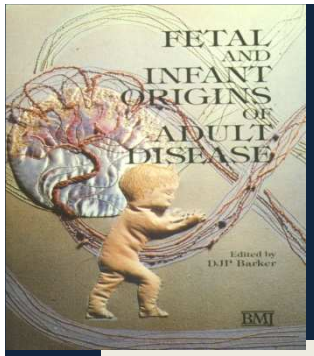
Am J Respir Crit Care Med Vol 177. pp 567–573, 2008



Epigenetic mechanisms .. include ***genomic imprinting***, ***histone modification***, **altered DNA methylation of regulatory sequences** in Th and other genes, and **regulation by microRNA (miRNA)**, which may change asthma risk after conception via environmentally mediated epigenetic disruption of gene expression…

Differential DNA methylation of promoter regions of reprogrammable genes may be an important mechanism in establishing the imprint. Another proposed mechanism is induction of **histone modifications**, a process that is reversible and may be associated with chromatin remodeling and gene transcription.

Oxidant-generating systems and proinflammatory mediators, some of which are implicated in asthma, may regulate ***histone acetylation*** : exposure to **H_2O_2** caused an **increase in histone acetyltransferase (HAT)** activity that promoted **acetylation** and **induced chromatin remodeling**…



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)

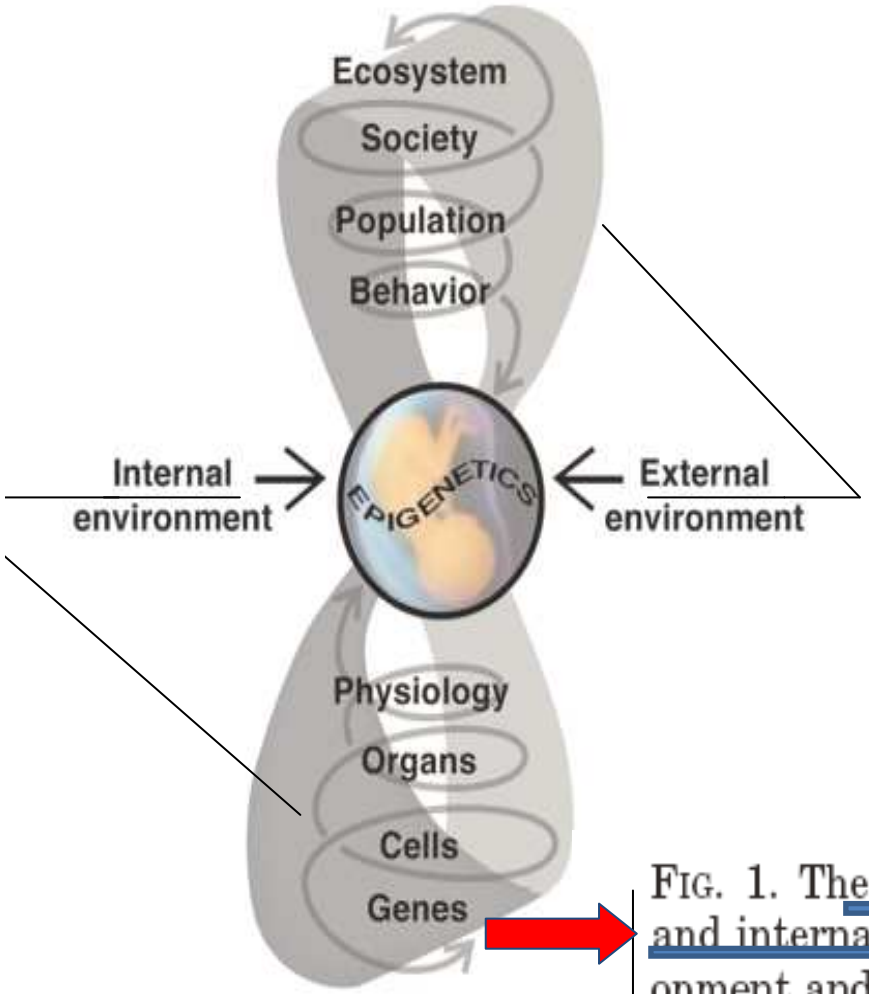
Szyf, M. **The Dynamic Epigenome and its Implications in Toxicology** Toxicol. Sci. 2007 100: 7-23

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*** (→ del ***riassetto 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 sviluppo …)

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



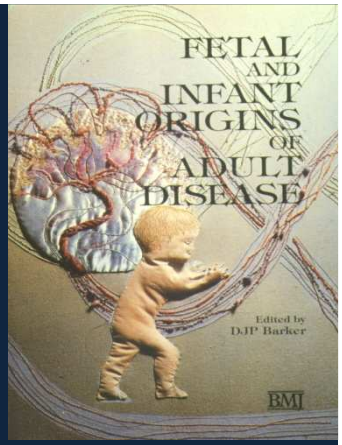
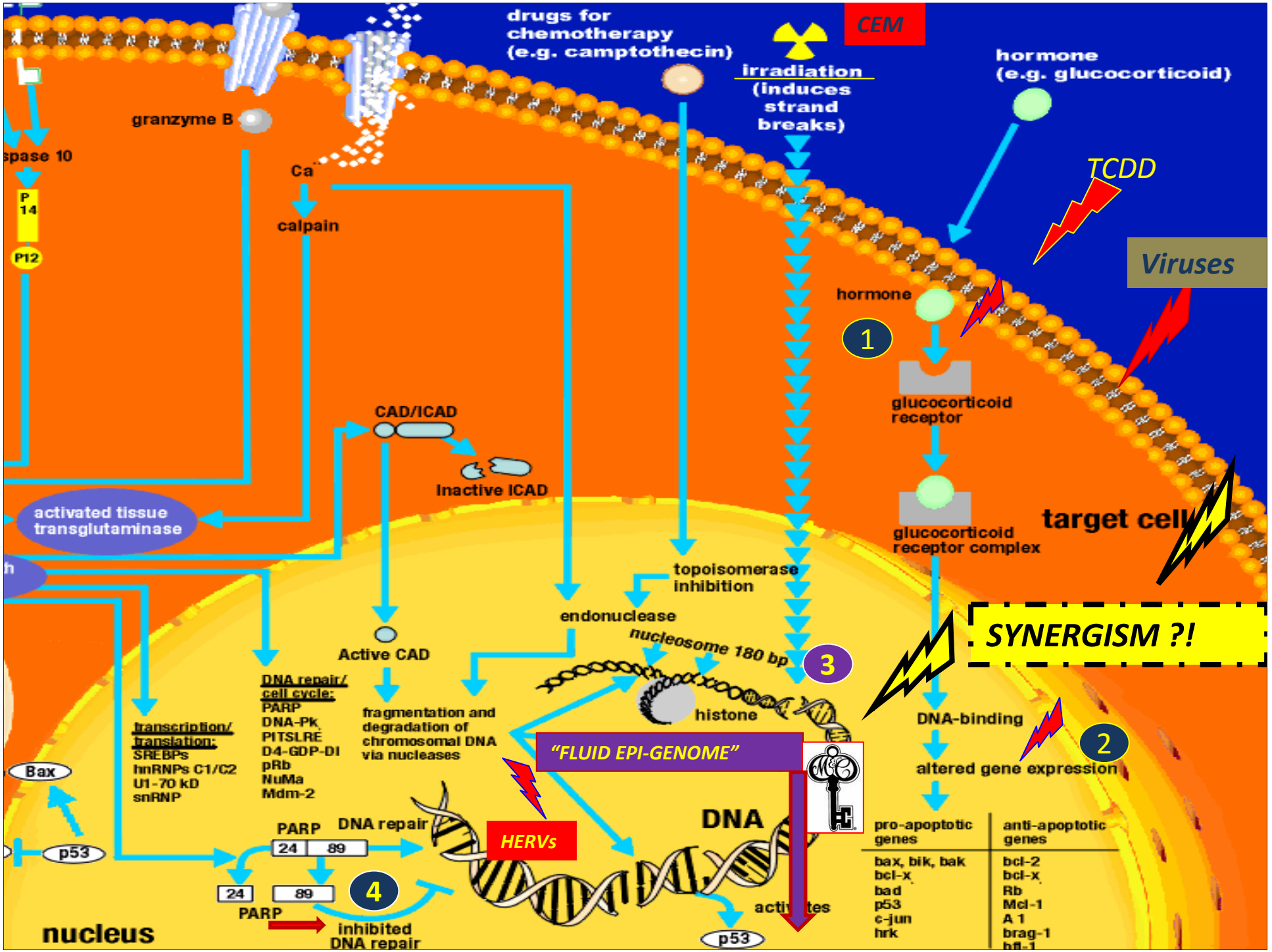


FIG. 1. The fetus is particularly vulnerable to changes in the external and internal environments, which interact to influence fetal development and have both immediate and life-long consequences. Such environmentally induced changes can occur at all levels of biological organization, from the molecular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


drugs for chemotherapy (e.g. camptothecin)
CEM
irradiation (induces strand breaks)
hormone (e.g. glucocorticoid)
granzyme B
spase 10
P 14
P12
Ca
calpain
TCDD
Viruses
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
SYNERGISM ?!
DNA-binding
2
altered gene expression
DNA repair/ cell cycle:
PARP
DNA-Pk
PITSLRE
D4-GDP-DI
pRb
NuMa
Mdm-2
transcription/ translation:
SREBPs
hnRNPs C1/C2
U1-70 kD
snRNP
fragmentation and degradation of chromosomal DNA via nucleases
"FLUID EPI-GENOME"
Bax
p53
PARP
DNA repair
24
89
HERVs
DNA
4
PARP
inhibited DNA repair
p53
nucleus
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

- E’ importante sottolineare fin d’ora che quanto cercheremo di illustrare **non** deve essere letto *semplicemente* come un approfondimento di nozioni acquisite da decenni

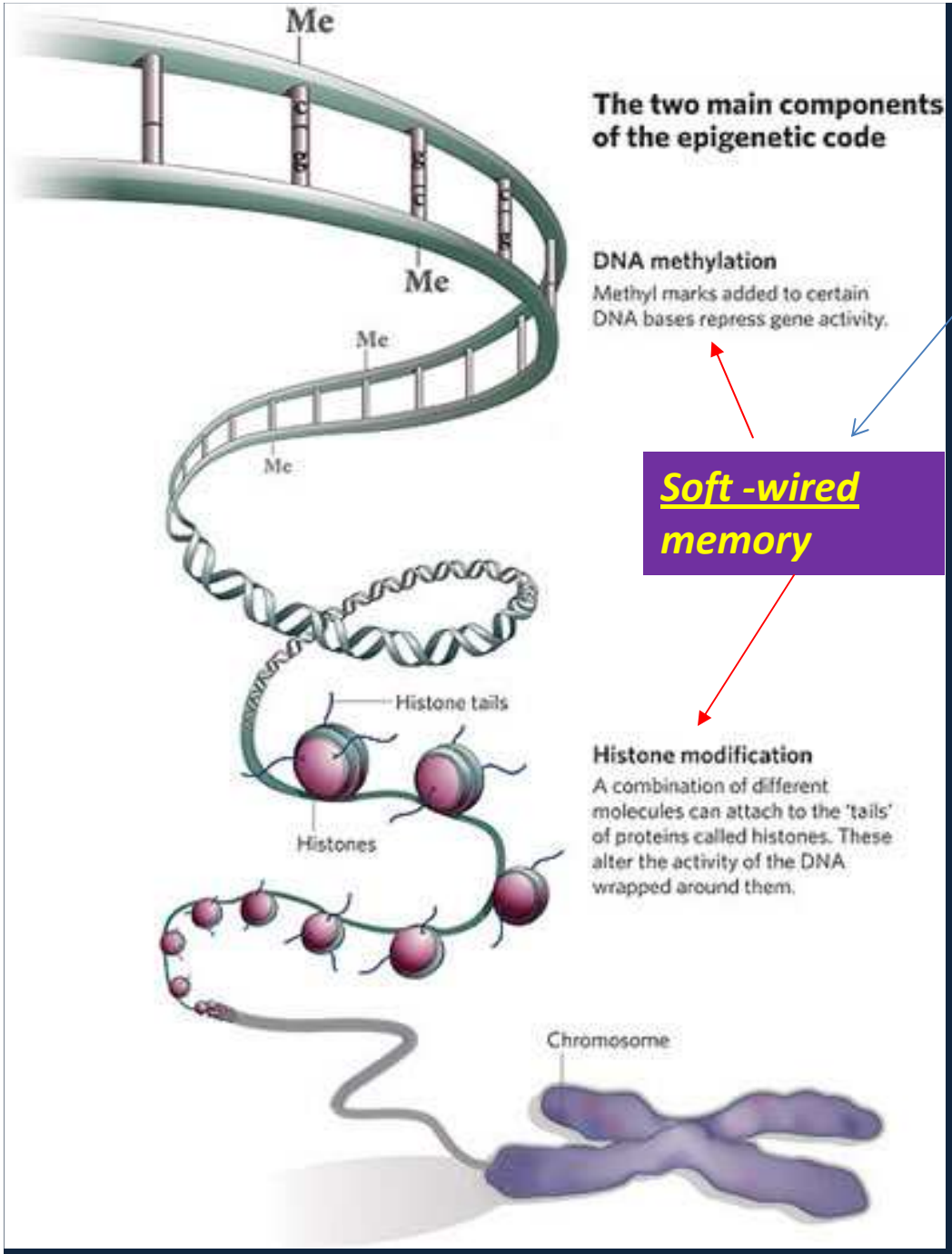
  e concernenti:

  - una + spiccata **sensibilità dell’embrione-feto** e più in generale dell’**organismo in via di sviluppo** (nozione intuitiva e documentata da innumerevoli studi tossicologici ed epidemiologici) **ad agenti ambientali geno-tossici**
  - l’altrettanto ben documentata capacità di alcuni agenti fisici (***radiazioni ionizzanti*** ecc.) e chimici (***IPA***, ***metalli pesanti*** ecc.) **di danneggiare in modo “casuale” il Dna**

xeno-biotici

- Quella cui faremo riferimento è la sempre meglio documentata capacità di singoli **agenti/fattori esogeni** (ad es. ***metalli pesanti/endocrine disruptors***)

  di **interagire direttamente con gli enzimi e i complessi proteici** deputati alla **metilazione del Dna**
  e alle **modifiche post-traduzionali degli istoni**,
  modulando l'assetto epi-genetico
  e la **conformazione cromatinica** delle singole cellule e favorendo/impedendo **l'accesso**
  - dei complessi trascrizionali alle sequenze regolatrici e codificanti
  - e degli **enzimi di riparazione** alle basi/sequenze danneggiate



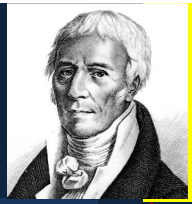
http://www.nature.com/news/2006/060508/images/441143a-i2.0.jpg

Soft -wired memory

- L'**ambiente** agisce più direttamente sull'**epigenoma** (assetto cromatinico-*hystone code*, metilazione DNA, RNA minori..)
- e attraverso questo sul **genoma**
- Possiamo anche dire che **lo sviluppo** 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.

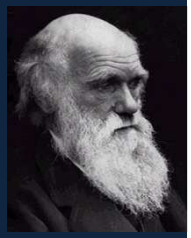
Il **genoma dello scimpanzé è per il 98.77% identico** a quello umano.
In media, un **gene codificante una proteina** in un uomo differisce dal suo **ortologo** nello scimpanzé per **due sole sostituzioni aminoacidiche**
..quasi **un terzo dei geni umani** hanno esattamente **la stessa traduzione proteica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



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

Species ***phylogeny***

Evo



From the Tree of the Life Website, University of Arizona

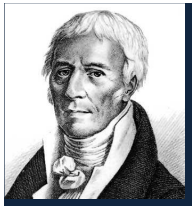
Orangutan

Gorilla

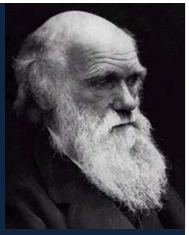
Chimpanzee

Human

Sanger Institute



Chimpanzee-human divergence



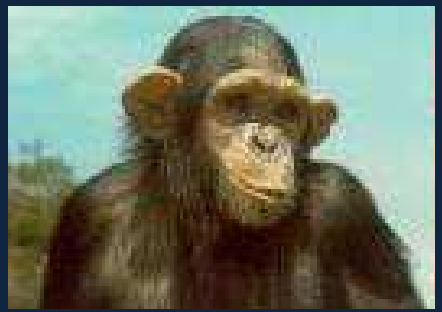
Evo

6-8 million years

Hominids or hominins

Chimpanzees

Humans



Brain:
a *<u>rapidly evolving Organ ?</u>*

Broad phenotypic variation in humans

Their DNA sequences differ by 0.1%

(1 in 1,000 base pairs are different)

Richard M. Myers
Stanford University School of Medicine

Epigenetic modifications : a molecular environmental effect

Nature

Genetics

Critical determinants of the epigenome

Nurture

Environment

Devo

Acute enviroemental events

Daily (low intensity) enviromental events

Celiac Disease

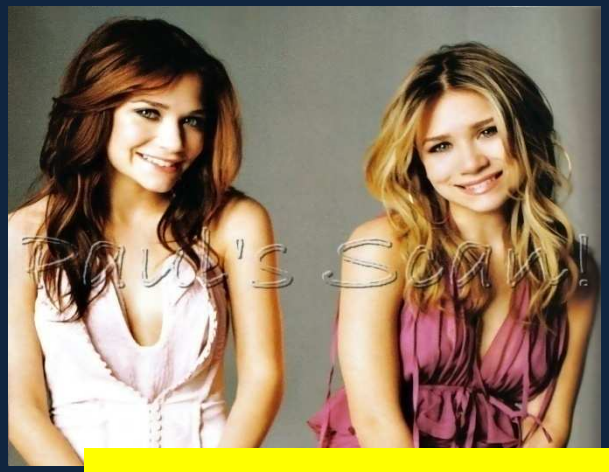
Why this disease is concordant in only **60%** to **70%** of **identical twins.**

Genetic Mutations etc.

Epi-Mutations

CHANGING EPIGENOME

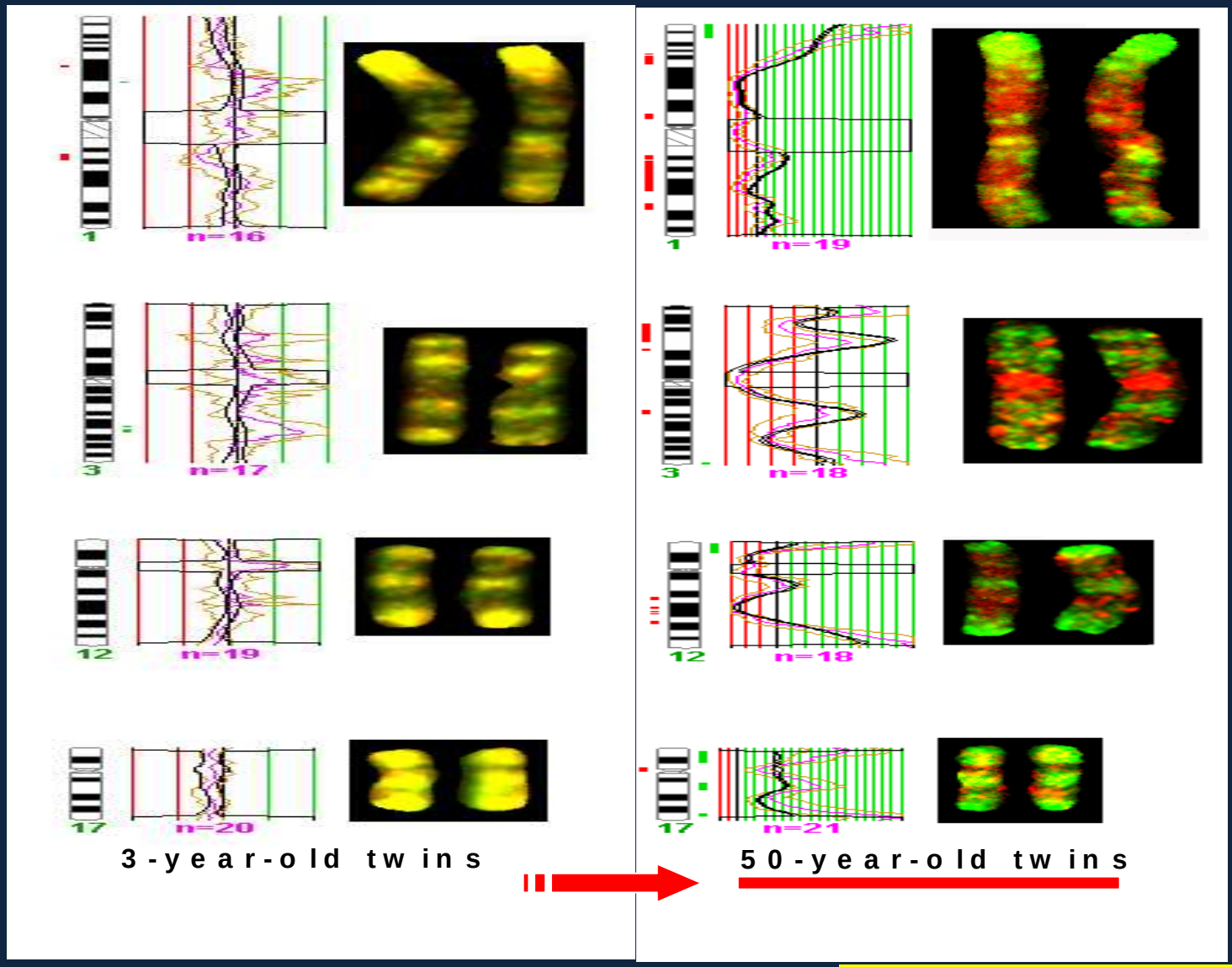
*And **Alzheimer Disease ?***



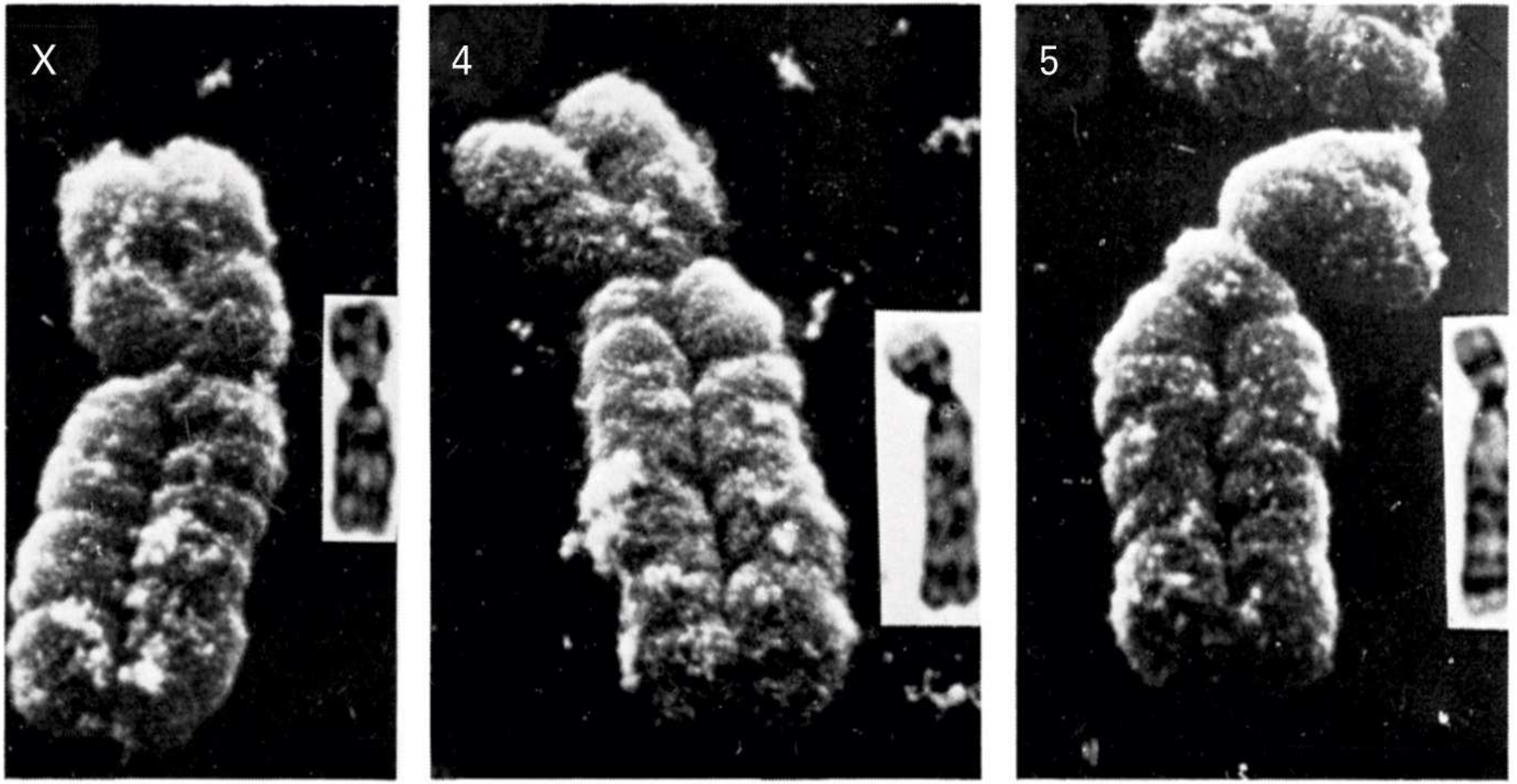
Instituto de Salud Carlos III

Fraga et al., PNAS. 2005.

Epigenetic differences in homozygotic twins



Fraga et al., PNAS. 2005.


X
4
5

Interphase chromosomes

Mitotic chromosome

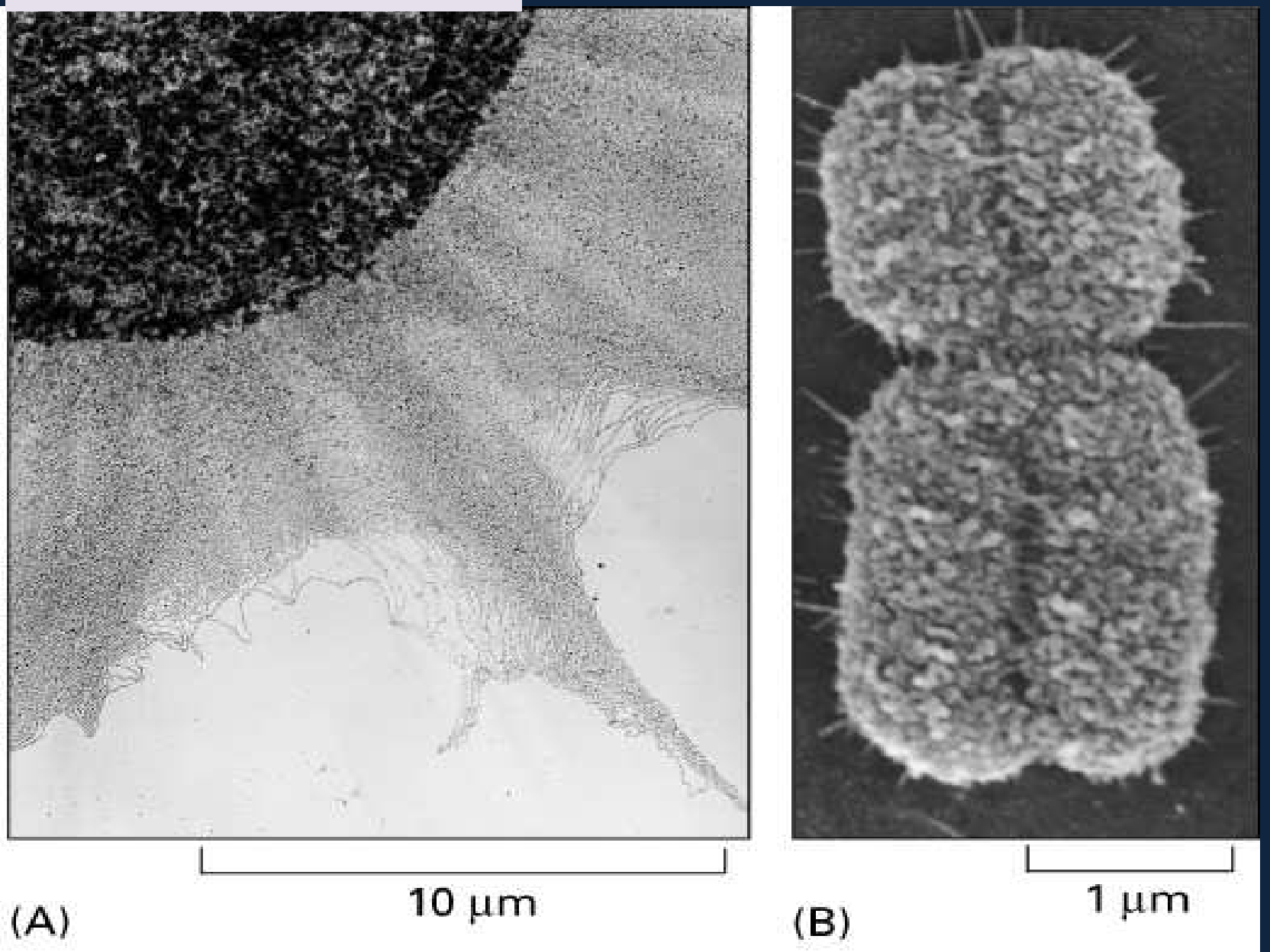
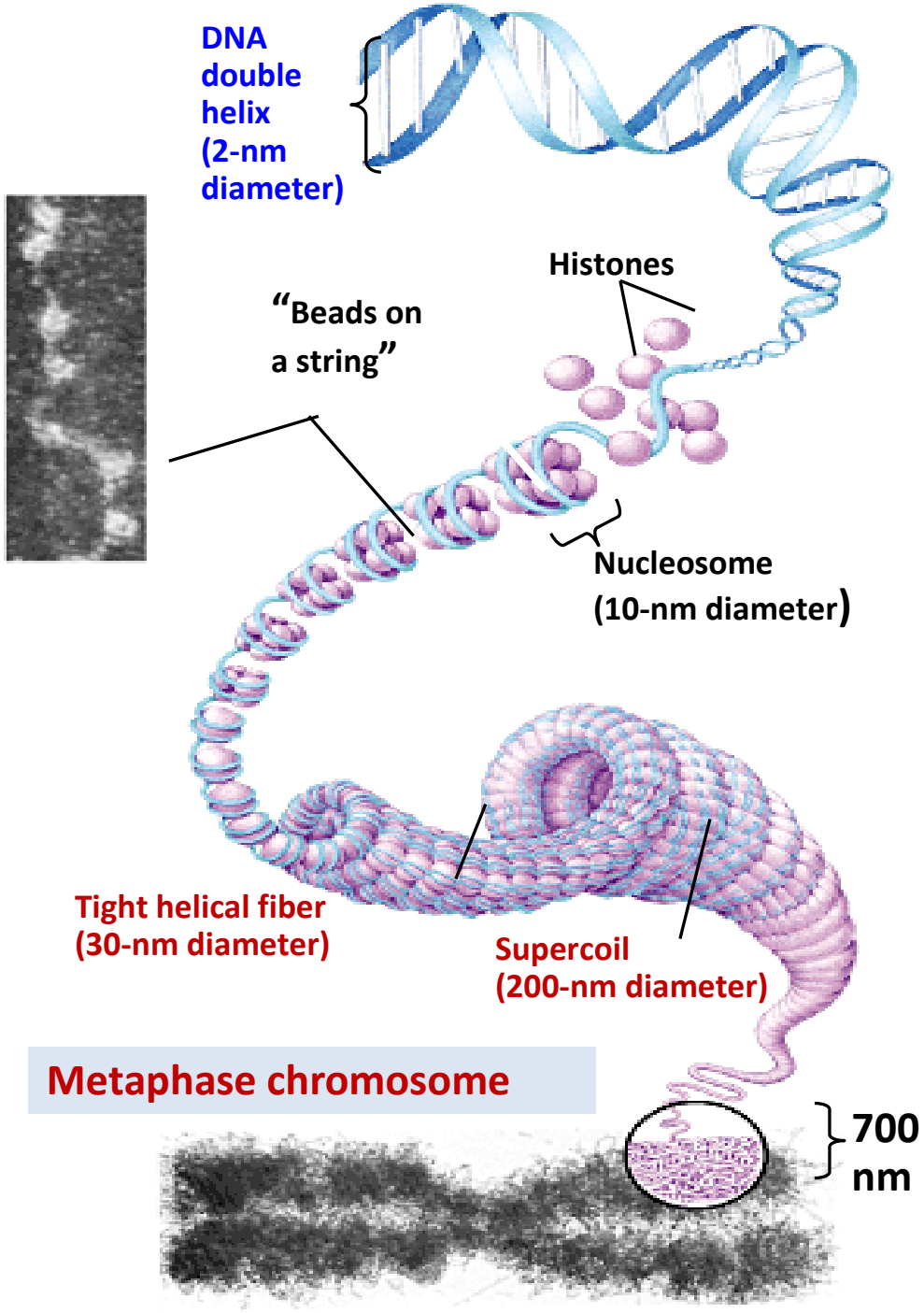


Figure 4–21. Molecular Biology of the Cell, 4th Edition.



Euchromatin

Heterochromatin

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

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

Nuclear DNA is normally **tightly wrapped around histones rendering the DNA inaccessible to the general transcription machinery** and hence this **tight** association prevents transcription of DNA

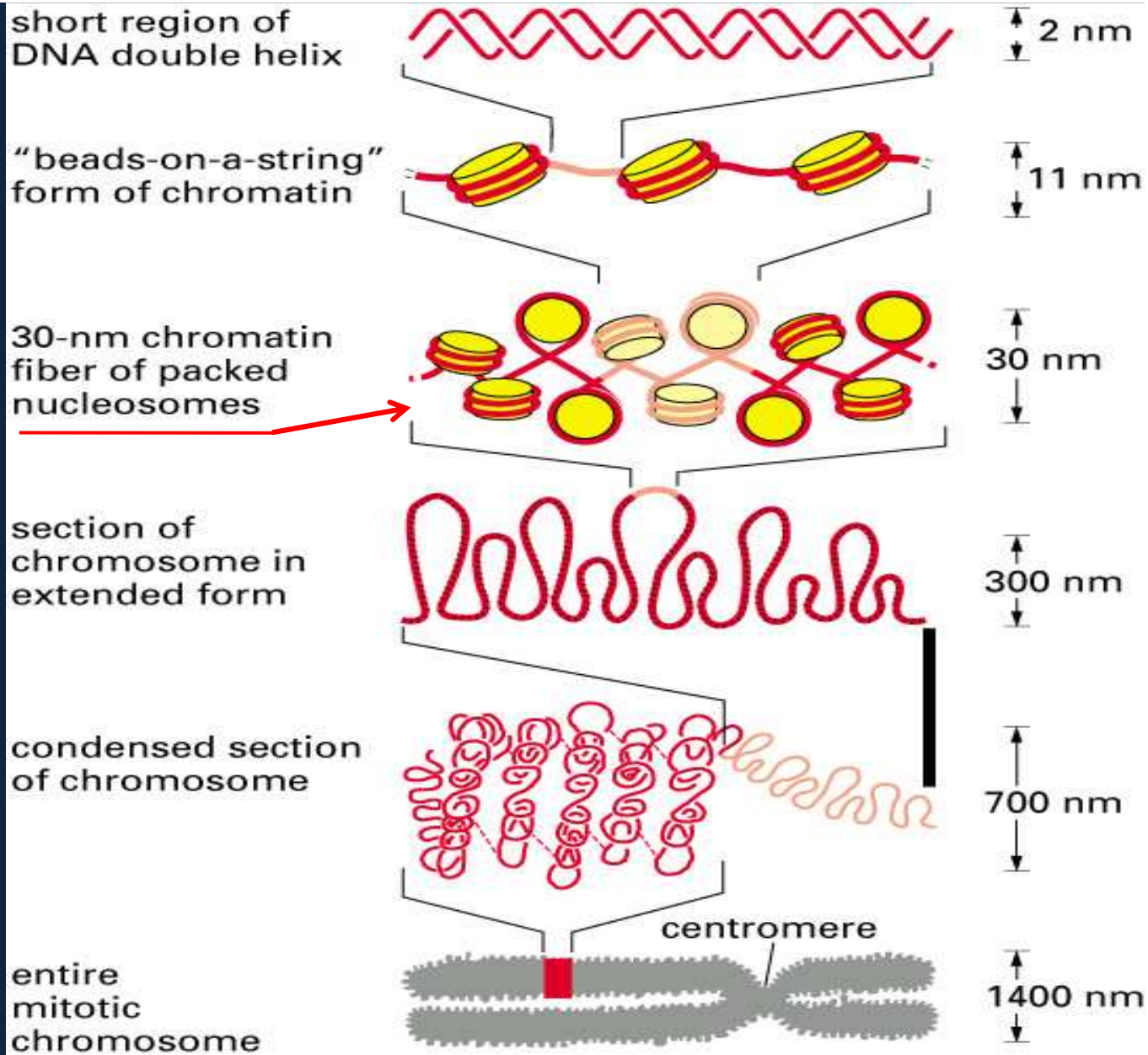


Figure 4–55. Molecular Biology of the Cell, 4th Edition.

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

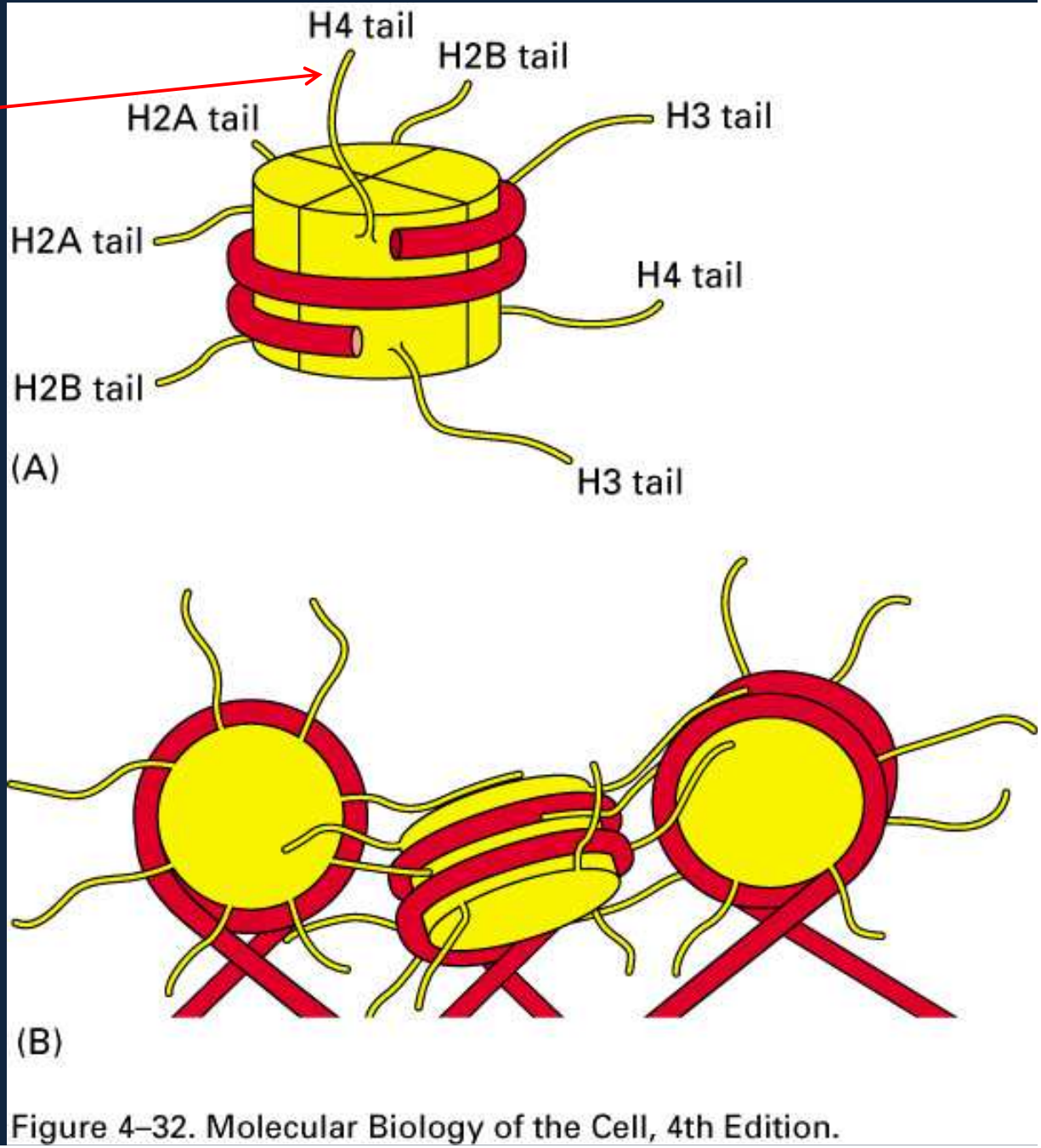


Figure 4–32. Molecular Biology of the Cell, 4th Edition.

Histone Tails
are subject to
a variety of
covalent modifications

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

E.g. generally,
Histone Acetylation *is associated with* ***transcriptionally active genes***
Deacetylation is associated with **inactive genes (= gene silencing)**

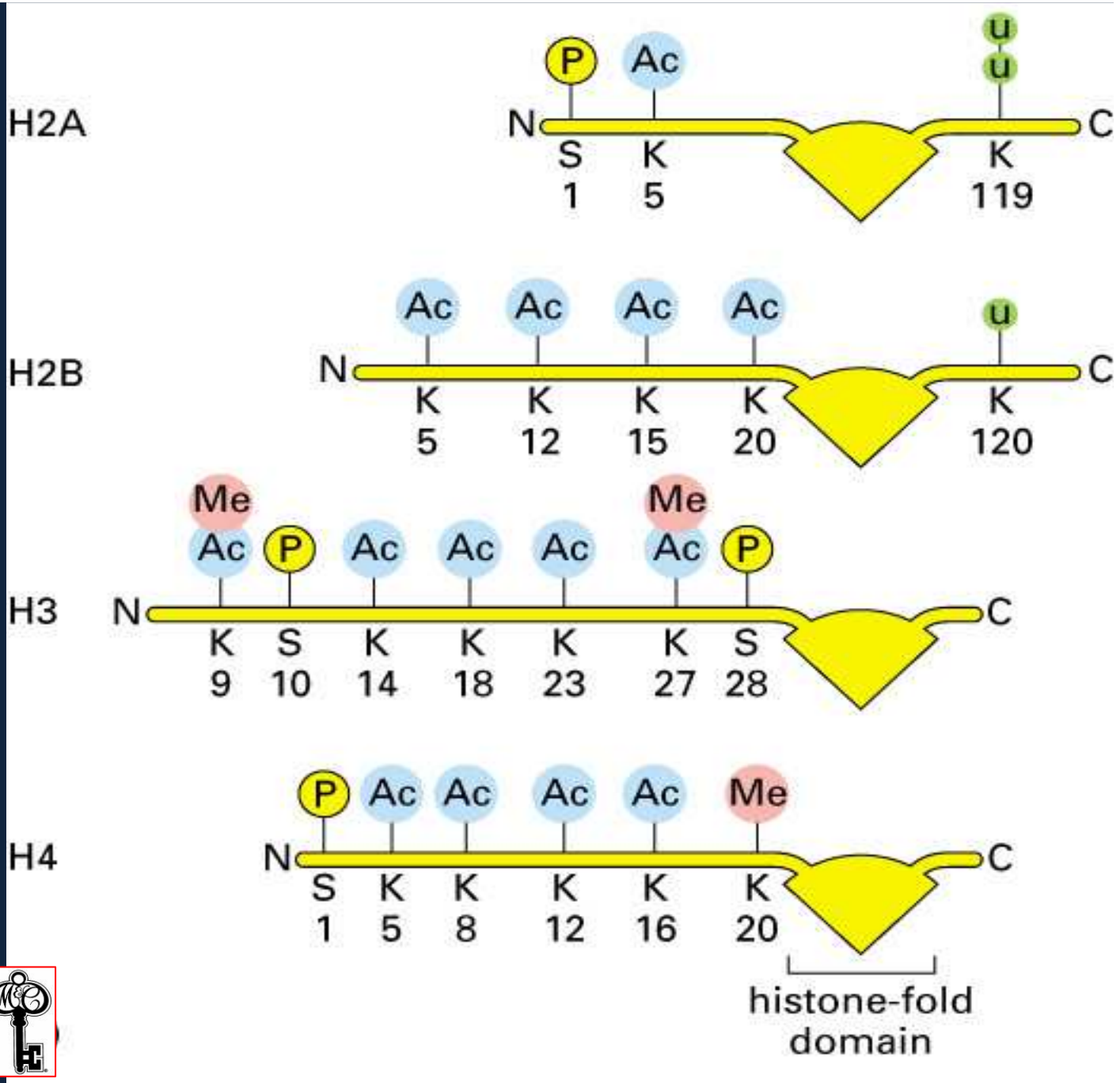
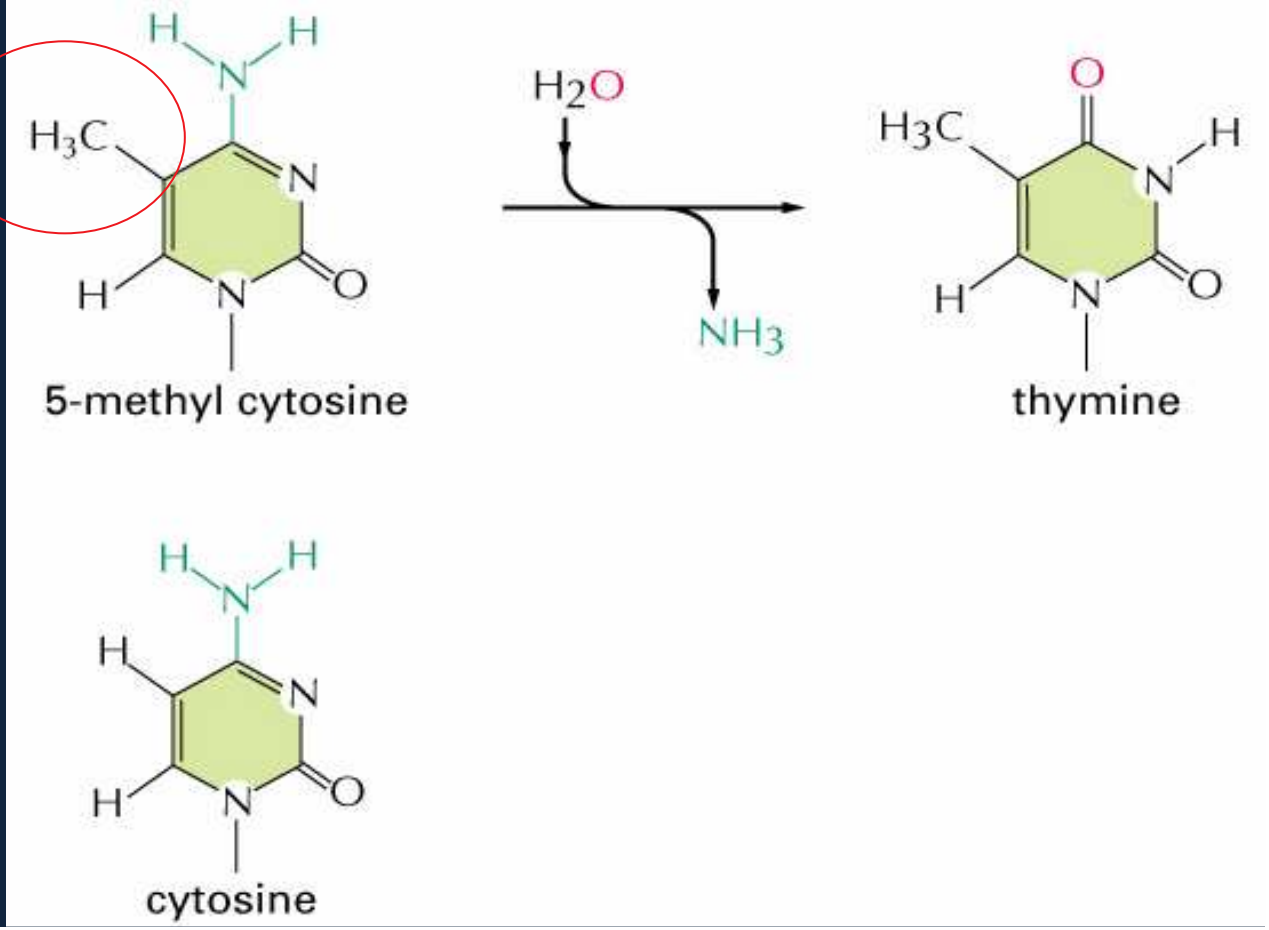


Figure 4–35 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

DNA methylation

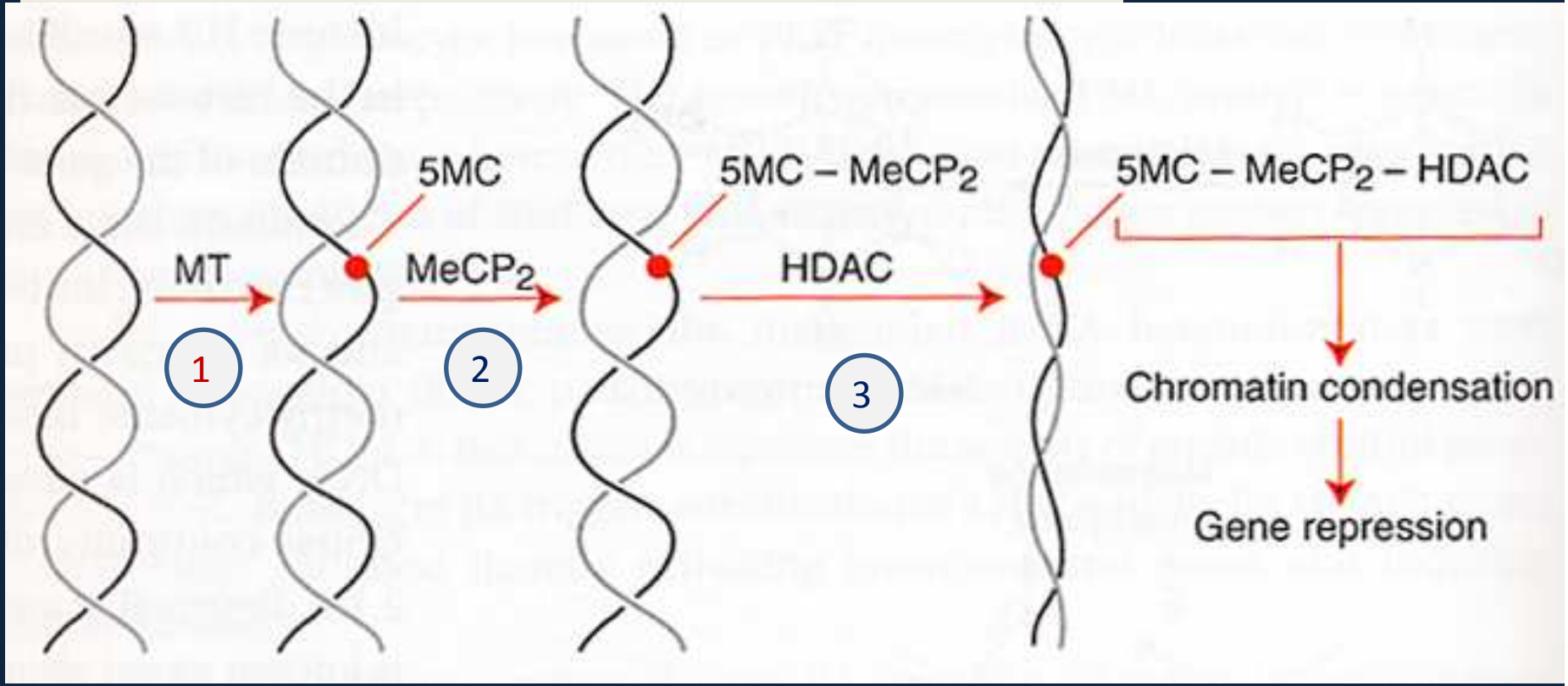
Covalent modification of the DNA is also important for gene silencing human cells. **Most genes have GC rich areas of DNA in their promoter regions.**
These are referred to as **CpG islands.**
Methylation of the C residues within the CpG islands leads to gene silencing

(highly *unstable* base)

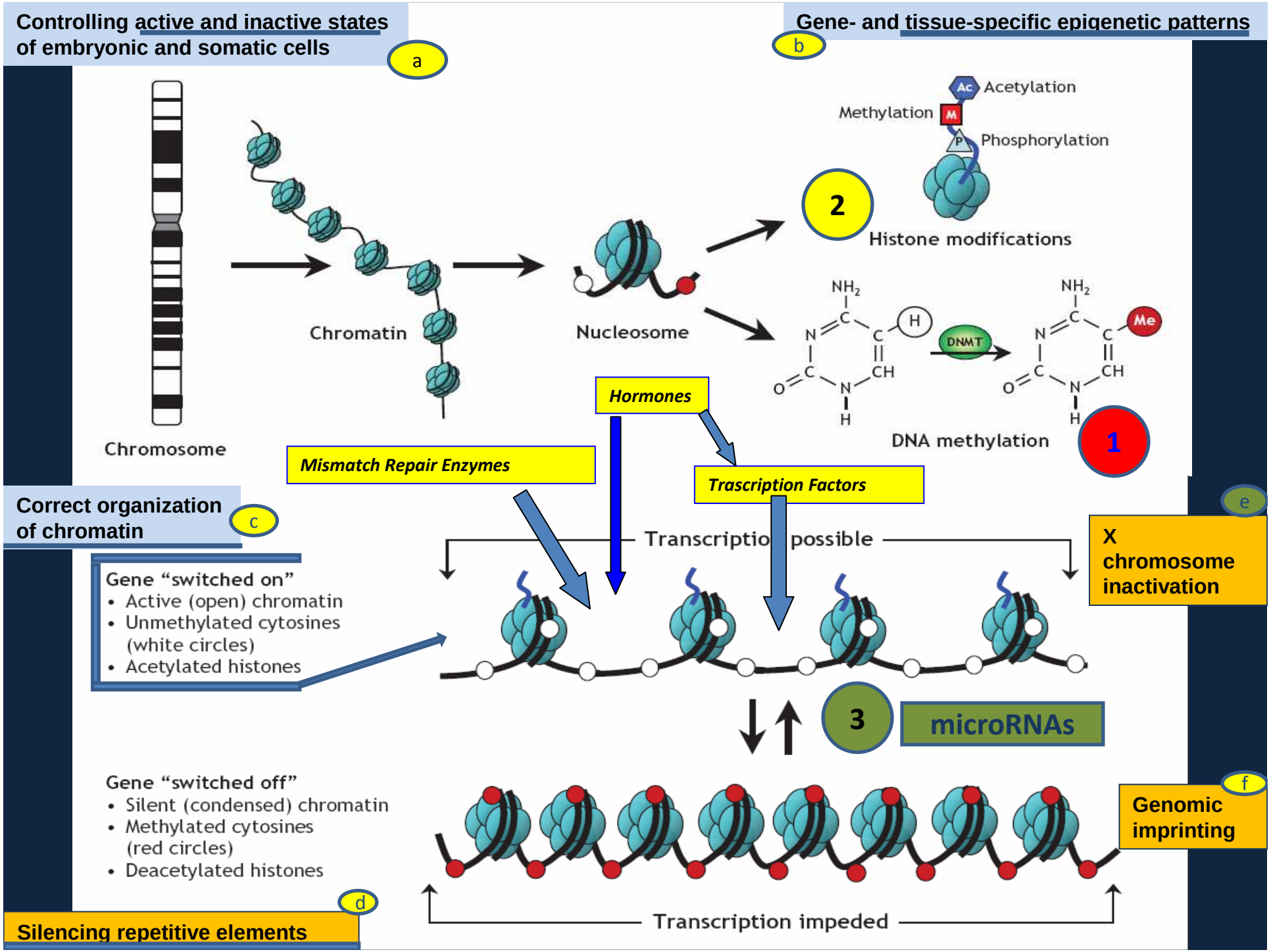


Continua interazione tra "*codice istonico*" e modifiche covalenti del DNA

The presence of **5-methylcytosine** leads to the **silencing of genes in that local area of the chromosome**



MT = DNA methyltransferase
HDAC = HistoneDeacetylase
MeCP2 = Methyl-CpG-binding protein


Controlling active and inactive states of embryonic and somatic cells
a
Chromosome
Chromatin
Nucleosome
Gene- and tissue-specific epigenetic patterns
b
Acetylation
Methylation
Phosphorylation
2
Histone modifications
DNMT
DNA methylation
1
Hormones
Mismatch Repair Enzymes
Trascription Factors
Correct organization of chromatin
c
Gene "switched on"
• Active (open) chromatin
• Unmethylated cytosines (white circles)
• Acetylated histones
Transcriptio possible
e
X chromosome inactivation
3
microRNAs
Gene "switched off"
• Silent (condensed) chromatin
• Methylated cytosines (red circles)
• Deacetylated histones
f
Genomic imprinting
d
Silencing repetitive elements
Transcription impeded

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

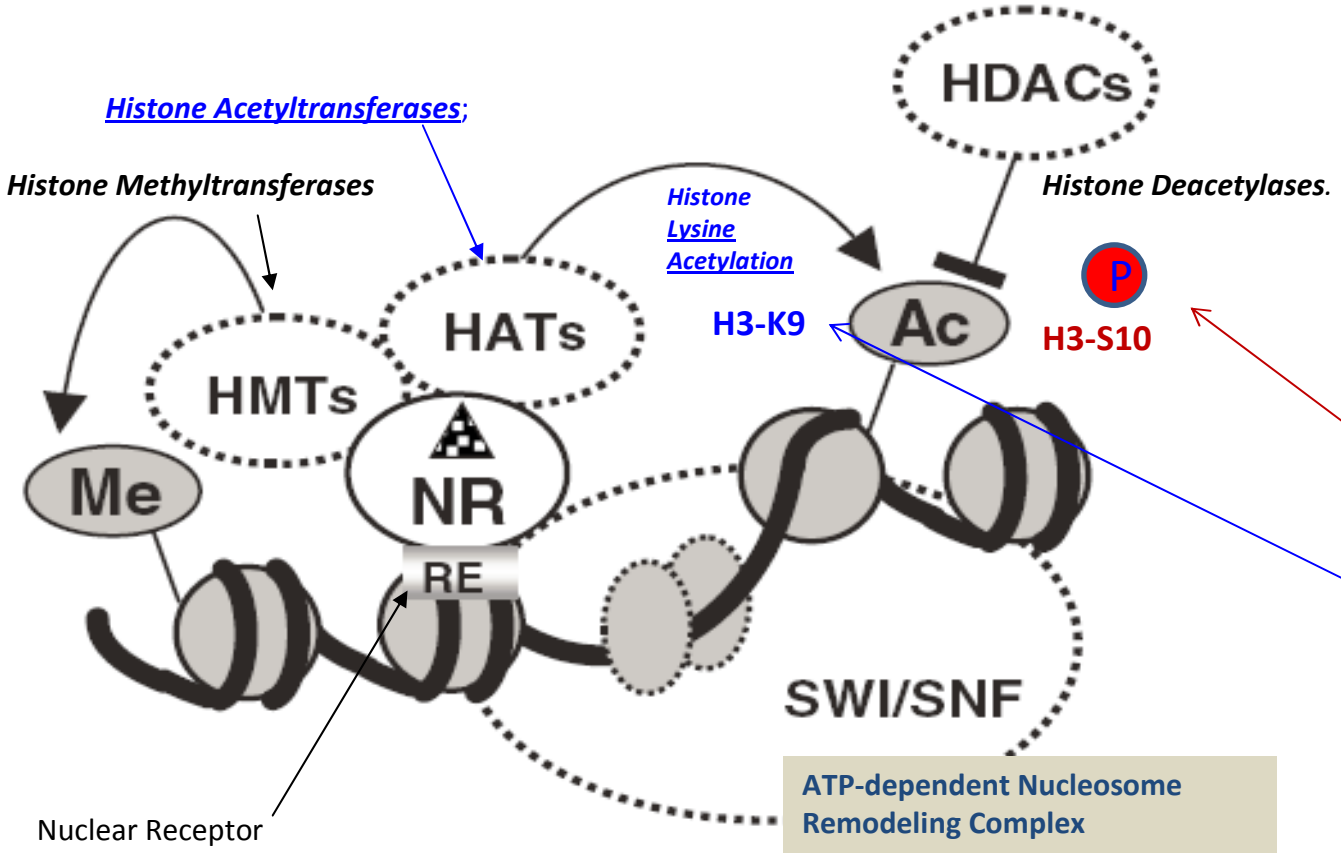
The Role of Chromatin in Molecular Mechanisms of Toxicity

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.

Modification of chromatin structure by histone modifying and nucleosome remodelling proteins



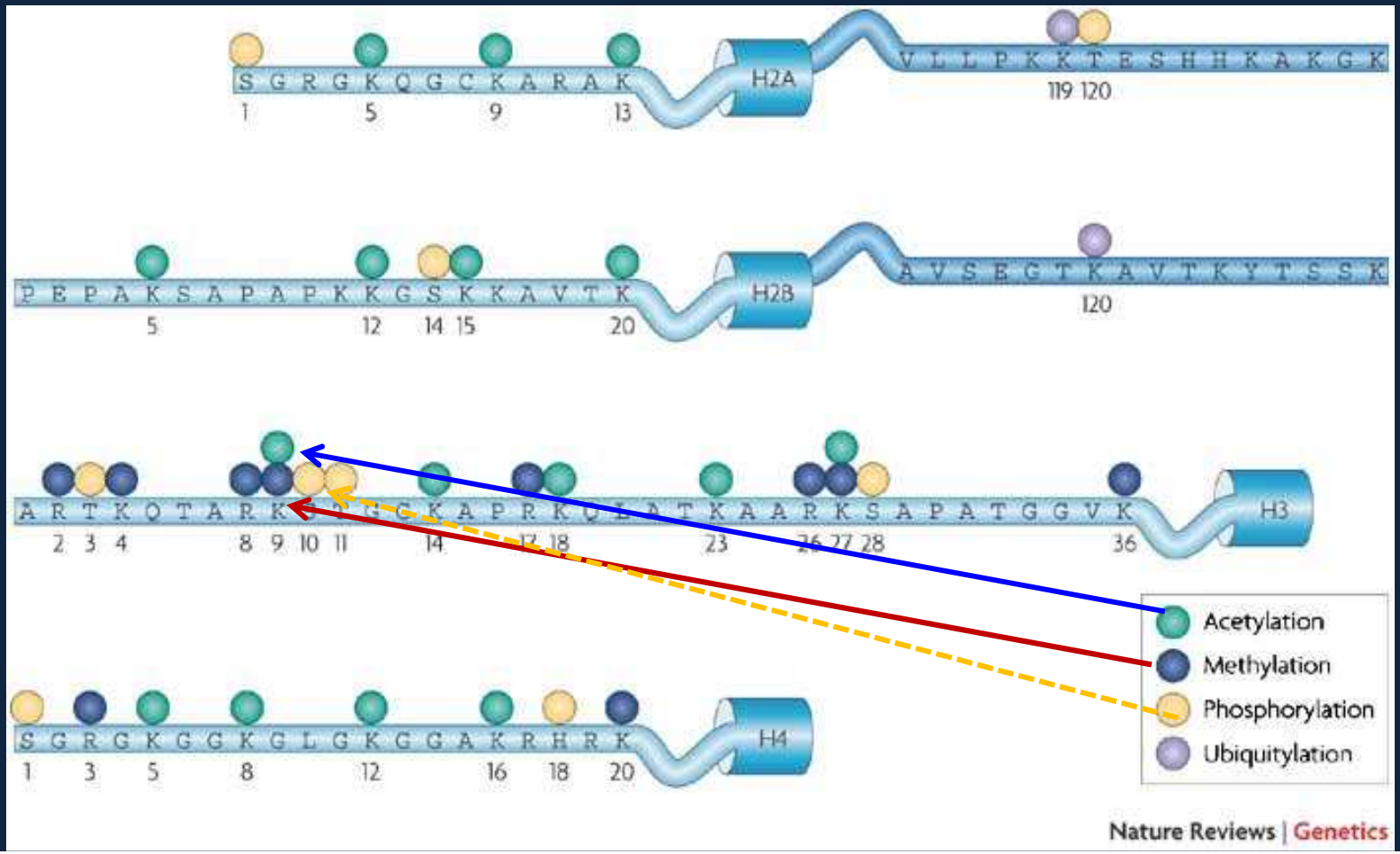
These modifications are believed to be essential for the full transcriptional response to stress-inducing chemicals

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

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

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

Some modifications, such as **histone lysine methylation**, are known to **recruit specific binding proteins** (for example, **HP1** to **methylated histone H3 lysine 9** and **PRC1** to **methylated histone H3 lysine 27**), whereas ***acetylation*** at various residues is **believed to have a more structural role, making the nucleosome structure 'looser' and more accessible to transcription factors.**

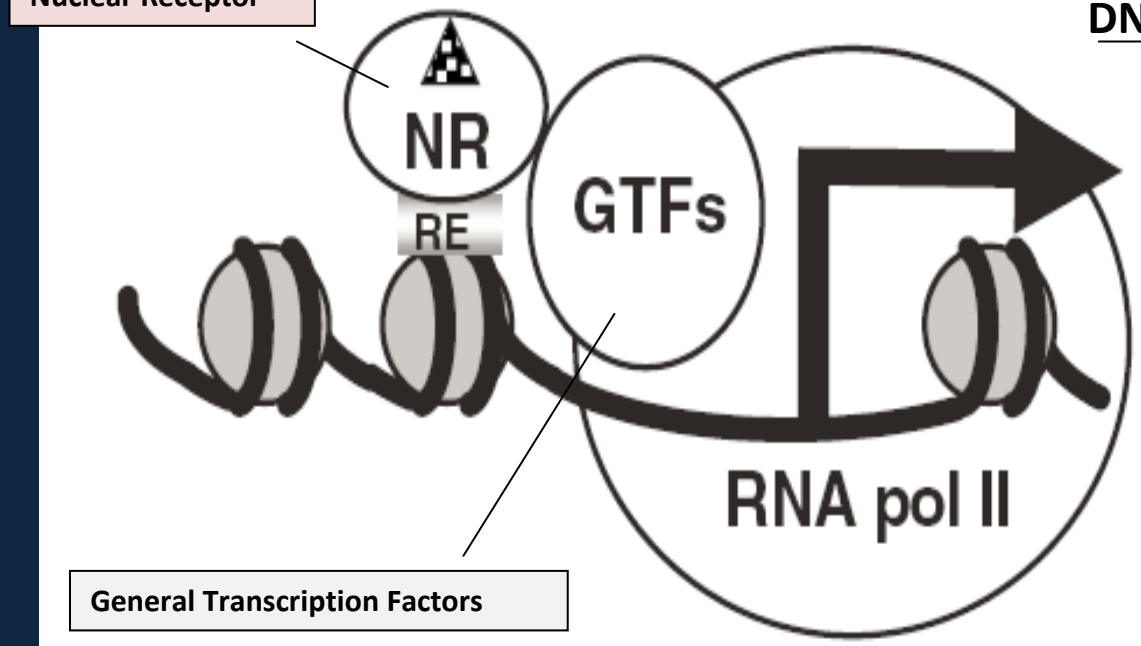


This **makes DNA sequences at the transcriptional start site accessible to RNA polymerase II** and the general transcription machinery and facilitates the initiation of ***gene transcription*** (or ***DNA repair***).

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

and

DNA Repair

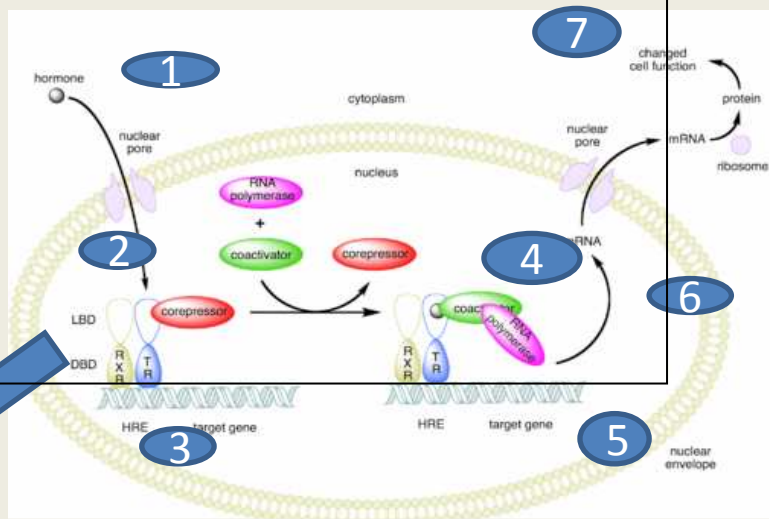


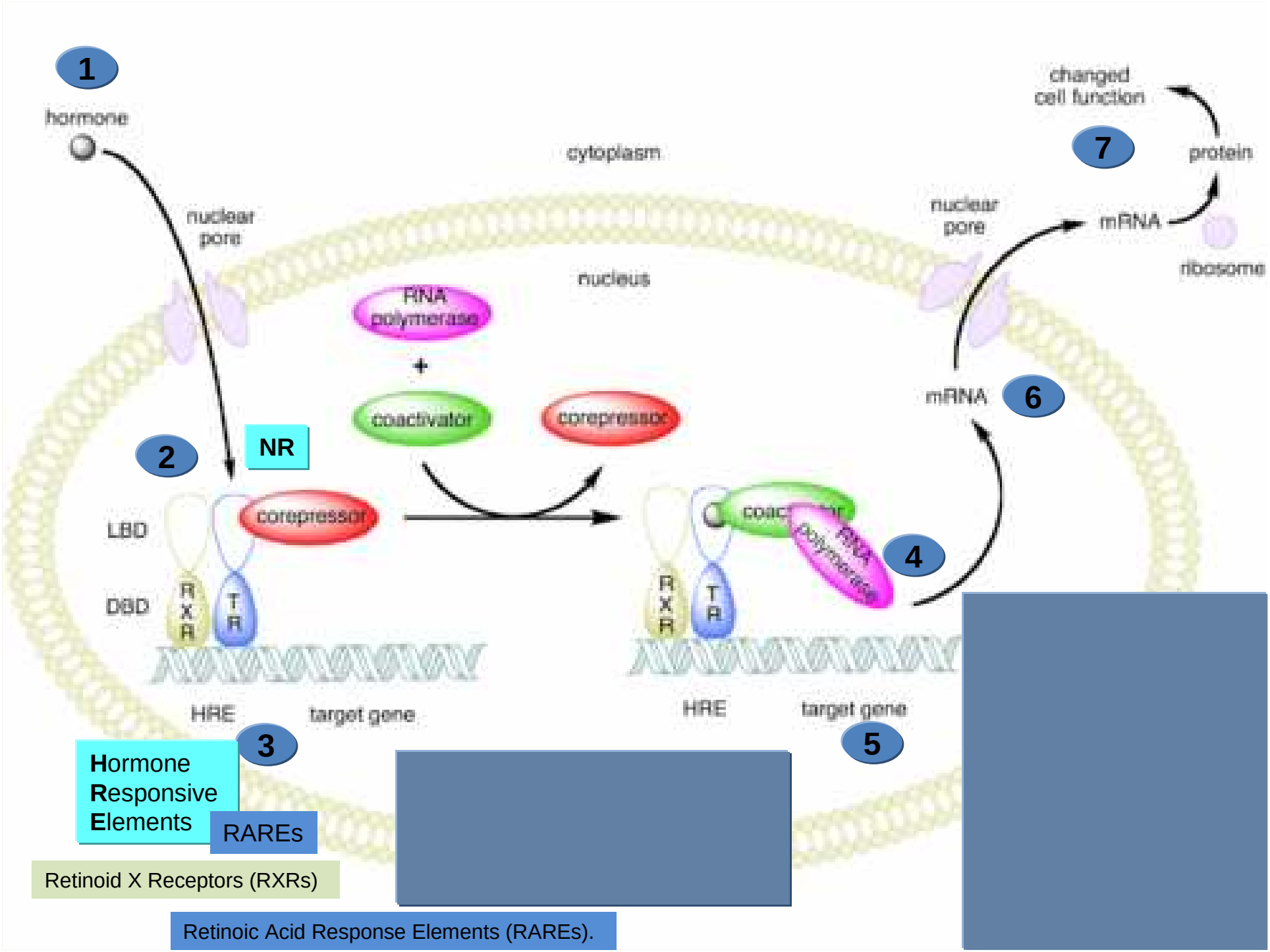
In **an analogous manner to the chromatin decompaction** that accompanies recruitment of ***RNA polymerase II*** during gene activation, **DNA excision repair** is associated with **increased histone acetylation** and localized **chromatin remodeling**

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 da tempo)..

- ***sia*** che si tratti di ***processi fisiologici***,
- ***sia*** che si tratti di ***meccanismi tossicologici e potenzialmente patogenetici***, secondo lo schema:

1. **Ormoni/UV/ Endocrine Disruptors →**
2. **recettori nucleari/fattori di trascrizione →**
3. legame al **Dna (*sequenze specifiche*)→**
4. riarrangiamento**(*epi*)genomico/cod. istonico →**
5. riarrangiamento genomico →
6. **trascrizione** (*proteine/Rna minori*) →
7. **differenziazione/proliferazione/ secrezione** *citochine/ormoni/enzimi…*




1
hormone
cytoplasm
changed cell function
7
protein
nuclear pore
nucleus
mRNA
ribosome
RNA polymerase
+
coactivator
corepressor
2
NR
corepressor
LBD
DBD
R X R
T R
HRE
target gene
3
Hormone Responsive Elements
RAREs
Retinoid X Receptors (RXRs)
Retinoic Acid Response Elements (RAREs).
mRNA
6
4
5

The toxic metal **nickel** can inhibit **HAT enzymes** and the **inhibition of histone acetylation by nickel compounds** *in vivo* has been associated with the **silencing of gene expression** (concomitant alterations in histone acetylation and gene expression appear to be important for **nickel-induced cellular transformation**)

Another **carcinogenic metal, chromium**, has recently been **shown to perturb HAT and HDAC enzymes** occupancy on PAH–inducible genes, resulting in the inhibition of their transcription…

Chromium is known to form DNA protein cross-links, and these might be responsible for **blocking the normal function of chromatin-modifying enzymes** during aryl hydrocarbon receptor–mediated gene activation…

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 condizione 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*** e ***neoplastiche*** (e **potrebbe/dovrebbe** essere, interpretata, come ***indotta/reattiva/adattativa*)**

Tutto ciò comporta **due conseguenze principali**:

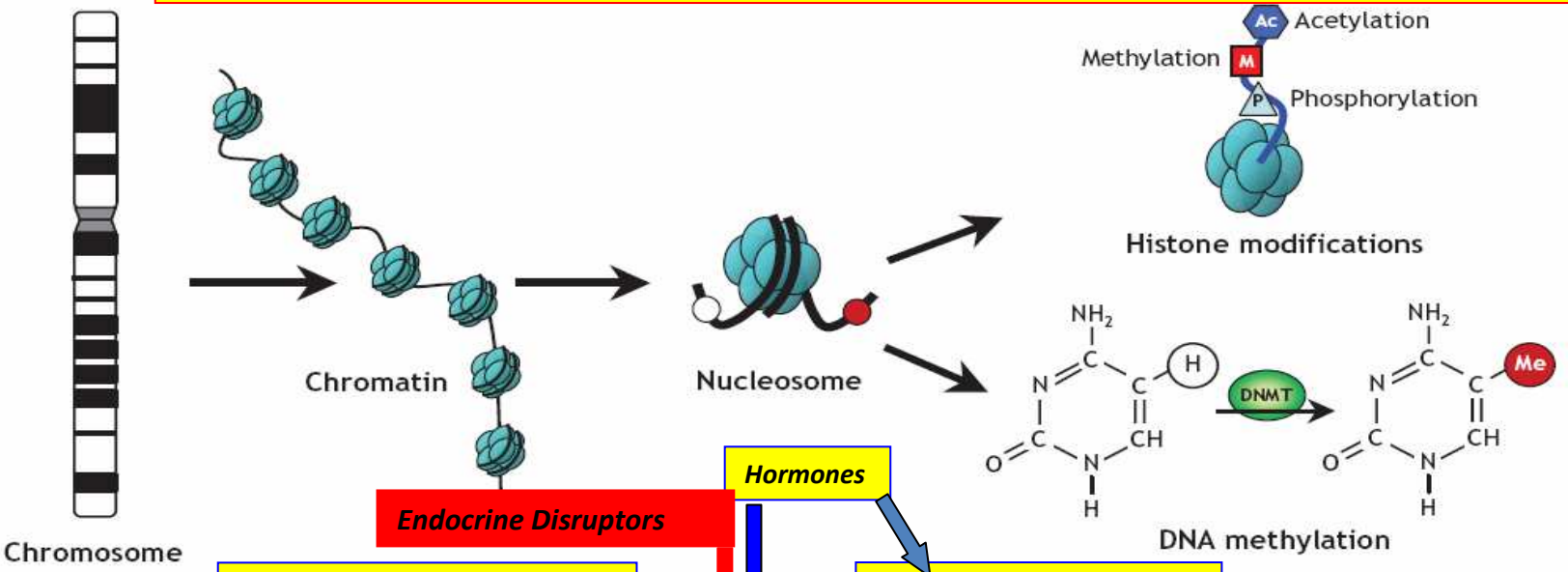
6a

da un lato la **sempre più ubiquitaria diffusione** in ambiente (e, quindi, in tessuti/cellule) di agenti e fattori esogeni in grado di sollecitare e (potenzialmente) danneggiare il Dna determina una condizione di ***stress epi-genomico* - cioè una instabilità "*reattiva/difensiva*" del genoma stesso** (direttamente connessa alla quantità/qualità delle sollecitazioni: si pensi ad es. all'azione di diretta induzione enzimatica da parte delle *diossine*) ed **un più facile accesso al Dna delle stesse *sostanze (geno)tossiche*** la cui azione si cerca di contrastare.

Può essere utile ricordare come un consimile stato di ***instabilità genomica* (ipometilazione diffusa, iper-metilazione delle sequenze *promoter* di geni onco-soppressori, specifiche combinazioni del "*codice istonico*")** sia di frequente riscontro nelle ***lesioni (pre)-neoplastiche*** (e potrebbe essere, interpretata, come *reattiva/difensiva*) e ***neoplastiche***

A

Global-DNA-hypomethylation resulting in **chromosomal instability** activates **oncogenes and transposons Specific P*romoter-hypermethylation*** inactivates **oncosuppressor-genes**



B

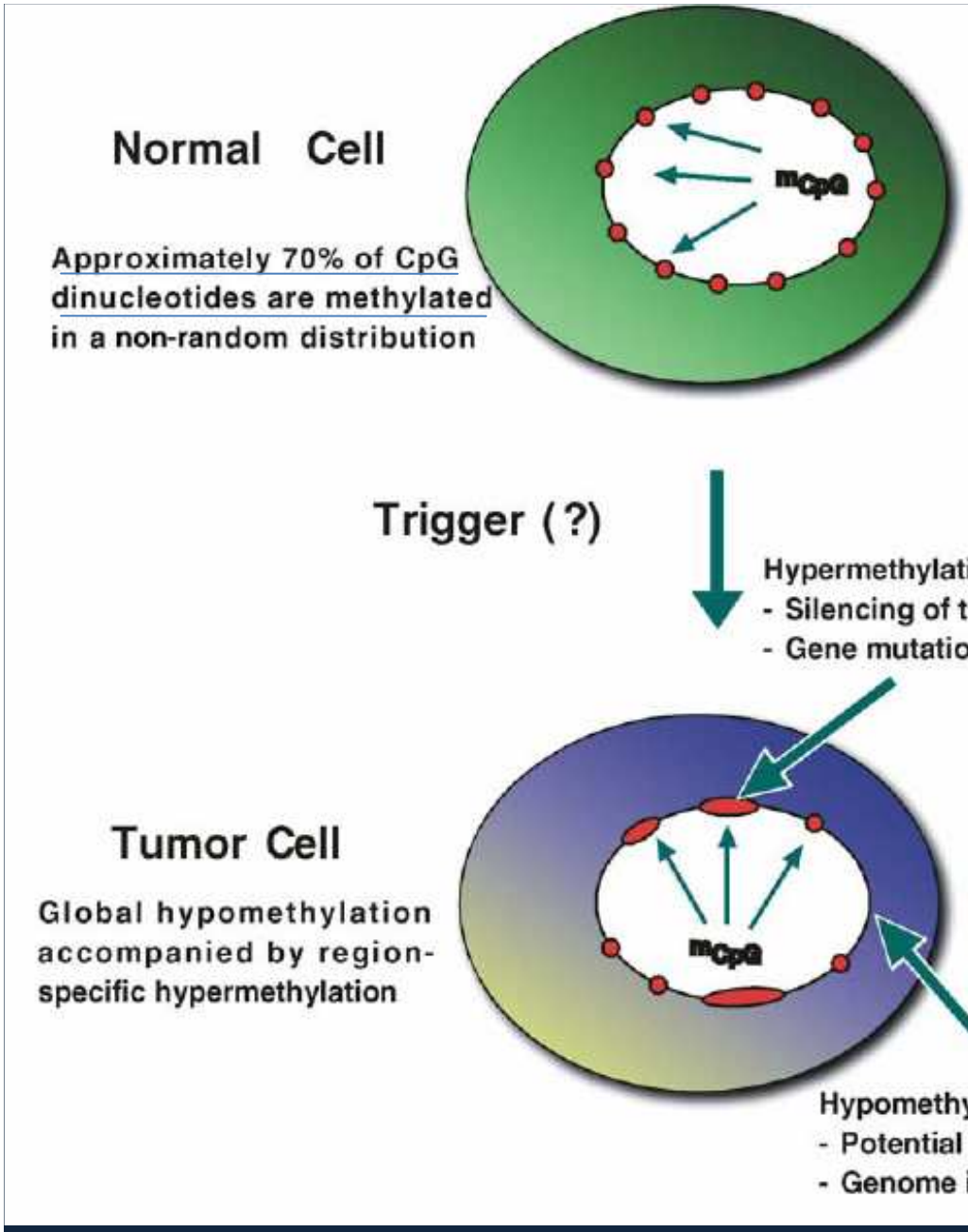
Gene "switched on"
- Active (open) chromatin
- Unmethylated cytosines (white circles)
- Acetylated histones

Transcriptio possible

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

Transcription impeded

The "methylation paradox" of cancer cells.



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

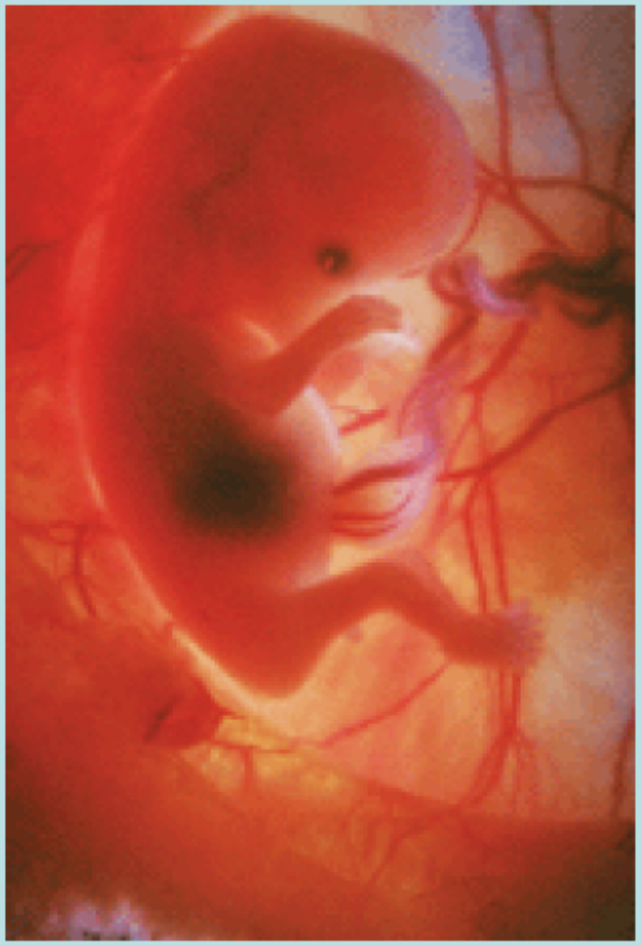
R Villa, F De Santis, A Gutierrez, S Minucci, PG Pelicci, L Di Croce
Epigenetic gene silencing in acute promyelocytic leukemia Biochem Pharmacol (2004) 68: 1247-54

Retrosequences activation…

6b

- ***d'altro canto*** il sempre maggiore riscontro dei **suddetti agenti tossici nel sangue materno e fetale** non può che avere effetti analoghi **sull'assetto epi-genetico delle cellule/tessuti fetali in via di sviluppo**:
- su queste basi è possibile ipotizzare che **tali meccanismi (alterazioni del *programming* fetale, cioè dell'assetto epi-genomico** a carico delle **cellule/tessuti "strategici": endocrino, immunitario** ecc.) svolgano un ruolo di tutto rilievo nell'ormai ben documentato **nesso tra sofferenza fetale e patologie cronico-degenerative dell'adulto**.
  [vedremo, del resto, come esistano studi tossicologici importanti che dimostrano come le **alterazioni programmatiche (epi-genetiche) fetali possano aprire la strada a patologie neoplastiche (come il *cancro del seno*) e neurodegenerative (come la *Malattia di Alzheimer*)**].

Developmental Programming



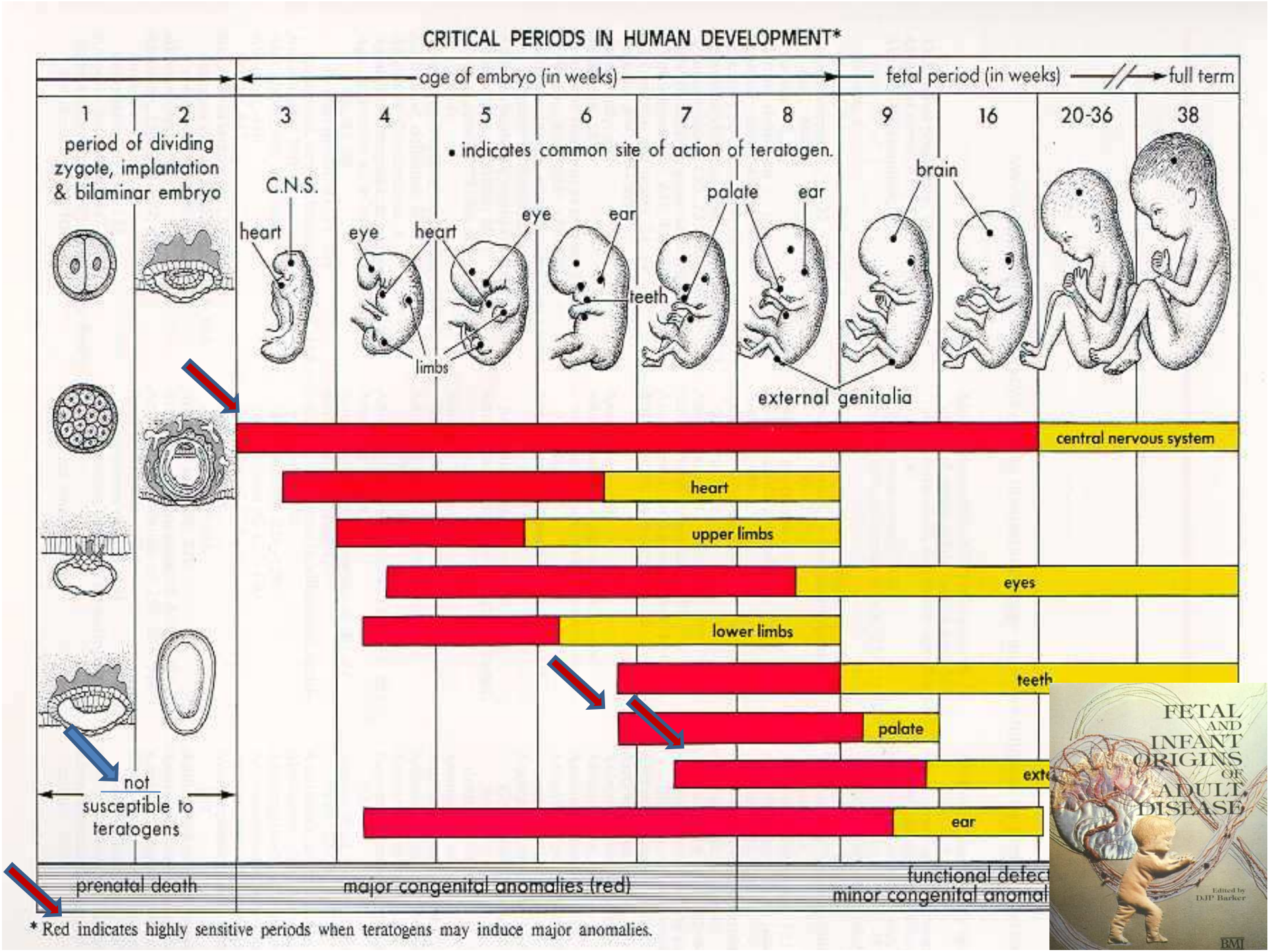
Exposure of developing tissues or organs to an adverse stimulus or insult during critical periods of development that can permanently reprogram normal physiological responses in such a way as to give rise to disease later in life

XXI secolo: drammatica trasformazione dell'**ambiente** → del **microambiente uterino**

- In relazione a quanto più ci interessa chiarire in questa sede **potremmo sintetizzare** il discorso in questi termini

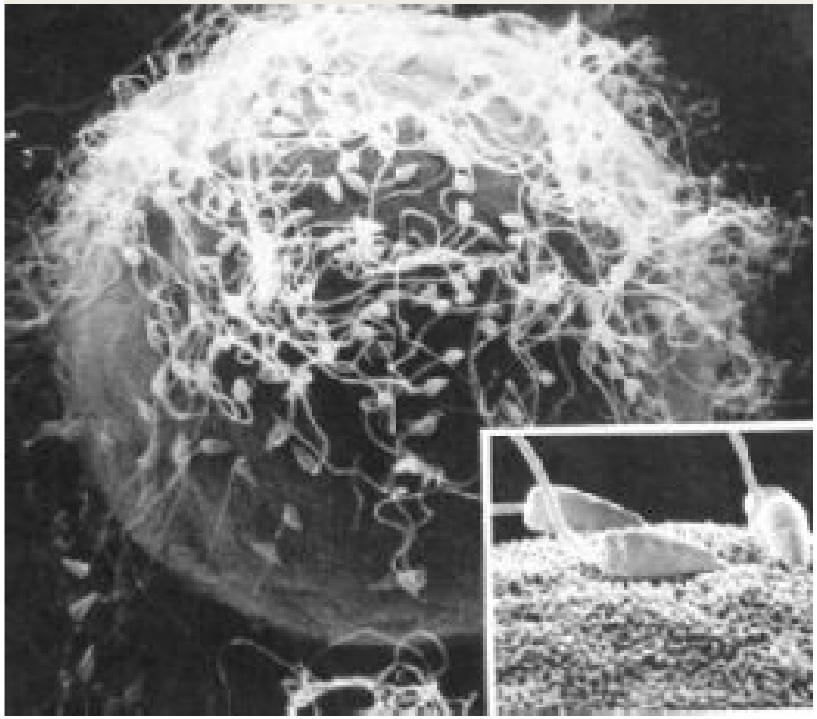
- **qualsiasi fenotipo – fisiologico o patologico** –
è il prodotto di un **lungo processo, individuale e collettivo**,
nel corso del quale **l'ambiente (in continua trasformazione) induce/modula/trasforma/plasma tanto i fenotipi, quanto i genotipi** (e gli uni per il tramite degli altri)

- esistono, in questi processi, alcuni momenti-chiave
che coincidono con le **fasi di massima plasticità evolutiva**
degli organismi stessi: quelli **in cui le cellule e i tessuti definiscono il proprio assetto epigenomico/programmatico,**
in relazione alle **condizioni (micro)ambientali**
in cui si trovano (→ ***sviluppo embrio-fetale***).


CRITICAL PERIODS IN HUMAN DEVELOPMENT*
age of embryo (in weeks)
fetal period (in weeks)
full term
1
2
3
4
5
6
7
8
9
16
20-36
38
period of dividing zygote, implantation & bilaminar embryo
• indicates common site of action of teratogen.
C.N.S.
heart
eye
heart
eye
ear
teeth
palate
ear
brain
limbs
external genitalia
central nervous system
heart
upper limbs
eyes
lower limbs
teeth
palate
ear
not susceptible to teratogens
prenatal death
major congenital anomalies (red)
functional defec
minor congenital anomal
* Red indicates highly sensitive periods when teratogens may induce major anomalies.

FETAL AND INFANT ORIGINS OF ADULT DISEASE
Edited by D.J.P. Barker
BMJ

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

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Early Nutrition, Epigenetic Changes at Transposons and Imprinted Genes, and Enhanced Susceptibility to Adult Chronic Diseases

Robert A. Waterland, PhD, and Randy L. Jirtle, PhD

Waterland R. *Nutrition*,
Volume 20, Issue 1, Pages 63-68

Several recent reviews surveying the promising field of nutrigenomics[1,2] have not discussed the important role that epigenetic mechanisms play at the nexus between nutrition and the genome. This is a glaring omission. Certainly, "nutrient–gene interactions" in humans enable various nutrients to transiently influence the expression of specific subsets of genes. In addition to these phenomena, however, it is becoming increasingly evident that by interacting with epigenetic mechanisms, which regulate chromatin conformation across entire genomic regions, transient nutritional stimuli at critical ontogenic stages can wield lasting influences on the expression of various genes.[3] Moreover, such epigenetic changes, if they occur in the gametes, may be heritable. This review focuses on early nutritional influences on cytosine methylation. It proposes that certain genomic regions, including genomically imprinted domains and specific transposon insertion sites, are especially labile to such influences. Considering the critical roles that genomically imprinted genes play in mammalian growth and development[4] and the huge proportion of our genome that is comprised of transposons,[5] early nutritional influences on these genomic components could have a substantial impact on human health. Genomic and epigenetic similarities between these distinct classes of elements are elaborated, and key areas of future research are discussed.

EARLY NUTRITION AND ADULT DISEASE

Extensive human epidemiologic data have indicated that prenatal and early postnatal nutrition influence adult susceptibility to diet-related chronic diseases including cardiovascular disease, type 2 diabetes, obesity, and cancer.[6–10] These epidemiologic data are bolstered by numerous studies in animal models[10,11] clearly showing that subtle nutritional influences during development can influence adult metabolism. Understanding the specific biologic mechanisms underlying such phenomena should enable early life nutritional interventions, or even corrective therapies, aimed at preventing chronic disease in humans. To help focus future mechanistic studies in this area, the term *metabolic imprinting* was proposed to encompass a subset of adaptive responses to early nutrition that is characterized by susceptibility limited to a critical ontogenic period and a persistent effect lasting into adulthood.

Epigenetics is the study of heritable changes in gene expression that are not mediated by DNA sequence alterations.[13] Because of their inherent malleability, epigenetic mechanisms are susceptible to environmental influences,[14] and as discussed below, this environmental susceptibility is expected to be enhanced during early development. Accordingly, nutritional perturbation of epigenetic gene regulation is a likely link between early nutrition and later metabolism and chronic disease susceptibility.[15–17]

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

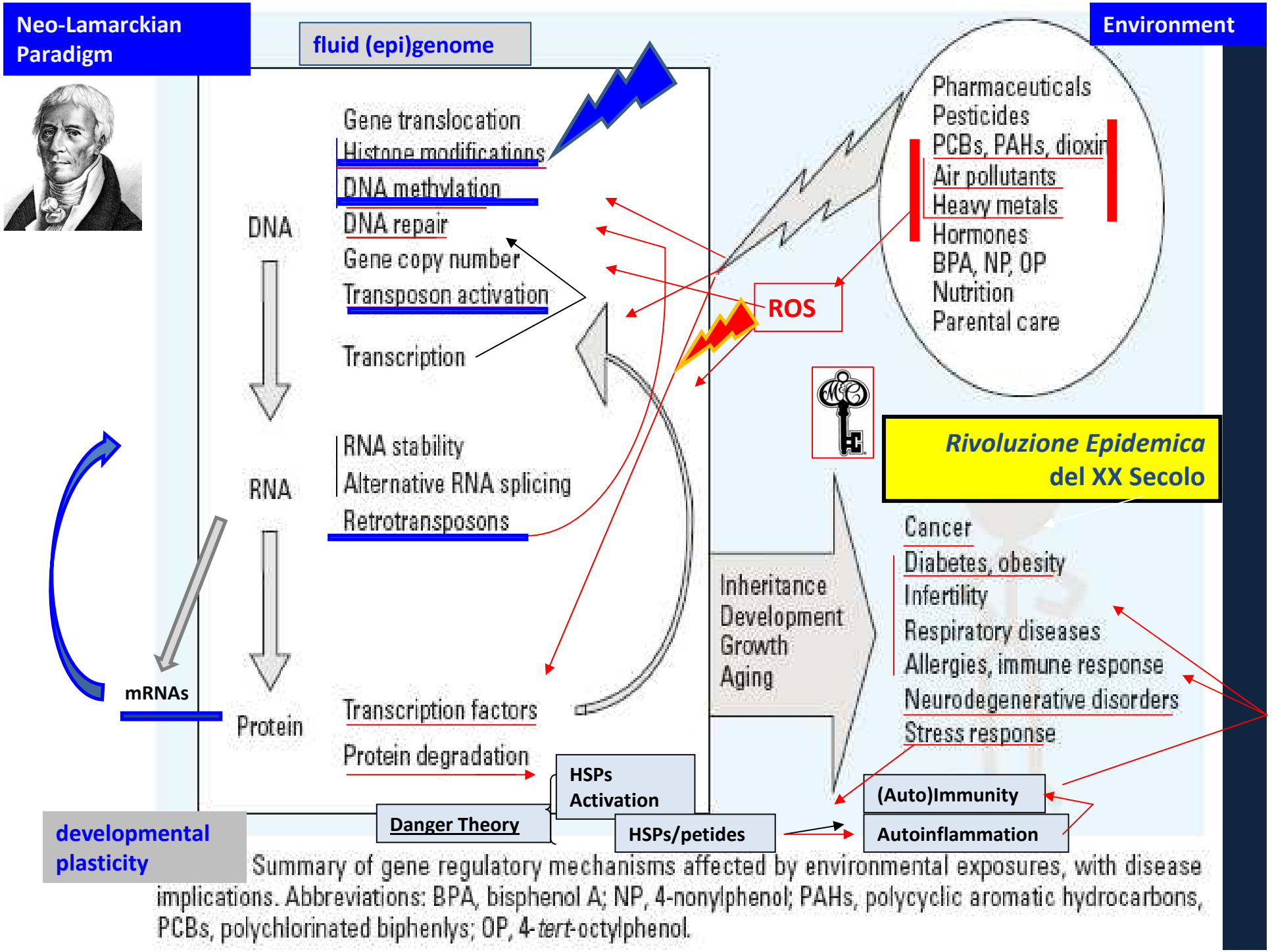
++ epigenetic patterns

Barker Hypothesis

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.

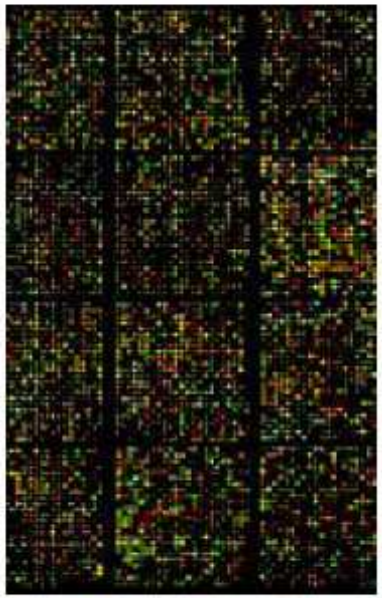
The purpose of this review is to identify points of gene expression regulation, occurring along the process described by the central dogma (DNA → RNA → protein), that have been shown to be affected by environmental factors, particularly contaminants (Figure 1). We have drawn on research that shows a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



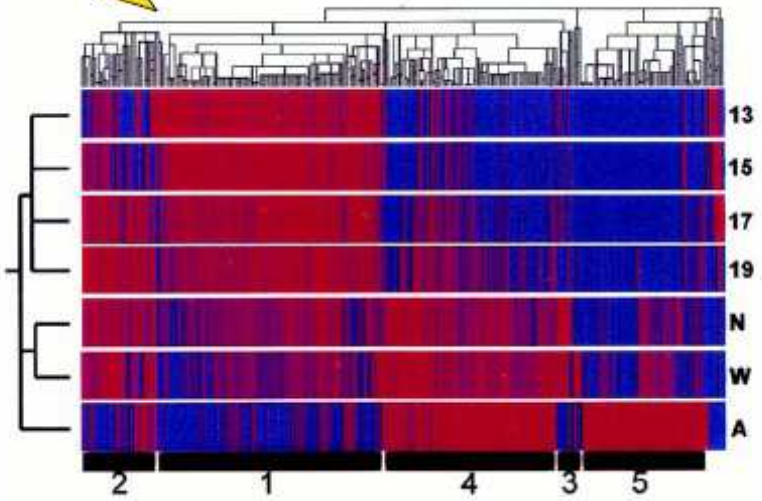
Summary of gene regulatory mechanisms affected by environmental exposures, with disease implications. Abbreviations: BPA, bisphenol A; NP, 4-nonylphenol; PAHs, polycyclic aromatic hydrocarbons, PCBs, polychlorinated biphenlys; OP, 4-*tert*-octylphenol.

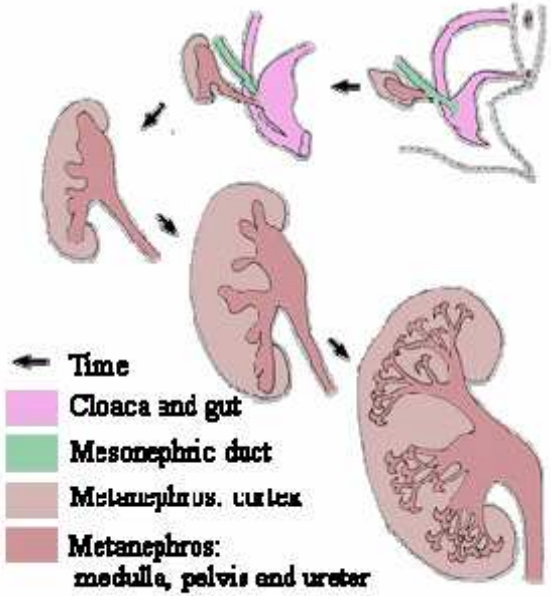
Why is the Developmental Period so Sensitive?

Isolate RNA from different stages of kidney development



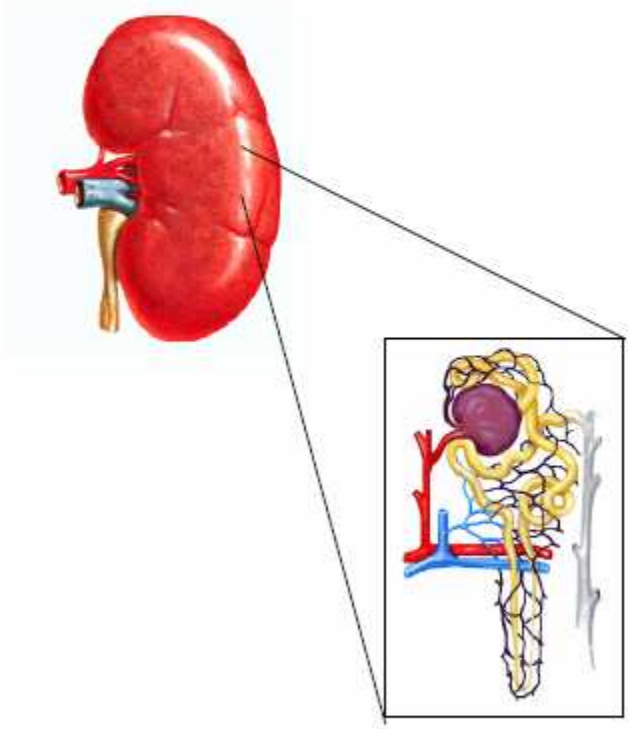
Microarray analysis and hierarchical clustering to identify differentially expressed genes





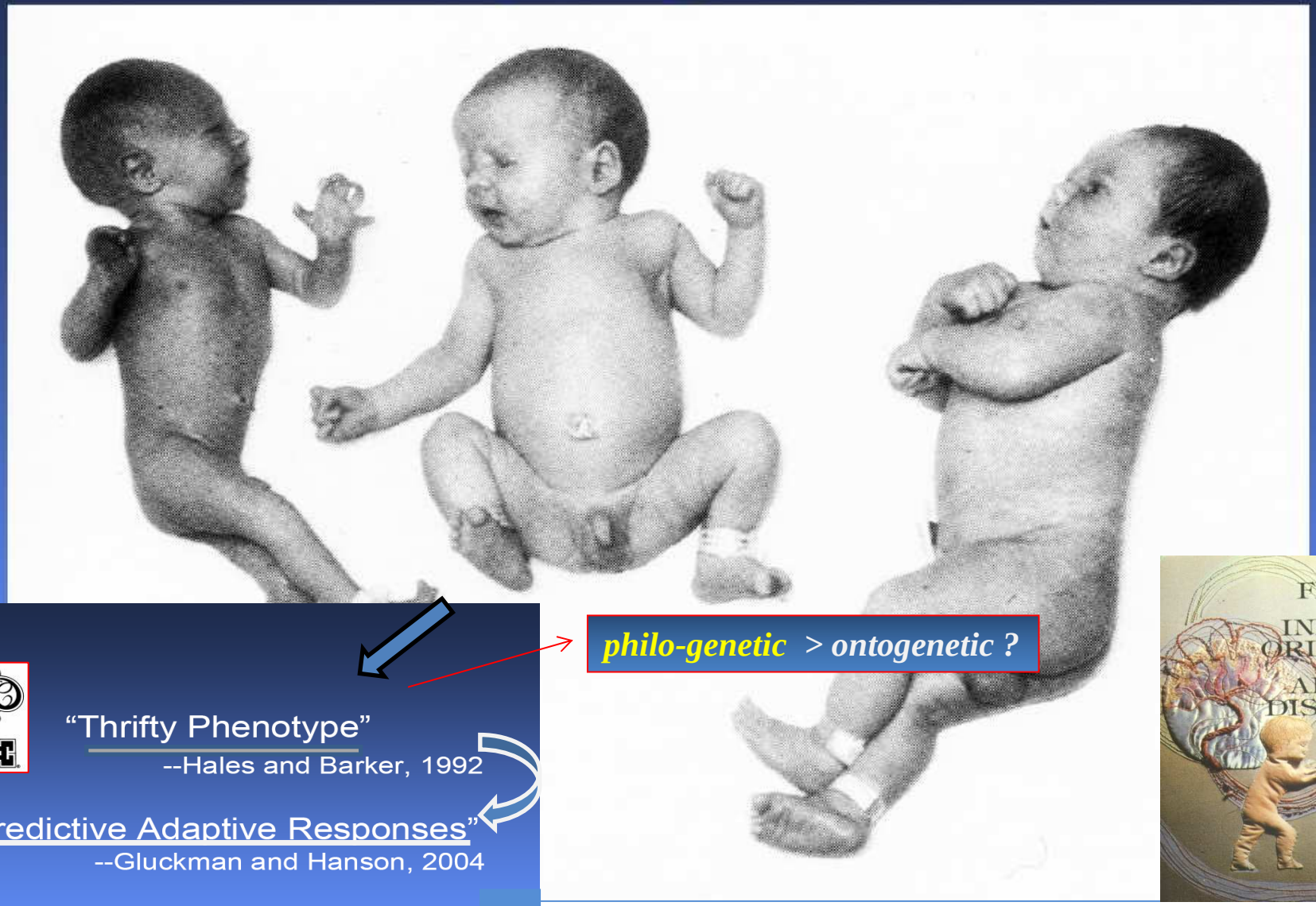
Organ development proceeds via an intricately orchestrated, temporal pattern of gene expression that is specific to the developing tissue. As a result, toxic exposures that perturb gene expression may have unique effects in the developing tissue or organ.

Relationship to Intrauterine Growth Retardation (IUGR) and Hypertension



- IUGR (or low protein diet in experimental animals) results in decreased nephron number
- This results in sodium retention and a compensatory increase in glomerular filtration rate (GFR) in the remaining nephrons
- Increased GFR leads to glomerulosclerosis, setting up a cycle of increasing GFR and glomerulosclerosis
- Ultimately more nephron loss occurs, leading to perturbed RAS and increased arterial blood pressure

Does Obesity Begin in the Womb?



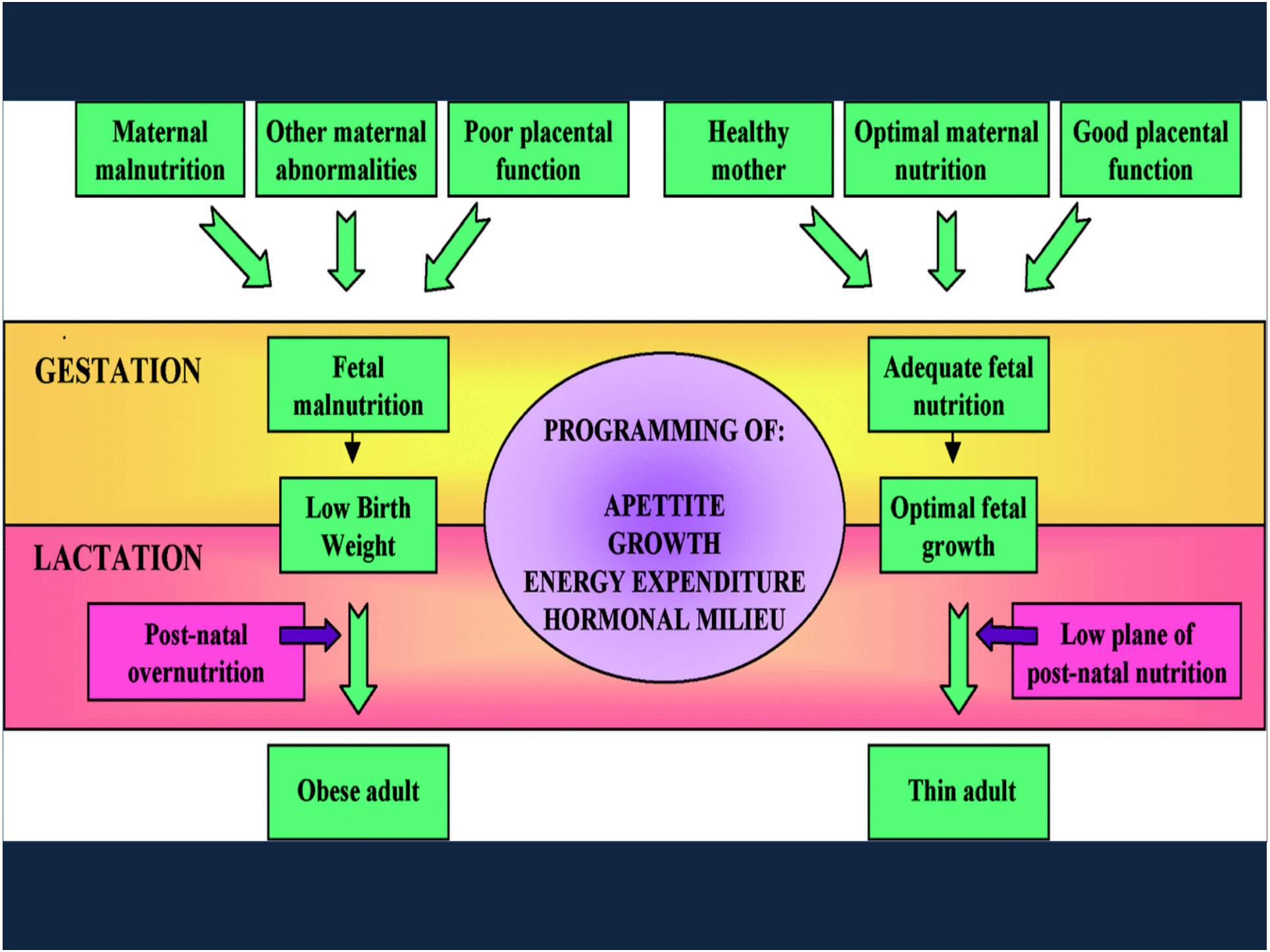
philo-genetic > *ontogenetic ?*

"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**


Maternal malnutrition
Other maternal abnormalities
Poor placental function
Healthy mother
Optimal maternal nutrition
Good placental function
GESTATION
Fetal malnutrition
Adequate fetal nutrition
PROGRAMMING OF:
APETTITE
GROWTH
ENERGY EXPENDITURE
HORMONAL MILIEU
Low Birth Weight
Optimal fetal growth
LACTATION
Post-natal overnutrition
Low plane of post-natal nutrition
Obese adult
Thin adult

"Thrifty Phenotype"

--Hales and Barker, 1992

"Predictive Adaptive Responses"

--Gluckman and Hanson, 2004

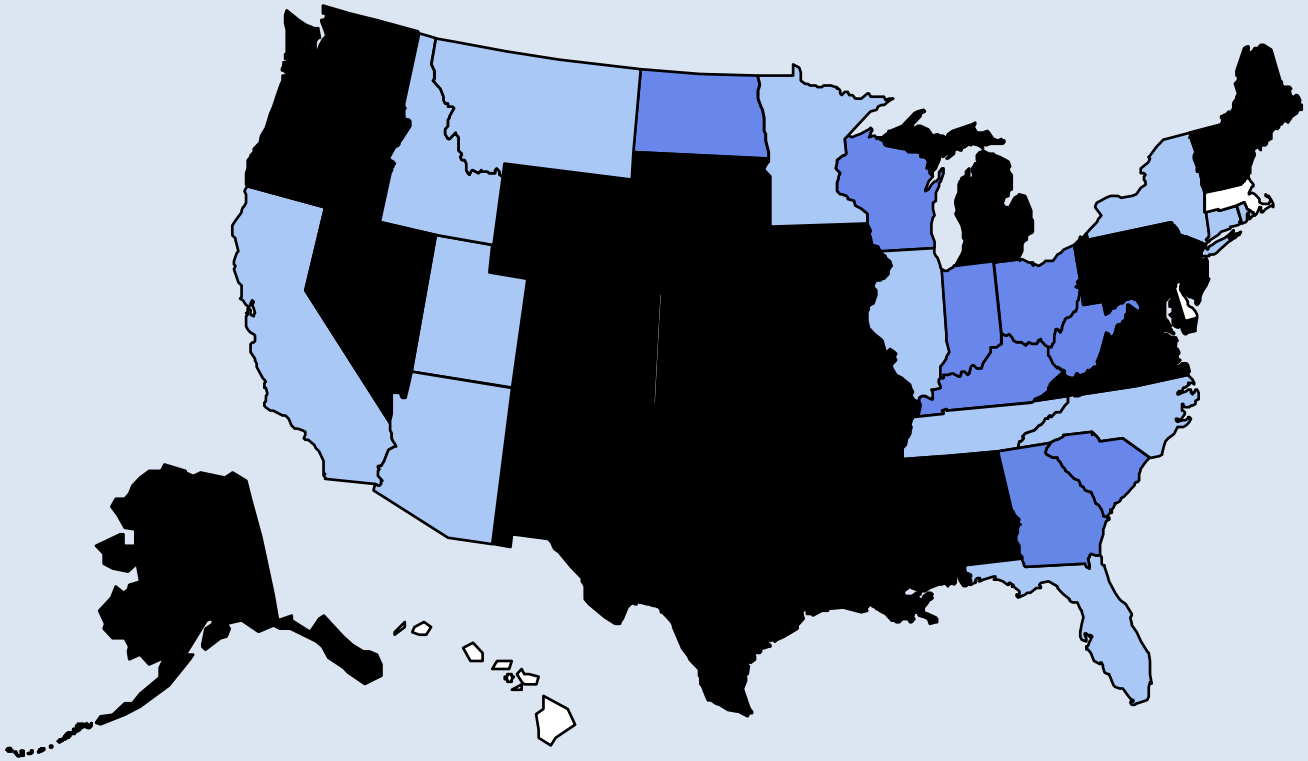
Potrebbe (dovrebbe ?) forse essere trasposta su un piano filo-genetico > ontogenetico evolutivo > devolutivo

L'epigenoma/fenotipo risparmiatore non è forse quello NATURALE ?

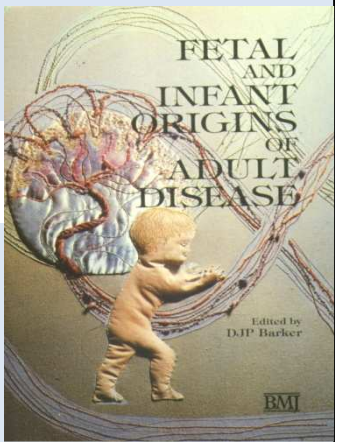
L'obesità non colpisce per questo solo gli animali in cattività ?

Obesity Trends* Among U.S. Adults 1985

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

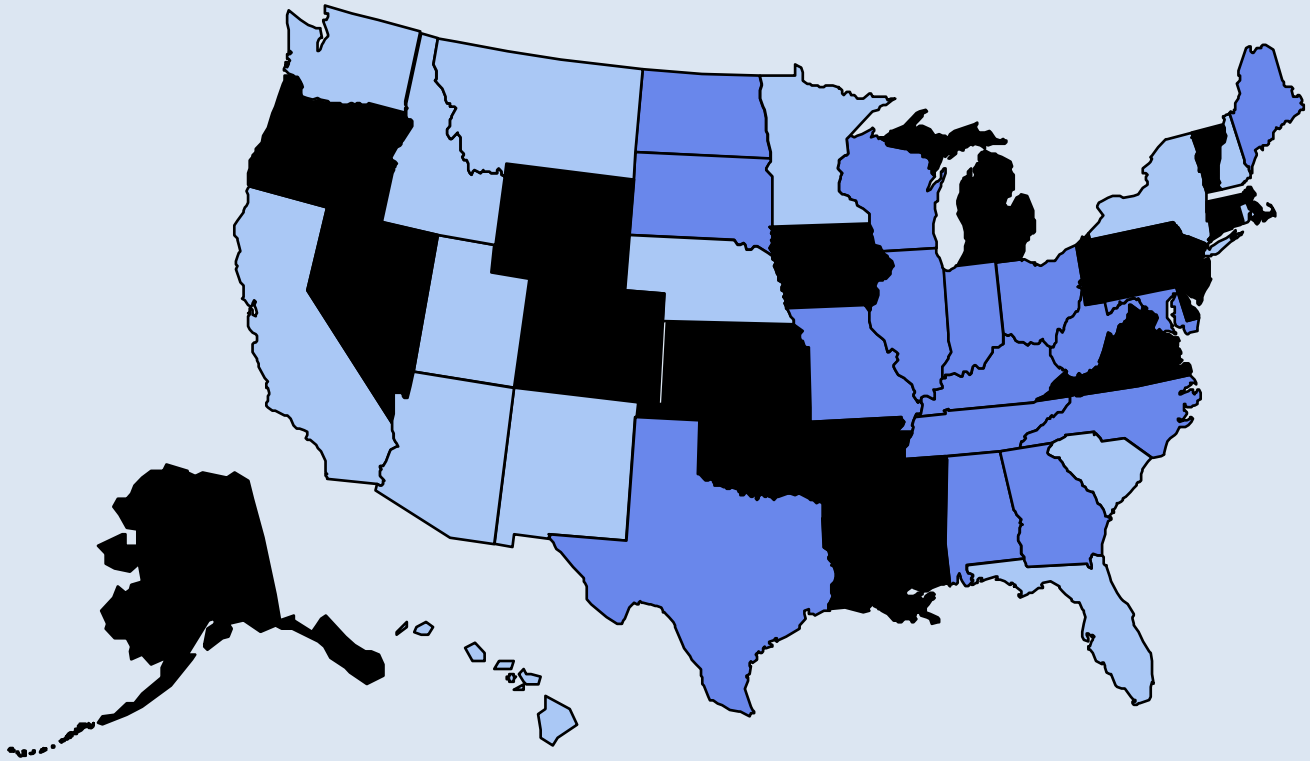


Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

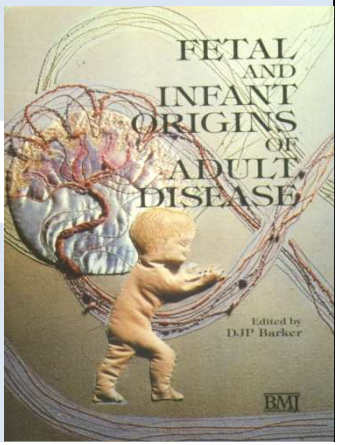


Obesity Trends* Among U.S. Adults 1987

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

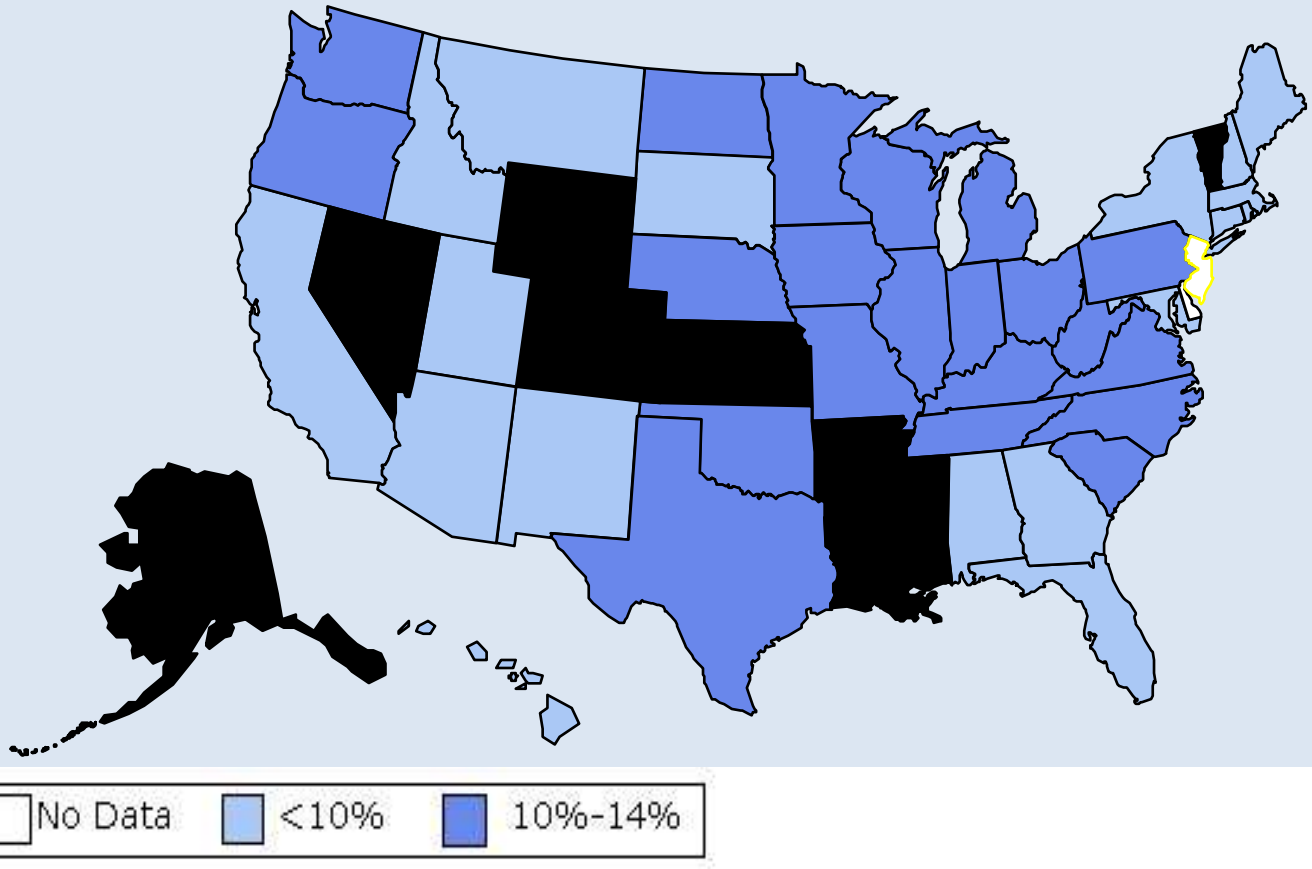


Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

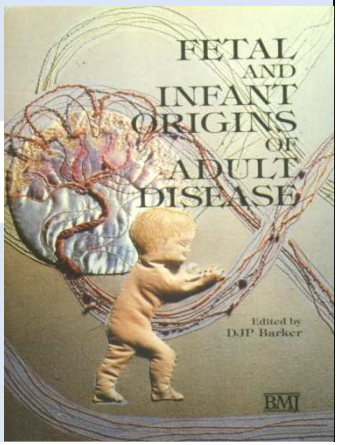


Obesity Trends* Among U.S. Adults 1989

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

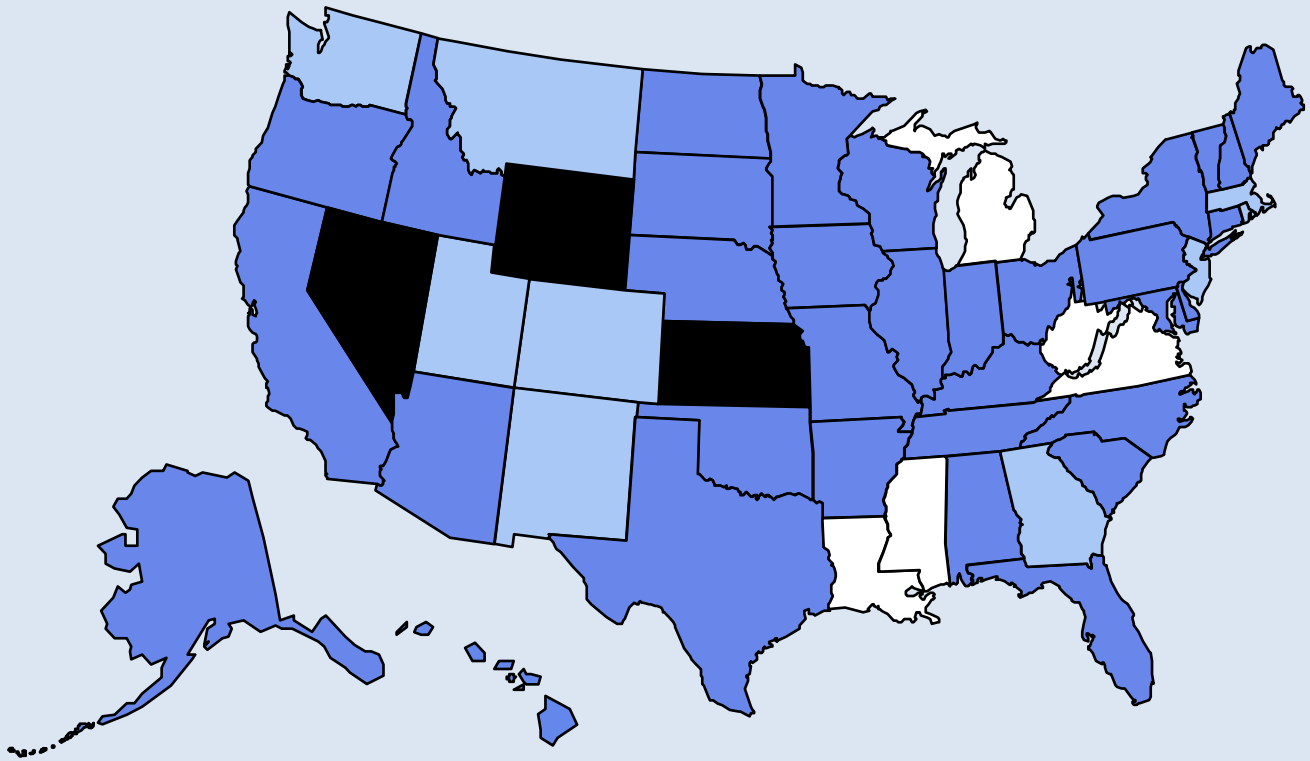


Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

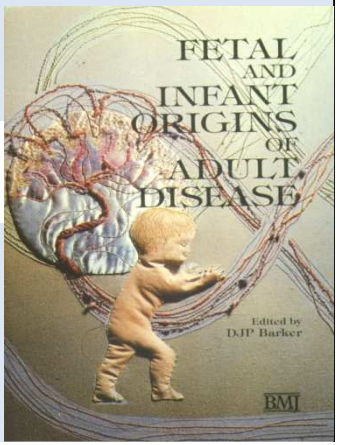


Obesity Trends* Among U.S. Adults 1991

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

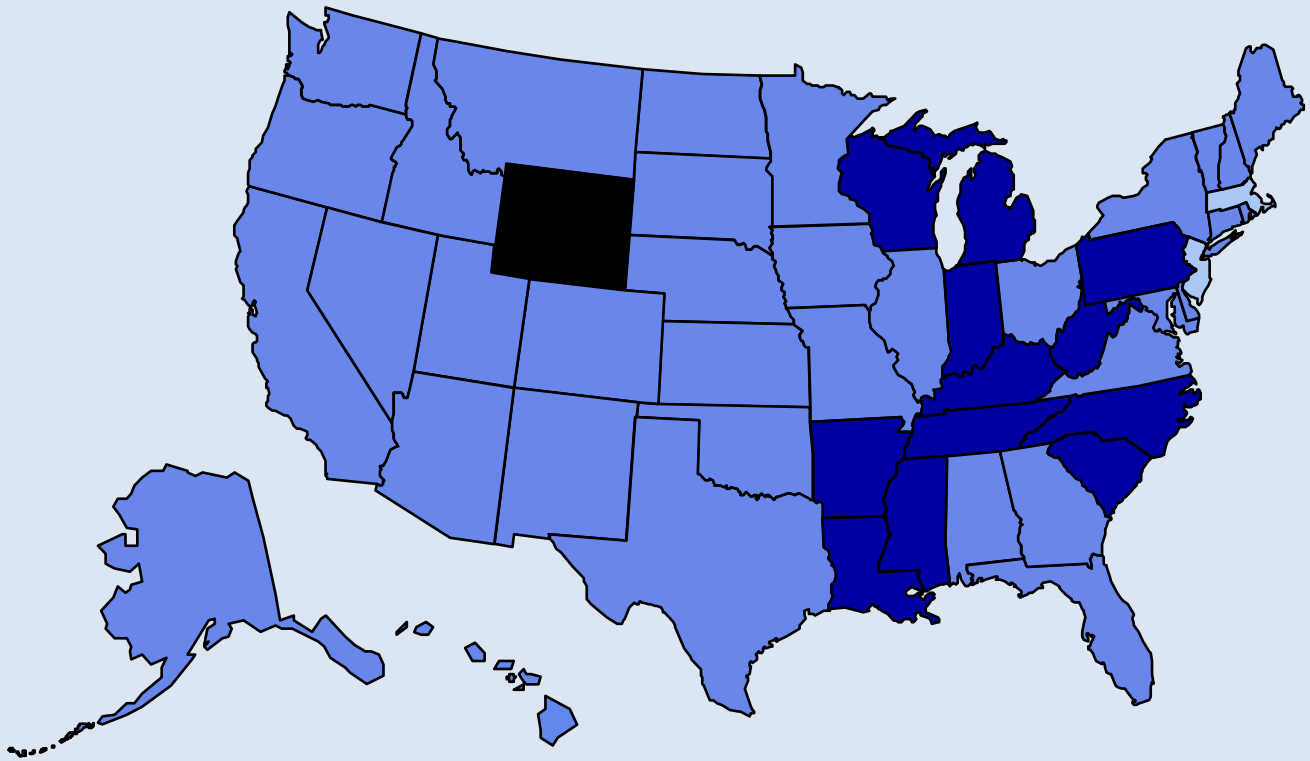


Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

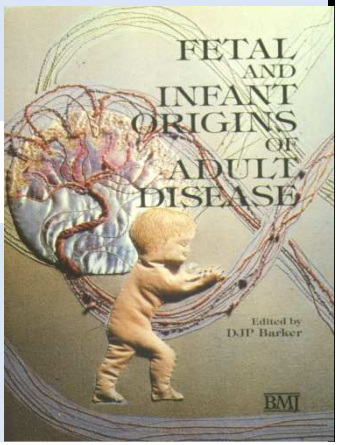


Obesity Trends* Among U.S. Adults 1993

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

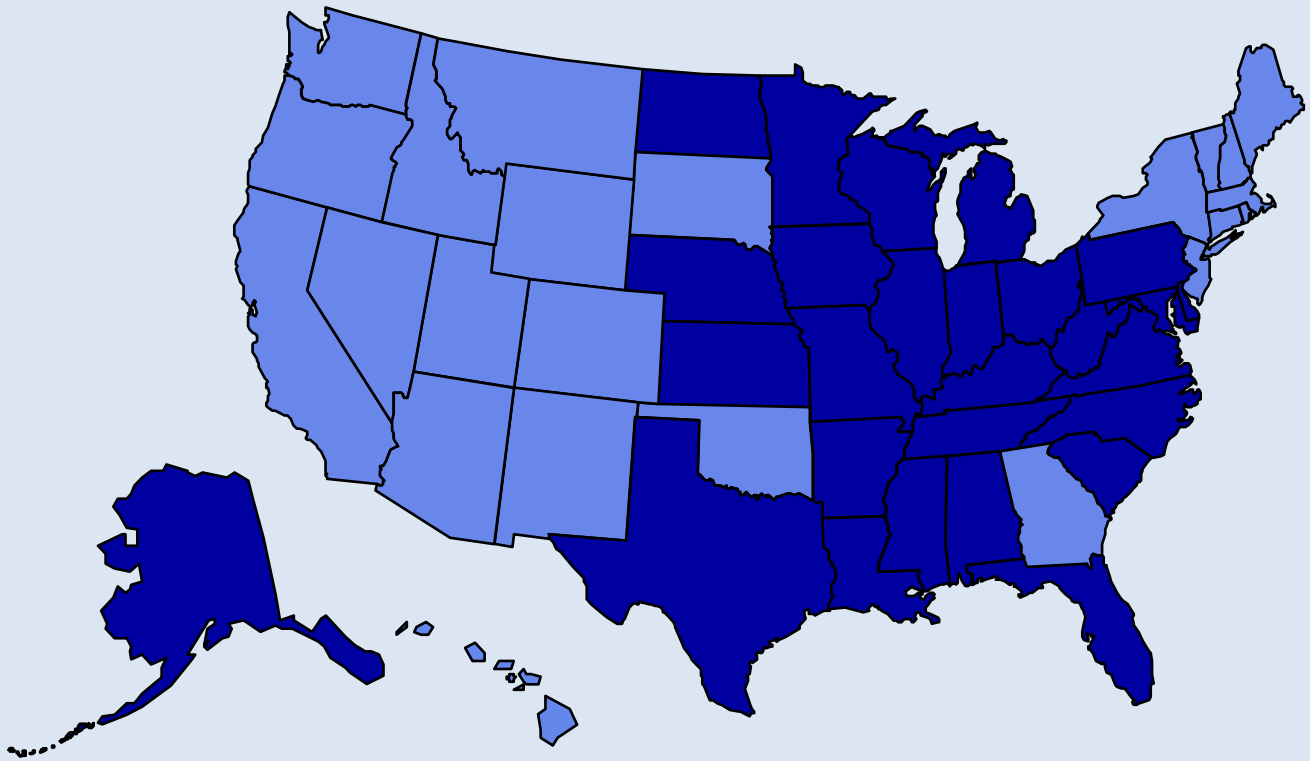


Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

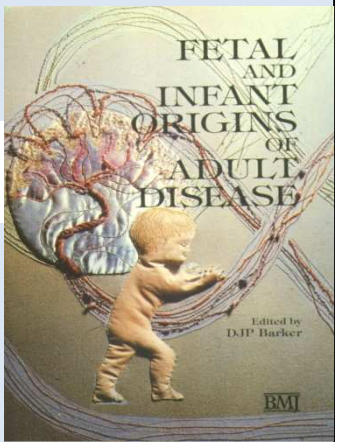


Obesity Trends* Among U.S. Adults 1995

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

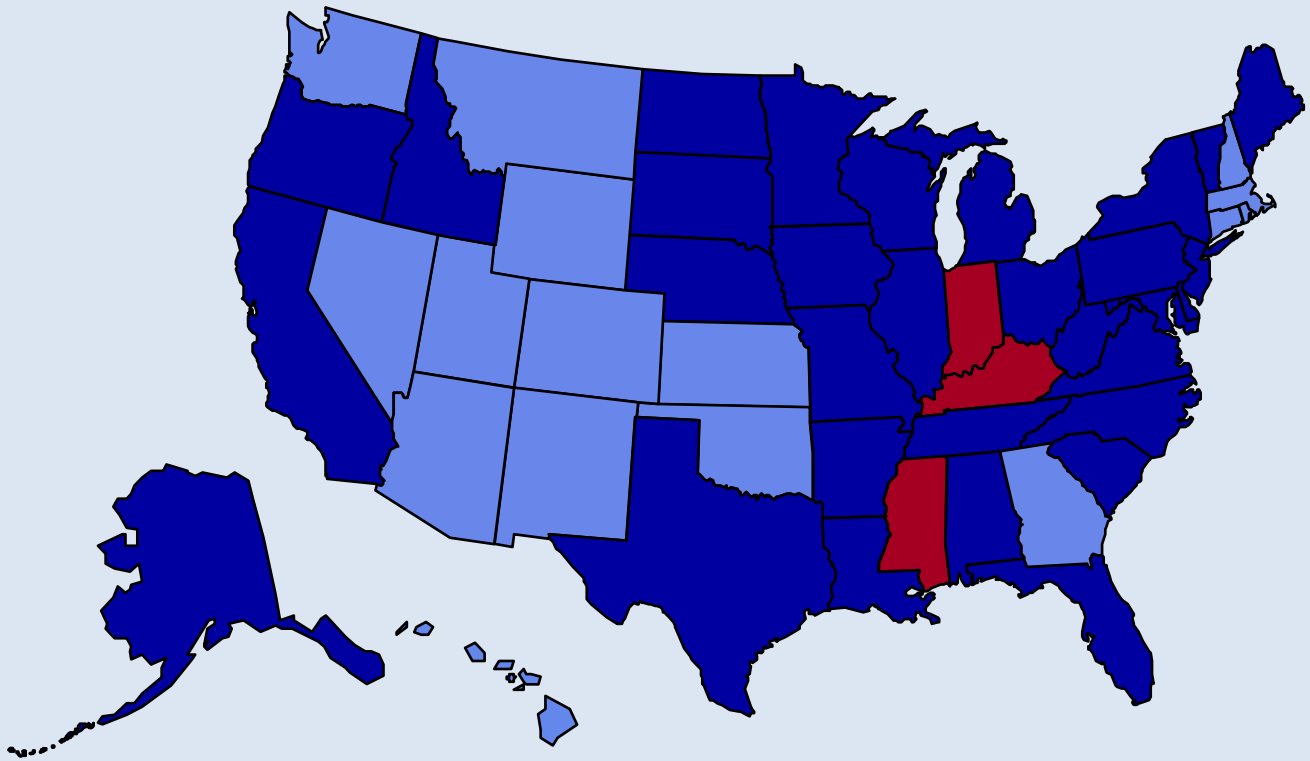


Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

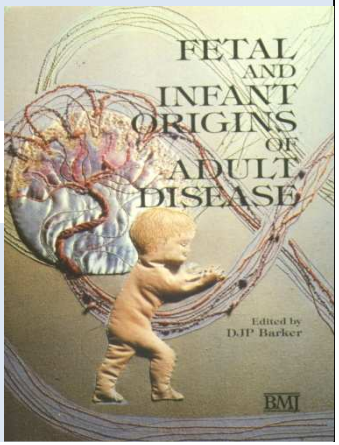


Obesity Trends* Among U.S. Adults 1997

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

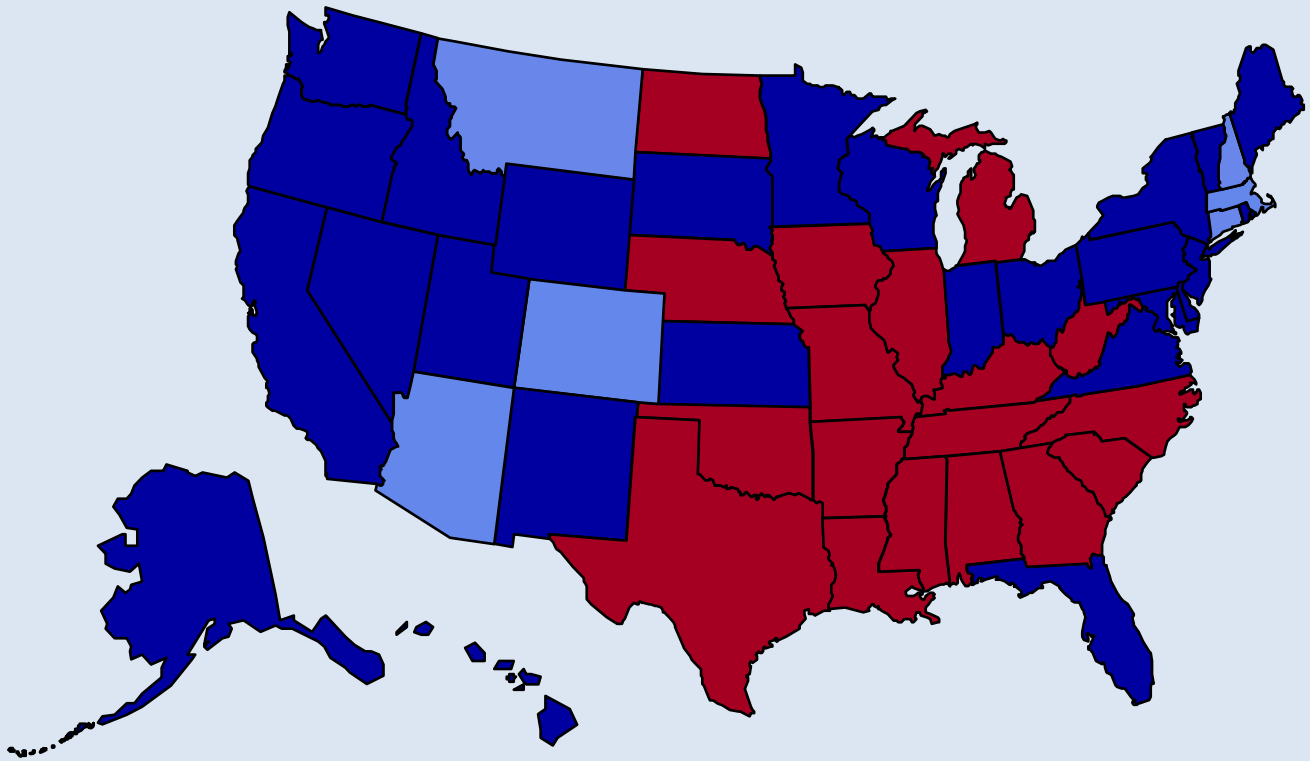


Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

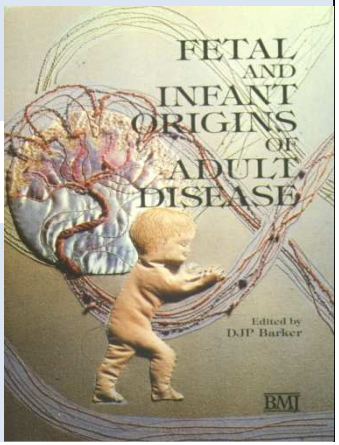


Obesity Trends* Among U.S. Adults 1999

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

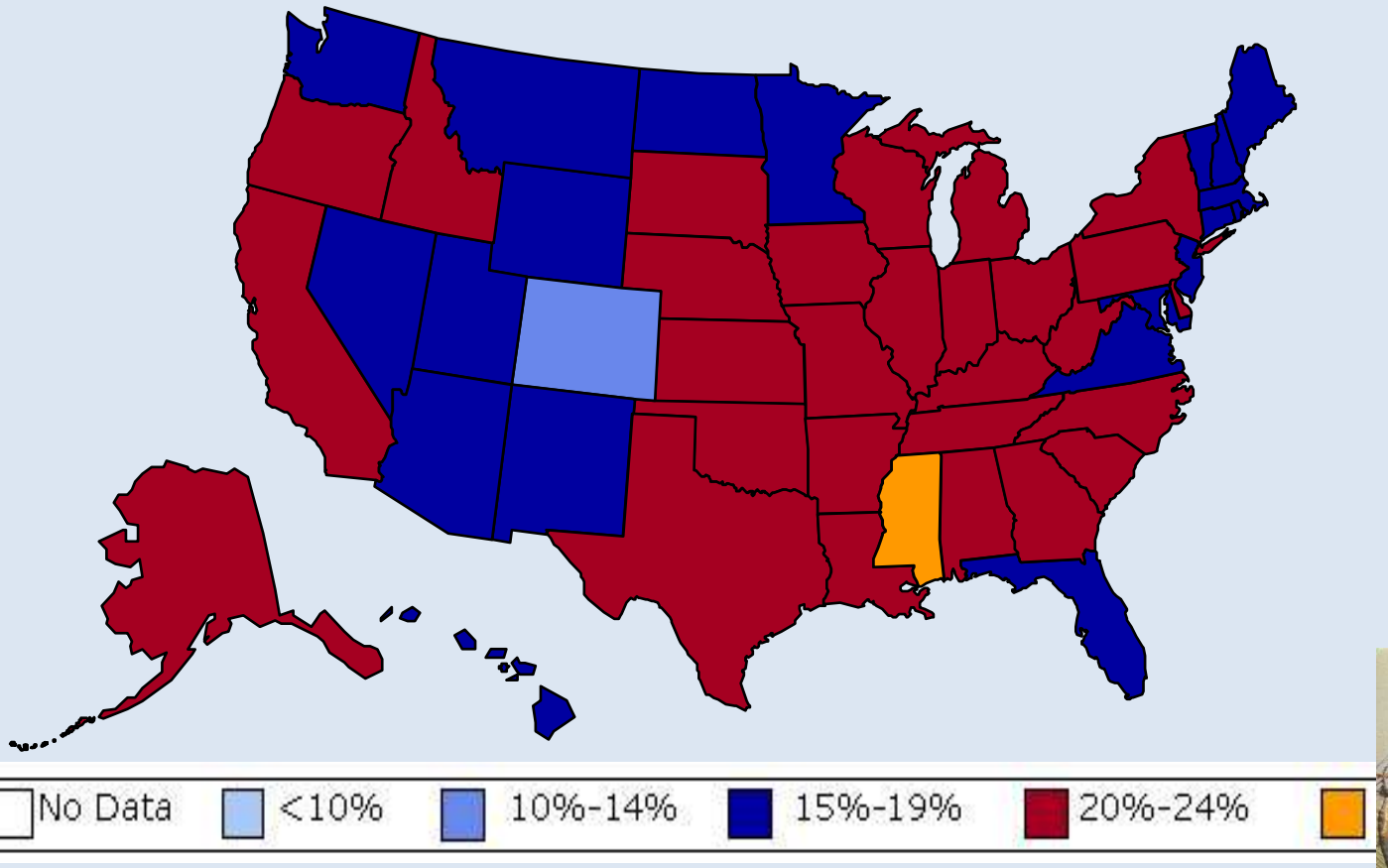


Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10

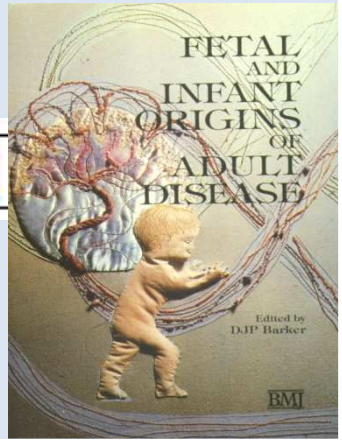


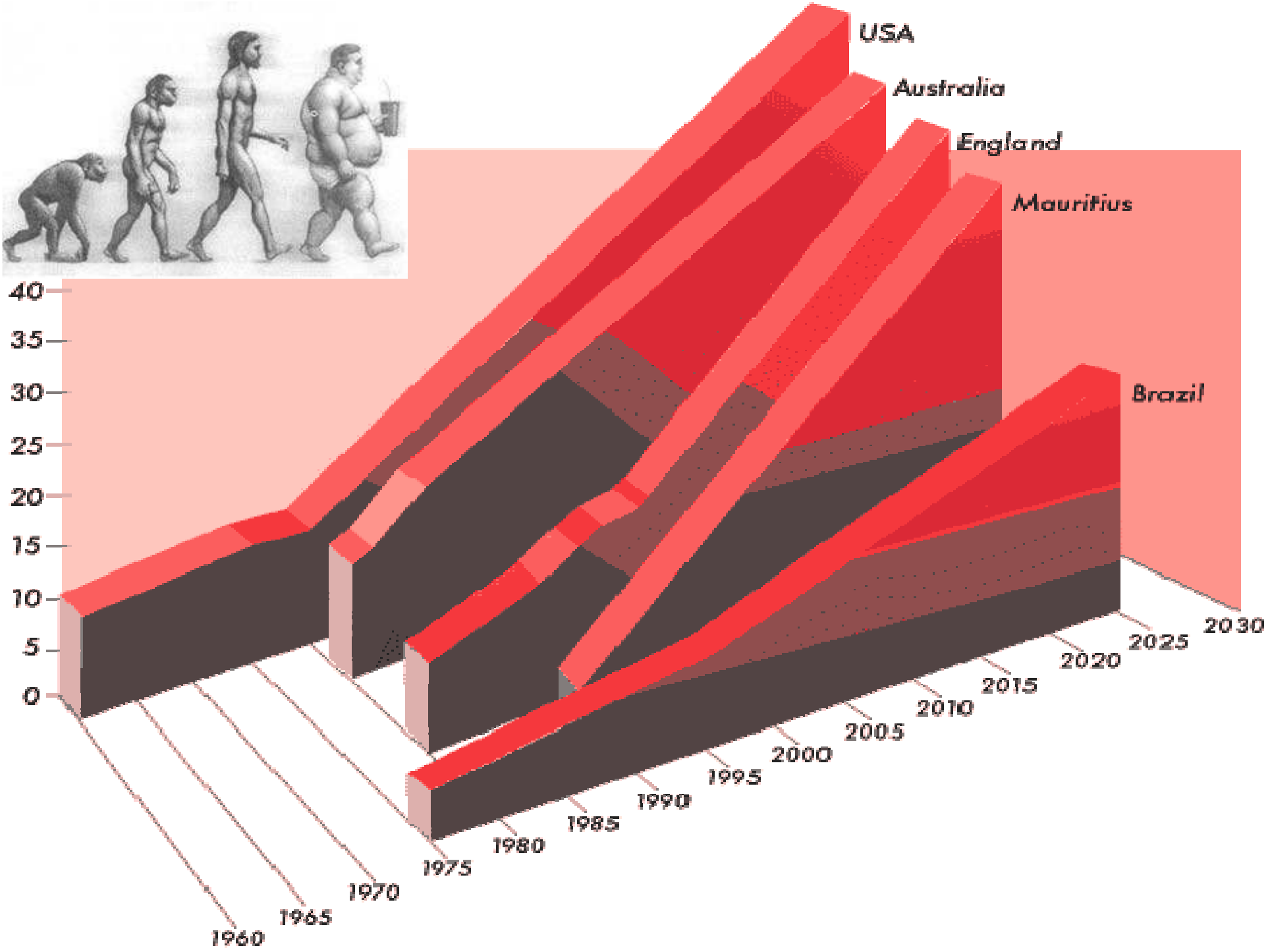
Obesity Trends* Among U.S. Adults 2001

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



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

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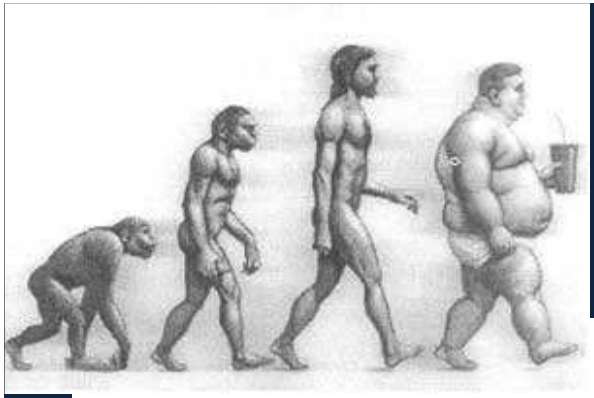


TOXICOLOGICAL SCIENCES 76, 247–249 (2003)
DOI: 10.1093/toxsci/kfg255

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

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

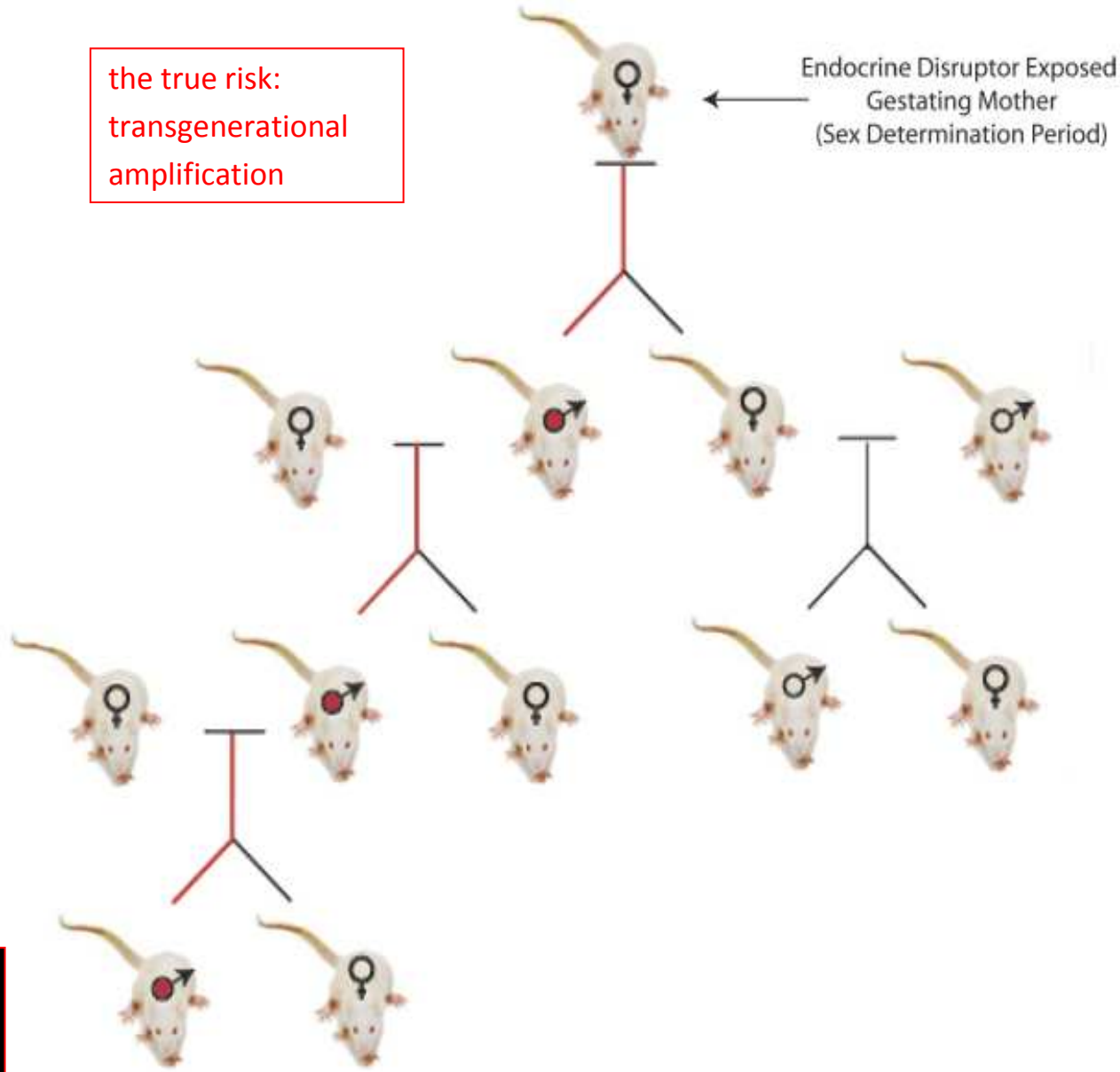
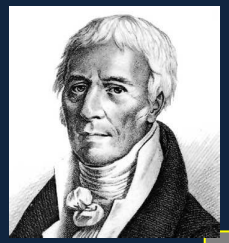


FIG. 1. Epigenetic transgenerational actions of endocrine disruptors through the male germ line.

Trasmissione ed
amplificazione
transgenerazionale
del danno



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

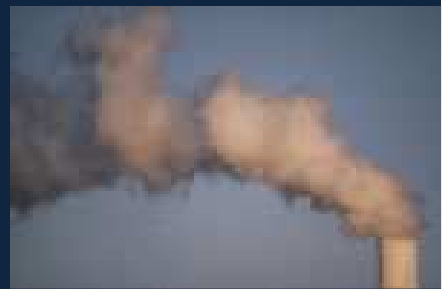
si passa dall' 1,5% dell''80

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



- **Variazioni nello stato di metilazione del DNA** sono state descritte in seguito ad esposizione ad **arsenico, bisfenolo A, dietilstilbestrolo, genisteina, metossicloro, TCDD** e **vinclozolina**;
- in particolare, studi condotti con **TCDD e vinclozolina** hanno causato **effetti transgenerazionali** in animali da laboratorio

Anway MD, Cupp AS, Uzumcu M, Skinner MK (2005) **"Epigenetic Transgenerational Actions of Endocrine Disruptors and Male Fertility"** Science, 308(5727):1466-1469.

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

Exposure → Health outcome

Prental Exposure to FP

pregnancy

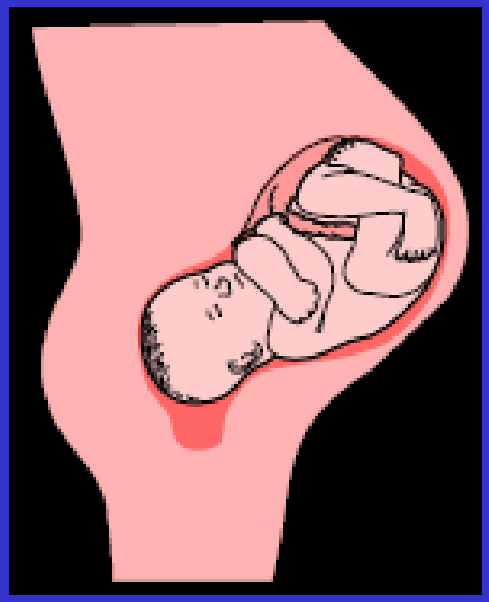
B C D

Interviews on prental nutrition

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

2. Important finding of the study is the protective effect of the fish consumption over the pregnancy period.



In the literature, there is an indication that long-chain polyunsaturated fatty acids (PUFA) supplementation from fish oil is beneficial for fetal development. The protective mechanism may involve antioxidant action of micronutrients and the free-radical scavenging action. It is assumed that increasing omega-3 fatty acids may lead to a reduced inflammatory status.

- **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.

- **Ambient air pollution and low birth weight in Connecticut and Massachusetts.**
- **Bell ML**, **Ebisu K**, **Belanger K**.
- School of Forestry and Environmental Studies, Yale University, New Haven, Connecticut 06511, USA. michelle.bell@yale.edu
- Environ Health Perspect. **2007** Jul;115(7):1118-24
- BACKGROUND: Several studies have examined whether air pollution affects birth weight; however results vary and many studies were focused on Southern California or were conducted outside of the United States. OBJECTIVES: **We investigated maternal exposure to particulate matter with aerodynamic diameter < 10, < 2.5 microm (PM(10), PM(2.5)), sulfur dioxide, nitrogen dioxide, and carbon monoxide and birth weight for 358,504 births** in Massachusetts and Connecticut from 1999 to 2002. METHODS: Analysis included logistic models for low birth weight (< 2,500 g) and linear models with birth weight as a continuous variable. Exposure was assigned as the average county-level concentration over gestation and each trimester based on mother's residence. We adjusted for gestational length, prenatal care, type of delivery, child's sex, birth order, weather, year, and mother's race, education, marital status, age, and tobacco use.
  RESULTS: An interquartile **increase in gestational exposure to NO(2), CO, PM(10), and PM(2.5) lowered birth weight by 8.9 g [95% confidence interval (CI), 7.0-10.8], 16.2 g (95% CI, 12.6-19.7), 8.2 g (95% CI, 5.3-11.1), and 14.7 g (95% CI, 12.3-17.1), respectively**. **Lower birth weight was associated with exposure in the third trimester for PM(10), the first and third trimesters for CO, the first trimester for NO(2) and SO(2), and the second and third trimesters for PM(2.5).** Effect estimates for PM(2.5) were higher for infants of black mothers than those of white mothers. CONCLUSIONS: Results indicate that **exposure to air pollution, even at low levels, may increase risk of low birth weight,** particularly for some segments of the population.

Table 3. Change in birth weight per IQR increase in pollution for the gestational period (95% confidence interval).

Pollutant	Difference in birth weight (g)	Odds ratio for low birth weight (< 2,500 g)
NO_2	–8.9 (–10.8 to –7.0)*	1.027 (1.002 to 1.051)**
CO	–16.2 (–19.7 to –12.6)*	1.028 (0.983 to 1.074)
SO_2	–0.9 (–4.4 to 2.6)	1.003 (0.961 to 1.046)
PM_{10}	–8.2 (–11.1 to –5.3)*	1.027 (0.991 to 1.064)
$PM_{2.5}$	–14.7 (–17.1 to –12.3)*	1.054 (1.022 to 1.087)**

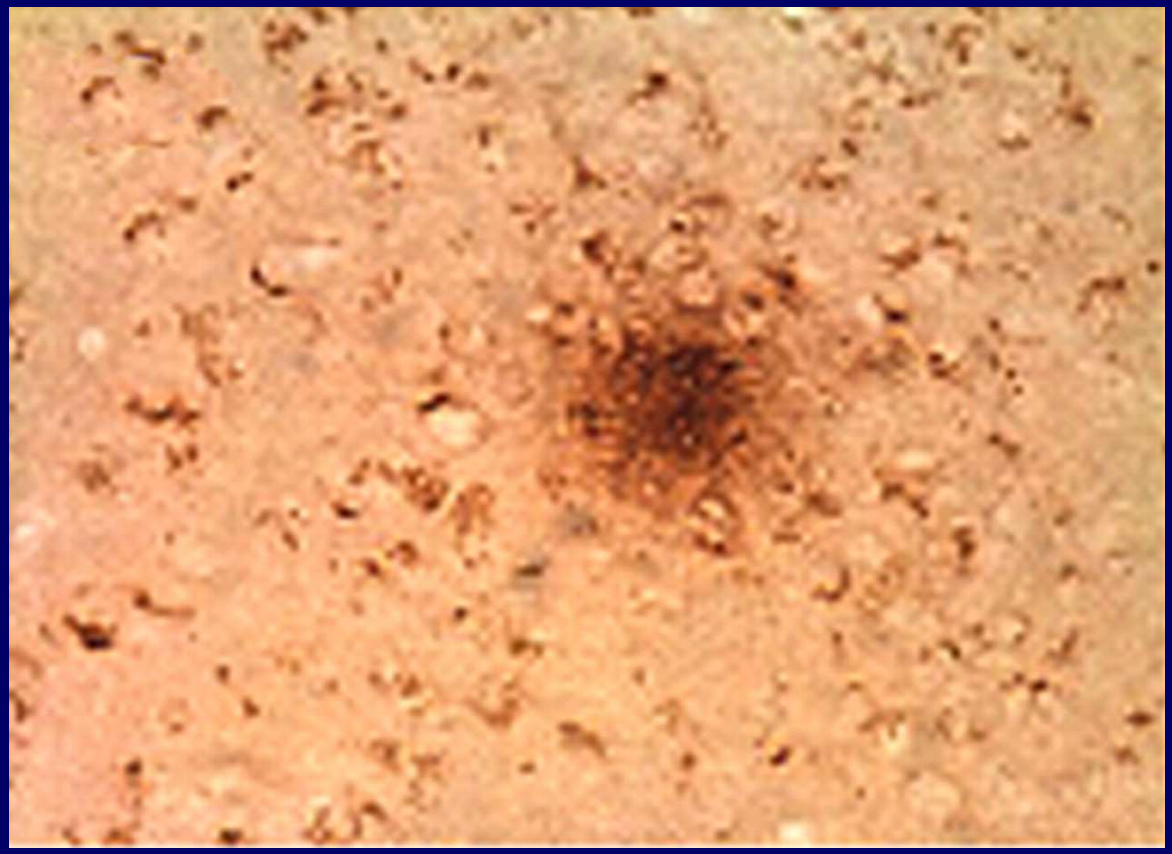
*$p < 0.001$; **$p < 0.05$.

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

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 manifestation 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.

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**.

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 assuma rilievo, in questo ambito **la componente cronica, connessa al perdurare 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 l'***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.

Atherosclerosis/KD

Obesity

Metabolic Syndrome

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

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.

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 la letteratura é ormai vastissima)…

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

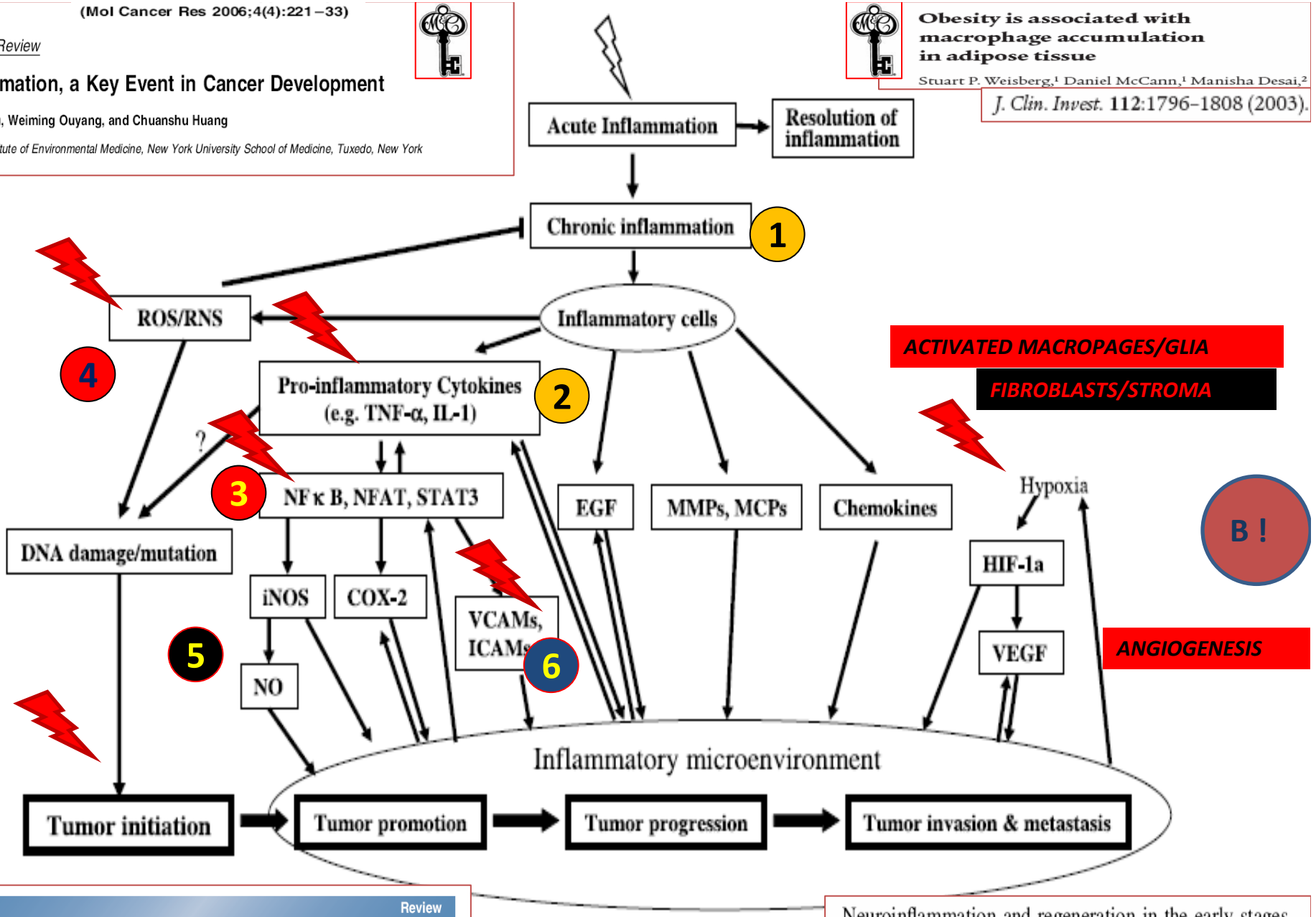
Haitian Lu, Weiming Ouyang, and Chuanshu Huang

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).



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

NF-κB IN CANCER: FROM INNOCENT BYSTANDER TO MAJOR CULPRIT

NATURE REVIEWS | CANCER
VOLUME 2 | APRIL 2002

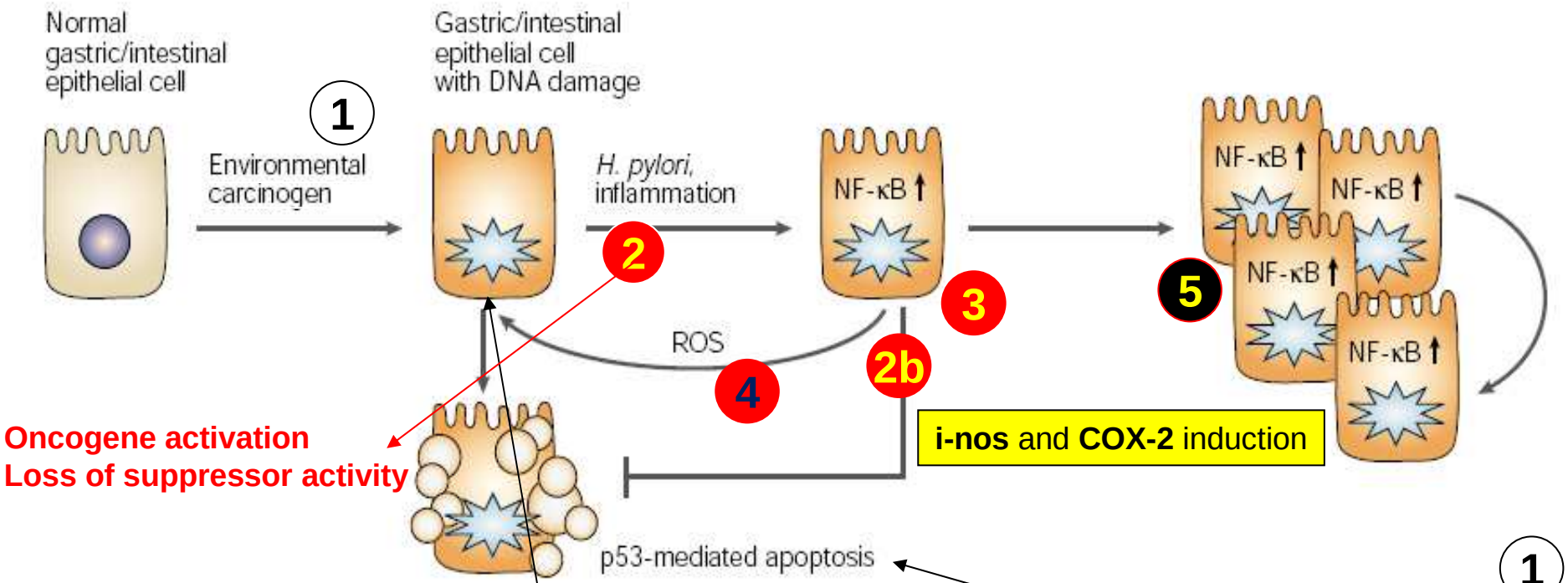
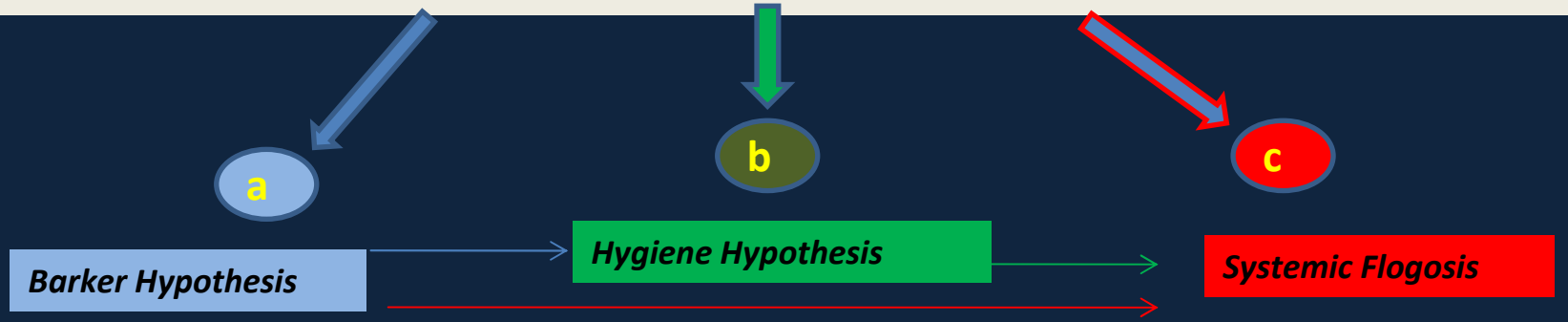


Figure 5 | **Role of NF-κB in gastric and colorectal cancers.** Exposure to environmental carcinogens in the diet can cause DNA damage to gastric or intestinal epithelial cells. Such cells are normally eliminated by p53-mediated apoptosis, but oncogene activation or loss of tumour-suppressor activity, coupled with *Helicobacter pylori* infection or inflammation, can lead to constitutive nuclear factor of κB (NF-κB) activation. NF-κB activation leads to production of enzymes such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2, which enhance the production of reactive oxygen species (ROS), leading to additional DNA damage. Finally, through enhanced production of growth factors and cytokines, NF-κB can lead to further proliferation of transformed cells.

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 **sequenziali:**

1

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 **micro-flora tipica dei principali alimenti** (a cominciare ovviamente dal **latte**) determinerebbe nel neonato **un'alterazione dell'ecosistema microbico e, quindi, dello sviluppo immunitario .**

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

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 e comprovata 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 conseguente all'inquinamento ambientale** (e in particolare alle **trasformazioni re-attive dell'epigenoma** che, paradossalmente nel tentativo di consentire l'intervento dei **sistemi enzimatici di riparazione**, determinano una condizione di **instabilità/vulnerabilità del genoma** stesso).

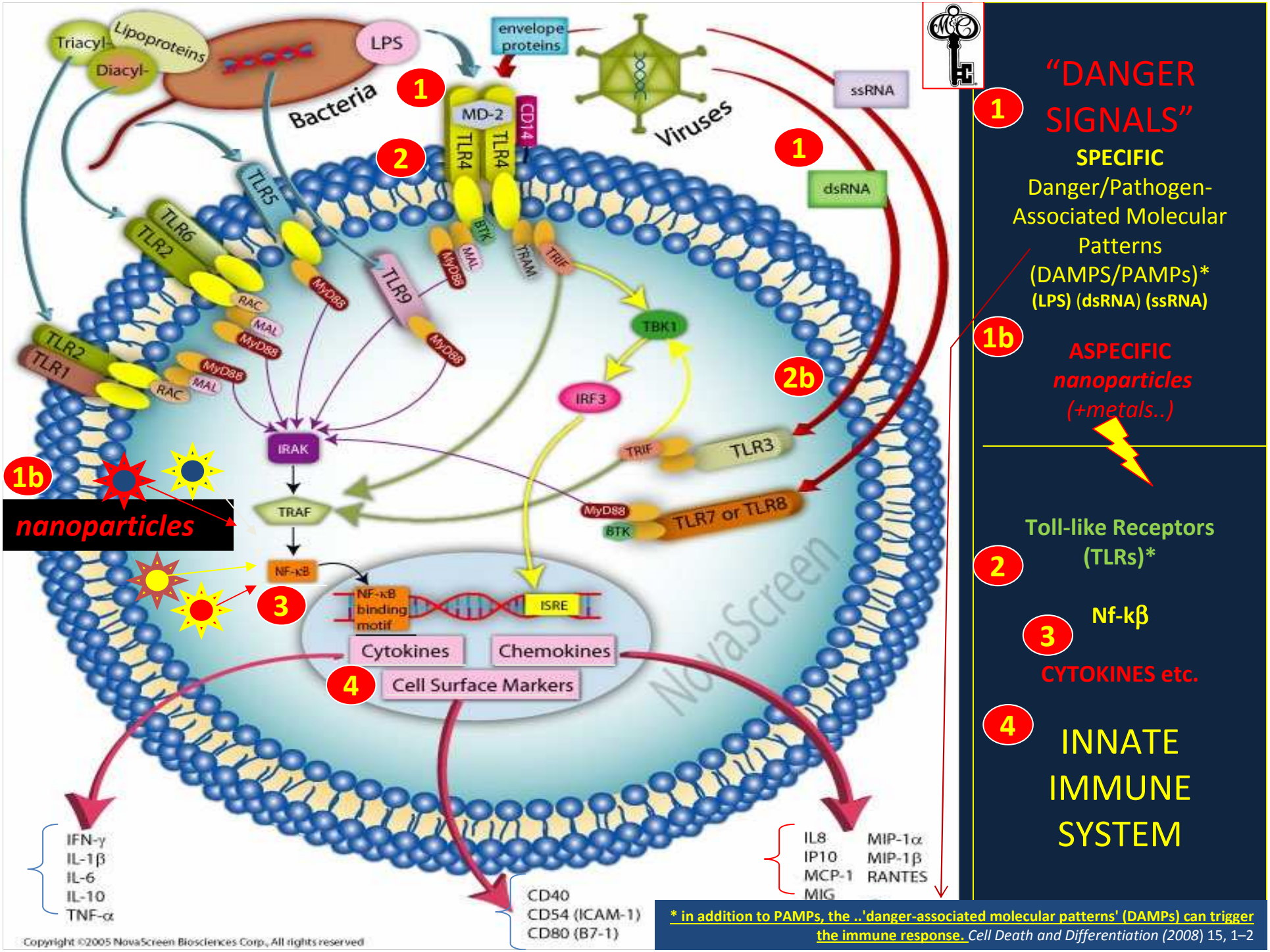
da 2
a 3

3

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) è 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 morte cellulare programmata*** …)

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



1 "DANGER SIGNALS"

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

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

Toll-like Receptors (TLRs)*

2

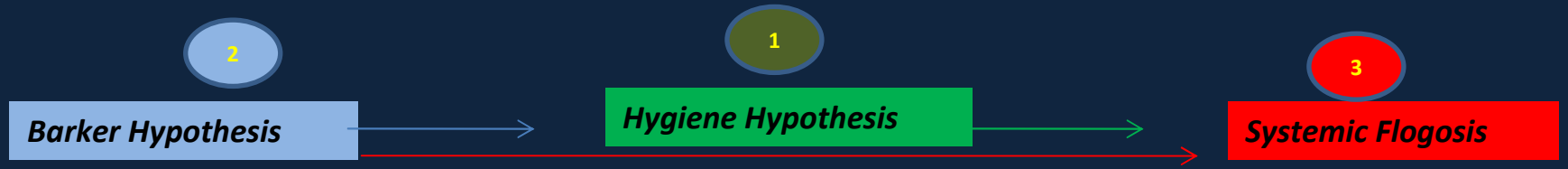
Nf-kβ

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 sorta 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 pesanti*** e ***particolato ultrafine*** – possano fare da ***trigger* patogenetico** nelle varie fasi del processo).

Development/Ontogenesis

Evolution/Philogenesis

- E' importante sottolineare fin d'ora come tutto questo rappresenti una conferma indiretta della validità del paradigma evolutivo ***neo-lamarchiano*** (tornato in auge tra i biologi evolutivi dopo decenni di ingiustificato ostracismo) secondo il quale l'**ambiente** non si limiterebbe a "**premiare**" le ***cellule*** e/o gli ***organismi*** cui **mutazioni casuali** abbiano accordato un vantaggio selettivo (come nel ***paradigma neo-darwinista***),

  ma svolgerebbe **un ruolo attivo/essenziale nella continua/diretta induzione/modulazione dell'assetto epi-genomico cellulare e quindi nei processi di sviluppo individuale (*ontogenesi*) e di evoluzione collettiva (*filogenesi*)** (il che, sia detto per inciso, potrebbe significare che gli agenti esogeni in grado di interferire in ambito *ontogenetico* potrebbero rilevarsi altrettanto dannosi in ambito *evolutivo*)

+

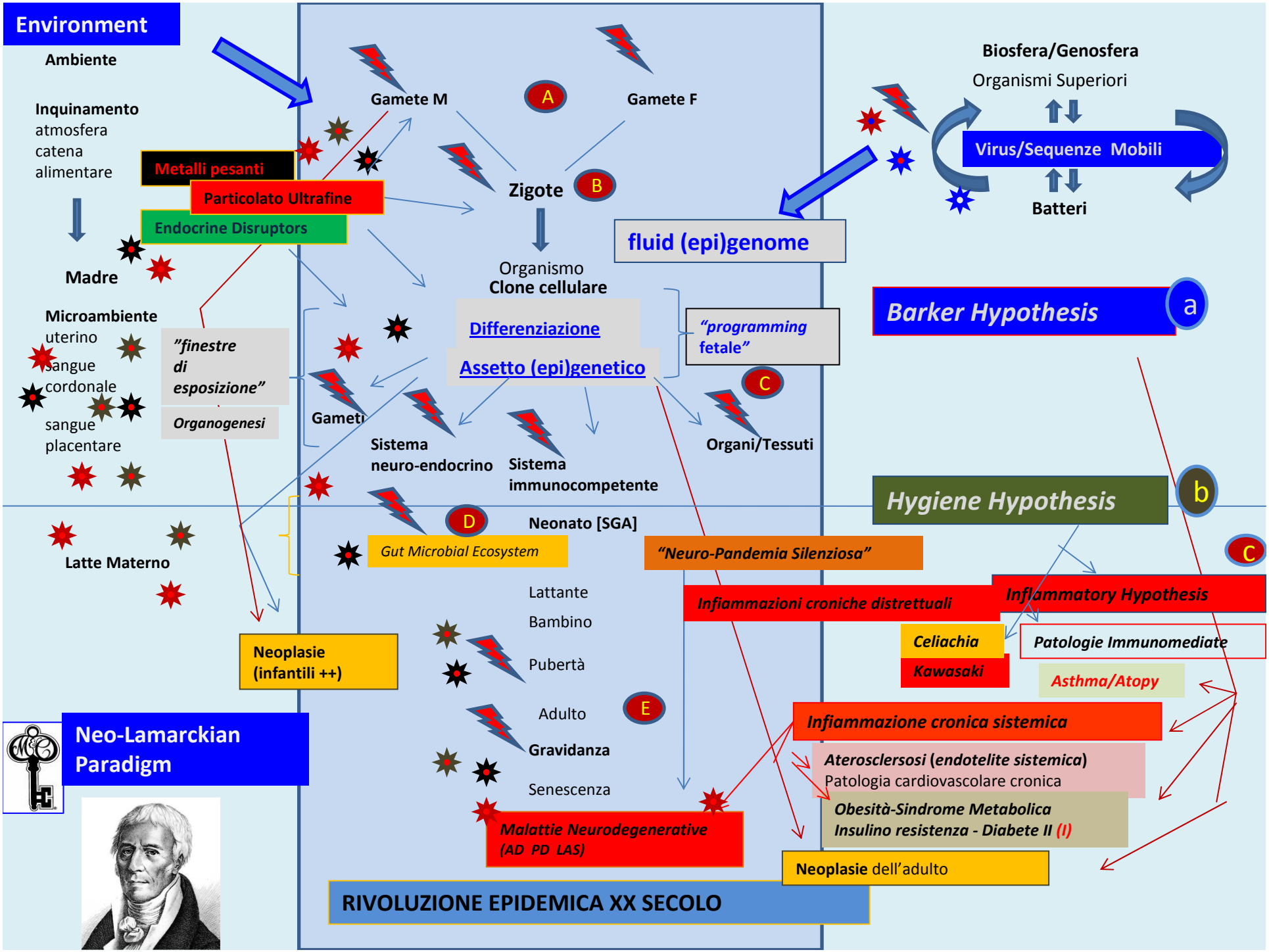
Environment

- Vedremo, inoltre, come l'utilizzo di un ***paradigma evolutivo neo-lamarchiano*** , risulti estremamente utile per una miglior comprensione dei **processi di cancerogenesi** (o, per meglio dire, come sia possibile riconoscere in un **processo neoplastico una distorsione del fisiologico processo di sviluppo che avrebbe origine in età fetale**)

+

Carcinogenesis

Soto A.M..**Does Breast Cancer Start in the Womb?** *Basic & Clinical Pharmacology & Toxicology* **102,**125–133


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

Sulla base di quanto detto fin qui dovrebbe essere evidente

A 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 catene alimentari di sostanze tossiche e**

B come 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**, sia di per se stessa specchio significativo e sintomatico di uno ***stress* (epi)-genomico e bio-evolutivo** che coinvolge l'uomo e l'intera biosfera).

***XENO*-BIOTICI**

Medical Hypotheses (2004) 62, 299–303

Neo-Lamarckian medicine.

Gorelick R.
School of Life Sciences, Arizona State University, Tempe, AZ 85287-4501, USA. cycac

Med Hypotheses. **2004;** 62(2):299-303

Darwinian medicine is the treatment of disease based on evolution. The underlying assumption of **Darwinian medicine** is that traits are coded by genes, which are often assumed to be sequences of DNA nucleotides.

The quantitative genetic ramification of this perspective is that traits, including disease susceptibility, are either caused by ***genes* or** by the ***environment***, with **genotype-by-environment interactions usually considered statistical artefacts.**

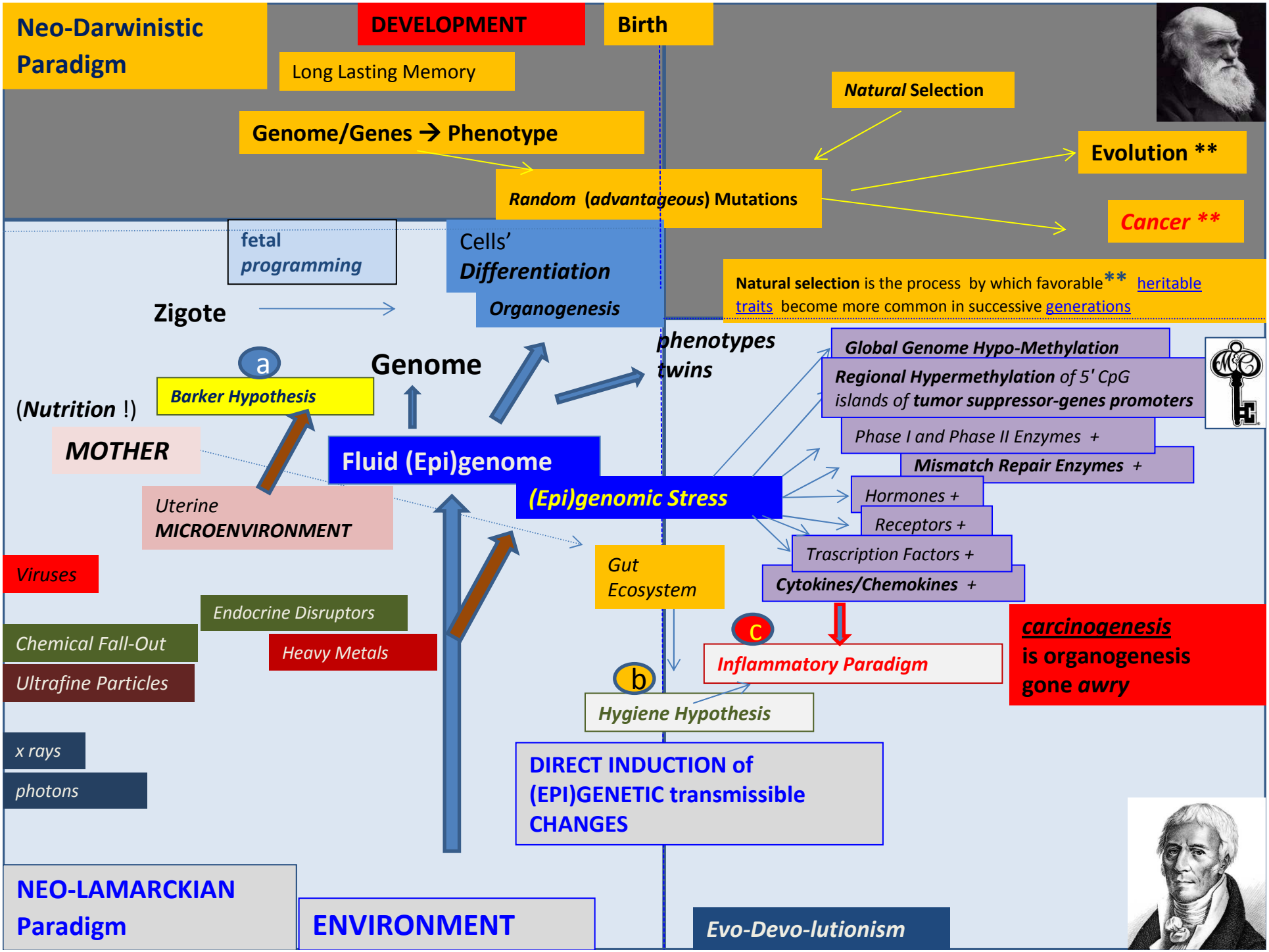
I emphasize also examining those **epigenetic signals that can be altered by environmental perturbations and then transmitted to subsequent generations**. Although seldom studied, **environmentally-alterable meiotically-heritable epigenetic signals exist and provide a mechanism underlying genotype-by-environment interactions**. **Environment of a parent can affect its descendants by heritably altering epigenetic signals. Neo-Lamarckian Medicine is the application of these evolutionary epigenetic notions to diseases** and could have enormous public health and environmental policy implications.

If industrial contaminants adversely affect organisms by meiotically-heritably altering their epigenetic signa…en cleaning up these contaminants will not remedy the problem.

Once contaminants have adversely altered an individual's epigenetic signals, this harm will be transmitted to future generations even if they are not exposed to the contaminant. Exposure to environmental shocks such as **free radicals or other carcinogens can alter cytosine methylation patterns on regulatory genes**. This can cause **cancer by up-regulating genes for cell division or by down-regulating tumour suppressor genes**.

Environmentally-alterable meiotically-heritable epigenetic signals could also underlie other diseases, such as diabetes, Prader-Willi syndrome, and many complex diseases. If environmentally-altered meiotically-heritable epigenetic effects are widespread - which is an important open empirical question - they have the potential to alter paradigmatic views of evolutionary medicine and the putative dichotomy of nature versus nurture.

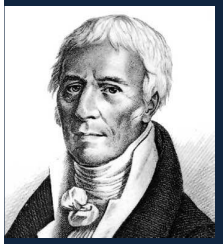
Neo-Lamarckian medicine would thereby shift emphasis from cure to prevention of diseases.


Neo-Darwinistic Paradigm
DEVELOPMENT
Birth
Long Lasting Memory
Natural Selection
Genome/Genes → Phenotype
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
phenotypes twins
Global Genome Hypo-Methylation
Regional Hypermethylation of 5' CpG islands of tumor suppressor-genes promoters
a
Genome
Barker Hypothesis
(Nutrition !)
MOTHER
Phase I and Phase II Enzymes +
Mismatch Repair Enzymes +
Fluid (Epi)genome
(Epi)genomic Stress
Hormones +
Receptors +
Uterine MICROENVIRONMENT
Trascription Factors +
Cytokines/Chemokines +
Gut Ecosystem
Viruses
Endocrine Disruptors
Chemical Fall-Out
Heavy Metals
Ultrafine Particles
c
Inflammatory Paradigm
carcinogenesis is organogenesis gone awry
b
Hygiene Hypothesis
x rays
photons
DIRECT INDUCTION of (EPI)GENETIC transmissible CHANGES
NEO-LAMARCKIAN Paradigm
ENVIRONMENT
Evo-Devo-lutionism

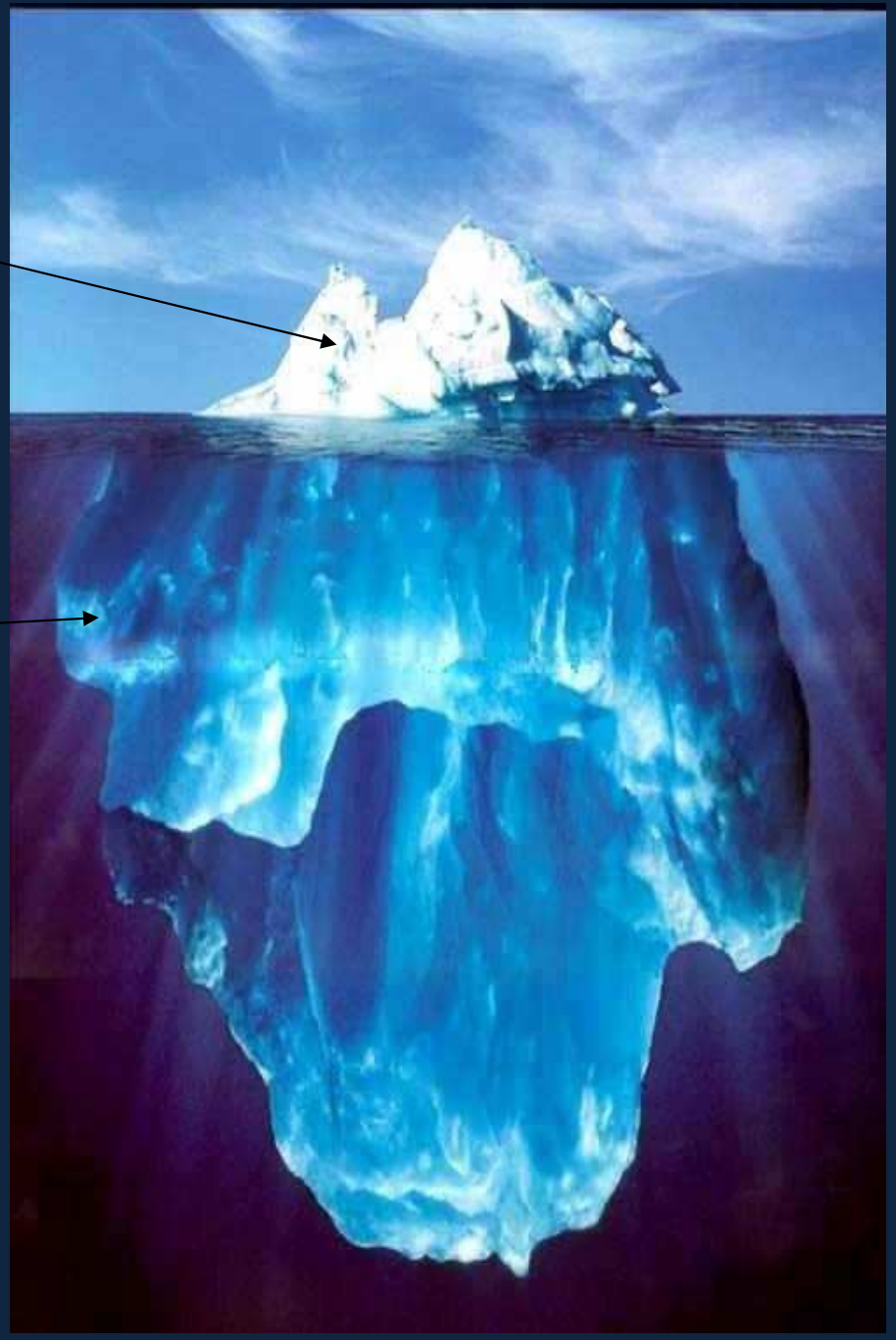
Patologie **cronico-degenerative** dell'adulto

Modifiche **epi-genetiche** fetali

(***programming*** fetale)



Amplificazione transgenerazionale del danno



Cancerogenesi ambientale

Il contributo della scienza medica alla
risoluzione dei problemi di inquinamento ambientale

CANCRO:
Il paradigma epigenetico

Ernesto Burgio
Comitato Scientifico
ISDE Italia