ISCRIZIONE
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- Partecipazione ai lavori scientifici
- Kit congressuale
- 4 Coffee break
- 2 Colazioni di lavoro (14 e 15 ottobre)
- Attestati di partecipazione
- Attestati E.C.M.*(agli aventi diritto)

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- Partecipazione ai lavori scientifici
- Attestati di partecipazione
- Attestati E.C.M.*(agli aventi diritto)

*Gli attestati riportanti i crediti E.C.M., saranno disponibili all'indirizzo www.pediatria.it/eventi entro 60 giorni dalla chiusura dell'evento.

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Edizione Speciale

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14 - 16 ottobre 2021
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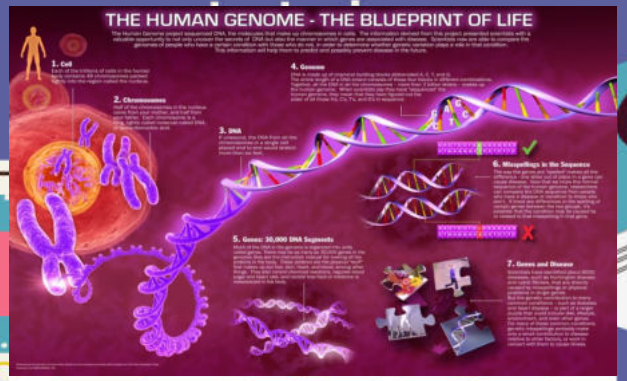
5° Congresso Nazionale **SIPEC**
Società Italiana di Pediatria Condivisa



(Epi) - Genetica
Ernesto Burgio

www.pediatria.it/eventi

SIPEC
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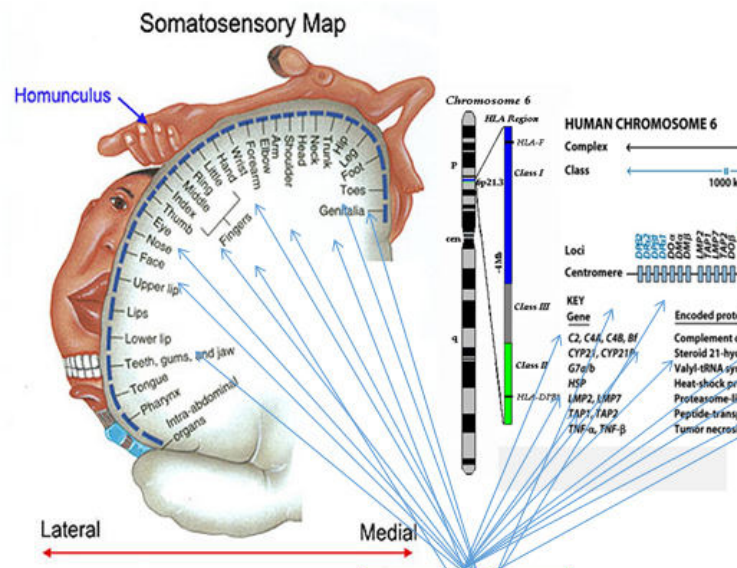
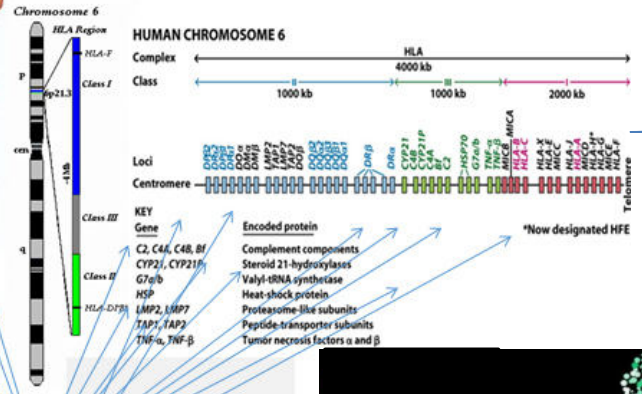
con il patrocinio di

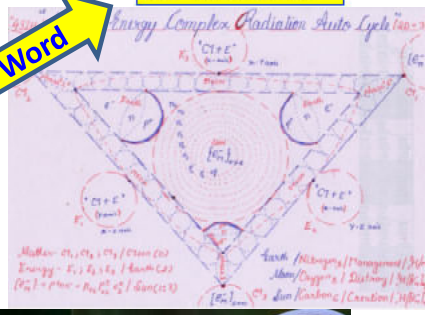


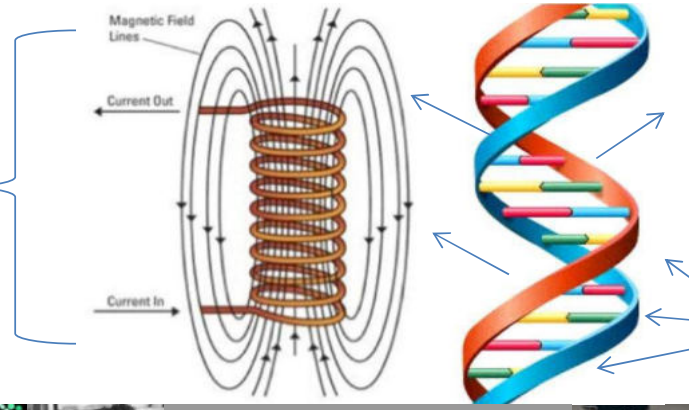


INFORMATION

3

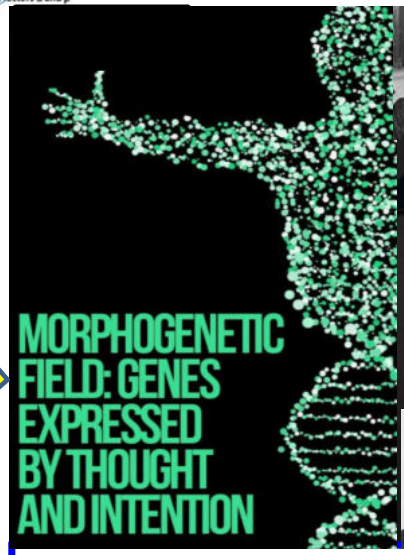
The Key Word

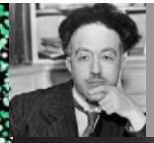




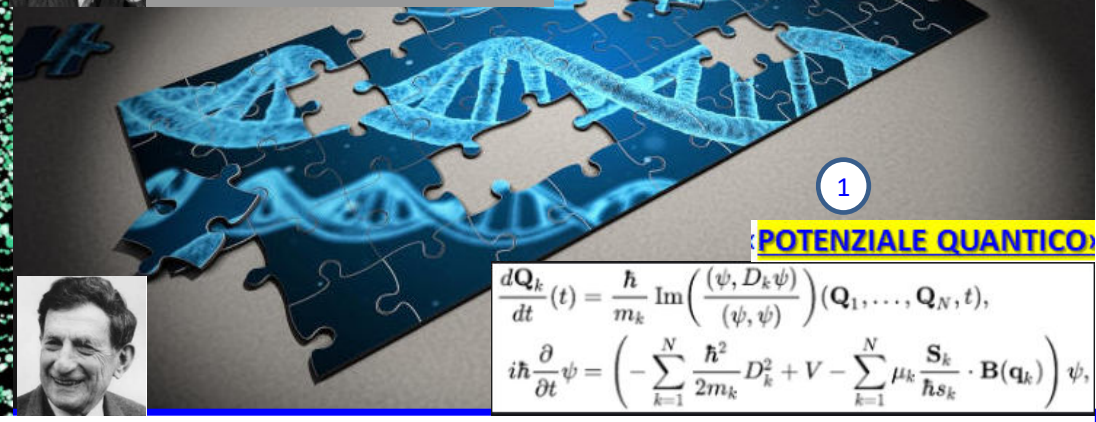
Il POTENZIALE QUANTICO (D. Bohm) è un NUOVO TIPO DI CAMPO CHE PERVADE LO SPAZIO-TEMPO INFLUENZANDO, COME SUBSTRATO PURAMENTE INFORMAZIONALE E NON ENERGETICO (!), TUTTI GLI OGGETTI DEL MONDO (QUANTISTICO) IN MODO INDIPENDENTE DALLA DISTANZA E DALL'INTENSITÀ DEL CAMPO STESSO

1





$$\lambda = \frac{h}{p} = \frac{h}{mv}\sqrt{1-\frac{v^2}{c^2}}$$

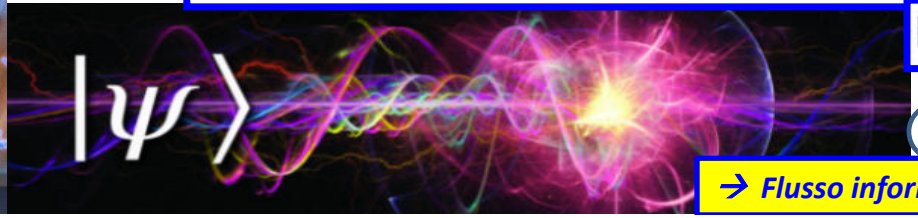


1

POTENZIALE QUANTICO

$$\frac{d\mathbf{Q}_k}{dt}(t) = \frac{\hbar}{m_k}\,\mathrm{Im}\left(\frac{(\psi, D_k\psi)}{(\psi,\psi)}\right)(\mathbf{Q}_1,\ldots,\mathbf{Q}_N,t),$$

$$i\hbar\frac{\partial}{\partial t}\psi = \left(-\sum_{k=1}^{N}\frac{\hbar^2}{2m_k}D_k^2 + V - \sum_{k=1}^{N}\mu_k\frac{\mathbf{S}_k}{\hbar s_k}\cdot\mathbf{B}(\mathbf{q}_k)\right)\psi,$$



2

→ *Flusso informazionale* →

La transizione epidemiologica del XXI secolo: dalla Genetica all'Epigenetica

Ernesto Burgio (ECERI, Brussels, Belgium

ECERI

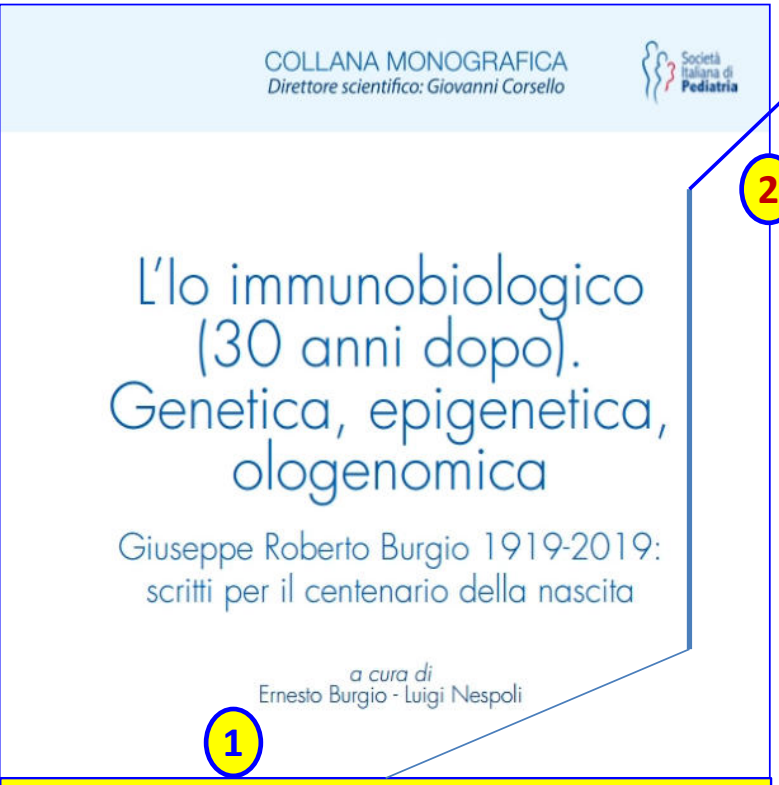
European Cancer and Environment Research Institute

18. CONCLUSIONI - L'IO *IN FIERI*

IMMUNOGENETICA - EPIGENETICA - METAGENOMICA - OLOGENOMICA

Ernesto Burgio, Luigi Nespoli

La ***teoria dell'informazione*** nell'ambito della biologia molecolare



1

…il termine ***informazione*** e molti altri strettamente connessi (si pensi a ***codice***, ***programma***, ***messaggio***, ***sequenza***, ***trascrizione***, ***traduzione***, ***edizione/editing***..) sono stati acquisiti in ambito biologico e rivestono ormai un ruolo-chiave, soprattutto nell'ambito della **biologia molecolare..**

2

L'introduzione del vocabolario informazionale in biologia molecolare risale, in realtà, all'inizio del secolo scorso, agli studi di **Morgan e Sturtevant sul materiale ereditario (1910-1915),** che misero in campo (sulla base degli **esperimenti mutazionali) un *modello lineare/mono-dimensionale*** delle molecole portatrici di informazione[v]. Si trattava ovviamente di una semplificazione, visto che nessuna molecola può avere carattere mono-dimensionale, ma la validità del modello venne sostanzialmente **confermato dagli esperimenti di Pontecorvo e Benzer negli anni 40'- 50'**[vi] e ne derivarono le **teorizzazioni di Gamow**[vii] **e Schrödinger** [viii] sulla natura del materiale genetico (è interessante notare che furono i fisici e non i biologi i primi a riflettere sulla struttura del programma e del codice genetico e questo non poteva che avere conseguenze significative).


Thomas Hunt Morgan


Alfred Sturtevant


Seymour Benzer


George Gamow

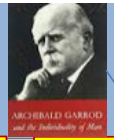

Erwin Schrödinger (

3

Così, **quando nel 1953 si arrivò alla identificazione della doppia elica si continuò a utilizzare il modello lineare**. La successiva decifrazione del codice genetico partì dalla **corrispondenza biunivoca tra due sequenze: la sequenza delle basi sul DNA e quella degli aminoacidi** sulle proteine. Si trattava di **semplificazioni utili, ma pericolose**, soprattutto in relazione al prodotto finale del processo, essendo le proteine morfo-funzionalmente alquanto diverse tra loro in relazione alla loro forma tridimensionale, oltre che alla loro sequenza amminoacidica.

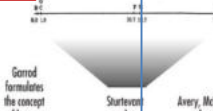
TIMELINE OF THE HUMAN GENOME PROJECT

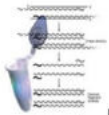
Human Genome Project - DAVID STREAMS

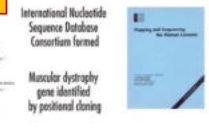


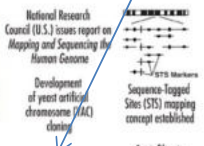
HUMAN GENOME ORGANISATION
HUGO

1865 | 1900 | 1905 | 1913 | 1944 | 1953 | 1966 | 1972 | 1977 | 1983 | 1985 | 1988









HGP
1990 2003

1913 THE FIRST LINEAR MAP OF GENES

1966 Nirenberg Genetic Code

1972 Cohen - Boyer **DNA Recombinant technology**

1977 Sanger DNA sequencing

First disease-gene mapped HUNTINGTON DISEASE

1985 Mullis PCR

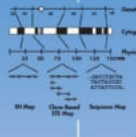
1990 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003

Human Genome Project (HGP) launched in the U.S.

Ethical, Legal, and Social Implications (ELSI) program founded at NIH and DOE

First gene for breast cancer (BRCA1) mapped

First U.S. Genome Centers established



Second-generation human genetic map developed

Rapid data release guidelines established by NIH and DOE

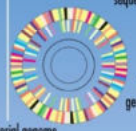
New five-year plan for the HGP in the U.S. published

Sanger Centre founded (later renamed Wellcome Trust Sanger Institute)

The Wellcome Trust

HGP's human genetic mapping goal achieved

HGP's human physical mapping goal achieved



First bacterial genome (*H. influenzae*) sequenced

U.S. Equal Employment Opportunity Commission issues policy on genetic discrimination in the workplace

First human gene map established

Pilot projects for human genome sequencing begin in U.S.

First archael genome sequenced

Yeast (*S. cerevisiae*) genome sequenced

HGP's mouse genetic mapping goal achieved

Bermuda principles for rapid and open data release established

DOE forms Joint Genome Institute

JGI

NCHGR becomes NHGRI

E. coli genome sequenced

Genoscope (French National Genome Sequencing Center) founded

Incorporation of 30,000 genes into human genome map

New five-year plan for the HGP in the U.S. published

RIKEN Genomic Sciences Center (Japan) established

Roundworm (*C. elegans*) genome sequenced

SNP initiative begins

GTGCT
GTCCT

Chinese National Human Genome Centers (in Beijing and Shanghai) established

Full-scale human sequencing begins

Sequence of first human chromosome (chromosome 22) completed

Draft version of human genome sequence completed

President Clinton and Prime Minister Blair support free access to genome information

Fruit fly (*D. melanogaster*) genome sequenced

Mustard cress (*A. thaliana*) genome sequenced

Draft version of human genome sequence published

10,000 full-length human cDNAs sequenced

Draft version of mouse genome sequence completed and published

Draft version of rat genome sequence completed

Draft version of rice genome sequence completed and published

Finished version of human genome sequence completed

HGP ends with all goals achieved

to be continued...

1994 First HGP mapping goal (LINKAGE MAP) is met.

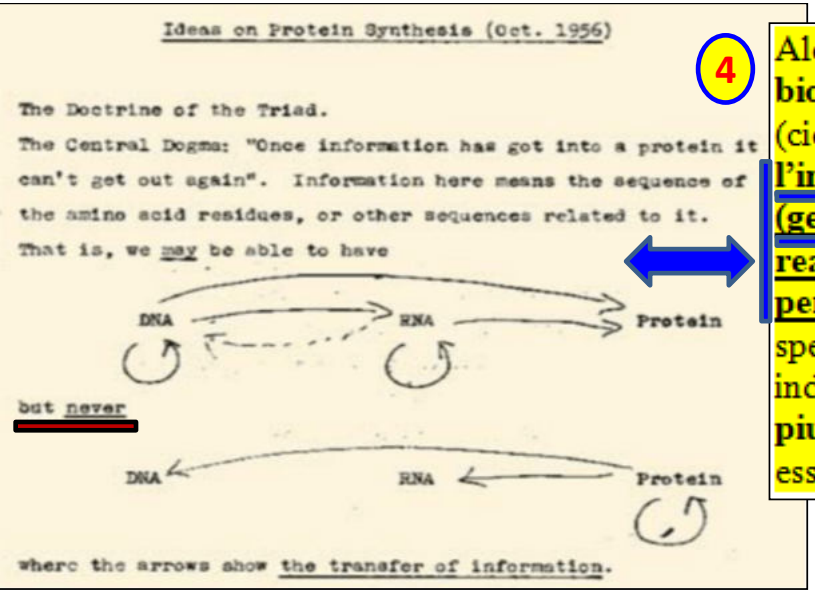
2000 Draft version of human genome sequence released

1990 HGP launched in the US

1995 First bacterial genome

1999 Complete sequence of human chromosome 22

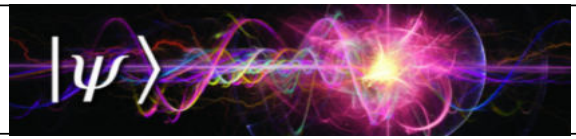
2003 Human genome sequence completed

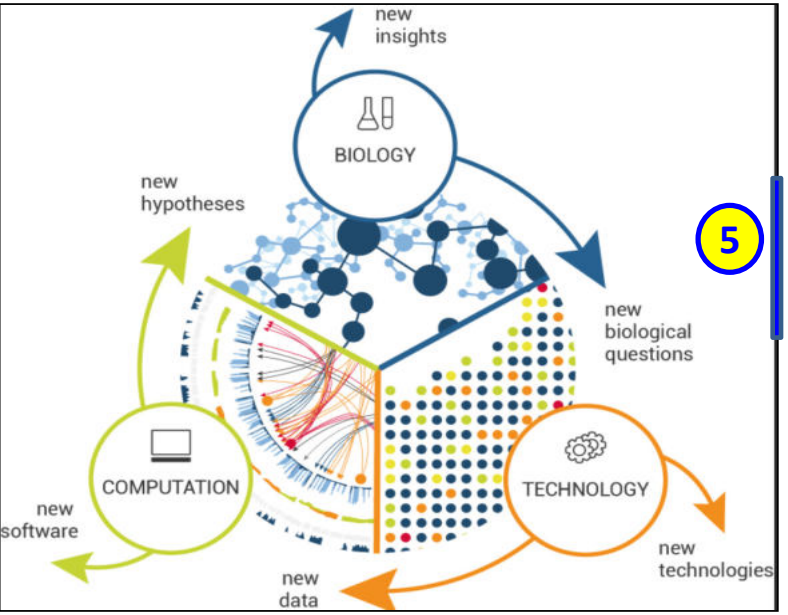


4

Alcuni anni dopo, sempre su queste basi, **Crick formulò il cosiddetto *Dogma centrale* della biologia**[ix], secondo il quale **l'informazione** andrebbe esclusivamente dal DNA verso le proteine (cioè dal DNA verso il fenotipo), che continua a dominare la scena, **anche se è ormai evidente che l'informazione viene dall'esterno e circola all'interno dei sistemi biologici (genomi/cellule/organismi), inducendoli a modificarsi**: provocando cioè **modifiche reattivo/adattativo/predittive nell'espressione, nella programmazione e, nel lungo periodo, persino nella sequenza del DNA**. E soprattutto, che la progressiva diversificazione e specializzazione degli organismi, **tanto nell'ambito della filogenesi, quanto dell'ontogenesi** individuale avviene grazie a una **diversa utilizzazione dell'informazione contenuta nel DNA, piuttosto che a variazioni quali/quantitative del contenuto di informazione dei genomi**, essendo il prodotto di **meccanismi *epigenetici*, piuttosto che *genetici*** *sensu stricto*.

→ *Flusso informazionale* →



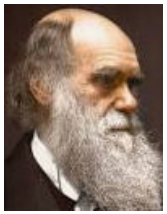


5

Va però detto che passare da una rappresentazione lineare ad una sistemica comporta una trasformazione del modello infinitamente più profonda. In un universo in continua movimento, in cui ogni molecola e ogni atomo vibrano e comunicano tra loro, bisognerebbe rappresentare non solo l'intero **organismo**, ma ogni **cellula** e ogni **molecola** e in particolare il **DNA/genoma come un sistema aperto/fluido/complesso in grado di processare l'informazione proveniente dall'esterno e di trasformarsi di conseguenza. Aperto**, nel senso che ricevendo continuamente informazioni chimico-fisiche (vibrazioni e segnali chimici) è in grado di elaborarli, processarli e di trasformarsi; **plastico/fluido** perché modificandosi continuamente può trasmettere, informazioni sempre diverse [fisiche, in forma di vibrazioni (campi elettromagnetici endogeni) e biochimiche/molecolari (in forma mRNA/proteine e RNA minori)][xvii] per corrispondere alle necessità dell'intero organismo; **complesso**, in quanto appunto costituito da **milioni di molecole in continua interazione e di circuiti complessi in grado di attivarsi/inattivarsi mediante meccanismi di *feedback* positivo e negativo**... all'interno di un organismo composto da milioni di cellule integrate e comunicanti tra loro e in continua trasformazione.

Natural Genetic Engineering

Nothing in Biology Makes Sense Except in the Light of Evolution



THEODOSIUS DOBZHANSKY

As recently as 1965, sheik Abd el Aziz bin Baz asked the king of Saudi Arabia to suppress a heresy that was spreading in his land. Wrote the sheik:

"The Holy Koran, the Prophet's teachings, the majority of Islamic scientists, and the actual facts all prove that the sun is running in its orbit . . . and that the earth is fixed and stable, spread out by God for his mankind. . . . Anyone who professed otherwise would utter a charge of falsehood toward God, the Koran, and the Prophet."

The good sheik evidently holds the Copernican theory to be a "mere theory," not a "fact." In this he is technically correct. A theory can be verified by a mass of facts, but it becomes a proven theory, not a fact. The sheik was perhaps unaware that the Space Age had begun before he asked the king to suppress the Copernican heresy. The sphericity of the earth had been seen by astronauts, and even by many earth-bound people on their television screens. Perhaps the sheik could retort that those who venture beyond the confines of God's earth suffer hallucinations, and that the earth is really flat.

Parts of the Copernican world model, such as the contention that the earth rotates around the sun, and not vice versa, have not been verified by direct observations even to the extent the sphericity of the earth has been. Yet scientists accept the model as an accurate representation of reality. Why? Because it makes sense of a multitude of facts which are otherwise meaningless or extravagant. To nonspecialists most of these facts are unfamiliar. Why then do we accept the "mere theory" that the earth is a sphere revolving around a spherical sun? Are we simply submitting to authority? Not quite: we know that those who took time to study the evidence found it convincing.

The good sheik is probably ignorant of the evidence. Even more likely, he is so hopelessly biased that no amount of evidence would impress him. Anyway, it would be sheer waste of time to attempt to convince him. The Koran and the Bible do not contradict Copernicus, nor does Copernicus contradict them. It is ludicrous to mistake the Bible and the Koran for primers of natural science. They treat of matters even more important: the meaning of man and his relations to God. They are written in poetic symbols that were understandable to people of the age when they were written, as well as to peoples of all other ages. The king of Arabia did not comply with the sheik's demand. He knew that some people fear enlightenment, because enlightenment threatens their vested interests. Education is not to be used to promote obscurantism.

The earth is not the geometric center of the universe, although it may be its spiritual center. It is a mere speck of dust in cosmic spaces. Contrary to Bishop Ussher's calculations, the world did not appear in approximately its present state in 4004 B.C. The estimates of the age of the universe given by modern cosmologists are still only rough approximations, which are revised (usually upward) as the methods of estimation are refined. Some cosmologists take the universe to be about 10 billion years old; others suppose that it may have existed, and will continue to exist, eternally. The origin of life on earth is dated tentatively between 3 and 5 billion years ago; manlike beings appeared relatively quite recently, between 2 and 4 million years ago. The

One of the world's leading geneticists, Theodosius Dobzhansky is professor emeritus, Rockefeller University, and adjunct professor of genetics, University of California, Davis 95616. Born in Russia, in 1900, he is a graduate of the University of Kiev and taught (with J. Philipchenko) at the University of Leningrad before coming to the U.S., in 1927; thereafter he taught at Columbia University and the California Institute of Technology before joining the Rockefeller faculty, in 1962. He has been president of the Genetics Society of America, the American Society of Naturalists, the Society for the Study of Evolution, the American Society of Zoologists, and the American Teilhard de Chardin Assoc... National Medal of Sci... for Distinguished Ach... 18 honorary doctorate... abroad. Among his ... Basis of Human Pro... (1962). The present p... convention.

Unity of Life

The unity of life is no less remarkable than its diversity. Most forms of life are similar in many respects. The universal biologic similarities are particularly striking in the biochemical dimension. From viruses to man, heredity is coded in just two, chemically related substances: DNA and RNA. The genetic code is as simple as it is universal. There are

...mainly on isotopes of ...le for such

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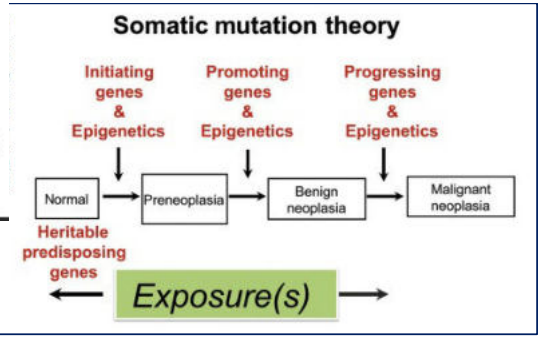
6



CANCER - SMT

Una delle frasi più citate, non sempre in modo corretto, della storia della biologia è quella di **Dobzhansky** secondo cui **non si può comprendere alcunché in campo biologico se non alla luce dell'evoluzione**. Ovviamente, i possibili fraintendimenti, anche in questo caso, dipendono essenzialmente dal modello adottato: in particolare dalla predilezione per **un modello strettamente competitivo/selettivo (*neodarwiniano*), oggi dominante**, o per **uno anche/essenzialmente istruttivo/costruttivo/cooperativo (*neolamarckiano*), oggi ostracizzato** dalla gran parte dei biologi. Senza entrare in eccessivi dettagli, è utile sottolineare come **nel primo caso si tenda a privilegiare un modello in cui è l'informazione contenuta nel DNA (e le sue minime variazioni stocastiche) a determinare le variazioni fenotipiche su cui opera la selezione naturale (come detto, in questo caso la *microevoluzione*/molecolare, determina la *macroevoluzione*)**. In un **modello istruttivo, costruttivo/cooperativo, invece, l'informazione proviene dall'ambiente** (inteso in senso lato) e **induce nel sistema modifiche sia fenotipiche, sia genotipiche reattive e potenzialmente adattative** (potremmo anche dire che in questo caso **è la distinzione stessa tra genotipo e fenotipo e non soltanto l'idea di un flusso informazionale essenzialmente diretto dal primo verso il secondo a perdere molto del suo significato**). Infine è importante notare che in **questo secondo caso le variazioni così acquisite e di conseguenza i "nuovi caratteri" si trasmettono direttamente da una generazione all'altra: il che rende infinitamente più rapido l'intero processo evolutivo.**

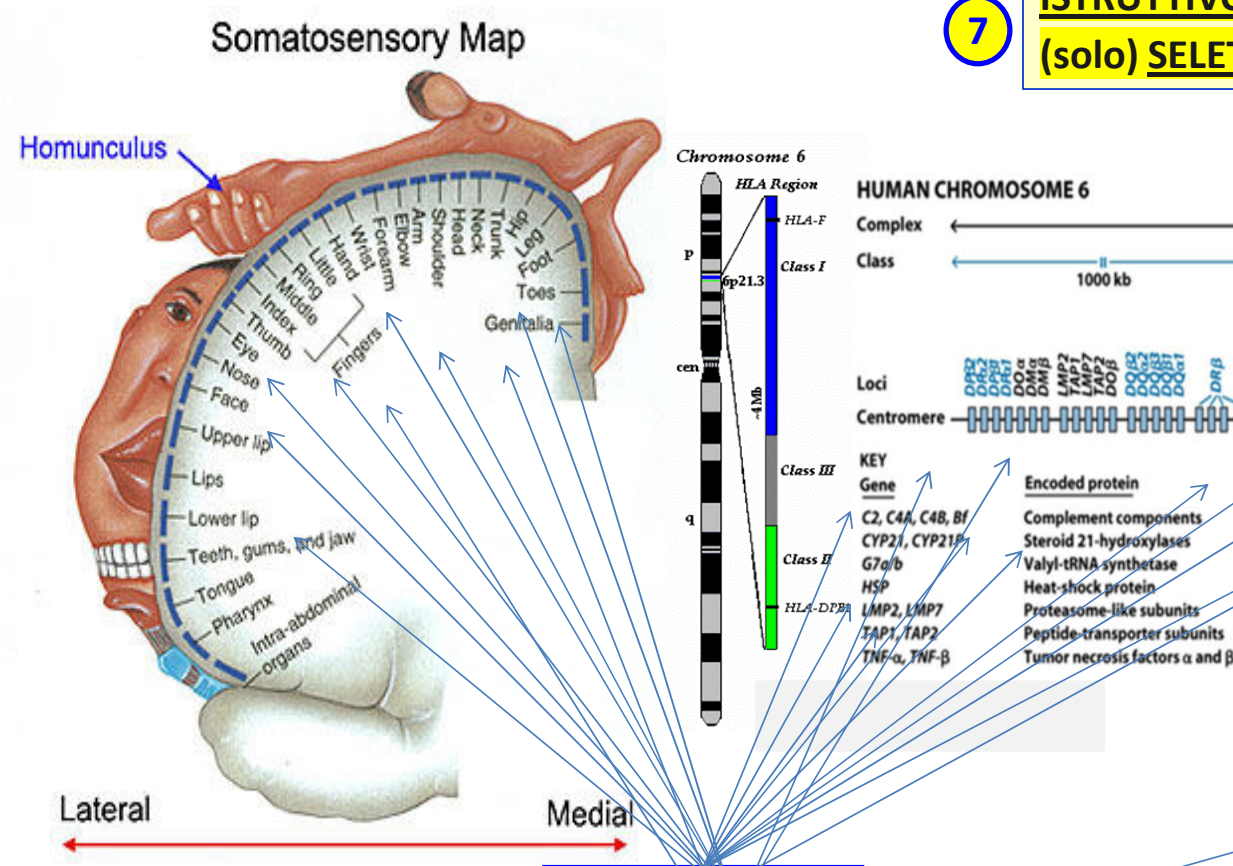
7

INVERTIRE IL FLUSSO DELLE INFORMAZIONI - anche in ambito evoluzionistico – permette di considerare ORGANISMI (E GENOMI) prodotti di INGEGNERIA (EPI)GENOMICA e COSTRUTTIVA (!)

INVERTIRE IL FLUSSO DELLE INFORMAZIONI - anche in ambito evoluzionistico – permette di considerare ORGANISMI (E GENOMI) prodotti di INGEGNERIA (EPI)GENOMICA e COSTRUTTIVA (!)

7

Verso un MODELLO EVOLUZIONISTICO ISTRUTTIVO E COSTRUTTIVO piuttosto che (solo) SELETTIVO



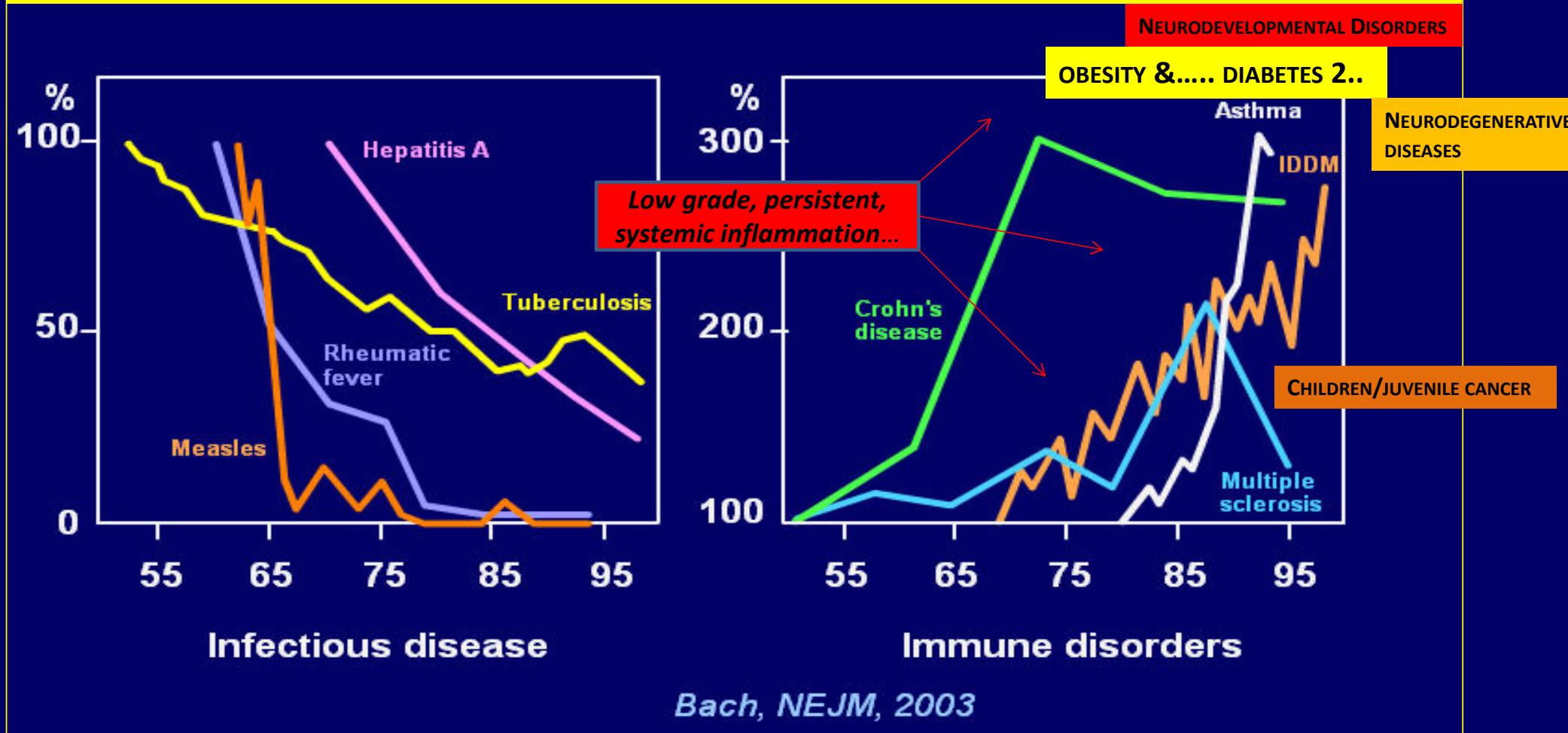
INFORMATION

Dawkins R, et al. ***Genomics of the major histocompatibility complex: haplotypes, duplication, retroviruses and disease*** Immunol Rev. (1999);167:275-304

È anche **ragionevole presumere** che le **250 megabasi più polimorfiche** e ricche di **sequenze codificanti funzionalmente interconnesse** tra loro di tutto il genoma umano, siano il ***prodotto di milioni di anni di ingegneria genetica naturale*** (evidenziata anche da una forte presenza di ***sequenze mobili***)

FOREWORD 1 The XXI Century's ***Epidemiological Transition***

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



Bach, NEJM, 2003

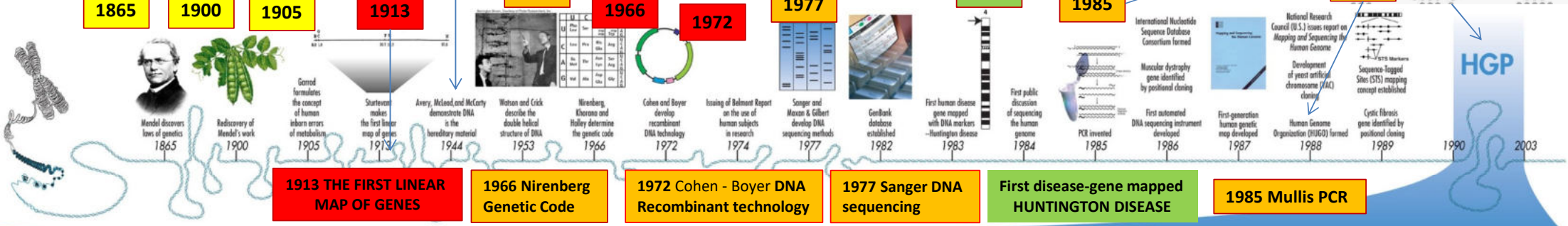
FOREWORD 2

TIMELINE OF THE HUMAN GENOME PROJECT

Human Genome Project - DAVID STREAMS

HUMAN GENOME ORGANISATION HUGO

1865 1900 1905 1913 1944 1953 1966 1972 1977 1983 1985 1988



1913 THE FIRST LINEAR MAP OF GENES

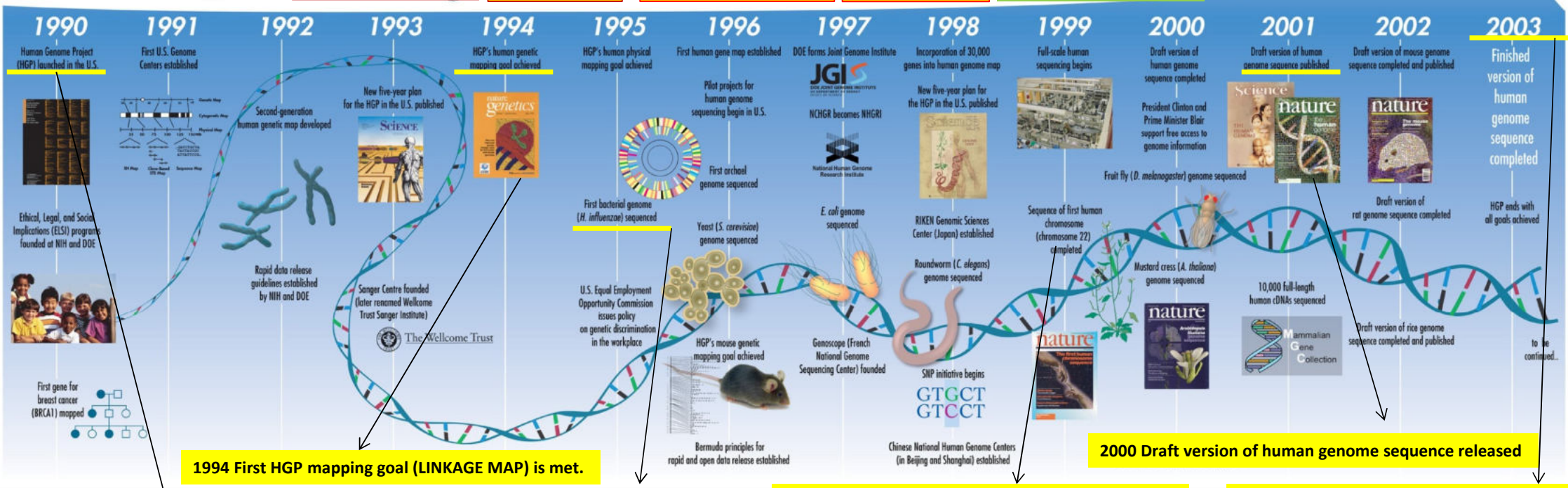
1966 Nirenberg Genetic Code

1972 Cohen - Boyer **DNA Recombinant technology**

1977 Sanger DNA sequencing

First disease-gene mapped HUNTINGTON DISEASE

1985 Mullis PCR



1994 First HGP mapping goal (LINKAGE MAP) is met.

2000 Draft version of human genome sequence released

1990 HGP launched in the US

1995 First bacterial genome

1999 Complete sequence of human chromosome 22

2003 Human genome sequence completed

THE HUMAN GENOME - THE BLUEPRINT OF LIFE

The Human Genome project sequenced DNA, the molecules that make up chromosomes in cells. The information derived from this project presented scientists with a valuable opportunity to not only uncover the secrets of DNA but also the manner in which genes are associated with disease. Scientists now are able to compare the genomes of people who have a certain condition with those who do not, in order to determine whether genetic variation plays a role in that condition. This information will help them to predict and possibly prevent disease in the future.

1. Cell

Each of the trillions of cells in the human body contains 46 chromosomes packed tightly into the region called the nucleus.

2. Chromosomes

Half of the chromosomes in the nucleus come from your mother, and half from your father. Each chromosome is a long, tightly coiled molecule called DNA, or deoxyribonucleic acid.

3. DNA

If unwound, the DNA from all the chromosomes in a single cell placed end to end would stretch more than six feet.

4. Genome

DNA is made up of chemical building blocks abbreviated A, C, T, and G. The entire length of a DNA strand consists of these four blocks in different combinations. Together, all the DNA in all the chromosomes -- more than 3 billion letters -- makes up the human genome. When scientists say they have "sequenced" the human genome, they mean that they have figured out the order of all those A's, C's, T's, and G's in sequence.

5. Genes: 30,000 DNA Segments

Much of the DNA in the genome is organized into units called genes. There may be as many as 30,000 genes in the genome; they are the instruction manual for making all the proteins in the body. These proteins are the physical "stuff" that makes up our hair, skin, heart, and blood, among other things. They also control chemical reactions, regulate blood sugar and heart rate, and control how food or medicine is metabolized in the body.

6. Misspellings in the Sequence

The way the genes are "spelled" makes all the difference - one letter out of place in a gene can cause disease. Now that we know the normal sequence of the human genome, researchers can compare the DNA sequence from people who have a disease or condition to those who don't. If there are differences in the spelling of certain genes between the two groups, it's possible that the condition may be caused by or related to that misspelling in that gene.

7. Genes and Disease

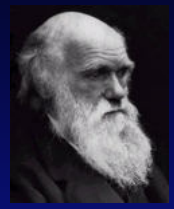
Scientists have identified about 6000 diseases, such as Huntington disease and cystic fibrosis, that are directly caused by misspellings or physical problems in single genes.
But the genetic contribution to many common conditions -- such as diabetes and heart disease -- is part of a larger puzzle that could include diet, lifestyle, environment, and even other genes.
For many of these common conditions, genetic misspellings probably make only a small contribution to disease relative to other factors, or work in concert with them to cause illness.

FOREWORD 3

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

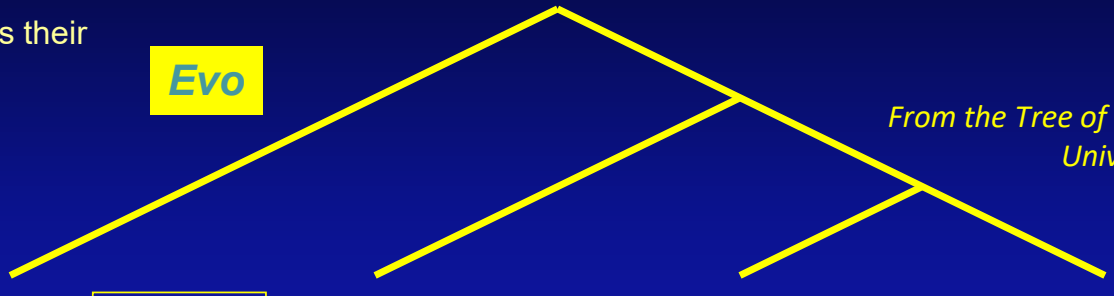
We are quite stable (for millions of years) both genetically and phenotypically

Species *phylogeny*



From the Tree of the Life Website, University of Arizona

Evo



Orangutan

Gorilla

Chimpanzee

Human

EPIGENETICS > GENETICS

Sanger Institute

FOREWORD 4

Nothing in Biology Makes Sense Except in the Light of Evolution

THEODOSIUS DOBZHANSKY

As recently as 1966, sheik Abd el Aziz bin Baz asked the king of Saudi Arabia to suppress a heresy that was spreading in his land. Wrote the sheik:

"The Holy Koran, the Prophet's teachings, the majority of Islamic scientists, and the actual facts all prove that the sun is running in its orbit . . . and that the earth is fixed and stable, spread out by God for his mankind. . . . Anyone who professed otherwise would utter a charge of falsehood toward God, the Koran, and the Prophet."

The good sheik evidently holds the Copernican theory to be a "mere theory," not a "fact." In this he is technically correct. A theory can be verified by a mass of facts, but it becomes a proven theory, not a fact. The sheik was perhaps unaware that the Space Age had begun before he asked the king to suppress the Copernican heresy. The sphericity of the earth had been seen by astronauts, and even by many earth-bound people on their television screens. Perhaps the sheik could retort that those who venture beyond the confines of God's earth suffer hallucinations, and that the earth is really flat.

Parts of the Copernican world model, such as the contention that the earth rotates around the sun, and not vice versa, have not been verified by direct observations even to the extent the sphericity of the earth has been. Yet scientists accept the model as an accurate representation of reality. Why? Because it makes sense of a multitude of facts which are otherwise meaningless or extravagant. To nonspecialists most of these facts are unfamiliar. Why then do we accept the "mere theory" that the earth is a sphere revolving around a spherical sun? Are we simply submitting to authority? Not quite: we know that those who took time to study the evidence found it convincing.

The good sheik is probably ignorant of the evidence. Even more likely, he is so hopelessly biased that no amount of evidence would impress him. Anyway, it would be sheer waste of time to attempt to convince him. The Koran and the Bible do not contradict Copernicus, nor does Copernicus contradict them. It is ludicrous to mistake the Bible and the Koran for primers of natural science. They treat of matters even more important: the meaning of man and his relations to God. They are written in poetic symbols that were understandable to people of the age when they were written, as well as to peoples of all other ages. The king of Arabia did not comply with the sheik's demand. He knew that some people fear enlightenment, because enlightenment threatens their vested interests. Education is not to be used to promote obscurantism.

The earth is not the geometric center of the universe, although it may be its spiritual center. It is a mere speck of dust in cosmic spaces. Contrary to Bishop Ussher's calculations, the world did not appear in approximately its present state in 4004 B.C. The estimates of the age of the universe given by modern cosmologists are still only rough approximations, which are revised (usually upward) as the methods of estimation are refined. Some cosmologists take the universe to be about 10 billion years old; others suppose that it may have existed, and will continue to exist, eternally. The origin of life on earth is dated tentatively between 3 and 5 billion years ago; manlike beings appeared relatively quite recently, between 2 and 4 million years ago. The estimates of the age of the earth, of the duration of the geologic and paleontologic eras, and of the antiquity of man's ancestors are now based mainly on radiometric evidence—the proportions of isotopes of certain chemical elements in rocks suitable for such studies.

One of the world's leading geneticists, Theodosius Dobzhansky is professor emeritus, Rockefeller University, and adjunct professor of genetics, University of California, Davis 95616. Born in Russia, in 1900, he is a graduate of the University of Kiev and taught (with J. Philipchenko) at the University of Leningrad before coming to the U.S., in 1927; thereafter he taught at Columbia University and the California Institute of Technology before joining the Rockefeller faculty, in 1962. He has been president of the Genetics Society of America, the American Society of Naturalists, the Society for the Study of Evolution, the American Society of Zoologists, and the American Teilhard de Chardin Association. Among his many honors are the National Medal of Science (1964) and the Gold Medal Award for Distinguished Achievement in Science (1969). He holds 18 honorary doctorates from universities in this country and abroad. Among his well-known books are *The Biological Basis of Human Freedom* (1956) and *Mankind Evolving* (1962). The present paper was presented at the 1972 AABT convention.

1 *Diversity of Living Beings*

The diversity and the unity of life are equally striking and meaningful aspects of the living world.

2 *Unity of Life*

The unity of life is no less remarkable than its diversity. Most forms of life are similar in many respects. The universal biologic similarities are particularly striking in the biochemical dimension. From viruses to man, heredity is coded in just two, chemically related substances: DNA and RNA. The genetic code is as simple as it is universal. There are

Minimal mutational distances between human cytochrome C and the cytochrome C of other living beings are as follows:

Monkey	1	Chicken	18
Dog	13	Penguin	18
Horse	17	Turtle	19
Donkey	16	Rattlesnake	20
Pig	13	Fish (tuna)	31
Rabbit	12	Fly	33
Kangaroo	12	Moth	36
Duck	17	Mold	63
Pigeon	16	Yeast	56

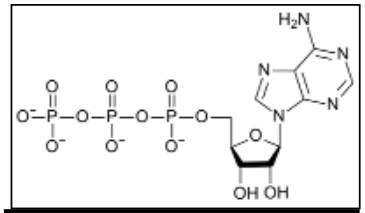
3 *Comparative Anatomy and Embryology*

The biochemical universals are the most impressive and the most recently discovered, but certainly they are not the only vestiges of creation by means of evolution. Comparative anatomy and embryology proclaim the evolutionary origins of the present inhabitants of the world. In 1555 Pierre Belon established the presence of homologous bones in the superficially very different skeletons of man and bird.

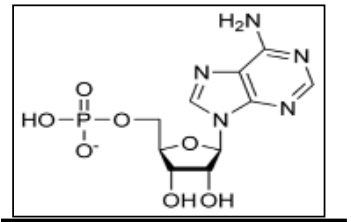
Strength and Acceptance of the Theory

Seen in the light of evolution, biology is, perhaps, intellectually the most satisfying and inspiring science. Without that light it becomes a pile of sundry facts—some of them interesting or curious but making no meaningful picture as a whole.

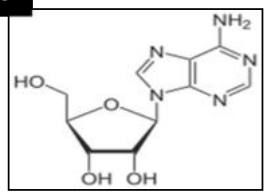
$E = Mc^2 = \mathbf{I}$



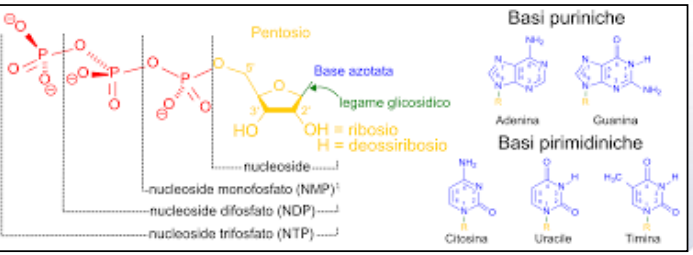
ATP - Adenosina trifosfato

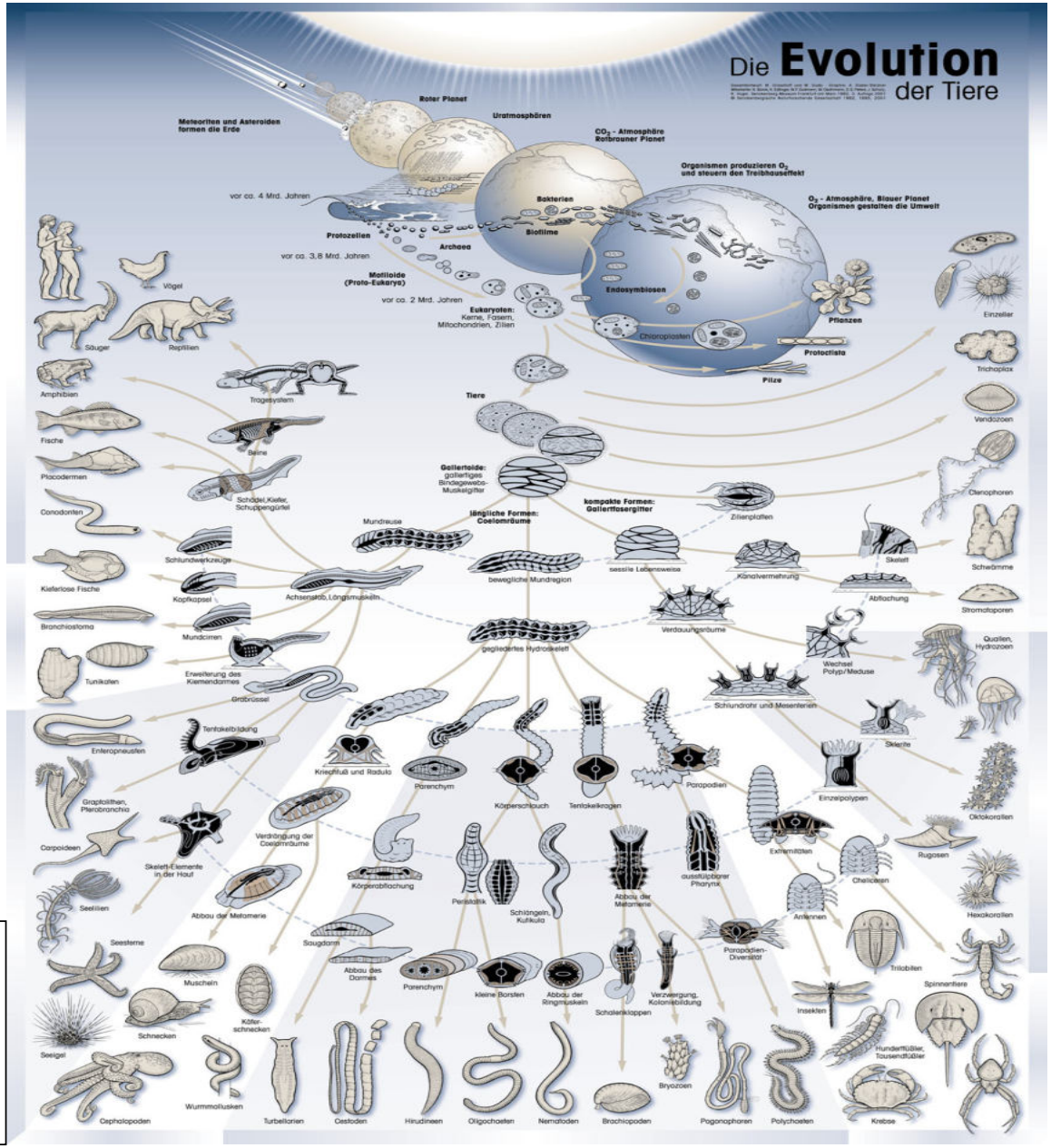


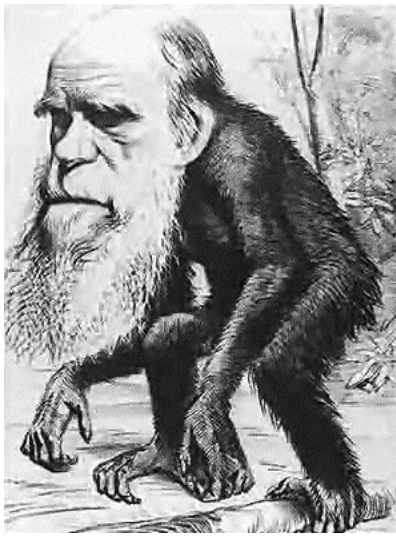
AMP - Adenosin monofosfato



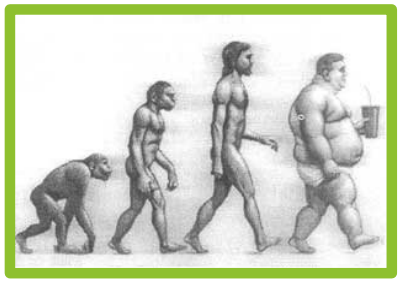
L'***adenosina*** è un nucleoside che ha un ruolo fondamentale
- sia nel **trasferimento di *Energia*** (ATP --> ADP),
- sia nella costituzione degli acidi nucleici (***Informazione***),
- sia nella **trasduzione del segnale** (cAMP = secondo messaggero)







FOREWORD 5



Phylogeny

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

Mismatch

Ontogeny

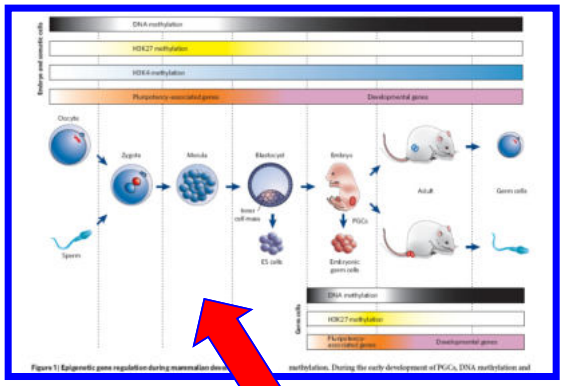
And of **9 months of an individual development**

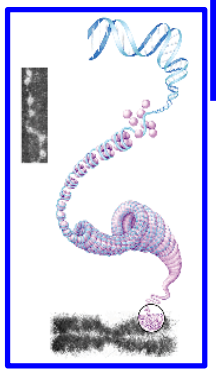
our **epigenome** being the product of nine months of ***cellular and tissue programming*** (**adaptive** to an environment that is rapidly changing)..

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

Devo-Evo

Ontogeny *recapitulates* (***anticipates***) ***Phylogeny***





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

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

FOREWORD 6

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Gene 345 (2005) 91–100

GENE
SECTION
EVOLUTIONARY GENOMICS

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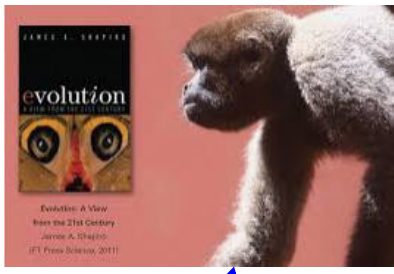
Review

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

James A. Shapiro

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



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

1 2 3 4 5

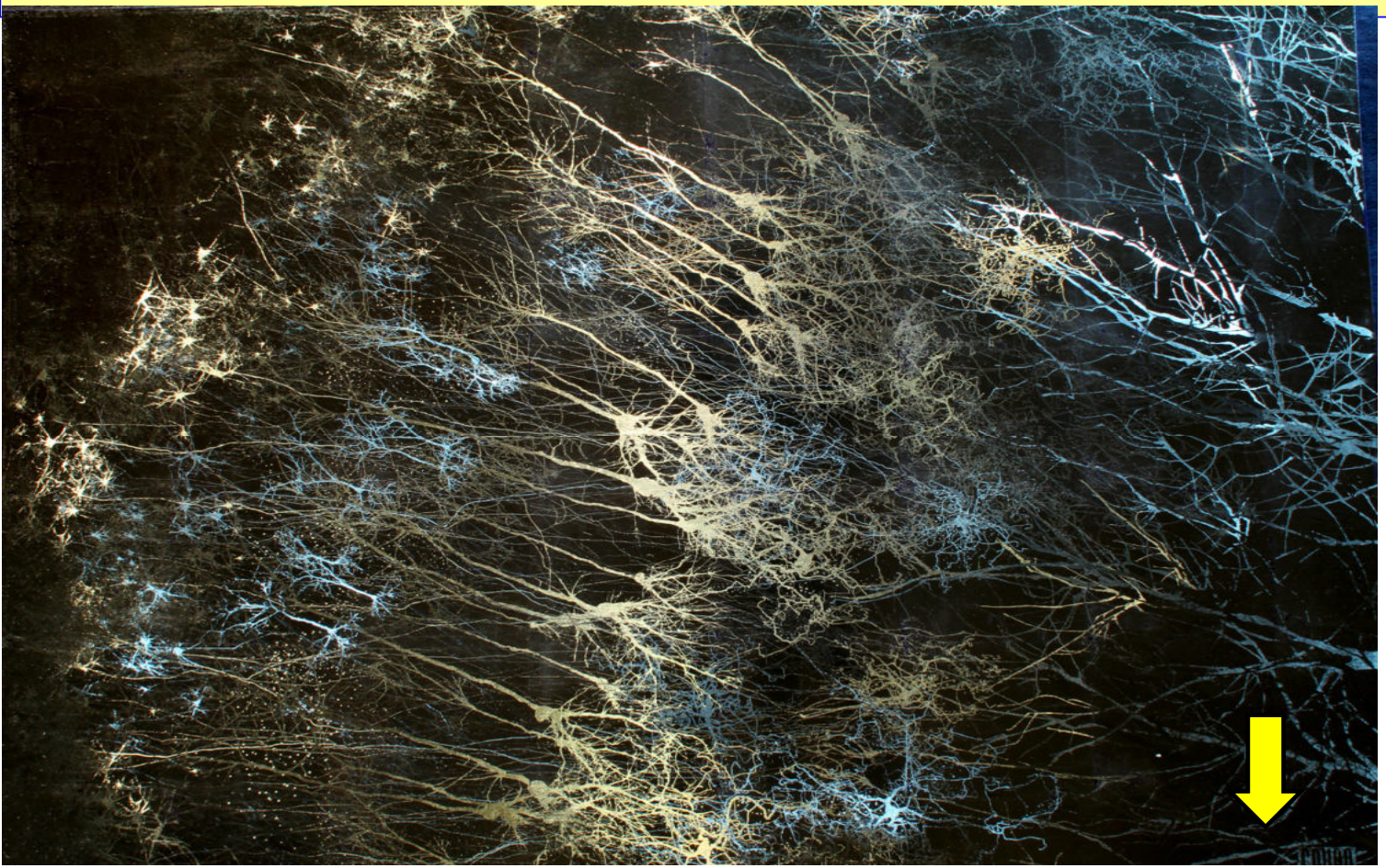
FOREWORD 7

.. *unlike your **genome**, which is **fixed from the moment of conception*** **(…)**
your **connectome* changes throughout your life**.

Neurons adjust…their connections (to one another) by ***strengthening*** or ***weakening*** them.

Neurons **reconnect by creating and eliminating synapses**, and **they rewire by growing and retracting branches**.

***You are more than your genes. You are your connectom* (*Sebastian Seung, MIT*).**



Seung S. ***Connectome: How the brain's wiring makes us who we are*** (2012)

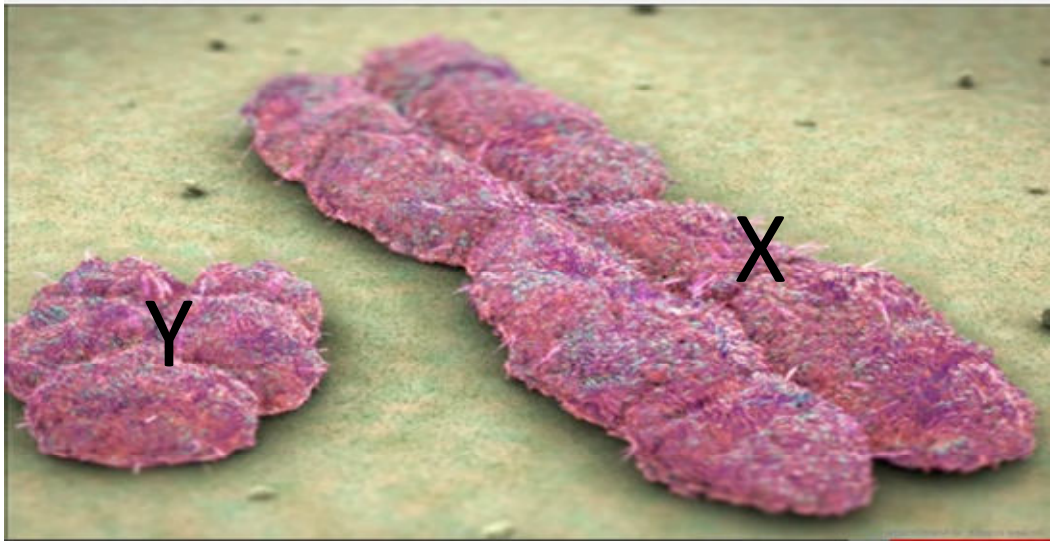
FOREWORD 8

DIMORFISMO SESSUALE

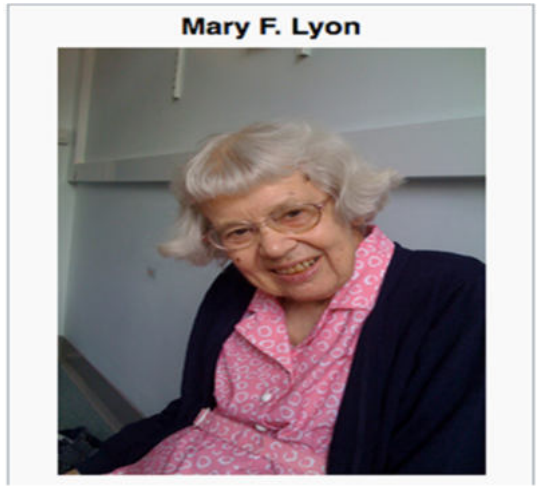
And yet this is not new!
Genetics : XY vs. XX

1861-1912

1905



1961



1921-2014

FOREWORD 9

A Symbiotic View Of Life: We Have Never Been Individuals

Scott F. Gilbert
Swarthmore College, sgilber1@swarthmore.edu

J. Sapp

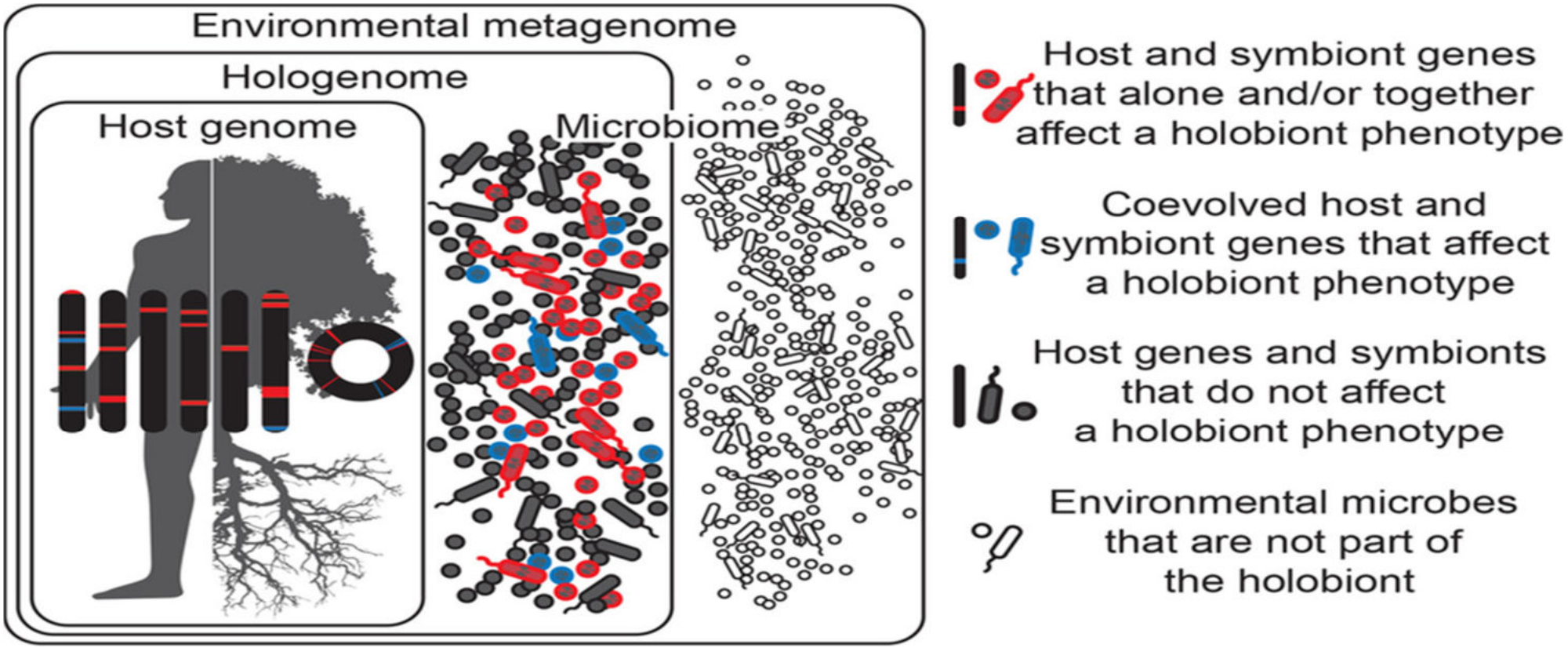
A. I. Tauber

CHICAGO JOURNALS

A Symbiotic View of Life: We Have Never Been Individuals
Author(s): Scott F. Gilbert, Jan Sapp and Alfred I. Tauber
Source: *The Quarterly Review of Biology*, Vol. 87, No. 4 (December 2012), pp. 325-341
Published by: The University of Chicago Press
Stable URL: http://www.jstor.org/stable/10.1086/668166

The notion of the "biological individual" is crucial to studies of genetics, immunology, evolution, development, anatomy, and physiology. Each of these biological subdisciplines has a specific conception of individuality, which has historically provided conceptual contexts for integrating newly acquired data. During the past decade, nucleic acid analysis, especially genomic sequencing and high-throughput RNA techniques, has challenged each of these disciplinary definitions by finding significant interactions of animals and plants with symbiotic microorganisms that disrupt the boundaries that heretofore had characterized the biological individual. Animals cannot be considered individuals by anatomical or physiological criteria because a diversity of symbionts are both present and functional in completing metabolic pathways and serving other physiological functions. Similarly, these new studies have shown that animal development is incomplete without symbionts. Symbionts also constitute a second mode of genetic inheritance, providing selectable genetic variation for natural selection. The immune system also develops, in part, in dialogue with symbionts and thereby functions as a mechanism for integrating microbes into the animal-cell community. Recognizing the "holobiont"-the multicellular eukaryote plus its colonies of persistent symbionts-as a critically important unit of anatomy, development, physiology, immunology, and evolution opens up new investigative avenues and conceptually challenges the ways in which the biological subdisciplines have heretofore characterized living entities.

Una **visione simbiotica della vita: non siamo mai stati «in-dividui»**
La nozione di "individuo biologico" è cruciale per gli studi **di genetica, immunologia, evoluzione, sviluppo, anatomia e fisiologia**... **Durante l'ultimo decennio, il sequenziamento genomico ha sfidato le varie definizioni** trovando **interazioni significative in animali e piante con i microrganismi simbiotici che rompono i confini che prima avevano caratterizzato l'individuo biologico.. lo sviluppo animale è incompleto senza simbionti**...
I simbionti costituiscono una **seconda modalità di ereditarietà genetica.. il sistema immunitario si sviluppa nel dialogo con i simbionti**. **Riconoscere l'olobionte - l'eucariota multicellulare più le sue colonie di simbionti persistenti - come unità di anatomia, sviluppo, fisiologia, immunologia ed evoluzione criticamente importanti** concettualmente **sfida i modi in cui le varie discipline biologiche hanno fino ad ora caratterizzato le entità viventi.**


Environmental metagenome
Hologenome
Host genome
Microbiome
Host and symbiont genes that alone and/or together affect a holobiont phenotype
Coevolved host and symbiont genes that affect a holobiont phenotype
Host genes and symbionts that do not affect a holobiont phenotype
Environmental microbes that are not part of the holobiont

FOREWORD 10

EPIGENETICS > GENETICS

Cosa è la "MALATTIA" ?

G. Fanconi " ***Non*** *vi sono* ***malattie nuove****.. nuovo è il modo di interpretarle*"
(Burgio-Notarangelo
Malattie Maestre**,** 2002
pag. 170)

- **M. Grmek**: da ***Vesalio*** e ***Sydenham*** → ***malattia come quadro sintomatologico ben definito = nuova ontologia***

Viruses ←→

PATHOCENOSIS *(cfr.* ***biocenosis****)*

Microbes **TLRs** → ***Natural Immunity***

"changing environment"

Gut Ecosystem

Immuno-systems

Biosphere

tolerance

Adaptive Immunity

Hypersensitivity

type I

type II

type III

type IV

type 0

Fluid Genosphere

Genetic background

Microbioma.. Epigenetics

Systemic (micro)vascular phlogosis

Kawasaki Disease
(*systemic* endothelitis)

Atherosclerosis
(**systemic** endothelitis)

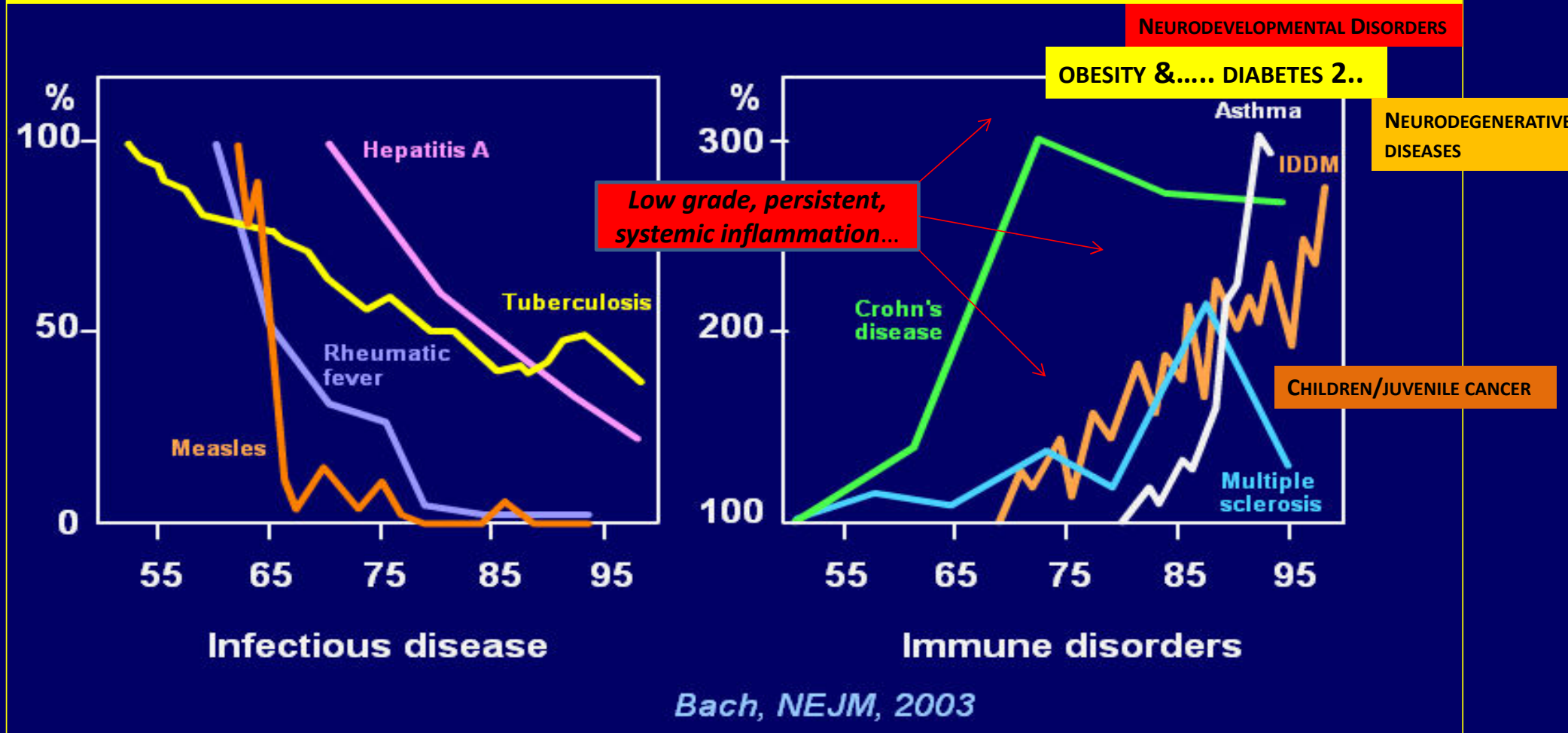
Coeliac Disease

Autism (?)

"Neurodegenerative" diseases

FOREWORD 1 The XXI Century's ***Epidemiological Transition***

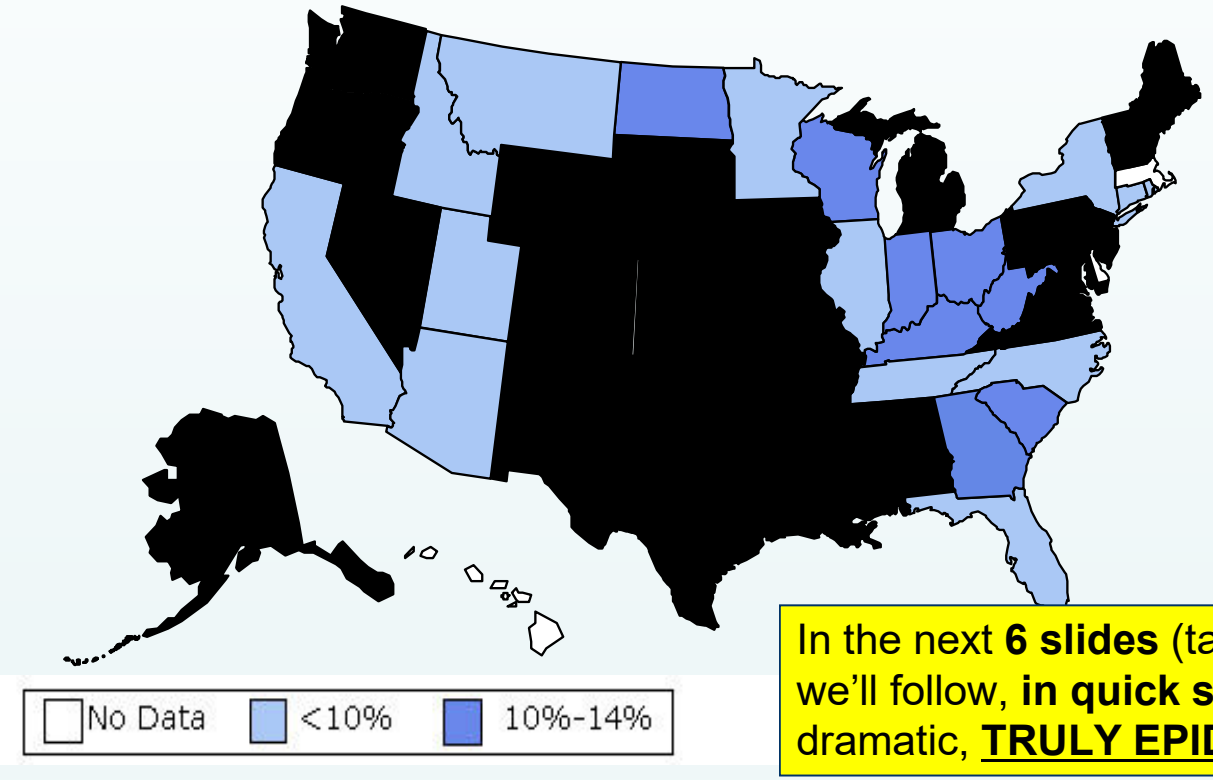
This is **a graph** taken from a famous article published **10 years ago on NEJM, showing the rapid decrease of the infectious/acute diseases** and the **simultaneous increase of the chronic/inflammatory diseases** in the North of the World



Bach, NEJM, 2003

Obesity Trends* Among U.S. Adults 1985

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

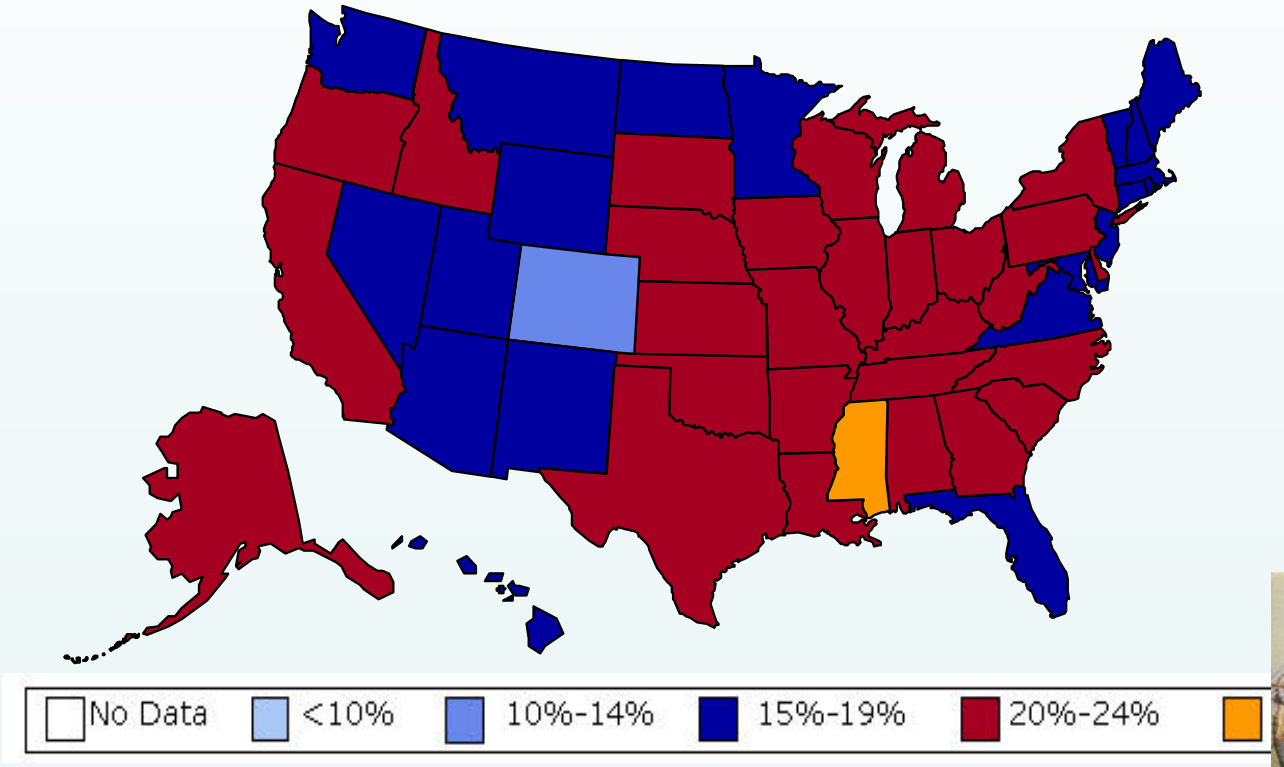


In the next **6 slides** (taken from **JAMA**) we'll follow, **in quick succession**, the dramatic, **TRULY EPIDEMIC SPREAD**

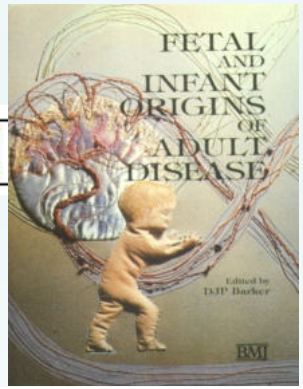
Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

Obesity Trends* Among U.S. Adults 2001

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



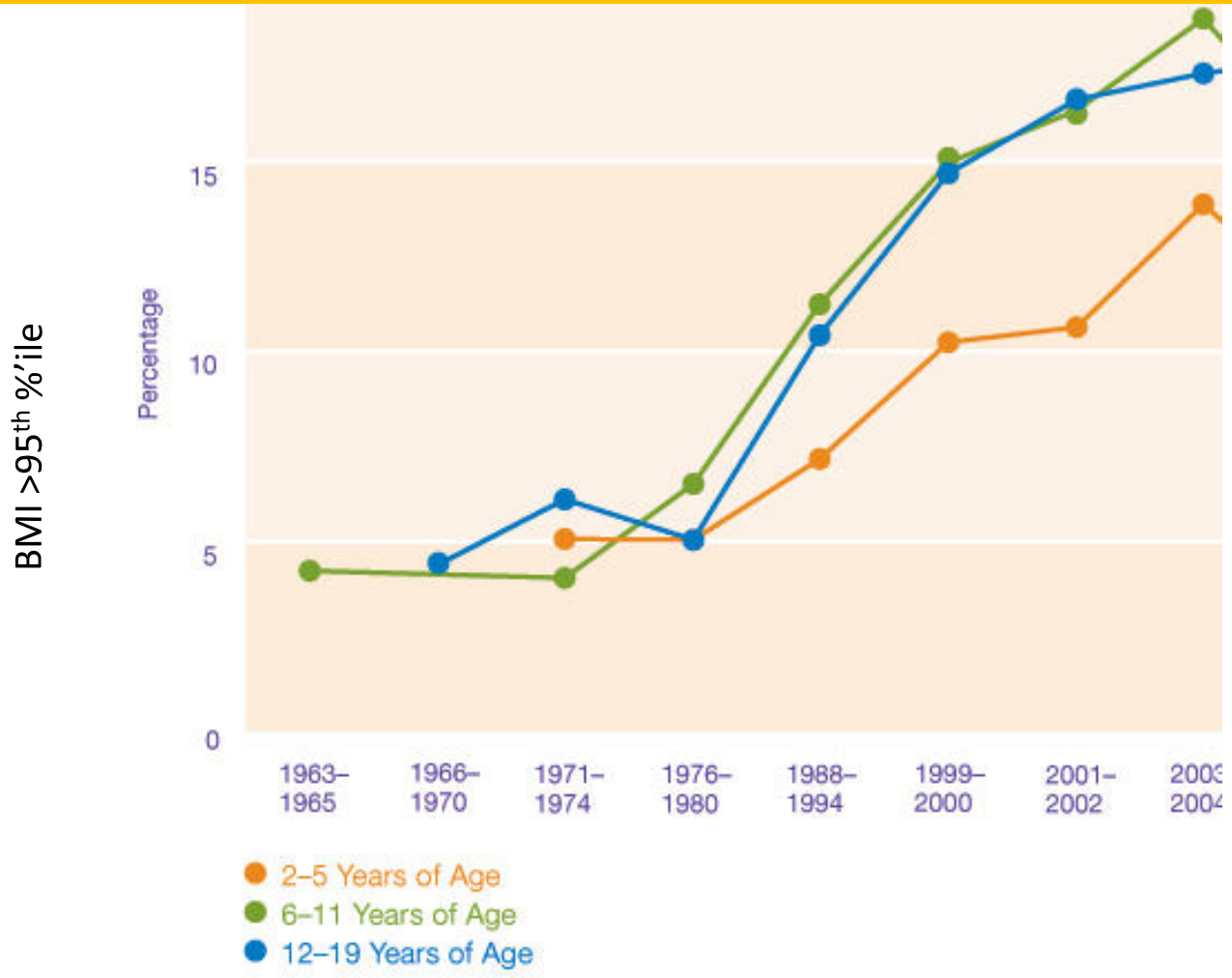
Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.



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

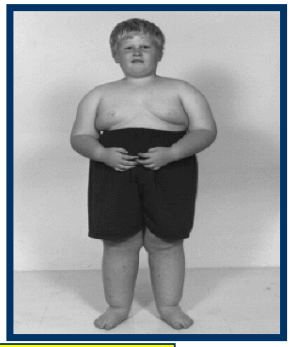
The Childhood Obesity Epidemic

Matthew W. Gillman, MD, SM



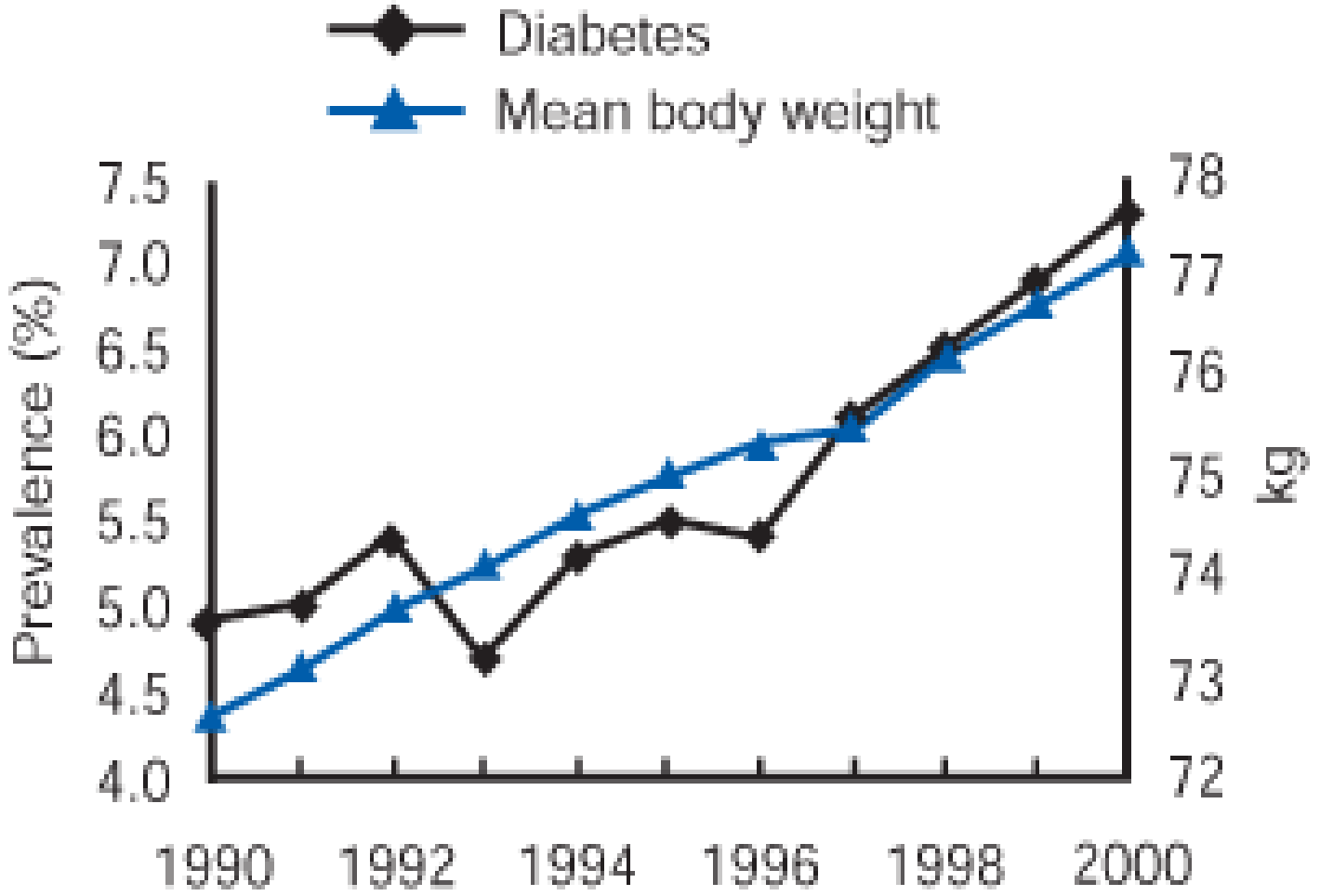
US DHHS, 2001; Hedley et al., 2004; Ogden et al., 2006, 2008

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



Prader Willi syndrome

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



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

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

Obesity and diabetes: from genetics to epigenetics

Ernesto Burgio · Angela Lopomo · Lucia Migliore

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

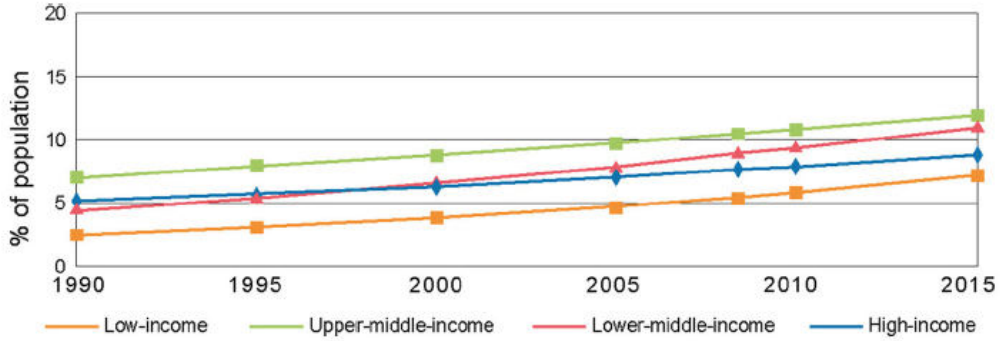


Fig. 1 Infant and young child overweight trends from 1990 to 2015, by World Bank income group (Adapted from WHO, 2010)

Genetic factors in obesity and diabetes

The obesogen hypothesis

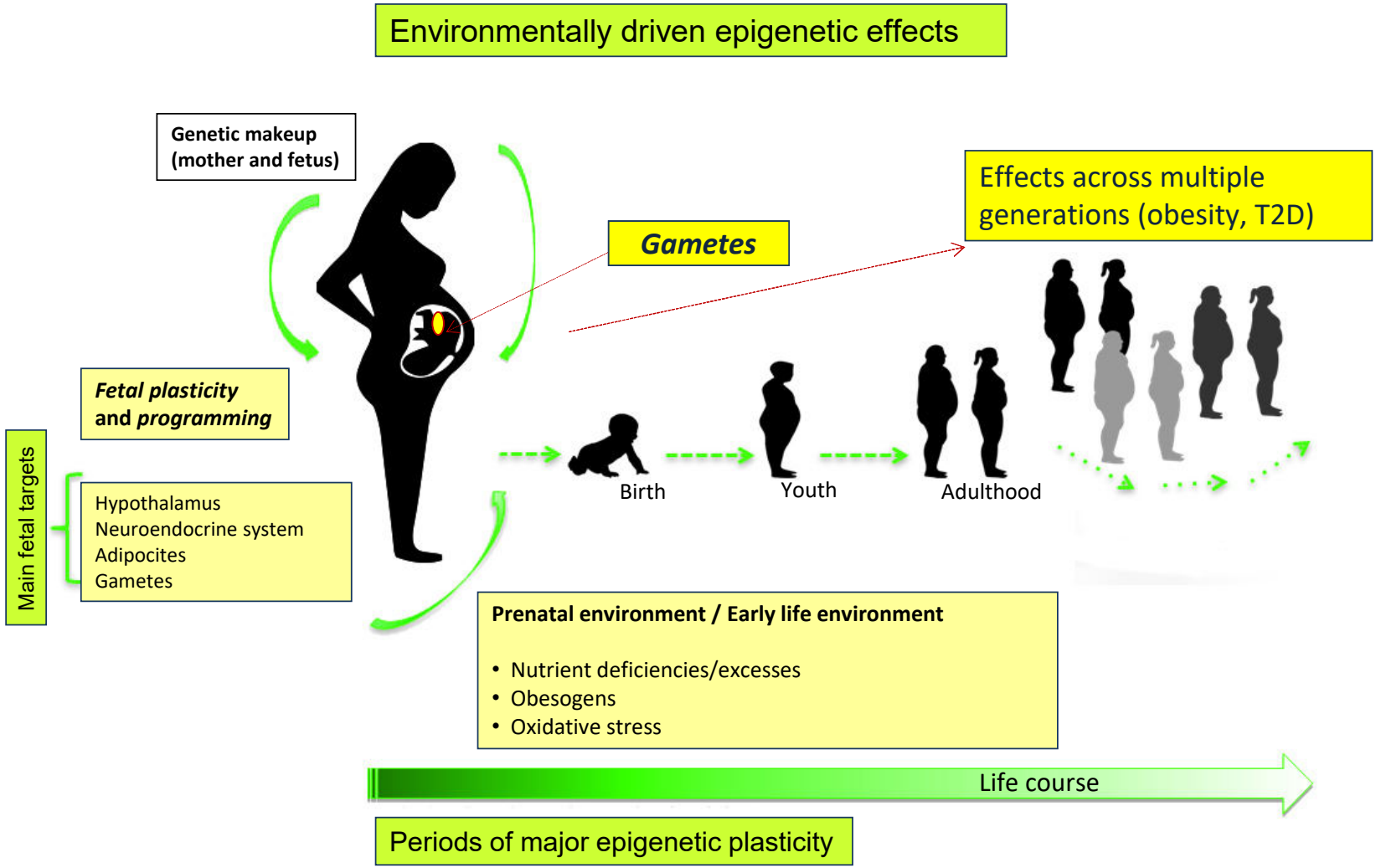
Epigenetic biomarkers

Beyond genetics

Diabetogens and diabetes epidemic

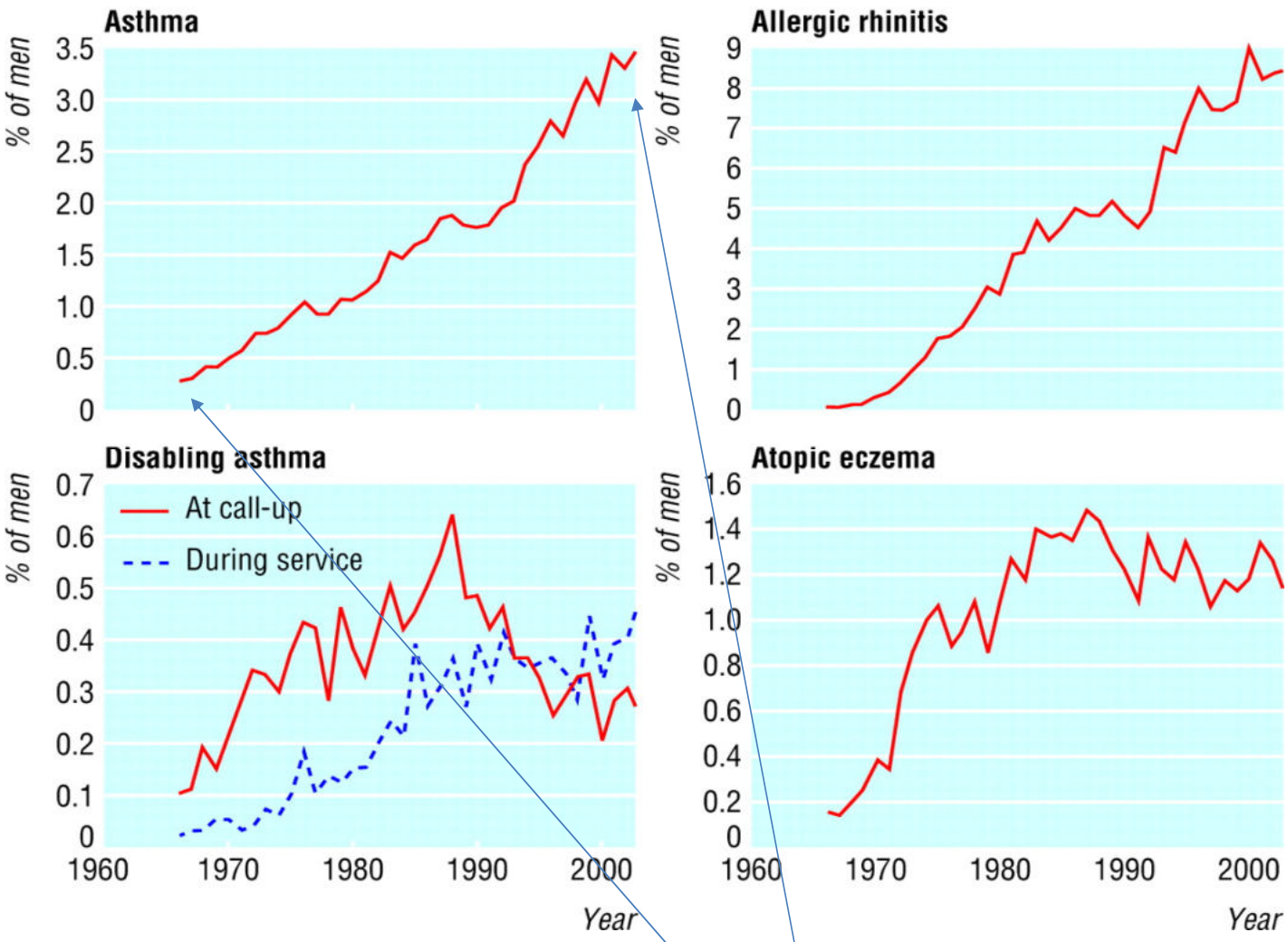
From genetics to epigenetics: fetal programming alterations

Is there a role for gut microbiota?



OBESITY AND DIABETES: FROM GENETICS TO EPIGENETICS (Mol Rep 2015)

Ernesto Burgio[1,2], Angela Lopomo[3,4] and Lucia Migliore[3]



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

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

WHAT IS EPIGENETICS

Could Epigenetics Explain the Origins of Allergic Disease?

Hypersensitivity begins in the womb

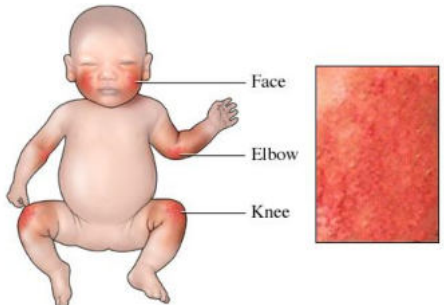
In a study examining **umbilical cord blood**, it was shown that **babies born to allergic mothers had a reduced number of Tregs**…and were at **high risk to develop sensitivity to food allergens and *atopic dermatitis*** (the start of atopic march) **during the first year of life**

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

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

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

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



Persistent cough: major causes

Pertussis

Asthma

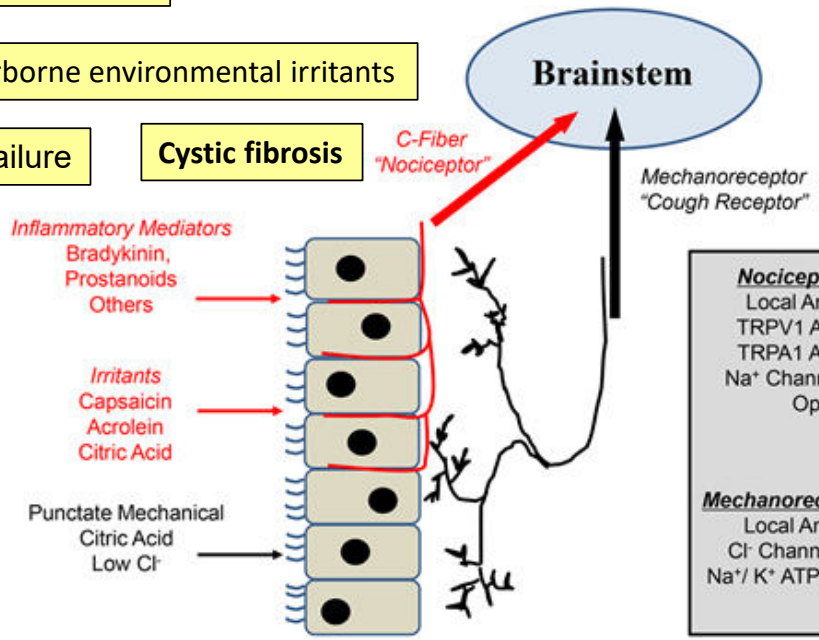
Lung infections

Postnasal drip

Airborne environmental irritants

Heart failure

Cystic fibrosis



Gastroesophageal reflux disease

Chronic bronchitis
Bronchiectasis

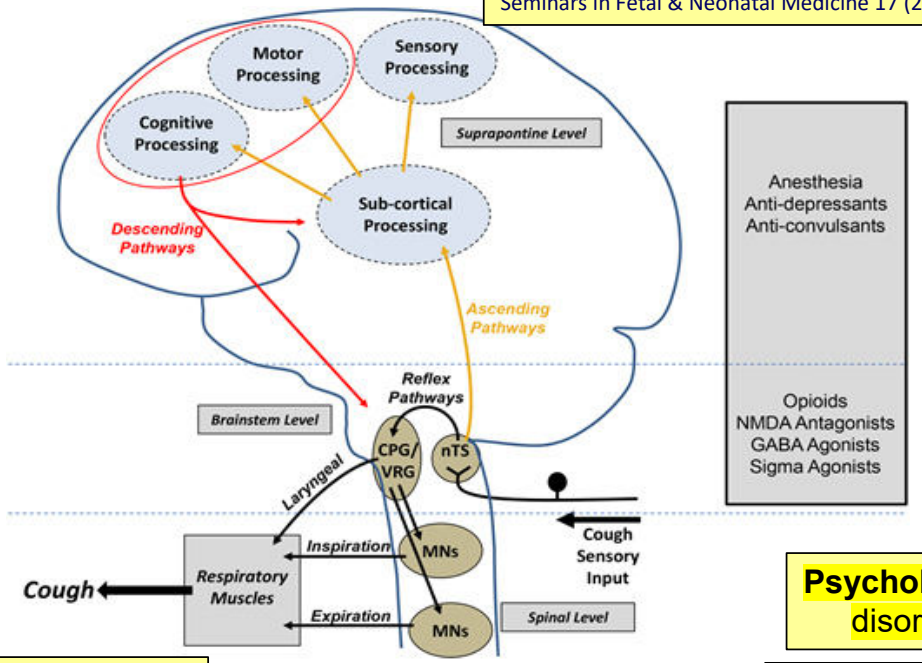
Lung cancer

Fetal Origins Hypothesis

Chronic obstructive pulmonary disease (COPD)

COPD is a major cause of morbidity and mortality worldwide and a significant challenge for adult physicians. However, **there is a misconception that COPD is a disease of only adult smokers. There is a growing body of evidence that chronic respiratory diseases such as COPD and ASTHMA have their origins in early life.**

Seminars in Fetal & Neonatal Medicine 17 (2012) 112e118



Tobacco smoke itself

Treatment with ACE inhibitors

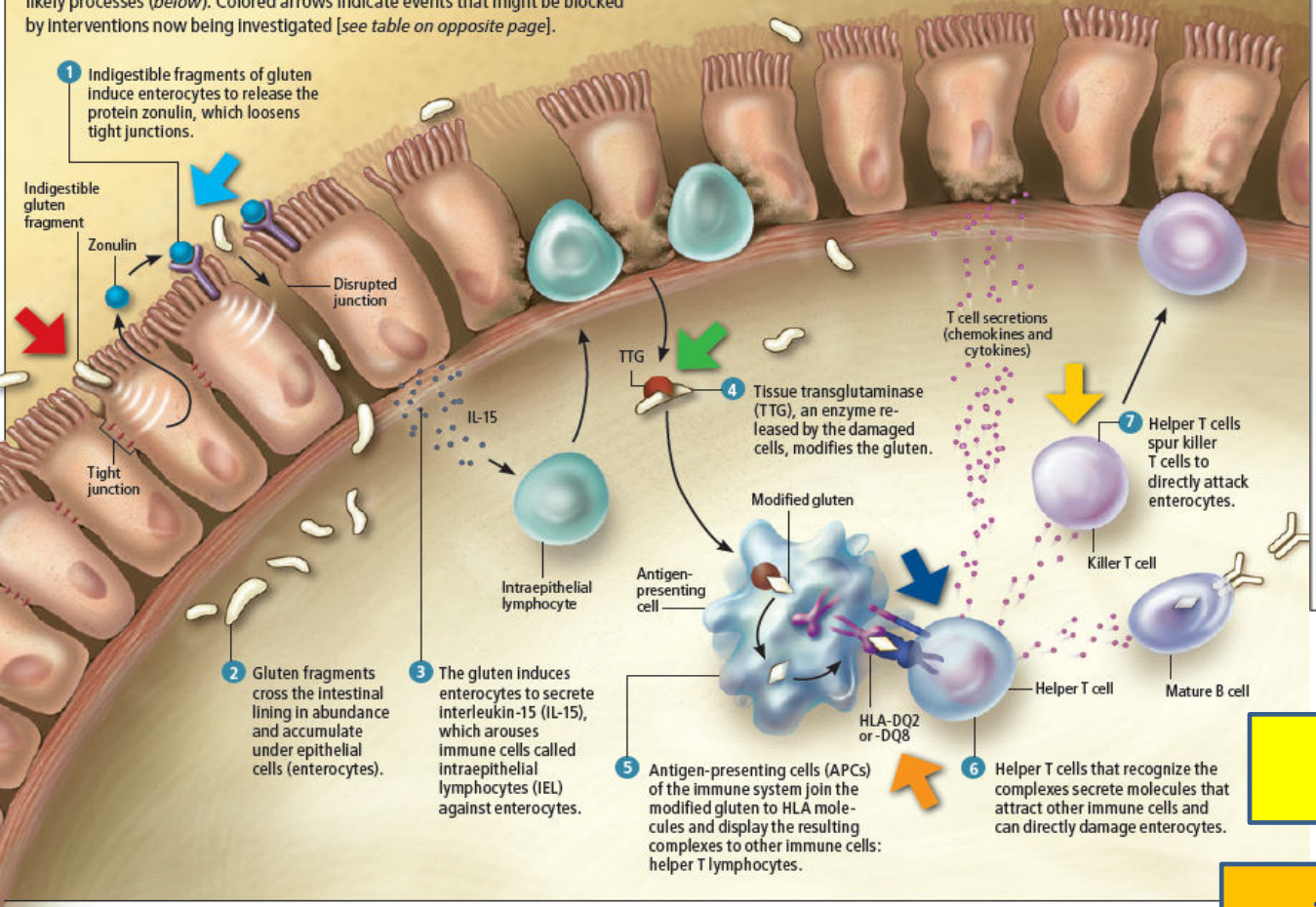
Psychological disorders

Psychogenic cough

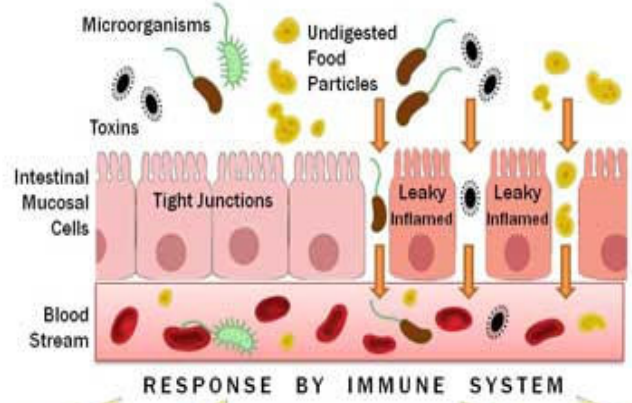
Neurogenic cough

THE INSIDE STORY

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



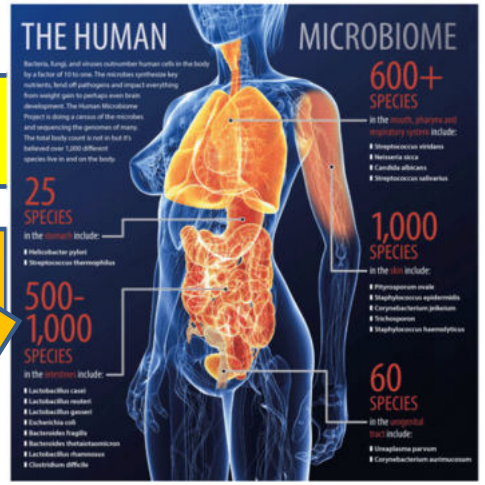
The Leaky Gut Syndrome



RESPONSE BY IMMUNE SYSTEM

Breach of Blood-Brain Barrier	Food Intolerances & Allergies	Autoimmunity & Inflammation	Malabsorption & Nutrient Deficiency

Metabolic Syndrome	Neurological Disorders	Autoimmune Disorders
Obesity, T2 Diabetes, Hypercholesterolemia, Hypertension	Depression, Anxiety, ADD, ADHD, Autism, Dementia, Epilepsy	Irritable bowel syndrome, Cronh's, Celiac, Allergies, Cancers



4 GUT PERMEABILITY

3 GUT ECOSYSTEM

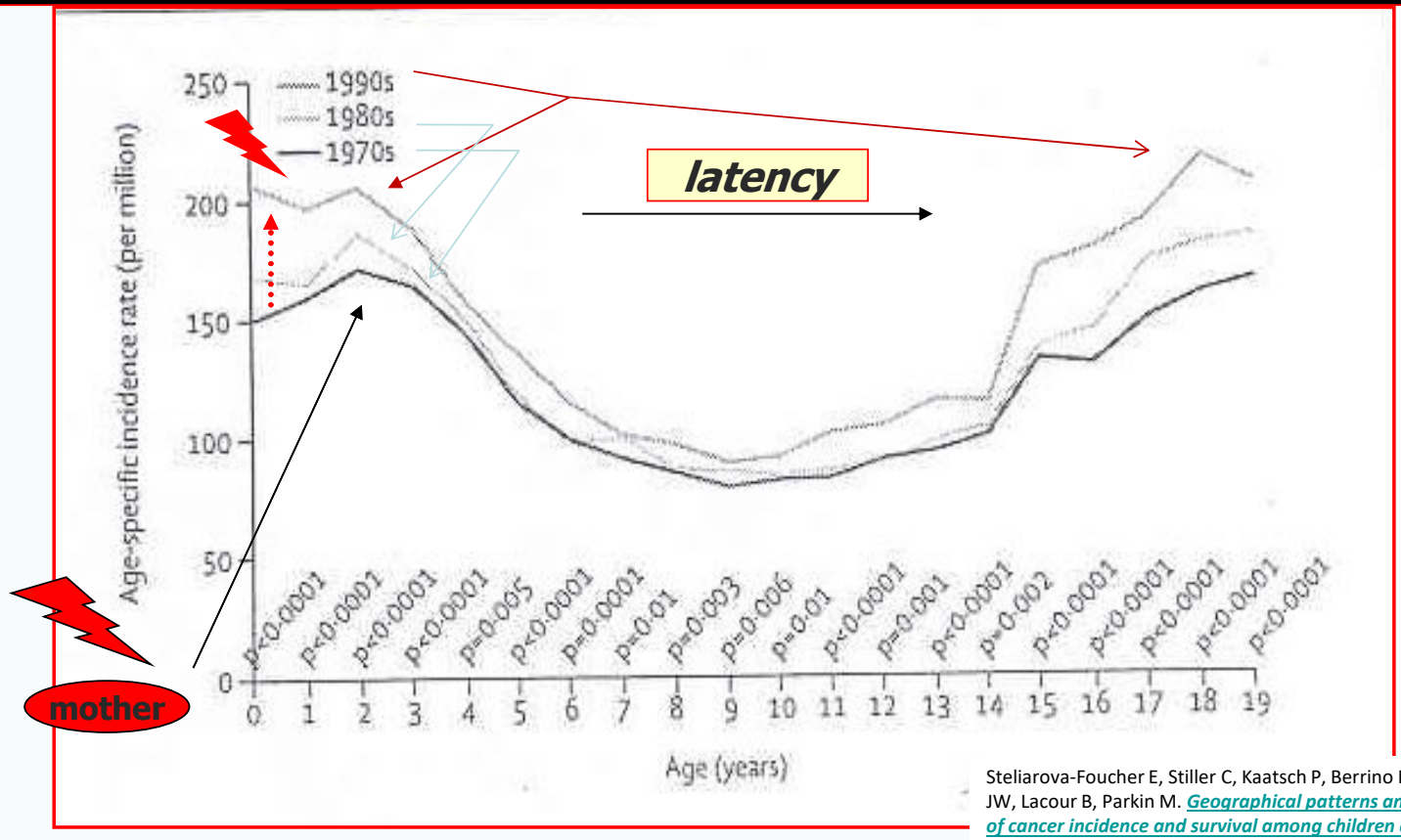
1 GLIADIN

2 DQ2 – DQ8

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

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

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



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

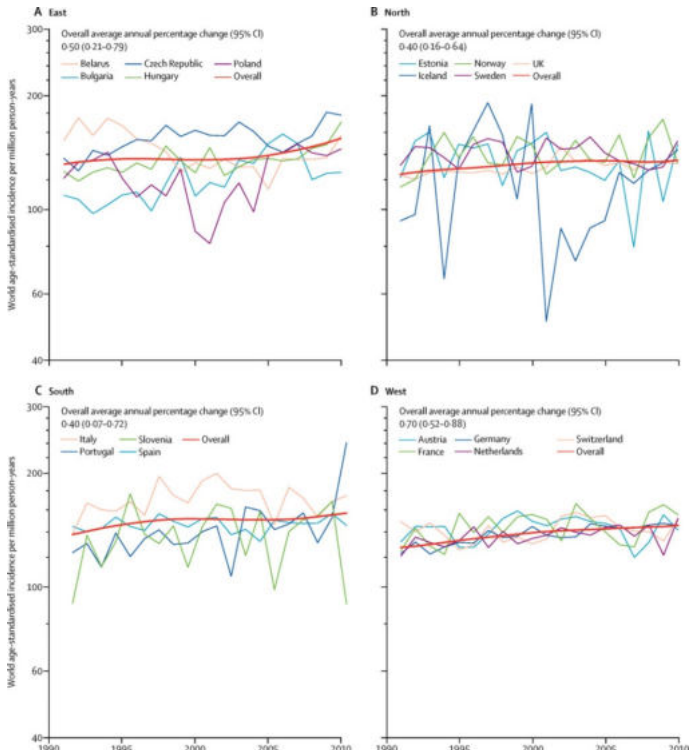
THE LANCET
Oncology
Volume 19, Issue 9, September 2018, Pages 1159-1169

Articles

Changing geographical patterns and trends in cancer incidence in children and adolescents in Europe, 1991–2010 (Automated Childhood Cancer Information System): a population-based study

Eva Steliarova-Foucher PhD [a], Miranda M Fidler PhD [a], Murielle Colombet MSc [a], Brigitte Lacour MD [b, c], Peter Kaatsch PhD [d], Marion Piñeros MD [a], Isabelle Soerjomataram PhD [a], Freddie Bray PhD [a], Prof Jan Willem Coebergh PhD [e], Rafael Peris-Bonet PhD [f], Charles A Stiller MSc [g]

The combined age-standardised incidence of leukaemia based on 48 458 cases in children was 46·9 (46·5–47·3) per million person-years and increased significantly by 0·66% (0·48–0·84) per year. The average overall incidence of leukaemia in adolescents was 23·6 (22·9–24·3) per million person-years, based on 4702 cases, and the average annual change was 0·93% (0·49–1·37). We also observed increasing incidence of lymphoma in adolescents (average annual change 1·04% [0·65–1·44], malignant CNS tumours in children (average annual change 0·49% [0·20–0·77]), and other tumours in both children (average annual change 0·56 [0·40–0·72]) and adolescents (average annual change 1·17 [0·82–1·53]).



.. incidence of leukaemia based on 48 458 cases in children was 46·9 (46·5–47·3) per million person-years and increased significantly by 0·66% (0·48–0·84) per year. The average overall incidence of leukaemia in adolescents was 23·6 (22·9–24·3) per million person-years, based on 4702 cases, and the average annual change was 0·93% (0·49–1·37)… We also observed increasing incidence of lymphoma in adolescents (average annual change 1·04% [0·65–1·44], malignant CNS tumours in children (average annual change 0·49% [0·20–0·77]), and other tumours in both children (average annual change 0·56 [0·40–0·72]) and adolescents (average annual change 1·17 [0·82–1·53]).

Executive Healthcare Management
www.executivehm.com

EHM Executive Healthcare

autism the great modern health concern

CDC Centers for Disease Control and Prevention

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

1980 1 : 1500

Autistic Disorder

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

Asperger Syndrome

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

Pervasive Developmental Disorder

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

2002 1 : 150

1 in 150 children in the US have an ASD CDC estimated ave~~meaning~~

2014 1 : 68

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

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

2006 1 : 110

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

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

about four-fifths notice by age 24 months

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

2008 1 : 88

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

Reports of autism cases per 1,000 children

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

2014 1 : 68

Sources: CDC | www.

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

AUTISM
(ASD :Autism Spectrum Disorders)

ASD is the fastest-growing developmental disorder in the world, the prevalence of diagnosis having increased by 600% over the last 20 years. New diagnosed cases (**incidence**) in US increased **from 15,580 in 1992 to 163.773 in 2003**

The estimated **prevalence was of 8-12 cases/1000 children in 2012..**

Chart showing the **increase in autism diagnosis (A)** ***versus*** **all disabilities (B)** (statistics based on data from the National Center for Health Statistics)

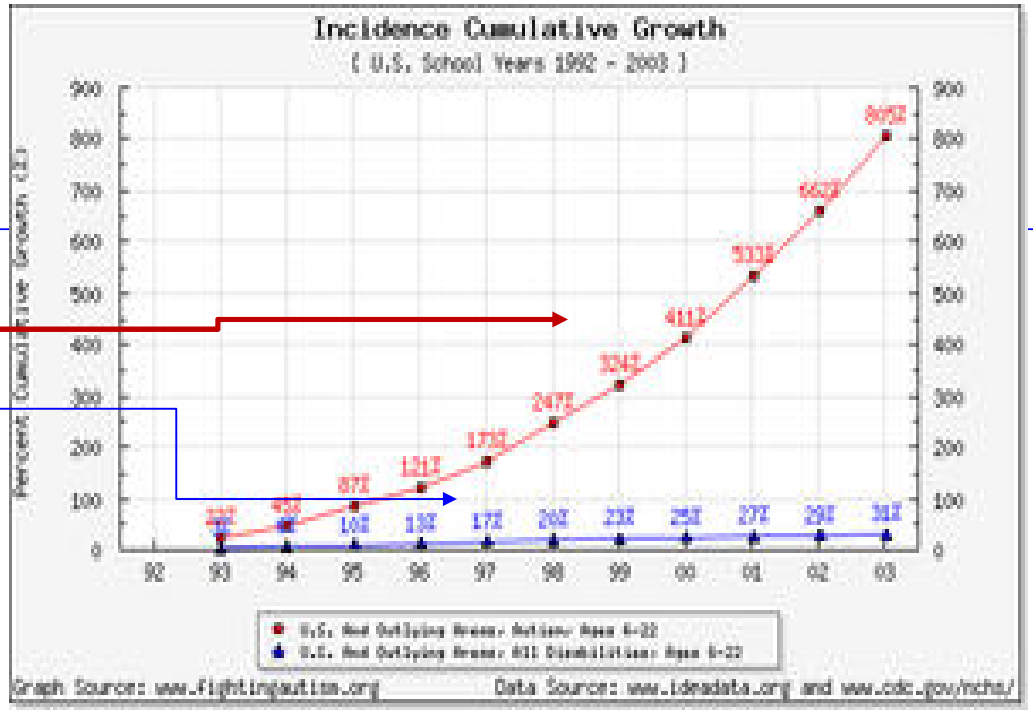
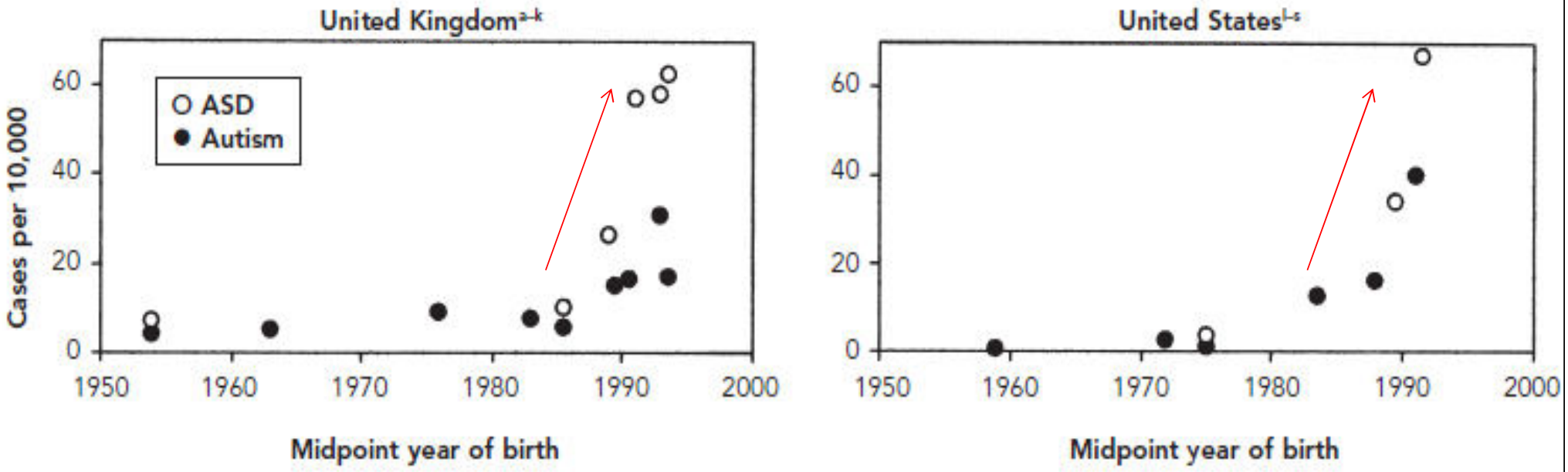


Figure 1. Reported prevalence of autism and autistic spectrum disorders (ASDs), by midpoint year of birth, United Kingdom and United States, 1954–1994



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

[a]Lotter 1966[35]

[b]Wing and Gould 1979[42]

[c]Deb and Prasad 1994[82]

[d]Webb et al. 1997[89]

[e]Taylor et al. 1999[20]

[k]Baird et al. 2000[78]

[l]Treffert 1970[36]

[m]Ritvo et al. 1989[53]

[n]Burd et al. 1987[45]

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

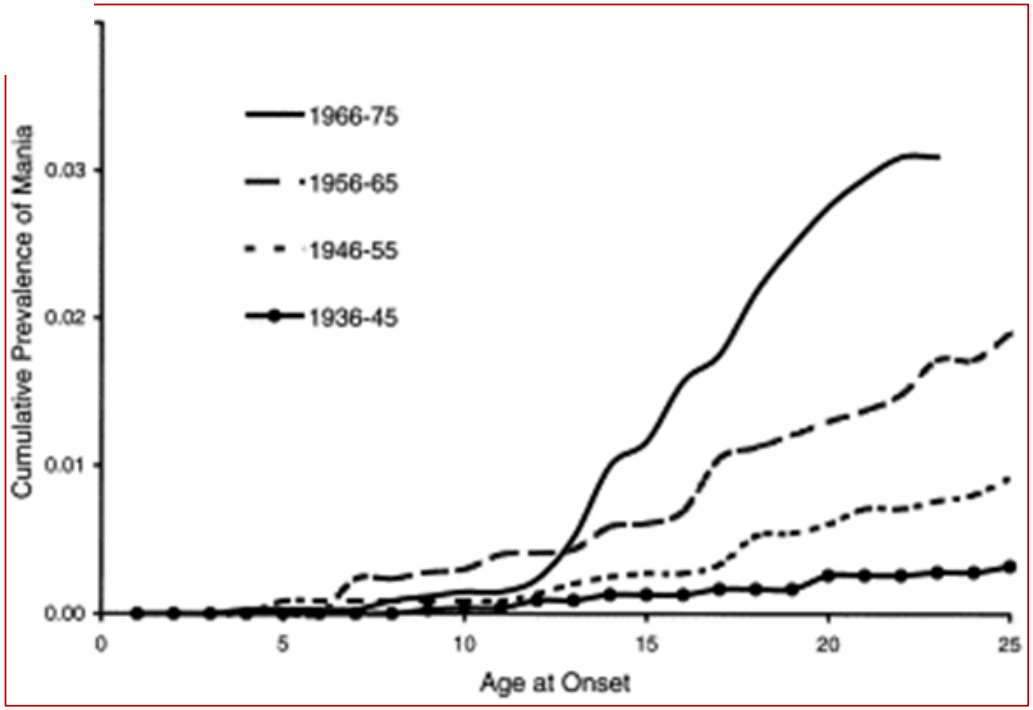
Biological Psychiatry
Volume 49, Issue 12, 15 June 2001, Pages 1002-1014

The unmet needs in diagnosis and treatment of mood disorders in children and adolescents

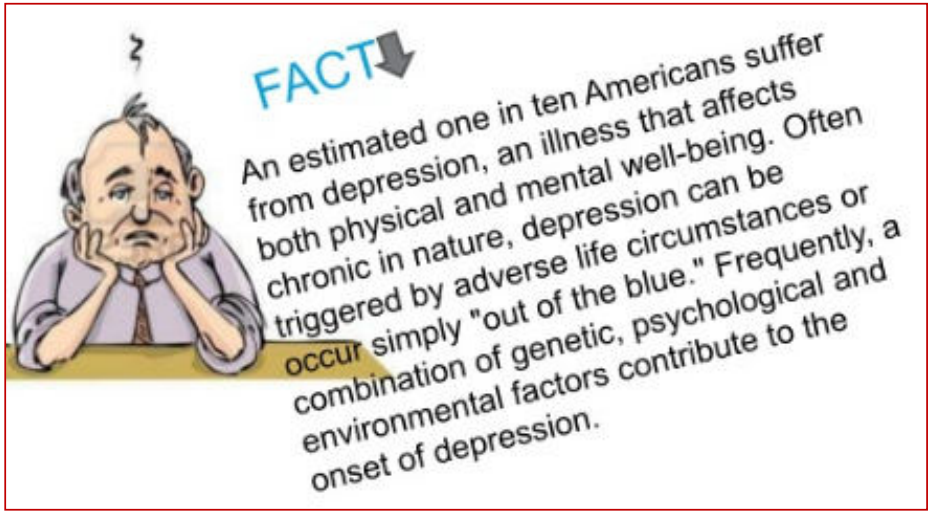
Mood disorders in children and adolescents: an epidemiologic perspective

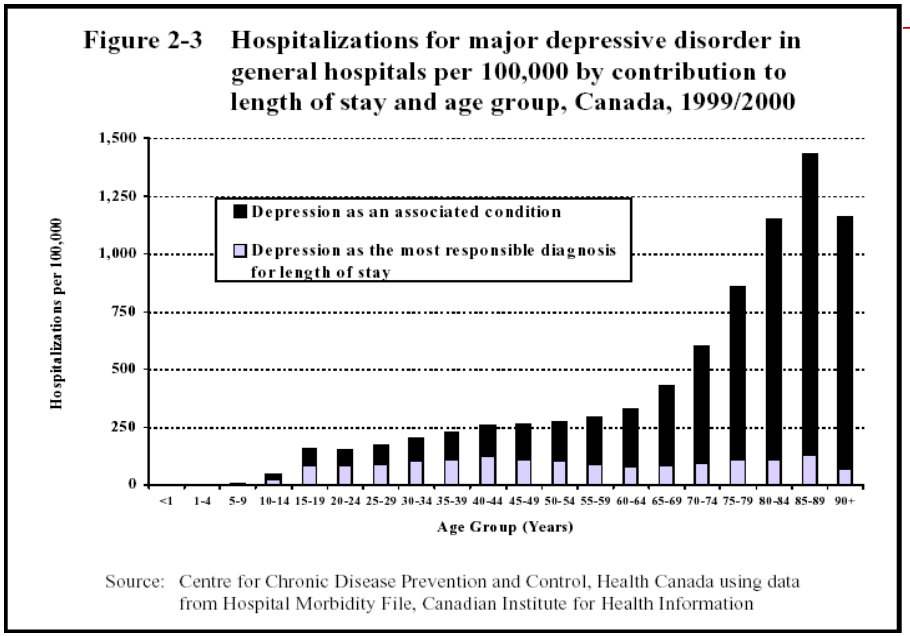
Ronald C Kessler [a], Shelli Avenevoli [b], Kathleen Ries Merikangas [b]

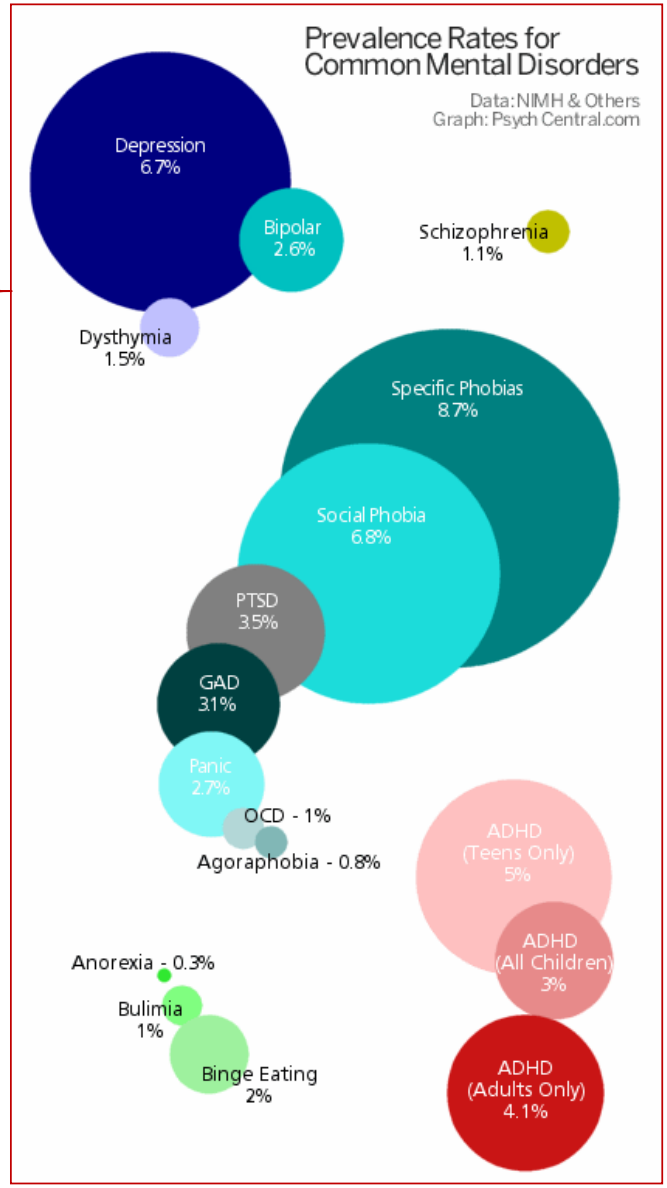
Adolescence is a time of increasing vulnerability for severe mental health disorders such as depression.
Epidemiological studies show that the **incidence of new cases of depression drastically increases with puberty..** Importantly, there is growing evidence that **sleep disturbance in adolescence may predict the development of depression**.. In addition to the increase in the prevalence of depression with the transition from childhood to adolescence, **there is also a secular trend of an increasing incidence of depression during adolescence since the 1960s**



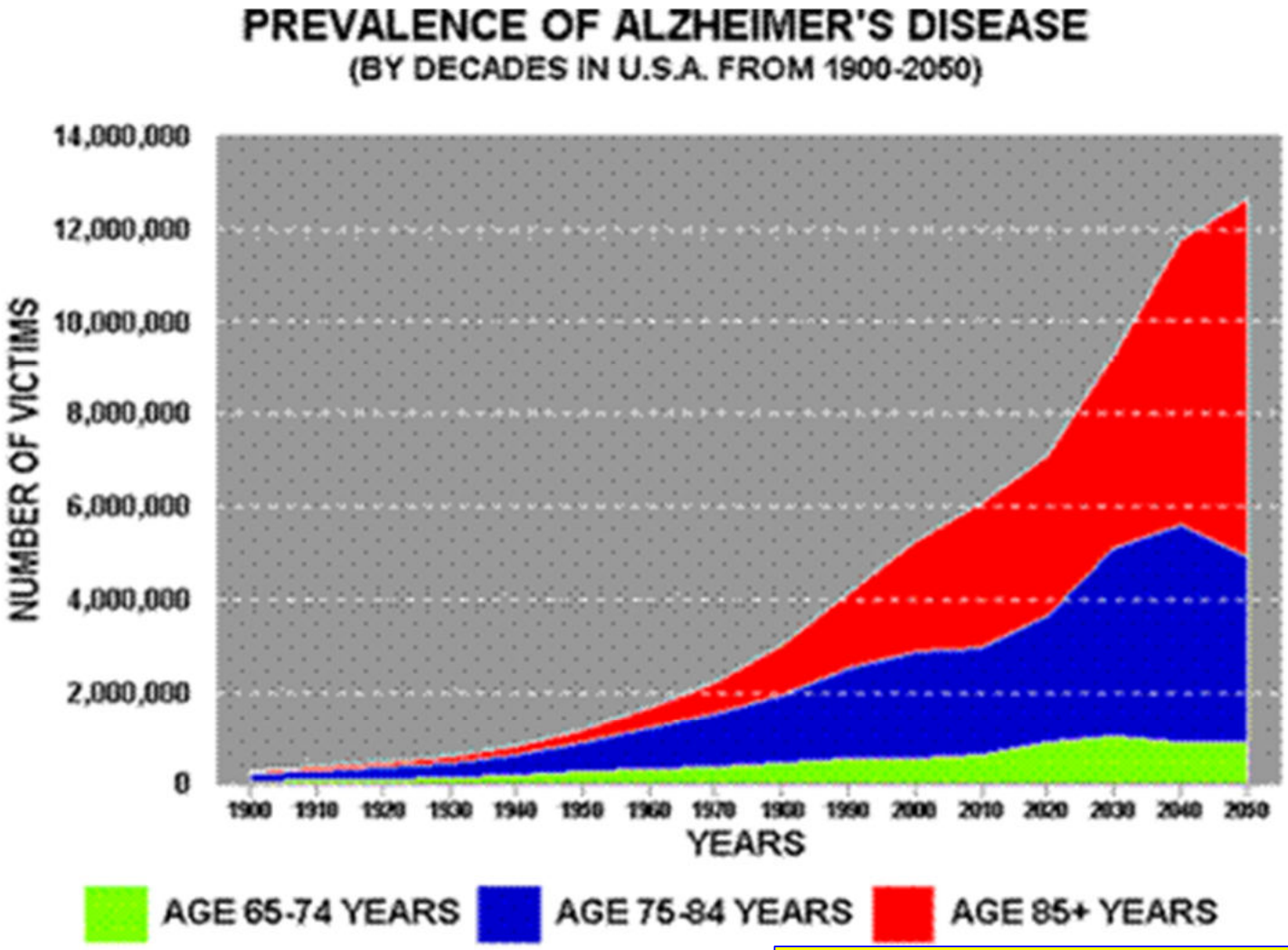
http://www.slideshare.net/CMoondog/depression-powerpoint-13945746







http://psychcentral.com/blog/archives/2009/10/05/prevalence-of-common-mental-disorders/

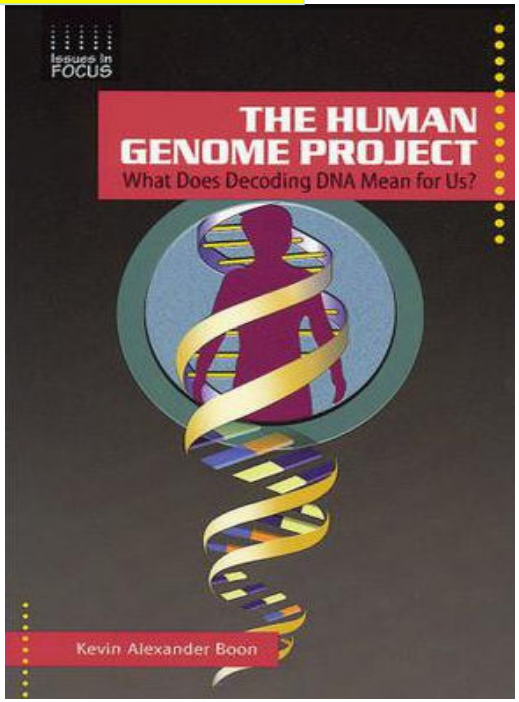


This graph portrays how many Americans over the age
Alzheimer's, and a projection of how many more will b

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

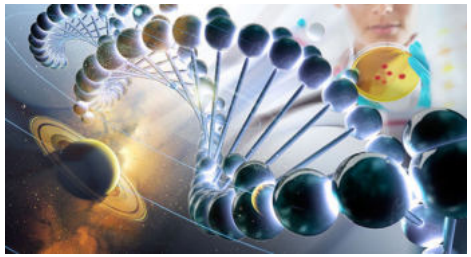
Since 2000 there has been a **66% increase in Alzheimer's diagnoses**.
6th leading cause of death in the United States.
5.4 million Americans are living with the disease.
15-20 million more Americans will be diagnosed by 2040

FOREWORD 2

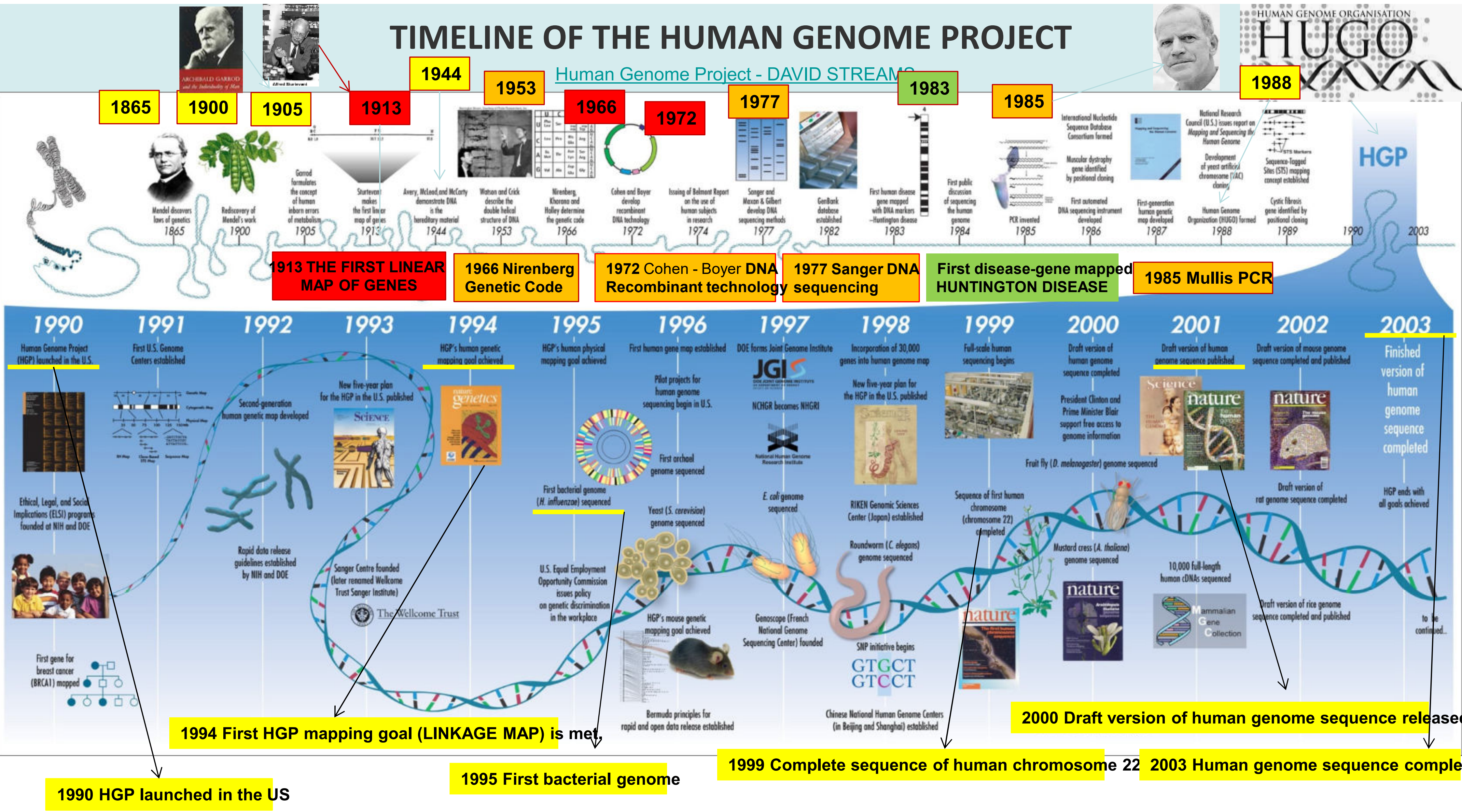


La **BIO-MEDICINA OCCIDENTALE/DOMINANTE** ha creduto di poter affrontare questa immensa problematica utilizzando **un modello semplice/semplicistico secondo il quale queste malattie sarebbero dovute a *errori del DNA **:** incidenti biologici **prodotti/indotti/rivelati** da **stili di vita poco corretti**.

- Uno degli obiettivi fondamentali di ***PROGETTO GENOMA***, il più grande progetto di tutti i tempi in campo biomedico, era SCOPRIRE QUESTI **SUPPOSTI ERRORI/DIFETTI DEL DNA** PREDISPONENTI O DIRETTAMENTE PATOGENETICI (A FINI DIAGNOSTICI E TERAPEUTICI…)



MA….IL **DNA** HA (**SUL PIANETA TERRA**) **4 MILIARDI DI ANNI: NON «SBAGLIA»** ….


TIMELINE OF THE HUMAN GENOME PROJECT
Human Genome Project - DAVID STREAMS
HUMAN GENOME ORGANISATION
HUGO
1865
1900
1905
1913
1944
1953
1966
1972
1977
1983
1985
1988
Mendel discovers laws of genetics 1865
Rediscovery of Mendel's work 1900
Garrod formulates the concept of human inborn errors of metabolism 1905
Sturtevant makes the first linear map of genes 1913
Avery, McLeod, and McCarty demonstrate DNA is the hereditary material 1944
Watson and Crick describe the double helical structure of DNA 1953
Nirenberg, Khorana and Holley determine the genetic code 1966
Cohen and Boyer develop recombinant DNA technology 1972
Issuing of Belmont Report on the use of human subjects in research 1974
Sanger and Maxam & Gilbert develop DNA sequencing methods 1977
GenBank database established 1982
First human disease gene mapped with DNA markers –Huntington disease 1983
First public discussion of sequencing the human genome 1984
PCR invented 1985
International Nucleotide Sequence Database Consortium formed
Muscular dystrophy gene identified by positional cloning
First automated DNA sequencing instrument developed 1986
First-generation human genetic map developed 1987
National Research Council (U.S.) issues report on Mapping and Sequencing the Human Genome
Development of yeast artificial chromosome (YAC) cloning
Human Genome Organization (HUGO) formed 1988
Sequence-Tagged Sites (STS) mapping concept established
Cystic fibrosis gene identified by positional cloning 1989
1990
2003
HGP
1913 THE FIRST LINEAR MAP OF GENES
1966 Nirenberg Genetic Code
1972 Cohen - Boyer DNA Recombinant technology
1977 Sanger DNA sequencing
First disease-gene mapped HUNTINGTON DISEASE
1985 Mullis PCR
1990
Human Genome Project (HGP) launched in the U.S.
Ethical, Legal, and Social Implications (ELSI) programs founded at NIH and DOE
First gene for breast cancer (BRCA1) mapped
1991
First U.S. Genome Centers established
1992
Second-generation human genetic map developed
Rapid data release guidelines established by NIH and DOE
1993
New five-year plan for the HGP in the U.S. published
Sanger Centre founded (later renamed Wellcome Trust Sanger Institute)
The Wellcome Trust
1994
HGP's human genetic mapping goal achieved
1995
HGP's human physical mapping goal achieved
First bacterial genome (H. influenzae) sequenced
U.S. Equal Employment Opportunity Commission issues policy on genetic discrimination in the workplace
1996
First human gene map established
Pilot projects for human genome sequencing begin in U.S.
First archael genome sequenced
Yeast (S. cerevisiae) genome sequenced
HGP's mouse genetic mapping goal achieved
Bermuda principles for rapid and open data release established
1997
DOE forms Joint Genome Institute
JGI
NCHGR becomes NHGRI
E. coli genome sequenced
Genoscope (French National Genome Sequencing Center) founded
1998
Incorporation of 30,000 genes into human genome map
New five-year plan for the HGP in the U.S. published
RIKEN Genomic Sciences Center (Japan) established
Roundworm (C. elegans) genome sequenced
SNP initiative begins
GTGCT
GTCCT
Chinese National Human Genome Centers (in Beijing and Shanghai) established
1999
Full-scale human sequencing begins
Sequence of first human chromosome (chromosome 22) completed
2000
Draft version of human genome sequence completed
President Clinton and Prime Minister Blair support free access to genome information
Fruit fly (D. melanogaster) genome sequenced
Mustard cress (A. thaliana) genome sequenced
2001
Draft version of human genome sequence published
10,000 full-length human cDNAs sequenced
Mammalian Gene Collection
2002
Draft version of mouse genome sequence completed and published
Draft version of rat genome sequence completed
Draft version of rice genome sequence completed and published
2003
Finished version of human genome sequence completed
HGP ends with all goals achieved
to be continued...
1990 HGP launched in the US
1994 First HGP mapping goal (LINKAGE MAP) is met,
1995 First bacterial genome
1999 Complete sequence of human chromosome 22
2000 Draft version of human genome sequence released
2003 Human genome sequence comple

THE HUMAN GENOME - THE BLUEPRINT OF LIFE

The Human Genome project sequenced DNA, the molecules that make up chromosomes in cells. The information derived from this project presented scientists with a valuable opportunity to not only uncover the secrets of DNA but also the manner in which genes are associated with disease. Scientists now are able to compare the genomes of people who have a certain condition with those who do not, in order to determine whether genetic variation plays a role in that condition. This information will help them to predict and possibly prevent disease in the future.

1. Cell

Each of the trillions of cells in the human body contains 46 chromosomes packed tightly into the region called the nucleus.

2. Chromosomes

Half of the chromosomes in the nucleus come from your mother, and half from your father. Each chromosome is a long, tightly coiled molecule called DNA, or deoxyribonucleic acid.

3. DNA

If unwound, the DNA from all the chromosomes in a single cell placed end to end would stretch more than six feet.

4. Genome

DNA is made up of chemical building blocks abbreviated A, C, T, and G. The entire length of a DNA strand consists of these four blocks in different combinations. Together, all the DNA in all the chromosomes -- more than 3 billion letters -- makes up the human genome. When scientists say they have "sequenced" the human genome, they mean that they have figured out the order of all those A's, C's, T's, and G's in sequence.

5. Genes: 30,000 DNA Segments

Much of the DNA in the genome is organized into units called genes. There may be as many as 30,000 genes in the genome; they are the instruction manual for making all the proteins in the body. These proteins are the physical "stuff" that makes up our hair, skin, heart, and blood, among other things. They also control chemical reactions, regulate blood sugar and heart rate, and control how food or medicine is metabolized in the body.

6. Misspellings in the Sequence

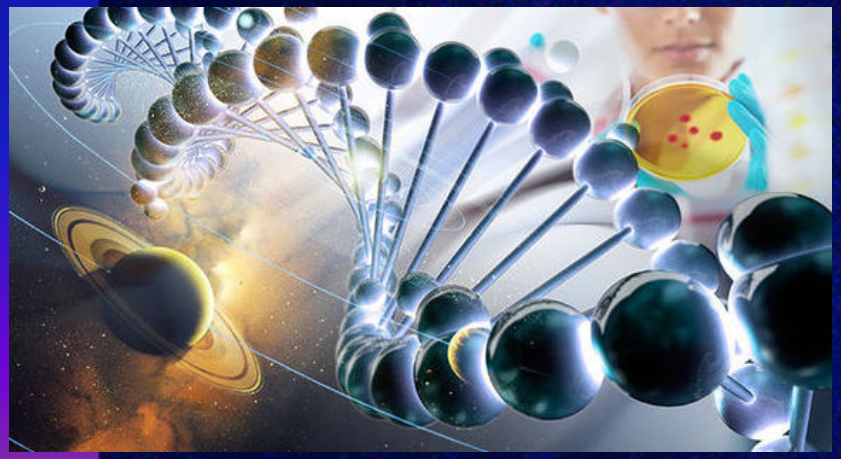
The way the genes are "spelled" makes all the difference - one letter out of place in a gene can cause disease. Now that we know the normal sequence of the human genome, researchers can compare the DNA sequence from people who have a disease or condition to those who don't. If there are differences in the spelling of certain genes between the two groups, it's possible that the condition may be caused by or related to that misspelling in that gene.

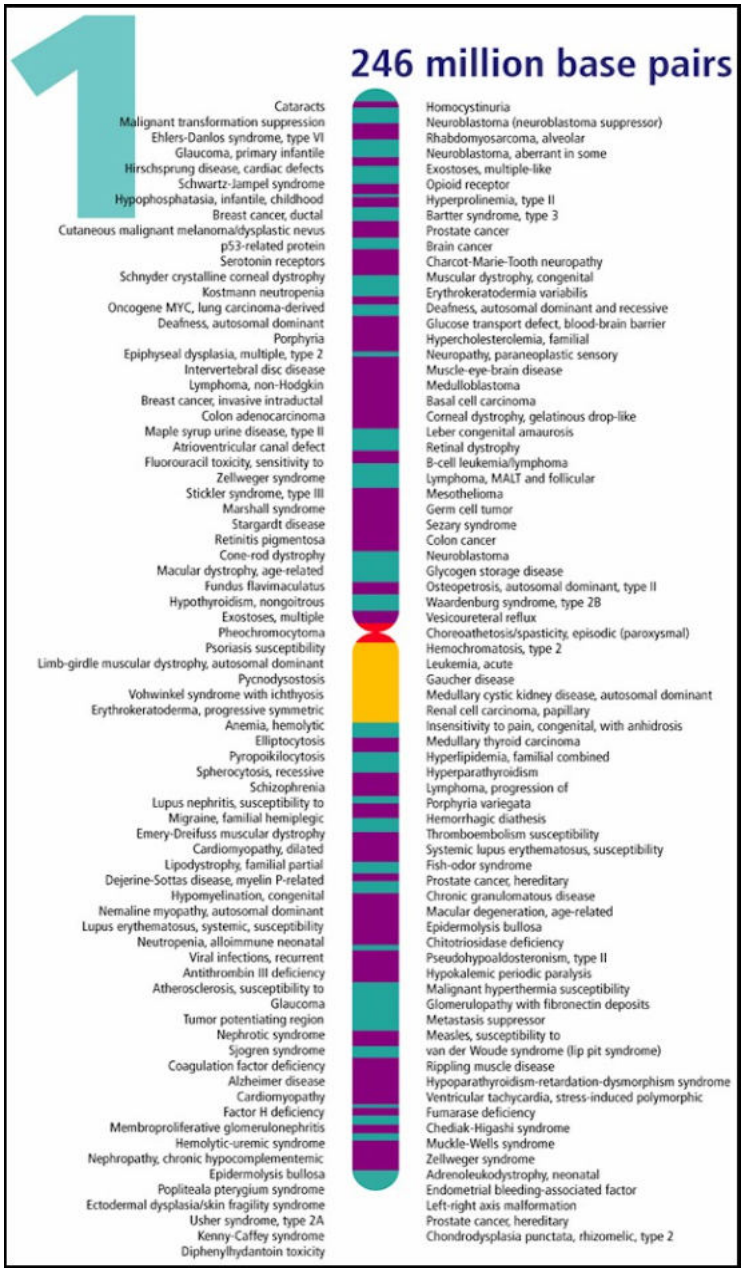
7. Genes and Disease

Scientists have identified about 6000 diseases, such as Huntington disease and cystic fibrosis, that are directly caused by misspellings or physical problems in single genes.
But the genetic contribution to many common conditions -- such as diabetes and heart disease -- is part of a larger puzzle that could include diet, lifestyle, environment, and even other genes.
For many of these common conditions, genetic misspellings probably make only a small contribution to disease relative to other factors, or work in concert with them to cause illness.

HUMAN GENOME PROJECT

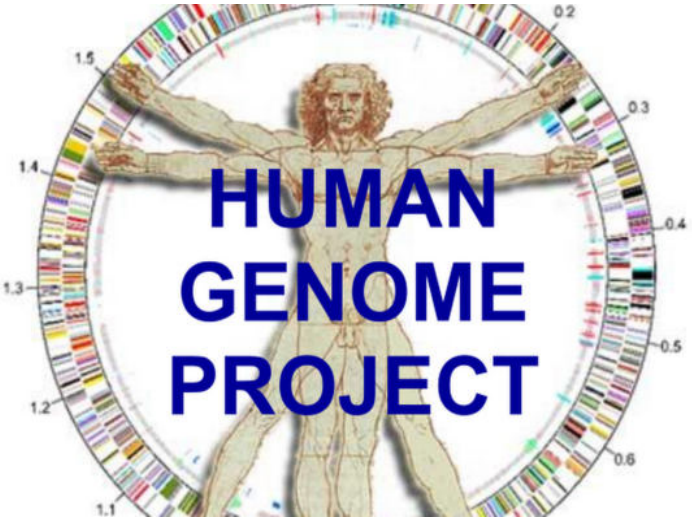
Ma….il **DNA** ha (**sul pianeta Terra**)
4 miliardi di anni: NON sbaglia….





q-arm

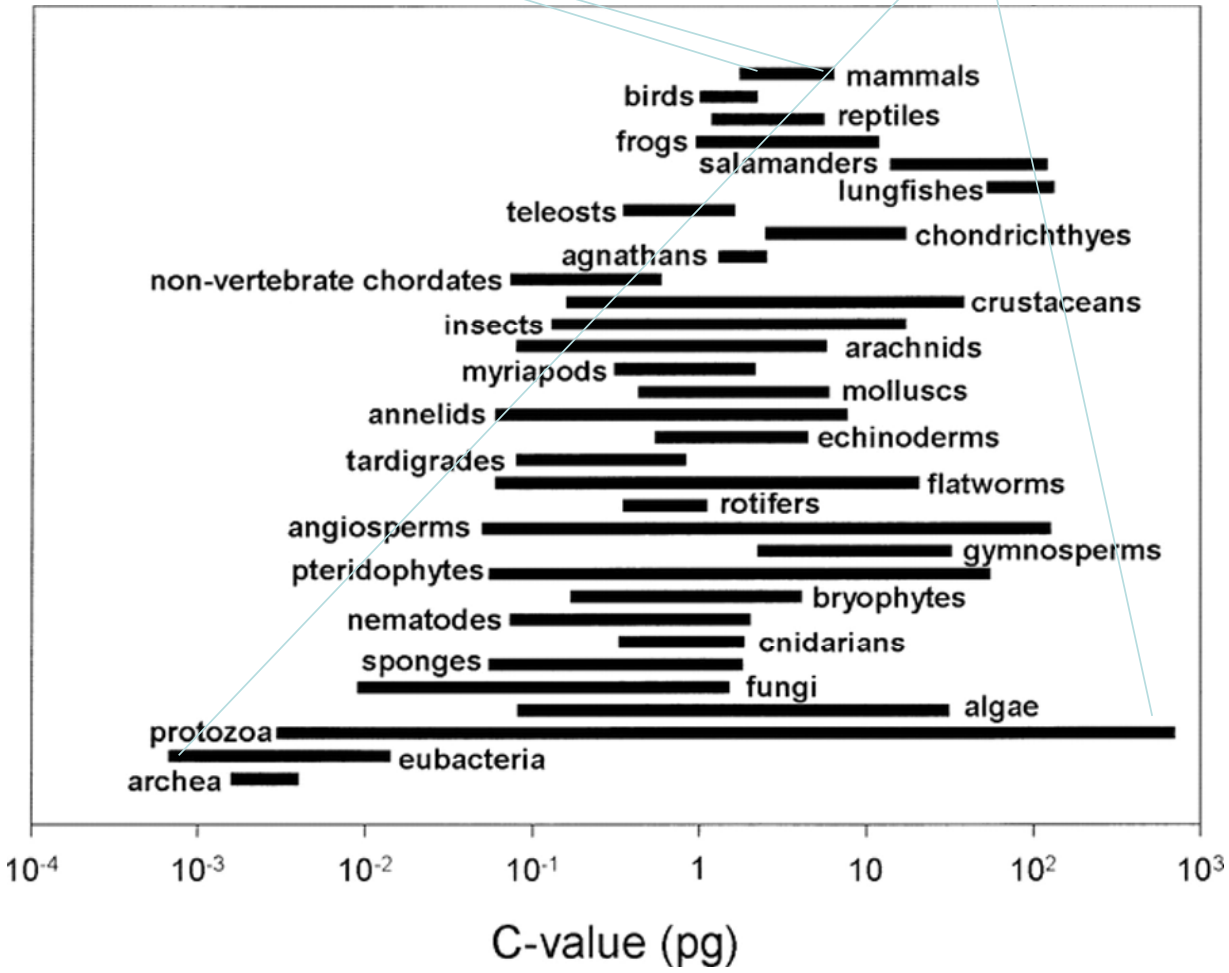
ASPM: a brain size determinant
F5: coagulation factor V (proaccelerin, labile factor)
FMO3: flavin containing monooxygenase 3
GBA: glucosidase, beta; acid (includes glucosylceramidase)
GLC1A: gene for glaucoma
HFE2: hemochromatosis type 2 (juvenile)
HPC1: gene for prostate cancer
IRF6: gene for connective tissue formation
LMNA: lamin A/C
MPZ: myelin protein zero (Charcot-Marie-Tooth neuropathy 1B)
MTR: 5-methyltetrahydrofolate-homocysteine methyltransferase
PPOX: protoporphyrinogen oxidase
PSEN2: presenilin 2 (Alzheimer disease 4)
SDHB: succinate dehydrogenase complex subunit B
TNNT2: cardiac troponin T2
USH2A: Usher syndrome 2A (autosomal recessive, mild)

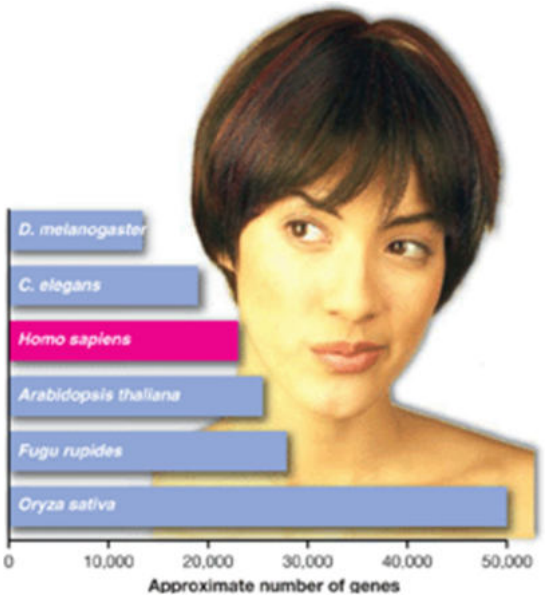


p-Arm

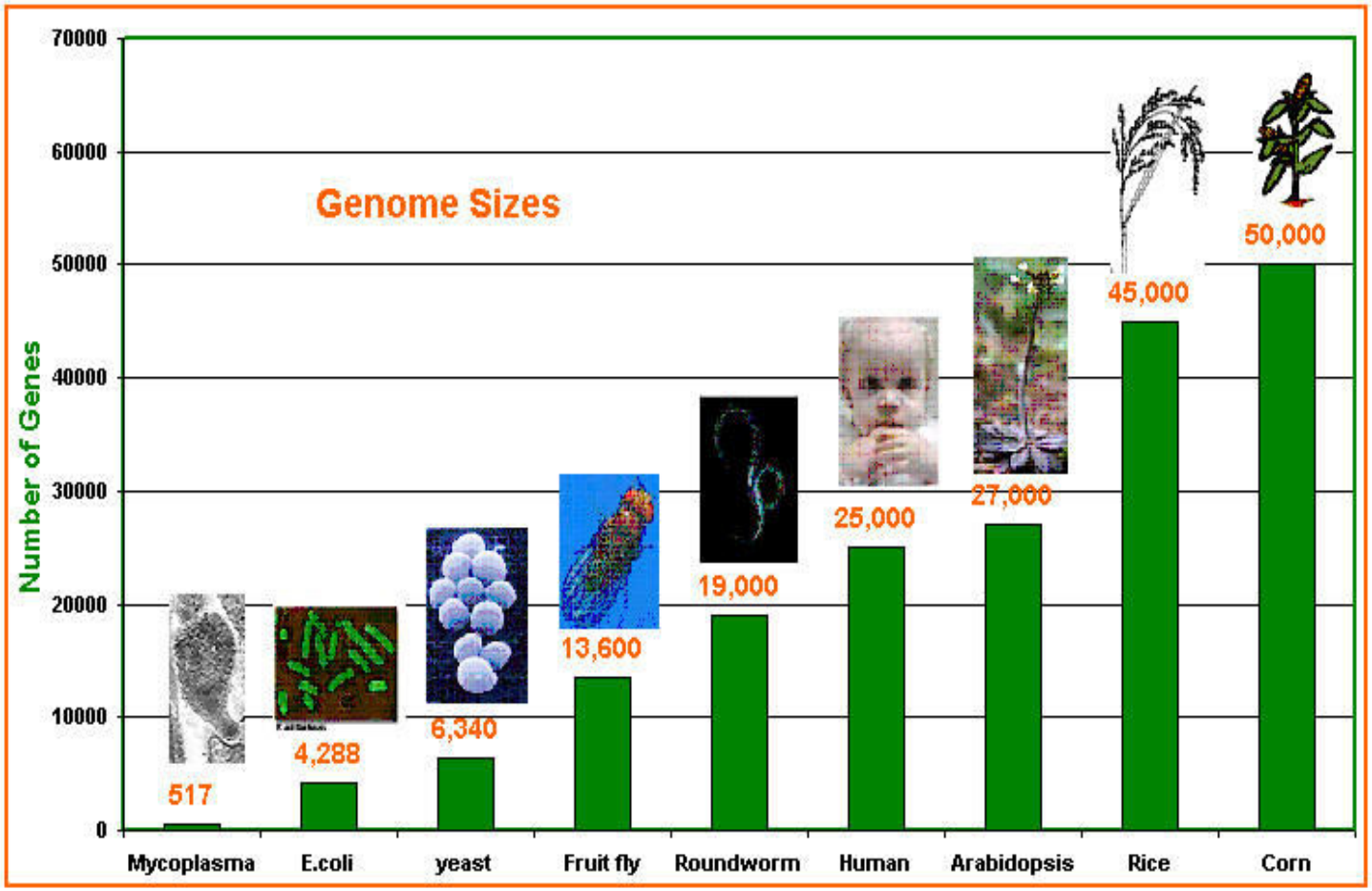
ACADM: acyl-Coenzyme A dehydrogenase, C-4 to C-12 straight chain
- COL11A1: collagen, type XI, alpha 1
- CPT2: carnitine palmitoyltransferase II
- DBT: dihydrolipoamide branched chain transacylase E2
- : DIRAS family, GTP-binding RAS-like 3
- : espin (autosomal recessive deafness 36)
- GALE: UDP-galactose-4-epimerase
- GJB3: gap junction protein, beta 3, 31kDa (connexin 31)
- : 3-hydroxymethyl-3-methylglutaryl-Coenzyme A lyase (hydroxymethylglutaricaciduria)
- KCNQ4: potassium voltage-gated channel, KQT-like subfamily, member 4
- KIF1B: kinesin family member 1B
- MFN2: mitofusin 2
- MTHFR: 5,10-methylenetetrahydrofolate reductase (NADPH)
- MUTYH: mutY homolog (E. coli)
- NGF: Nerve Growth Factor
- PARK7: Parkinson disease (autosomal recessive, early onset) 7
- PINK1: PTEN induced putative kinase 1
- PLOD1: procollagen-lysine 1, 2-oxoglutarate 5-dioxygenase 1
- TSHB: thyroid stimulating hormone, beta
- UROD: uroporphyrinogen decarboxylase (the gene for porphyria cutanea tarda)

The **C-value enigma** or **C-value paradox** is a term used to describe **the complex puzzle surrounding the extensive variation in nuclear genome size among eukaryotc species**. At the center of the C-value enigma is the observation that **genome size does not correlate with organismal complexity; for example, some single-celled protists have genomes much larger than that of humans.**



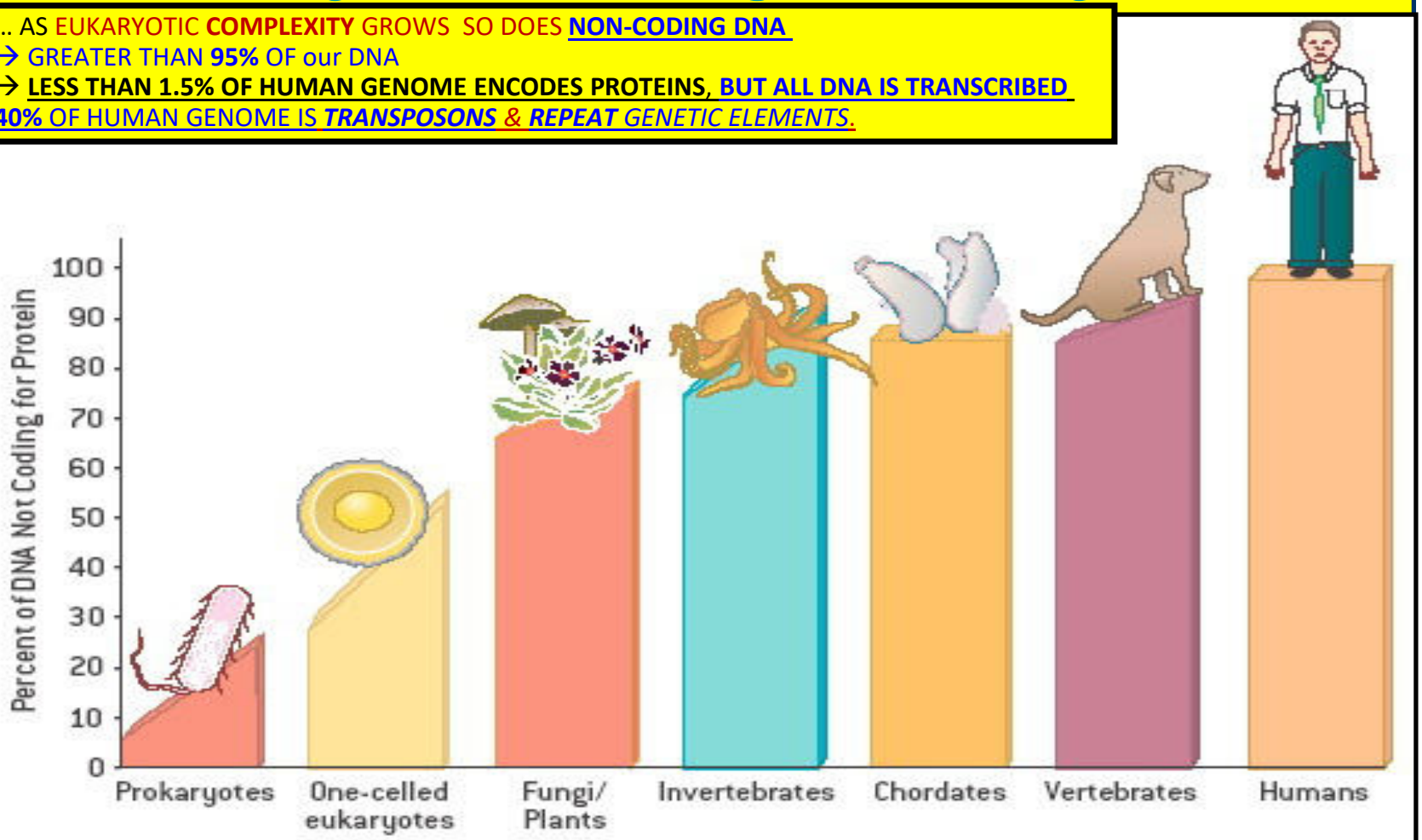


Prior to the human genome sequence, the expected gene number most commonly cited was 100,000, even though lower estimates were becoming increasingly common … As a result, the finding of **20,000-25,000 genes in the human genome** has inspired extensive commentary.
Some authors even characterized this ***as a new "G-value paradox" or "N-value paradox",*** in reference to the "C-value paradox"



Percentage of ***non-coding DNA*** during evolution

… AS EUKARYOTIC **COMPLEXITY** GROWS SO DOES **NON-CODING DNA**
→ GREATER THAN **95%** OF our DNA
→ **LESS THAN 1.5% OF HUMAN GENOME ENCODES PROTEINS, BUT ALL DNA IS TRANSCRIBED**
40% OF HUMAN GENOME IS ***TRANSPOSONS*** & ***REPEAT*** *GENETIC ELEMENTS*.



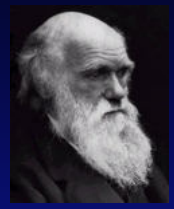
NONPROTEIN-CODING SEQUENCES make up only a small fraction of the DNA of prokaryotes. Among eukaryotes, as their complexity increases, generally so, too, does the proportion of their DNA that does not code for protein. The noncoding sequences have been considered junk, but perhaps it actually helps to explain organisms' complexity.

FOREWORD 3

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

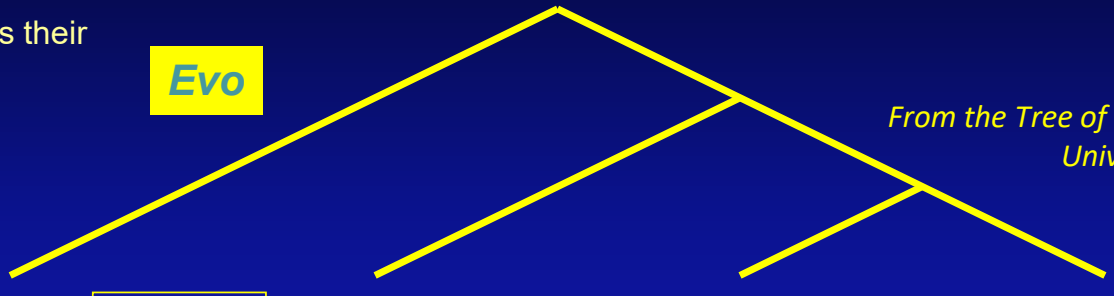
We are quite stable (for millions of years) both genetically and phenotypically

Species *phylogeny*



From the Tree of the Life Website, University of Arizona

Evo



Orangutan

Gorilla

Chimpanzee

Human

EPIGENETICS > GENETICS

Sanger Institute

FOREWORD 4

Nothing in Biology Makes Sense Except in the Light of Evolution

THEODOSIUS DOBZHANSKY

As recently as 1966, sheik Abd el Aziz bin Baz asked the king of Saudi Arabia to suppress a heresy that was spreading in his land. Wrote the sheik:

"The Holy Koran, the Prophet's teachings, the majority of Islamic scientists, and the actual facts all prove that the sun is running in its orbit . . . and that the earth is fixed and stable, spread out by God for his mankind. . . . Anyone who professed otherwise would utter a charge of falsehood toward God, the Koran, and the Prophet."

The good sheik evidently holds the Copernican theory to be a "mere theory," not a "fact." In this he is technically correct. A theory can be verified by a mass of facts, but it becomes a proven theory, not a fact. The sheik was perhaps unaware that the Space Age had begun before he asked the king to suppress the Copernican heresy. The sphericity of the earth had been seen by astronauts, and even by many earth-bound people on their television screens. Perhaps the sheik could retort that those who venture beyond the confines of God's earth suffer hallucinations, and that the earth is really flat.

Parts of the Copernican world model, such as the contention that the earth rotates around the sun, and not vice versa, have not been verified by direct observations even to the extent the sphericity of the earth has been. Yet scientists accept the model as an accurate representation of reality. Why? Because it makes sense of a multitude of facts which are otherwise meaningless or extravagant. To nonspecialists most of these facts are unfamiliar. Why then do we accept the "mere theory" that the earth is a sphere revolving around a spherical sun? Are we simply submitting to authority? Not quite: we know that those who took time to study the evidence found it convincing.

The good sheik is probably ignorant of the evidence. Even more likely, he is so hopelessly biased that no amount of evidence would impress him. Anyway, it would be sheer waste of time to attempt to convince him. The Koran and the Bible do not contradict Copernicus, nor does Copernicus contradict them. It is ludicrous to mistake the Bible and the Koran for primers of natural science. They treat of matters even more important: the meaning of man and his relations to God. They are written in poetic symbols that were understandable to people of the age when they were written, as well as to peoples of all other ages. The king of Arabia did not comply with the sheik's demand. He knew that some people fear enlightenment, because enlightenment threatens their vested interests. Education is not to be used to promote obscurantism.

The earth is not the geometric center of the universe, although it may be its spiritual center. It is a mere speck of dust in cosmic spaces. Contrary to Bishop Ussher's calculations, the world did not appear in approximately its present state in 4004 B.C. The estimates of the age of the universe given by modern cosmologists are still only rough approximations, which are revised (usually upward) as the methods of estimation are refined. Some cosmologists take the universe to be about 10 billion years old; others suppose that it may have existed, and will continue to exist, eternally. The origin of life on earth is dated tentatively between 3 and 5 billion years ago; manlike beings appeared relatively quite recently, between 2 and 4 million years ago. The estimates of the age of the earth, of the duration of the geologic and paleontologic eras, and of the antiquity of man's ancestors are now based mainly on radiometric evidence—the proportions of isotopes of certain chemical elements in rocks suitable for such studies.

One of the world's leading geneticists, Theodosius Dobzhansky is professor emeritus, Rockefeller University, and adjunct professor of genetics, University of California, Davis 95616. Born in Russia, in 1900, he is a graduate of the University of Kiev and taught (with J. Philipchenko) at the University of Leningrad before coming to the U.S., in 1927; thereafter he taught at Columbia University and the California Institute of Technology before joining the Rockefeller faculty, in 1962. He has been president of the Genetics Society of America, the American Society of Naturalists, the Society for the Study of Evolution, the American Society of Zoologists, and the American Teilhard de Chardin Association. Among his many honors are the National Medal of Science (1964) and the Gold Medal Award for Distinguished Achievement in Science (1969). He holds 18 honorary doctorates from universities in this country and abroad. Among his well-known books are *The Biological Basis of Human Freedom* (1956) and *Mankind Evolving* (1962). The present paper was presented at the 1972 AABT convention.

1 *Diversity of Living Beings*

The diversity and the unity of life are equally striking and meaningful aspects of the living world.

2 *Unity of Life*

The unity of life is no less remarkable than its diversity. Most forms of life are similar in many respects. The universal biologic similarities are particularly striking in the biochemical dimension. From viruses to man, heredity is coded in just two, chemically related substances: DNA and RNA. The genetic code is as simple as it is universal. There are

Minimal mutational distances between human cytochrome C and the cytochrome C of other living beings are as follows:

Monkey	1	Chicken	18
Dog	13	Penguin	18
Horse	17	Turtle	19
Donkey	16	Rattlesnake	20
Pig	13	Fish (tuna)	31
Rabbit	12	Fly	33
Kangaroo	12	Moth	36
Duck	17	Mold	63
Pigeon	16	Yeast	56

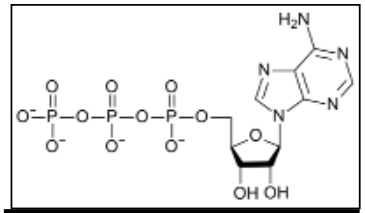
3 *Comparative Anatomy and Embryology*

The biochemical universals are the most impressive and the most recently discovered, but certainly they are not the only vestiges of creation by means of evolution. Comparative anatomy and embryology proclaim the evolutionary origins of the present inhabitants of the world. In 1555 Pierre Belon established the presence of homologous bones in the superficially very different skeletons of man and bird.

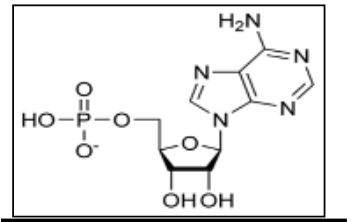
Strength and Acceptance of the Theory

Seen in the light of evolution, biology is, perhaps, intellectually the most satisfying and inspiring science. Without that light it becomes a pile of sundry facts—some of them interesting or curious but making no meaningful picture as a whole.

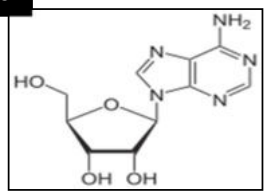
$E = Mc^2 = \mathbf{I}$



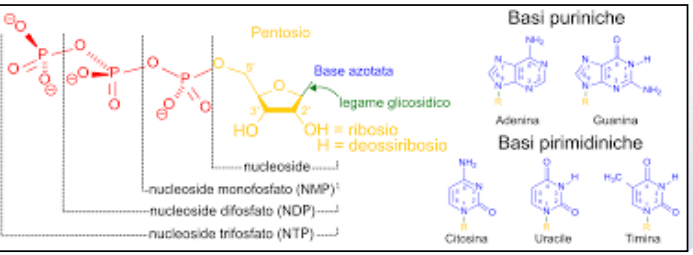
ATP - Adenosina trifosfato

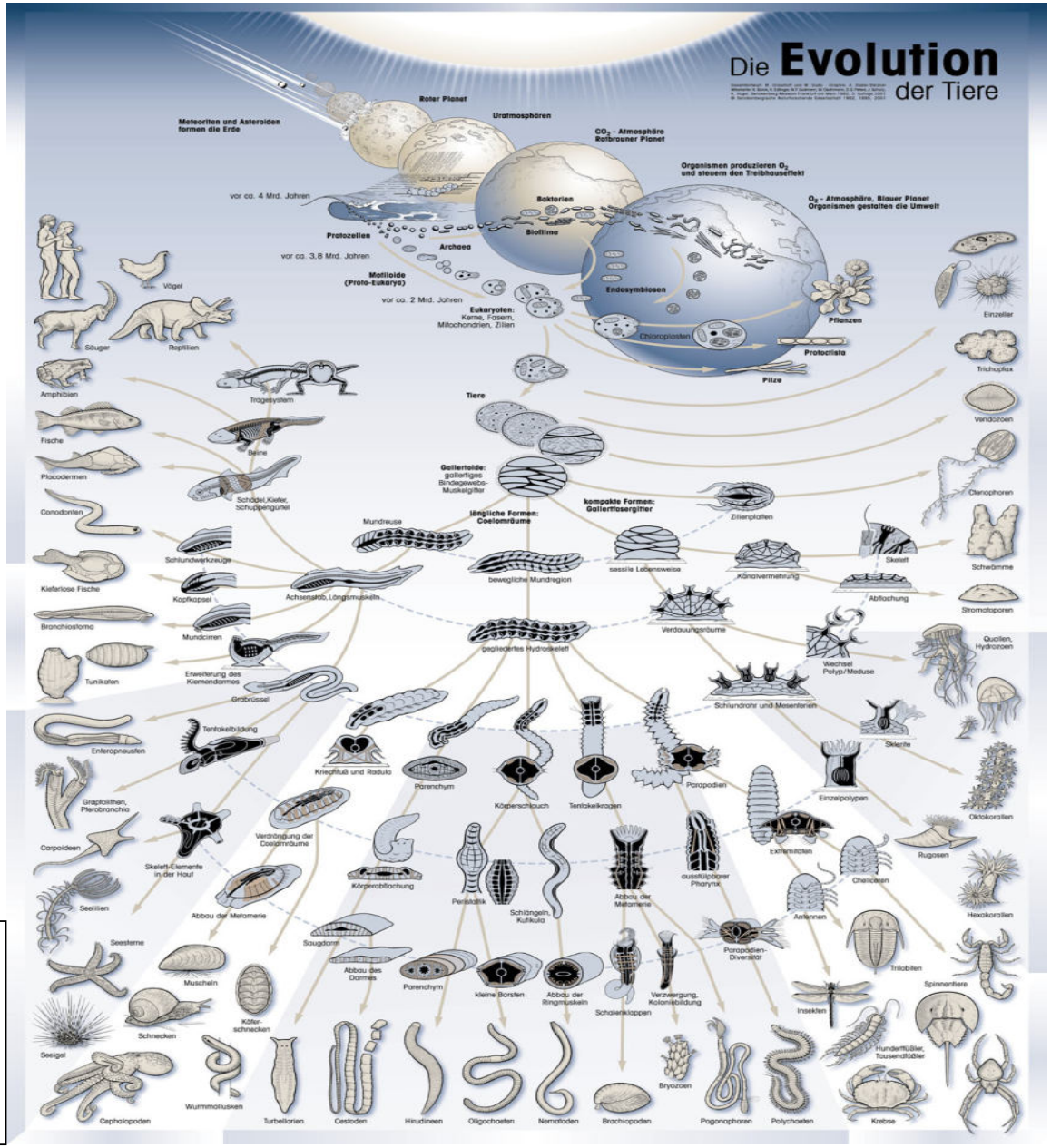


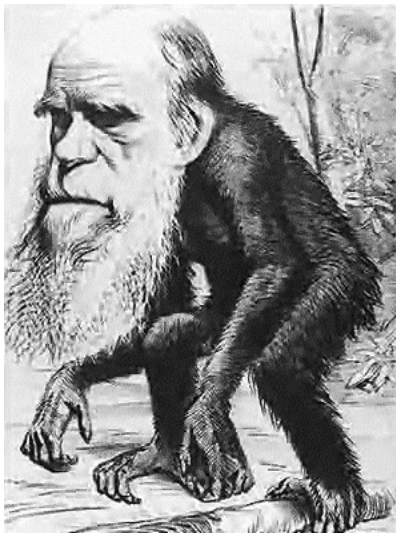
AMP - Adenosin monofosfato

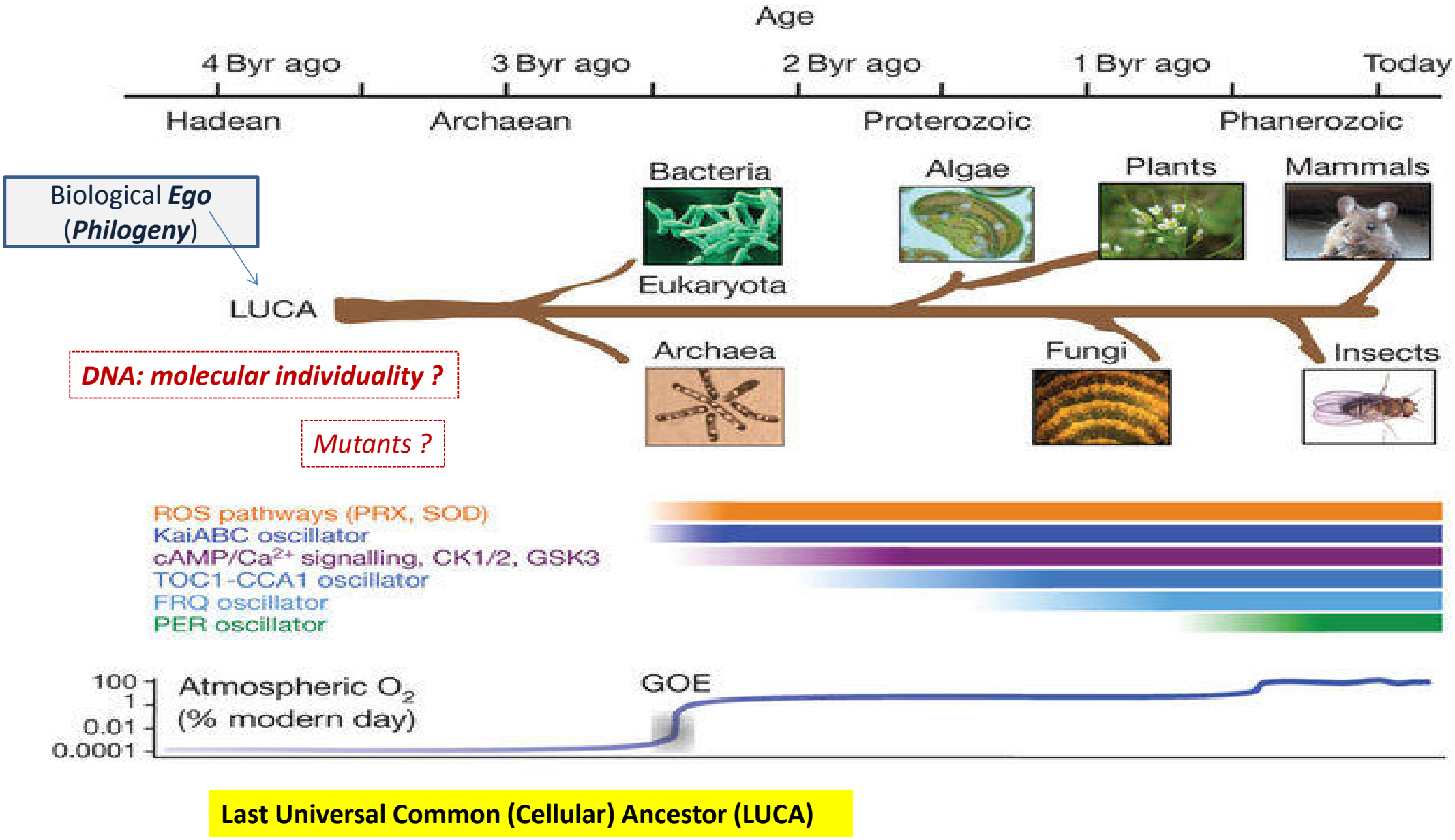


L'***adenosina*** è un nucleoside che ha un ruolo fondamentale
- sia nel **trasferimento di *Energia*** (ATP --> ADP),
- sia nella costituzione degli acidi nucleici (***Informazione***),
- sia nella **trasduzione del segnale** (cAMP = secondo messaggero)



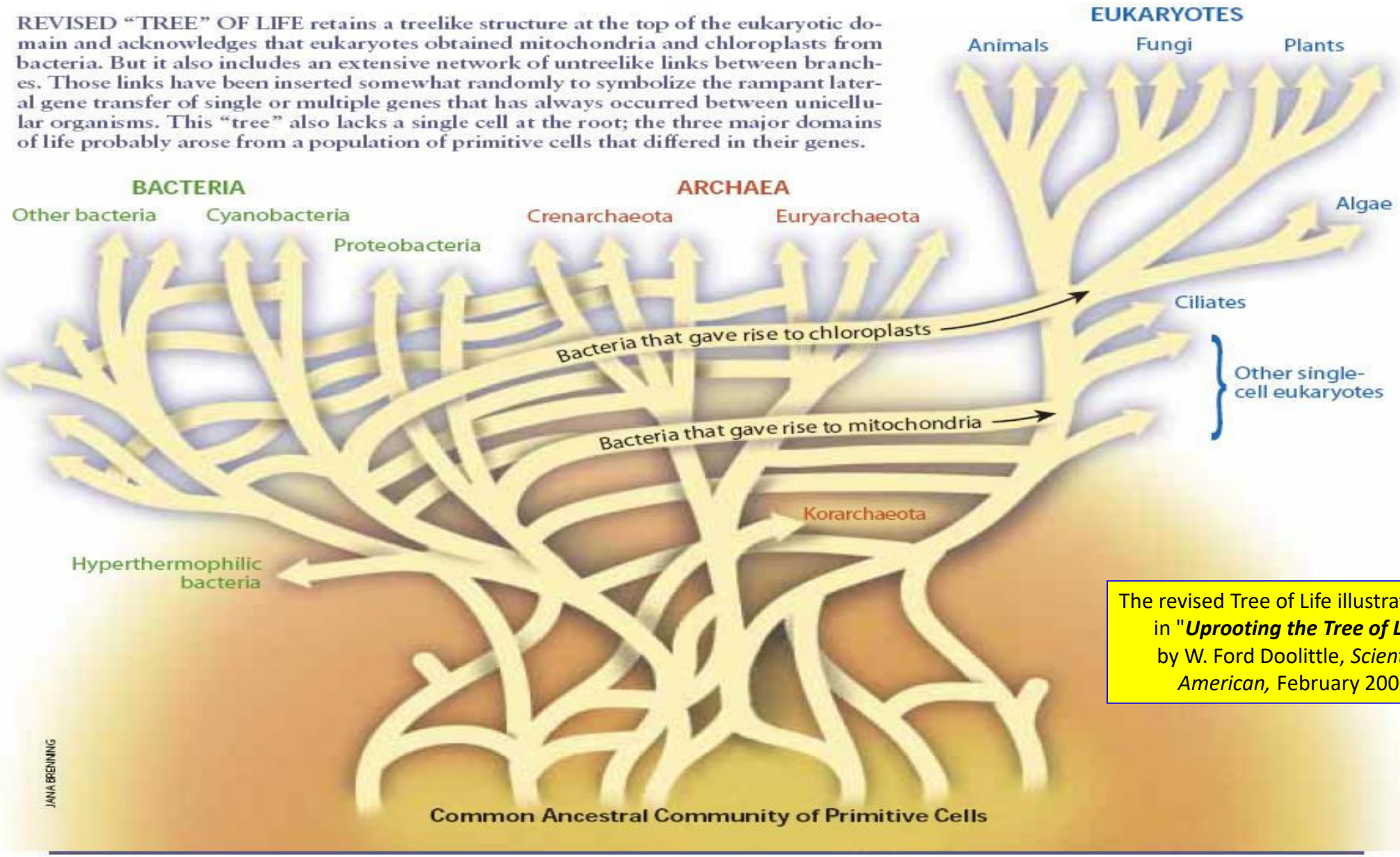




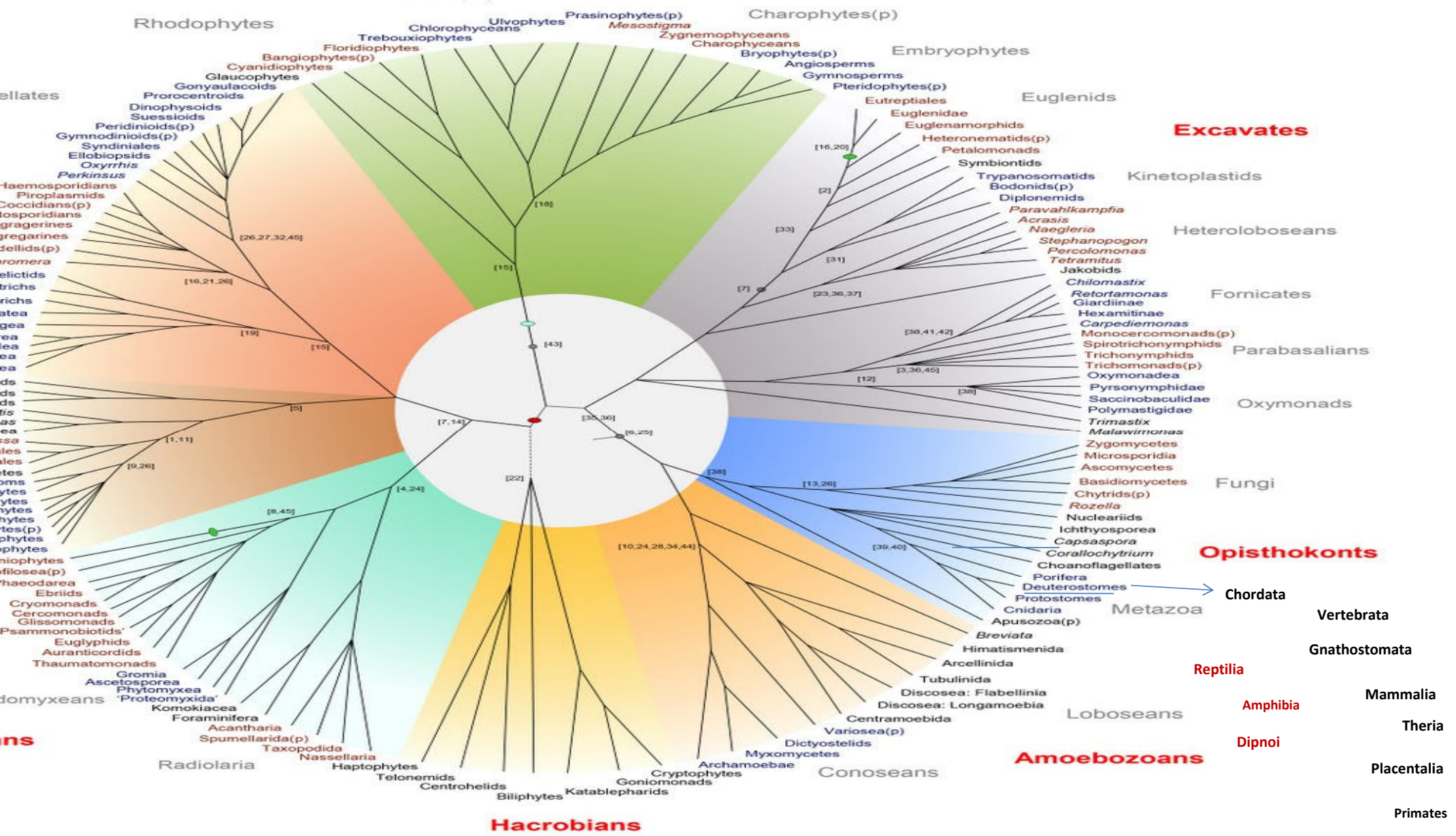


Last Universal Common (Cellular) Ancestor (LUCA)

REVISED "TREE" OF LIFE retains a treelike structure at the top of the eukaryotic domain and acknowledges that eukaryotes obtained mitochondria and chloroplasts from bacteria. But it also includes an extensive network of untreelike links between branches. Those links have been inserted somewhat randomly to symbolize the rampant lateral gene transfer of single or multiple genes that has always occurred between unicellular organisms. This "tree" also lacks a single cell at the root; the three major domains of life probably arose from a population of primitive cells that differed in their genes.



The revised Tree of Life illustrated in "***Uprooting the Tree of Life***" by W. Ford Doolittle, *Scientific American,* February 2000


Rhodophytes
Chlorophyceans
Ulvophytes
Prasinophytes(p)
Mesostigma
Charophytes(p)
Zygnemophyceans
Charophyceans
Trebouxiophytes
Floridiophytes
Bangiophytes(p)
Cyanidiophytes
Glaucophytes
Gonyaulacoids
Prorocentroids
Dinophysoids
Suessioids
Peridinioids(p)
Gymnodinioids(p)
Syndiniales
Ellobiopsids
Oxyrrhis
Perkinsus
Haemosporidians
Piroplasmids
Coccidians(p)
Hosporidians
gregarines
gregarines
dellids(p)
romera
elictids
richs
richs
atea
gea
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les
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hytes
tes(p)
phytes
phytes
niophytes
filosea(p)
haeodarea
Ebriids
Cryomonads
Cercomonads
Glissomonads
'Psammonobiotids'
Euglyphids
Auranticordids
Thaumatomonads
Gromia
Ascetosporea
Phytomyxea
'Proteomyxida'
domyxeans
Komokiacea
Foraminifera
Acantharia
Spumellarida(p)
Taxopodida
Nassellaria
ns
Radiolaria
Haptophytes
Telonemids
Centrohelids
Biliphytes
Katablepharids
Goniomonads
Cryptophytes
Archamoebae
Myxomycetes
Dictyostelids
Variosea(p)
Centramoebida
Discosea: Longamoebia
Discosea: Flabellinia
Tubulinida
Arcellinida
Himatismenida
Breviata
Apusozoa(p)
Cnidaria
Protostomes
Deuterostomes
Porifera
Choanoflagellates
Corallochytrium
Capsaspora
Ichthyosporea
Nucleariids
Rozella
Chytrids(p)
Basidiomycetes
Ascomycetes
Microsporidia
Zygomycetes
Malawimonas
Trimastix
Polymastigidae
Saccinobaculidae
Pyrsonymphidae
Oxymonadea
Trichomonads(p)
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Spirotrichonymphids
Monocercomonads(p)
Carpediemonas
Giardiinae
Retortamonas
Chilomastix
Jakobids
Tetramitus
Percolomonas
Stephanopogon
Naegleria
Acrasis
Paravahlkampfia
Diplonemids
Bodonids(p)
Trypanosomatids
Symbiontids
Petalomonads
Heteronematids(p)
Euglenamorphids
Euglenidae
Eutreptiales
Pteridophytes(p)
Gymnosperms
Angiosperms
Bryophytes(p)
Embryophytes
Hacrobians
Conoseans
Loboseans
Amoebozoans
Metazoa
Fungi
Opisthokonts
Euglenids
Kinetoplastids
Heteroloboseans
Fornicates
Parabasalians
Oxymonads
Excavates
Chordata
Vertebrata
Gnathostomata
Reptilia
Mammalia
Amphibia
Theria
Dipnoi
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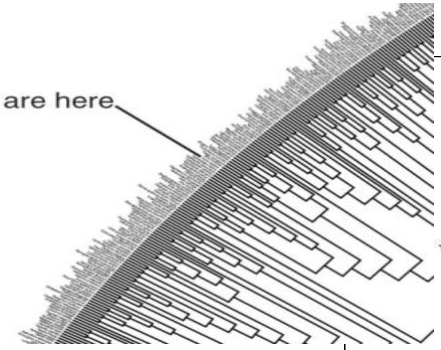
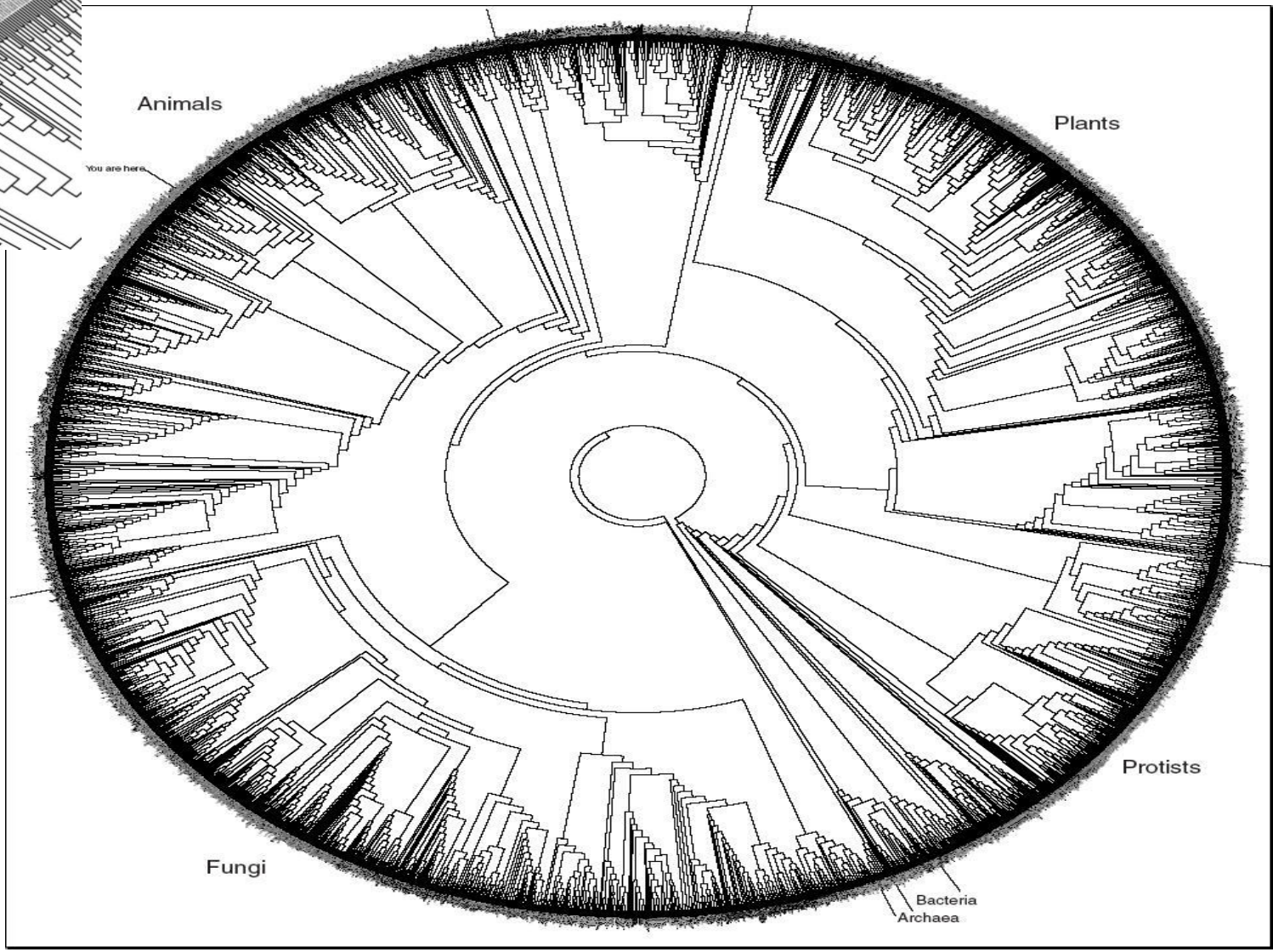
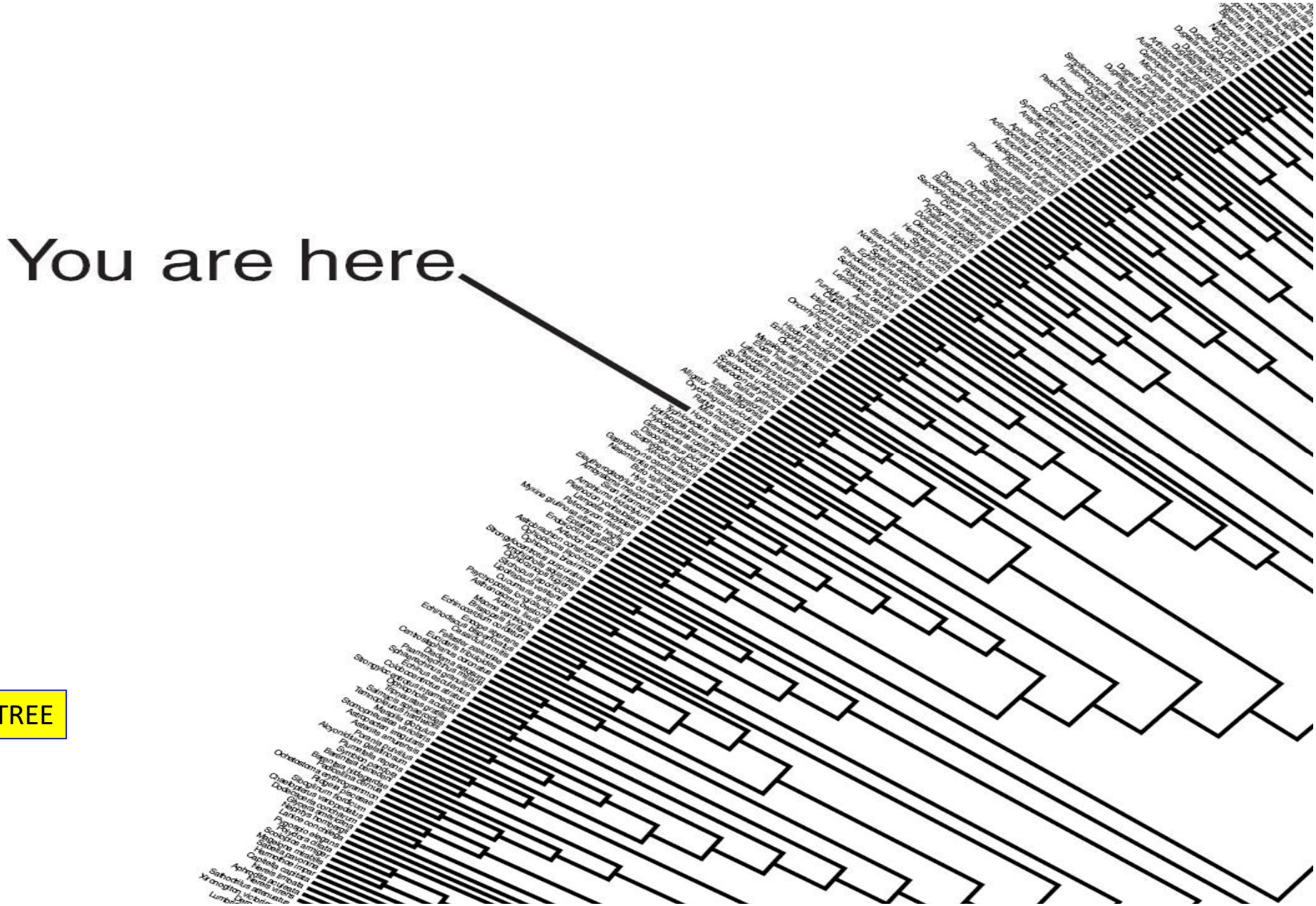




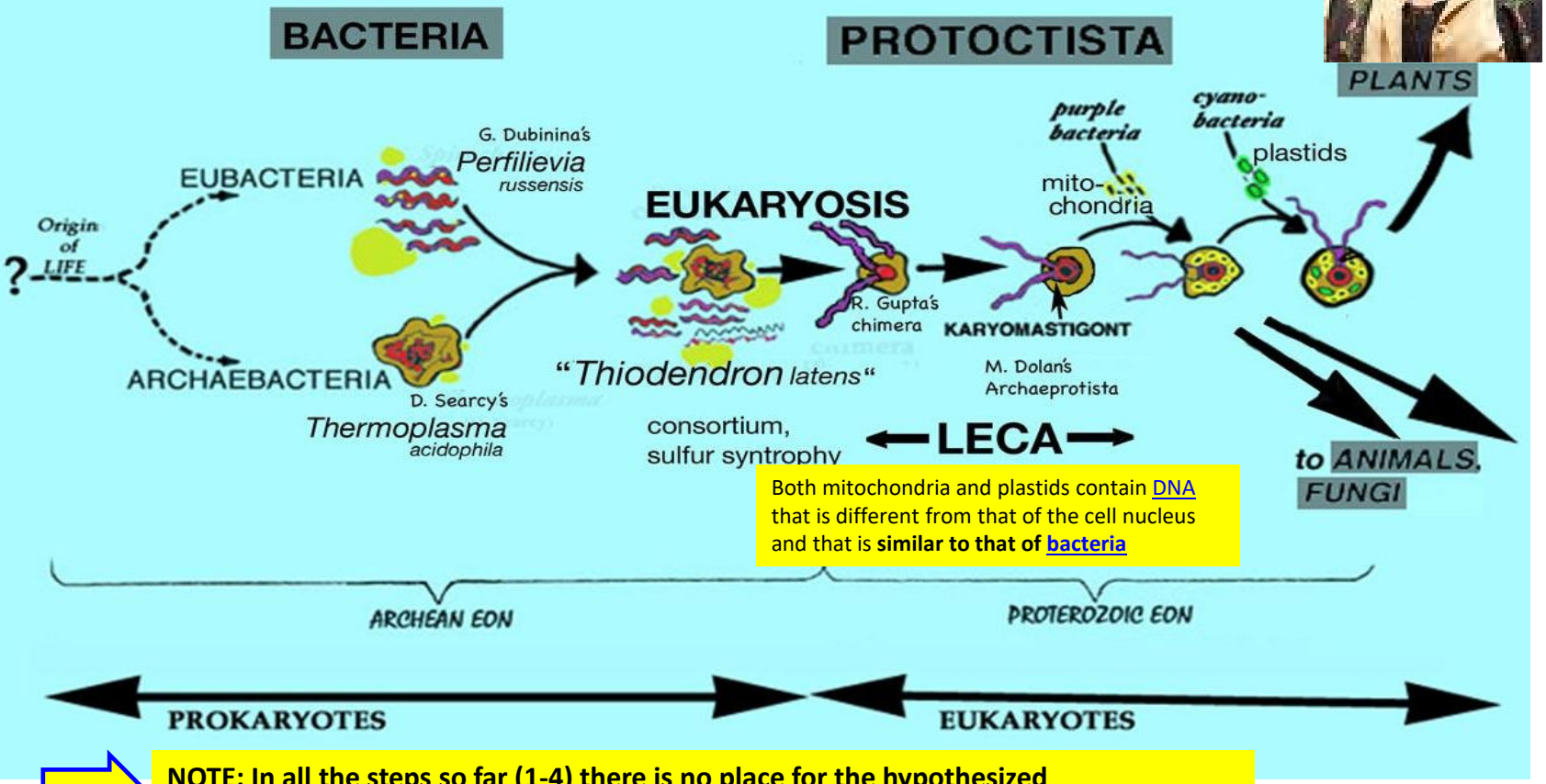
David Hillis TREE



David Hillis TREE

The incorporation of microbial symbionts, and the progressive formation of eukaryotic cells .. and then the formation of multicellular organisms, etc.

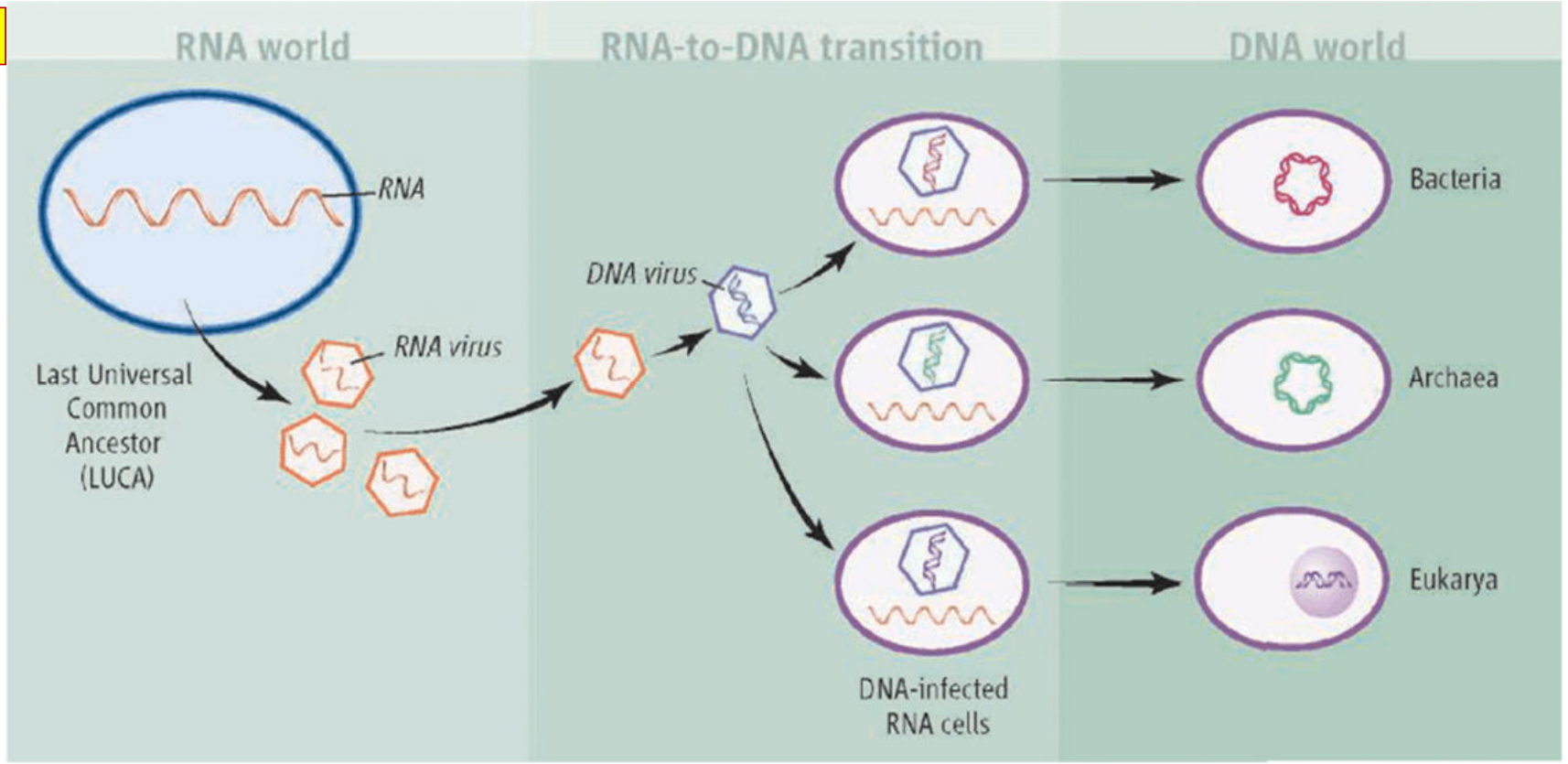
The **endosymbiotic theory** was first articulated by the Russian botanist Konstantin Mereschkowski in 1905 and substantiated with microbiological evidence by Lynn Margulis in 1967.. According to Margulis and Dorion Sagan "**Life did not take over the globe by combat, but by *networking*" (i.e., by *cooperation*).**



Both mitochondria and plastids contain DNA that is different from that of the cell nucleus and that is **similar to that of bacteria**

NOTE: In all the steps so far (1-4) there is no place for the hypothesized stochastic genetic mutations as a key driver of the process

And *Viruses*?



Forterre proposes that **all living organisms share a common ancestor that stored its genetic information in RNA. Some of its genes evolved into viruses**.
Later, **some of those viruses evolved DNA as a way to defend their genes from attack, and DNA-based viruses became incorporated into hosts**.
Host genes were then transferred onto viral chromosomes and shared. In the process, the three major domains of DNA-based life emerged

Did DNA Come From Viruses? ***SCIENCE*** *12 May 2006: vol. 312 no. 5775 870-872*

PROCEEDINGS OF THE AMERICAN PHILOSOPHICAL SOCIETY VOL. 148, NO. 3, SEPTEMBER 2004

Can Viruses Make Us Human?[1]

A hugely **underrated role** is played by the **(retro)viruses** and by **HGT** (horizontal transfer) of mobile sequences: in particular **in higher organisms major acquisitions and transformations are produced by gene insertions ..**

LUIS P. VILLARREAL
Director, Center for Virus Research
University of California at Irvine

THIS QUESTION WILL SEEM preposterous to most. Viruses are molecular genetic parasites and are mostly recognized for their ability to induce disease in their host. Their effect on host evolution has long been thought to be like that of a predator on its prey, eliminating the host with weakened defenses. How can we propose any constructive role for viruses? Many viruses, however, can infect their host in a stable and persisting manner, generally with no disease, often for the life of the host. Such viruses can bring to bear onto their host the viral seeds of genetic creation. For such persisting viruses to successfully colonize their host, they must superimpose a complex viral molecular genetic identity onto their host.

A ***key-example***: the ***placenta***. ***Syncytiotrophoblast*** being the **product of a protein encoded by a retrovirus… mammals are the "product" of the insertion** of retroviruses' in genomes of previous organisms...

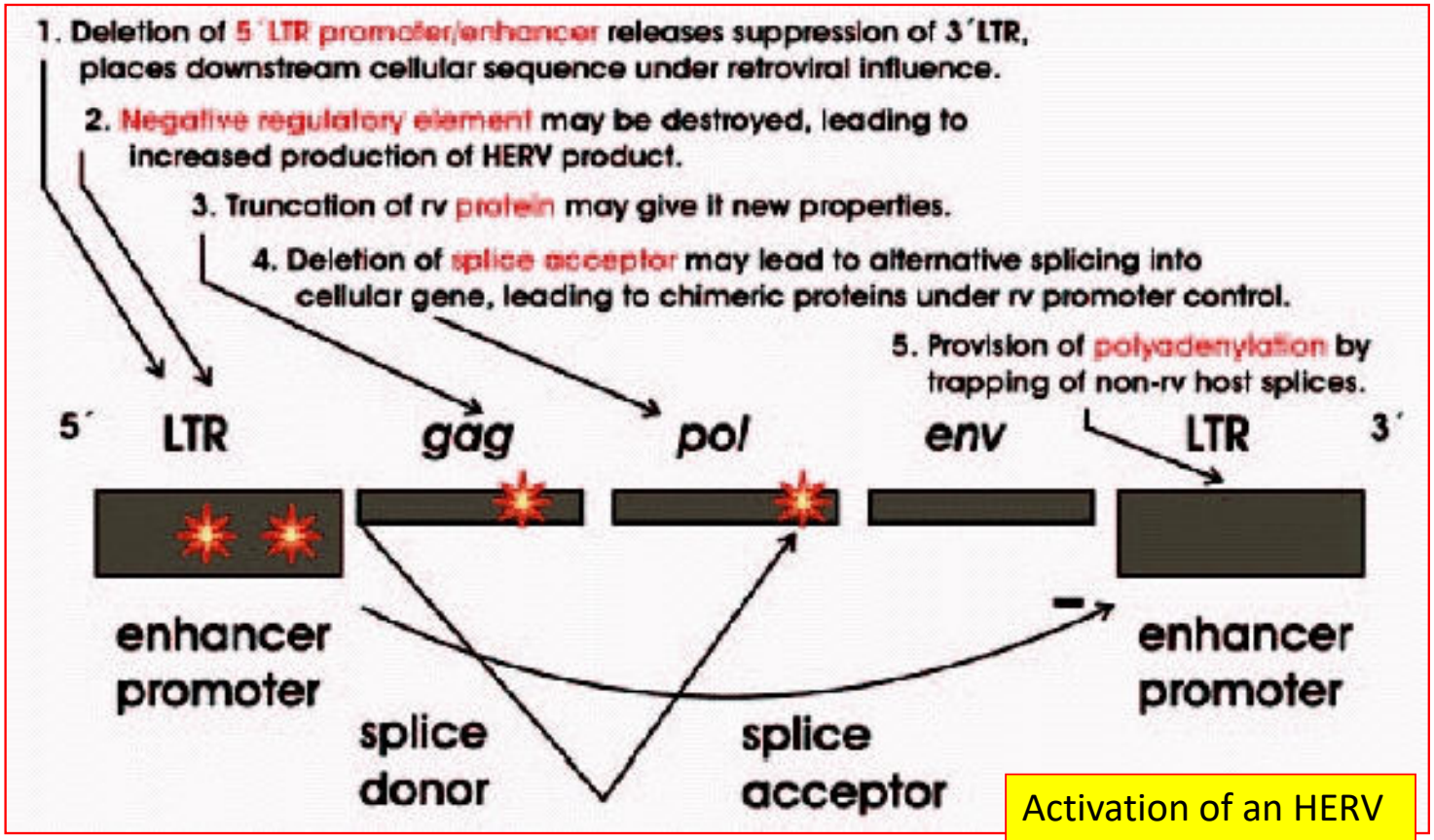
« Hotwiring the Human Genome: The Programming Language of Life | Main | MIT Scientists Mimic Plants' Energy Storage System -Discovery to Unleash Solar Revolution »

August 01, 2008

Were Ancient Viruses a Key to Human Evolution?

When the mapping of the human genome was completed in 2003, researchers discovered a shocking fact: our bodies are littered with the shards of retroviruses, fragments of the chemical code from which all genetic material is made. This discovery has created a new discipline, paleovirology, which seeks to better understand the impact of modern diseases by studying the genetic history of ancient viruses.

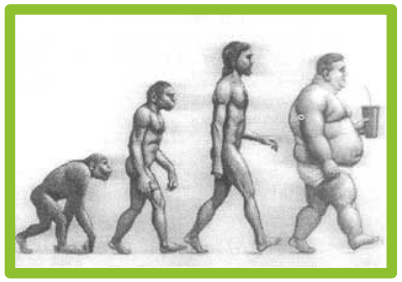
… playing a **reactive-adaptive role**.. **processing / engineering** the entire genome (→ Shapiro's ***Natural Genetic Engineering***)



Activation of an HERV through mutation

Retroviruses are our more intimate symbionts

FOREWORD 5



Phylogeny

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

Mismatch

Ontogeny

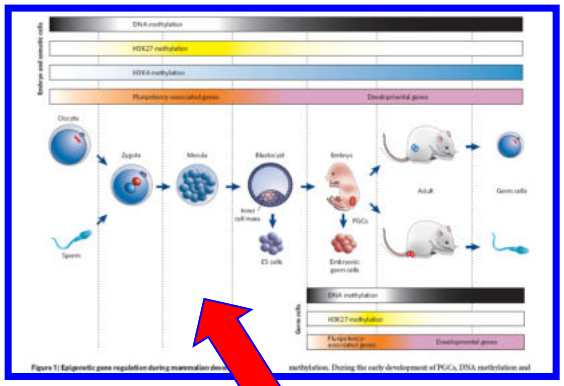
And of **9 months of an individual development**

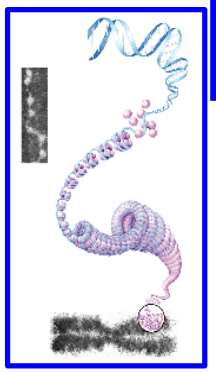
our **epigenome** being the product of nine months of ***cellular and tissue programming*** (**adaptive** to an environment that is rapidly changing)..

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

Devo-Evo

Ontogeny *recapitulates* (***anticipates***) ***Phylogeny***

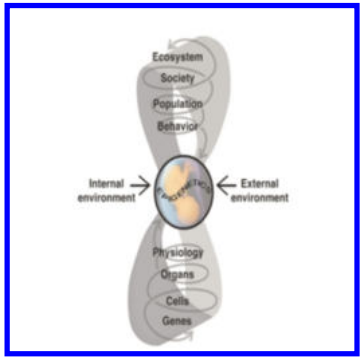




A ***major risk***: the **EDCs** and other ***xenobiotics*** (***not*** being the product of ***molecular coevolution***) can interfere at this level, acting as ***pseudo-morphogens***

The 7 keywords: from genetics to *epigenetics*

3



Fetal programming

2

Environment

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

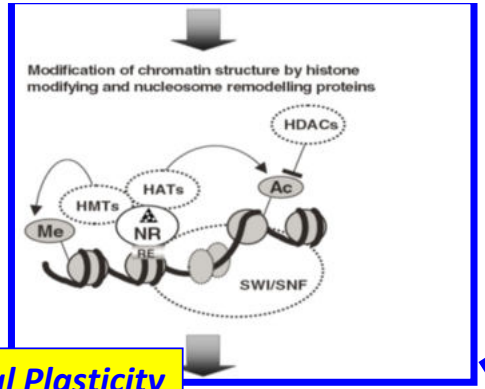
1

From Genetics to Epigenetics

Ontogeny*

4

Developmental Plasticity

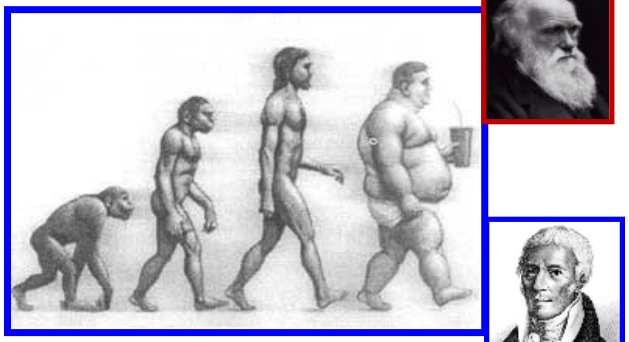


Phylogeny*

Evolutionary Medicine

5

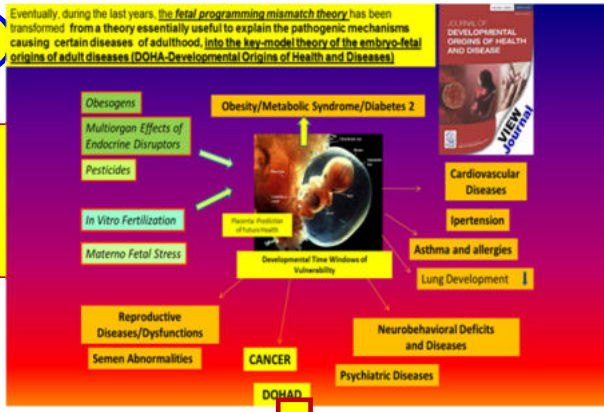
Devo → Evo



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

Epi-genetic Mismatch DOHA

6



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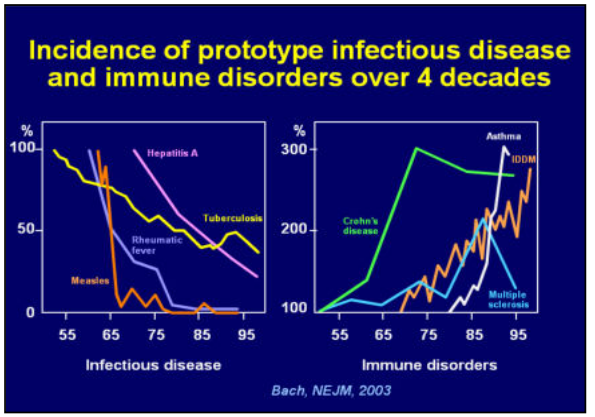
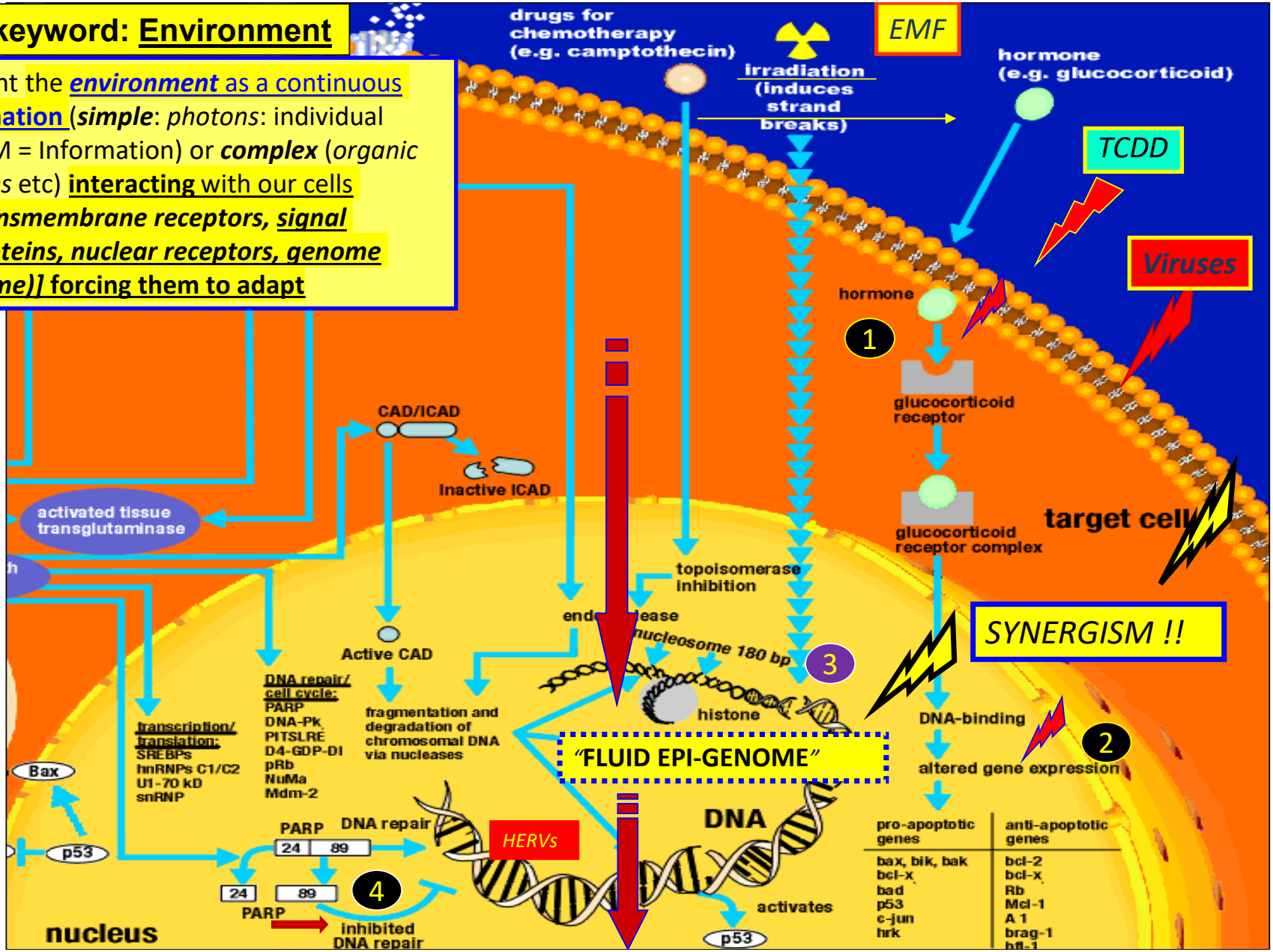


XXI Century Epidemiological Transition

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

The **second keyword: Environment**

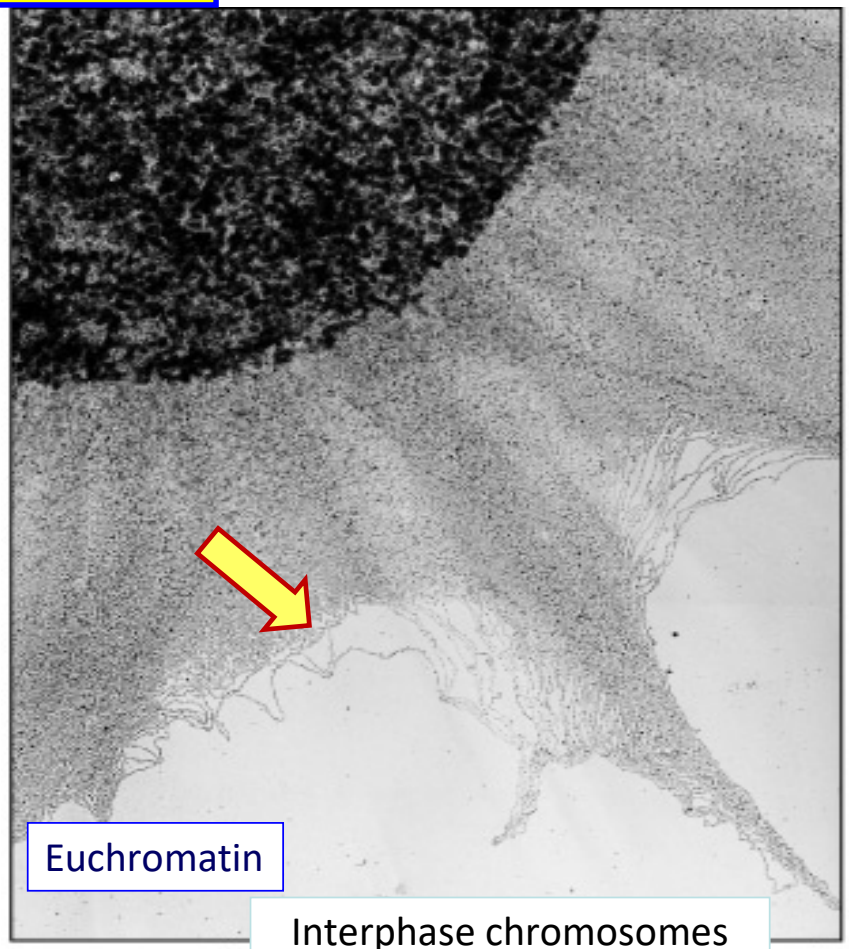
We may represent the ***environment*** as a continuous stream of **information** (***simple***: *photons*: individual packages of E = M = Information) or ***complex*** (*organic molecules, viruses* etc) **interacting** with our cells [***membrane /transmembrane receptors, signal transduction proteins,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

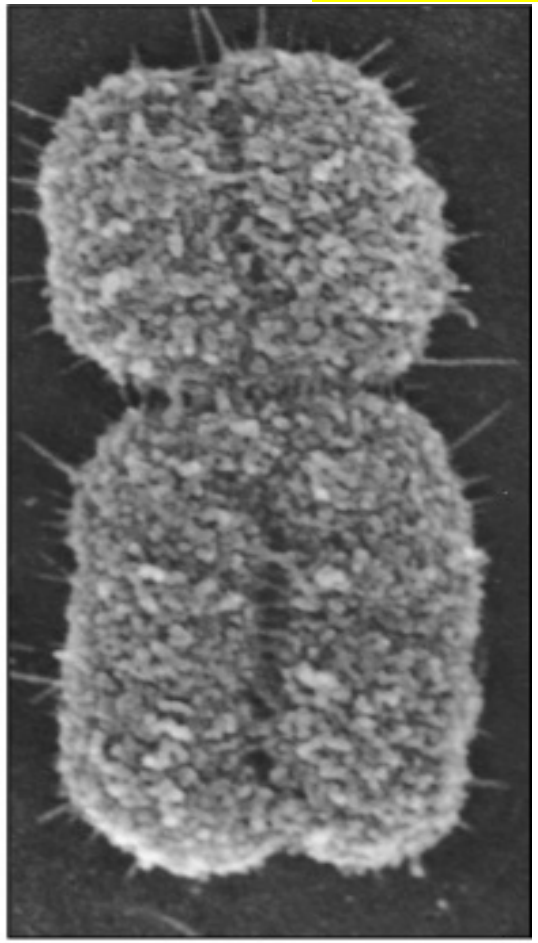


The first keyword: **Epigenetics**

Heterochromatin

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



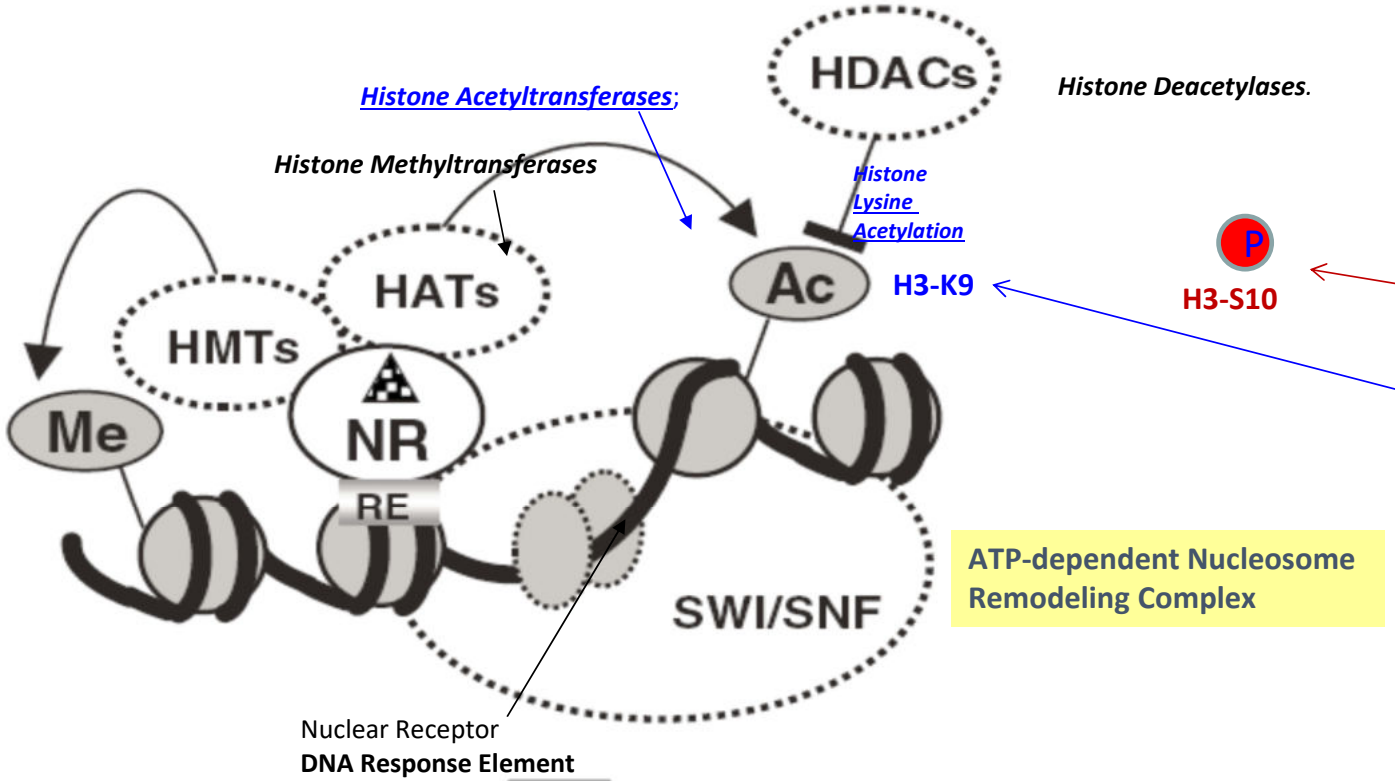


Mitotic chromosome

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

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

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



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

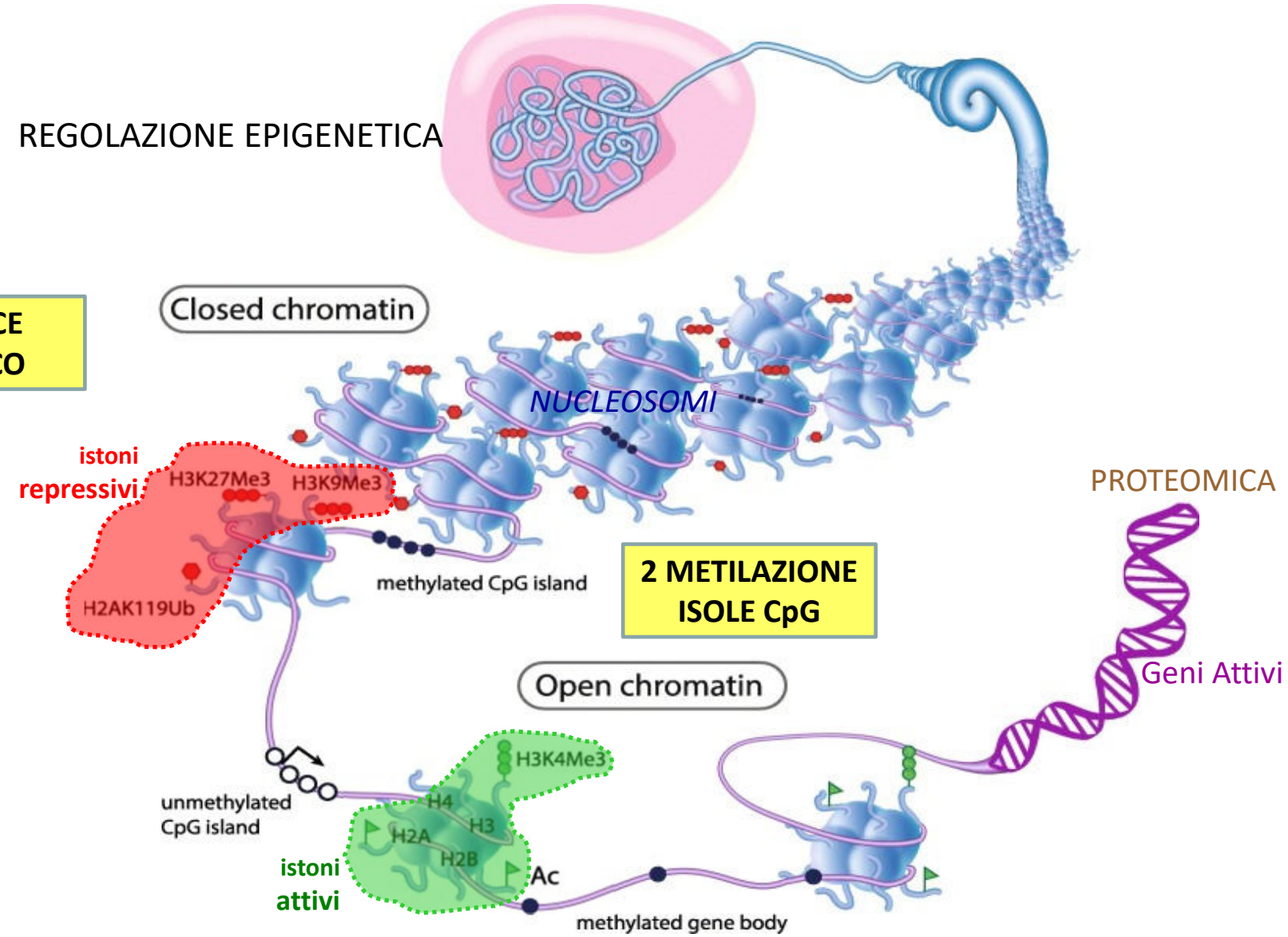
The resulting **rapid, defensive alterations in gene activity require the transmission of a signal directly to the histones** present in the **chromatin of stress response genes**:

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

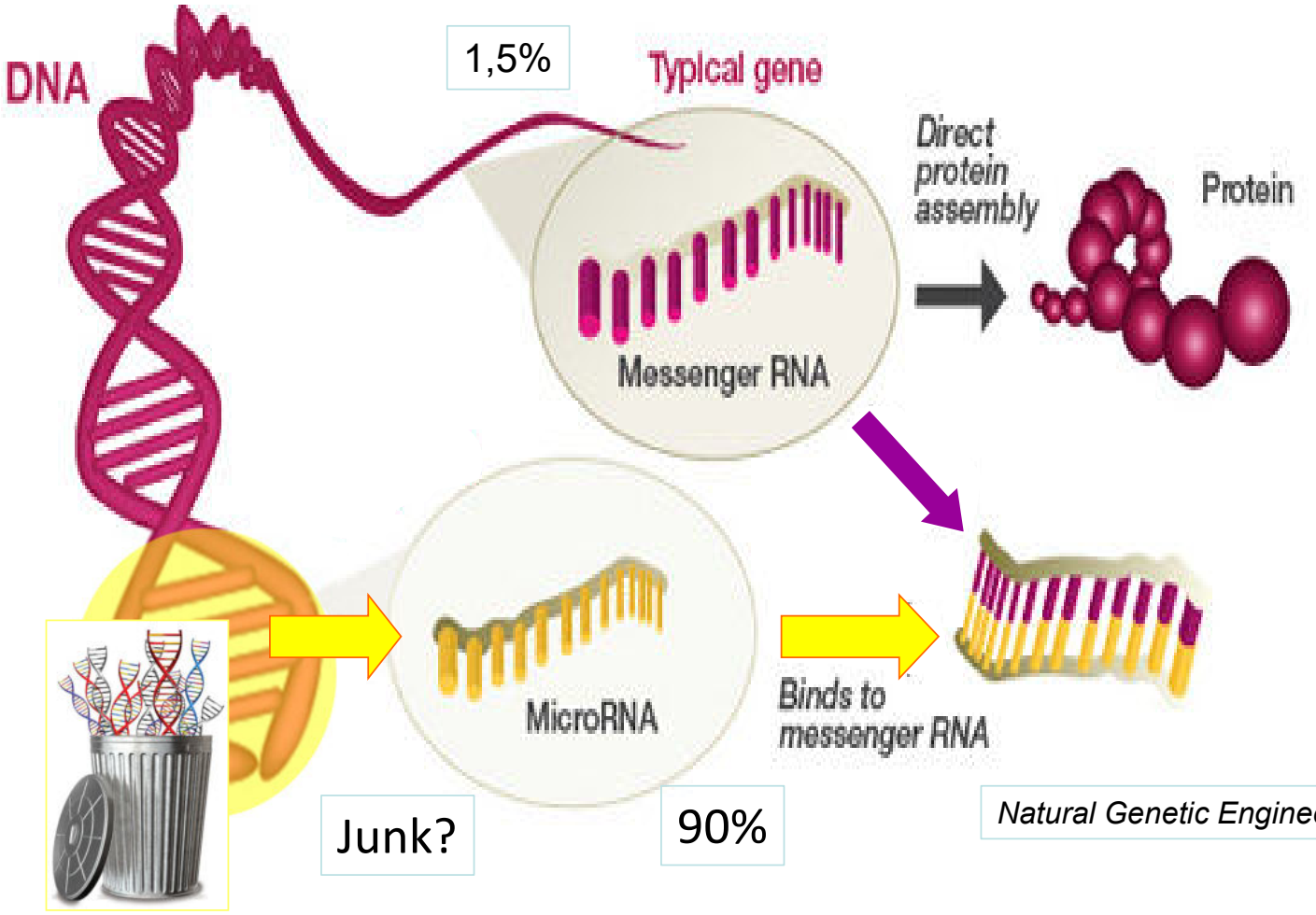
Chromatin itself is the direct target of many toxicants… toxicant-induced perturbations in chromatin structure may precipitate adverse effects.. Forcing the genome to change

REGOLAZIONE EPIGENETICA

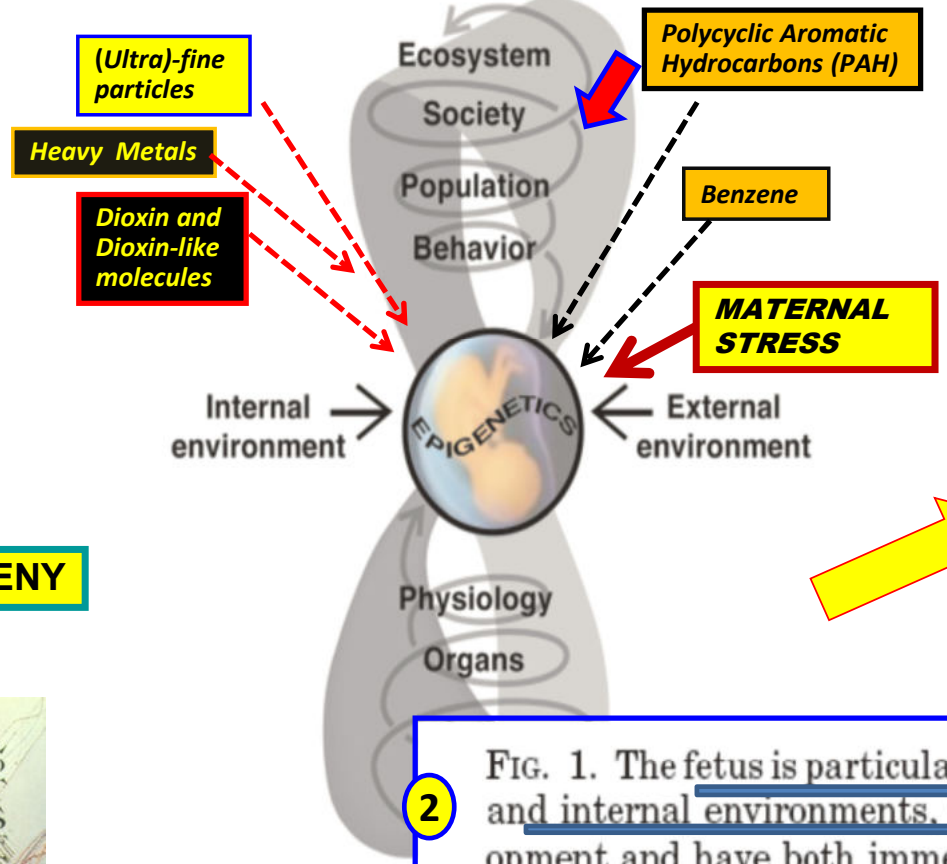
1 CODICE ISTONICO



I microRNA (miRNA) comprendono una specie di RNA corto non codificante che regola l'espressione genica post-trascrizionale



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



ONTOGENY

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

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

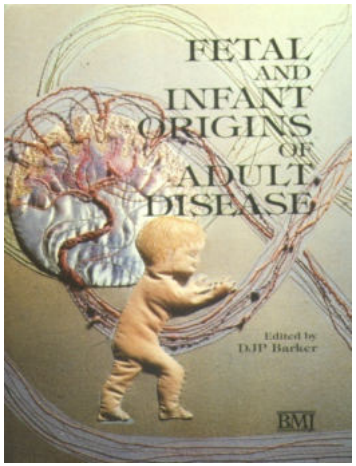


FIG. 1. The fetus is particularly vulnerable to changes in the external and internal environments, which interact to influence fetal development and have both immediate and life-long consequences. Such environmentally induced changes can occur at all levels of biological organization, from the molecular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

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

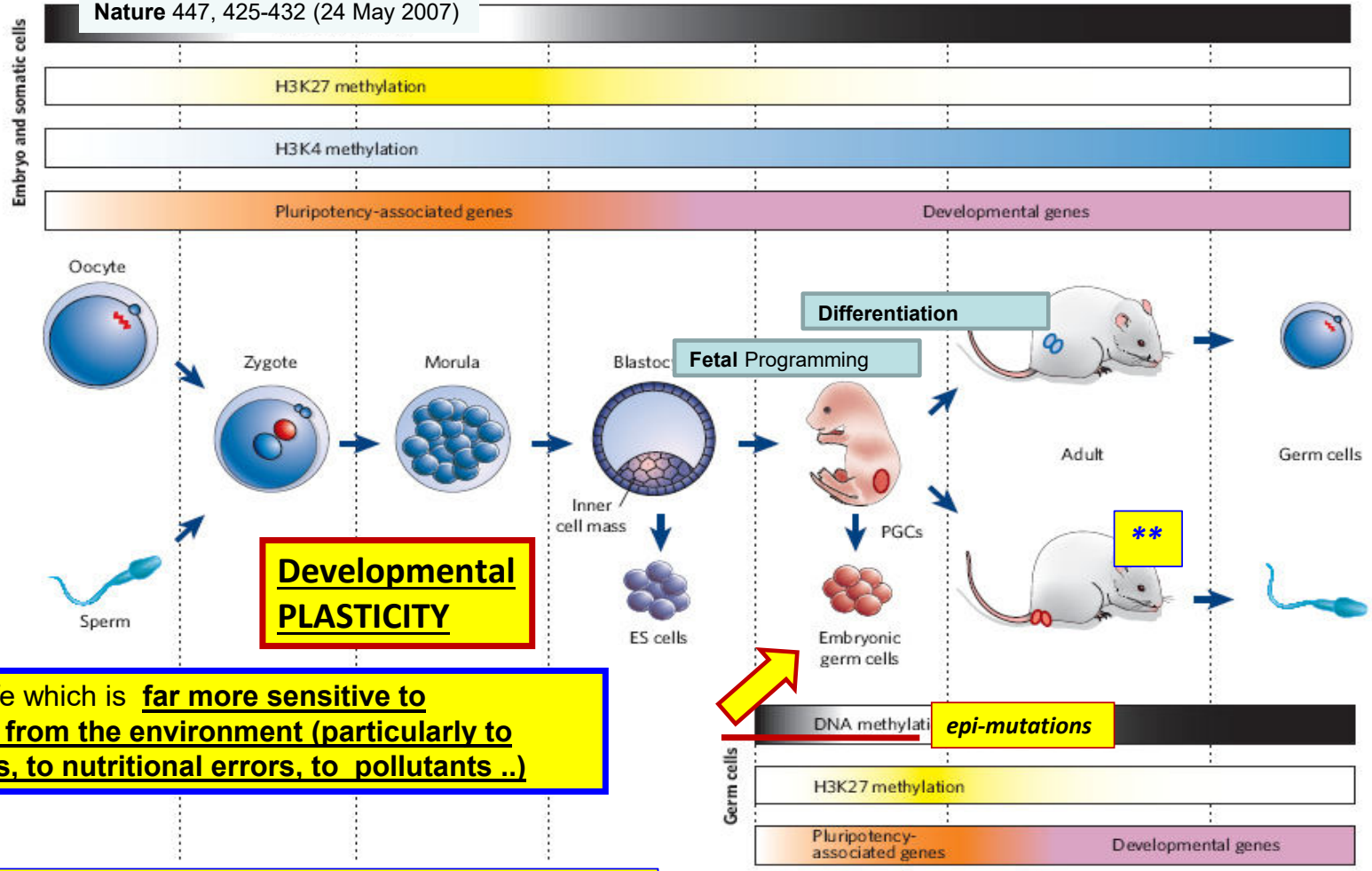
Cellular Differentiation*: an *epigentic process

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

1 ⇩ 2

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

Stability and flexibility of epigenetic gene regulation in mammalian development



Developmental PLASTICITY

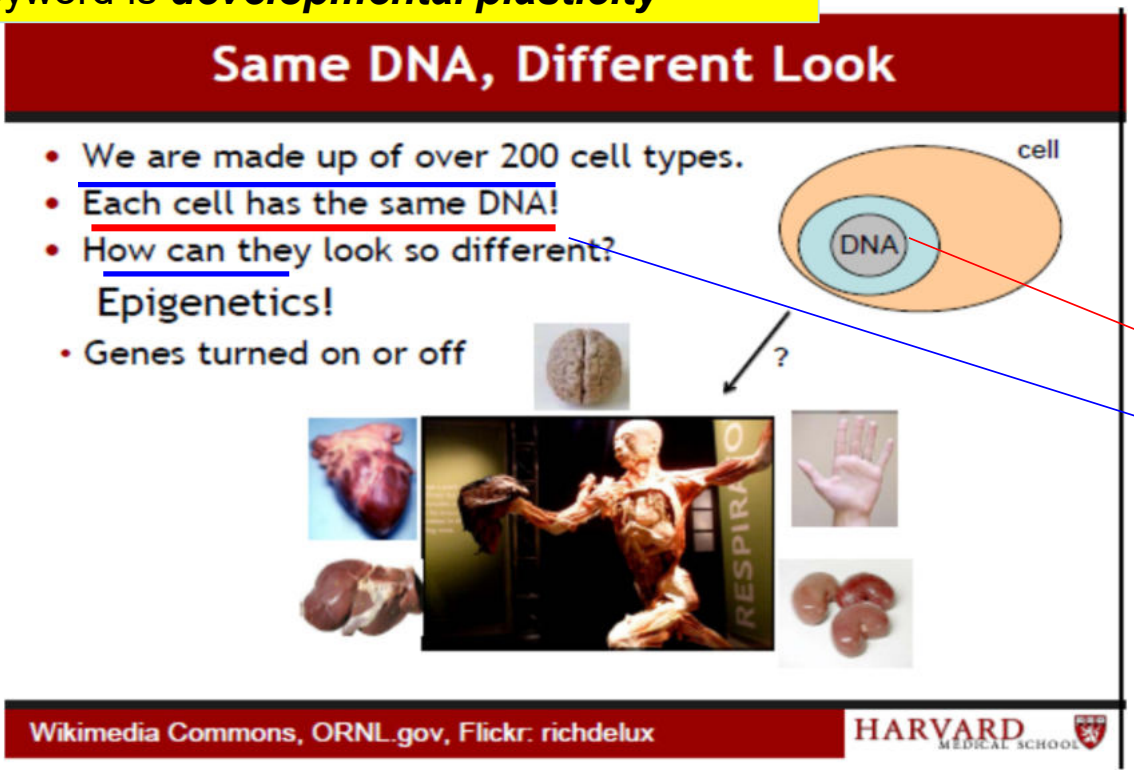
3

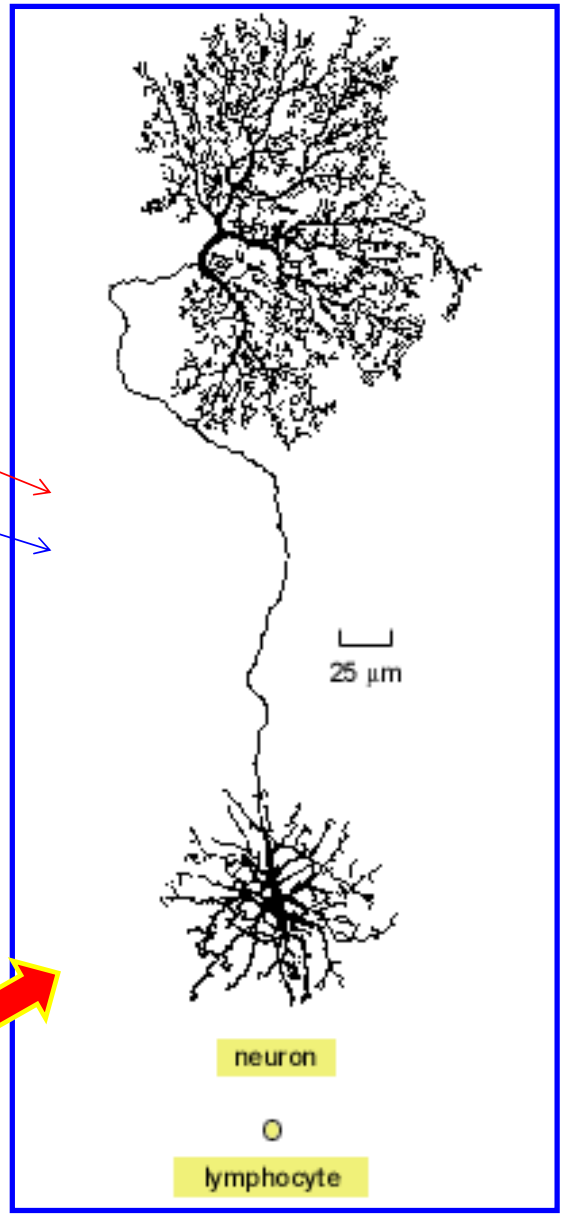
This is the stage of life which is **far more sensitive to information coming from the environment (particularly to maternal-fetal stress, to nutritional errors, to pollutants ..)**

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

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

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





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

A Bee's Royal Diet

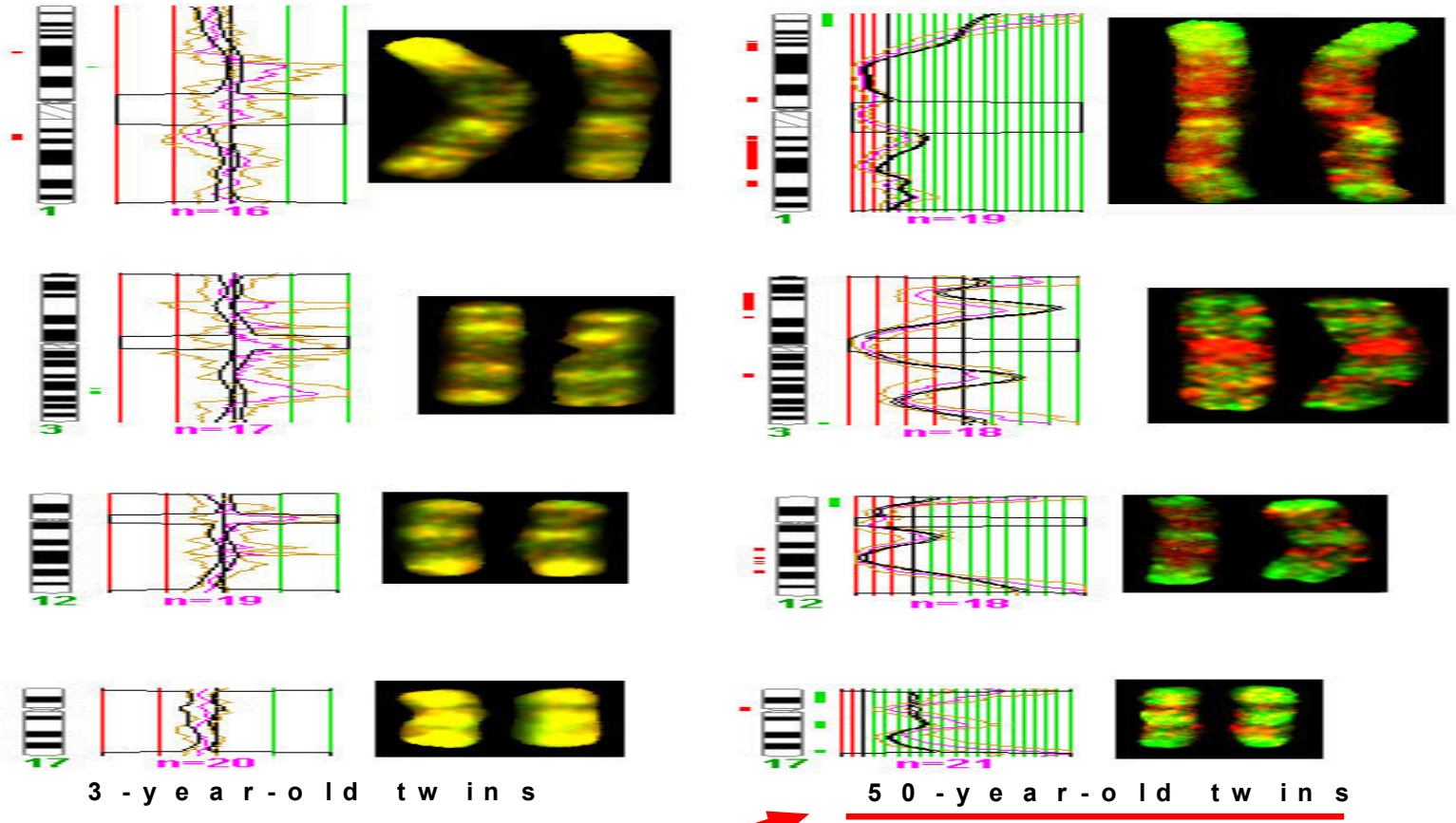
Kucharski R., Maleszka J., Foret S., Maleszka R. ***Nutritional Control of Reproductive Status in Honeybees via DNA Methylation***
Science (2008) 319: 1827-1830

Queen Bee Larvae: Queens are raised in specially-constructed cells called "queen cups," which are filled with royal jelly.

The **larvae** that develop into ***workers*** and ***queens*** are **genetically identical**.
But **as a result of the royal jelly diet, the queen will develop functional ovaries and a larger abdomen** for egg laying

Epigenetic differences in homozygotic twins

… although **twins are epigenetically indistinguishable during the early years** of life, … **older monozygous twins exhibited remarkable differences in** their **overall content and genomic distribution** of **5-methylcytosine DNA and histone acetylation**, affecting their gene-expression portrait.



Epigenetic differences arise during the lifetime of monozygotic twins

Fraga et al., PNAS. Jul 26 (2005);102(30):10604-9..

Epigenetic modifications : a molecular environmentally induced 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

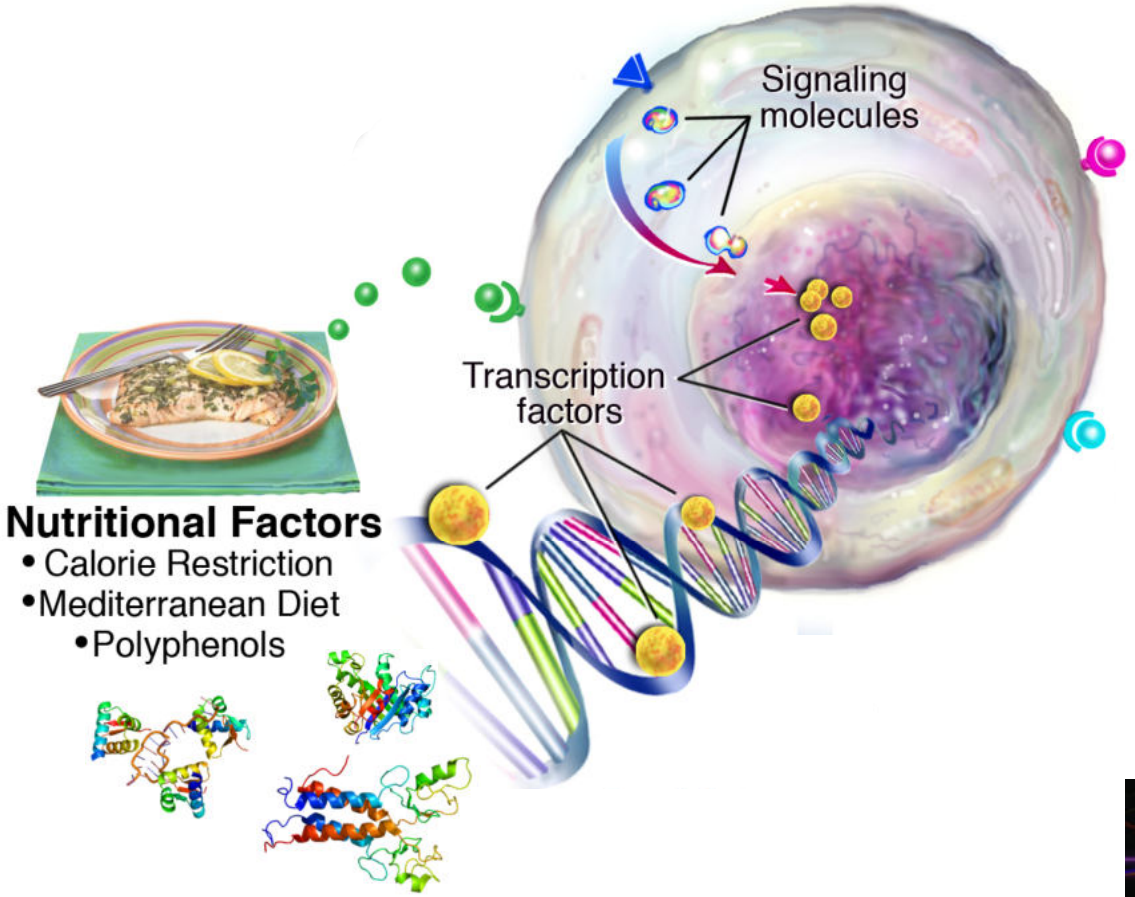
And Alzheimer Disease ?

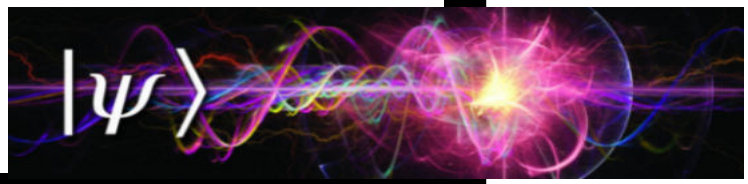
1

Fraga et al., PNAS. 2005.

ALTHOUGH TWINS ARE EPIGENETICALLY INDISTINGUISHABLE DURING THE EARLY YEARS OF LIFE…

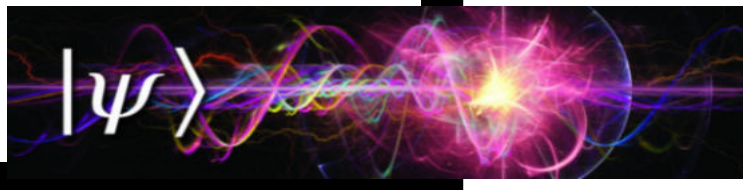
Epigenetics and Gene Activation
for Improved Health and Longevity



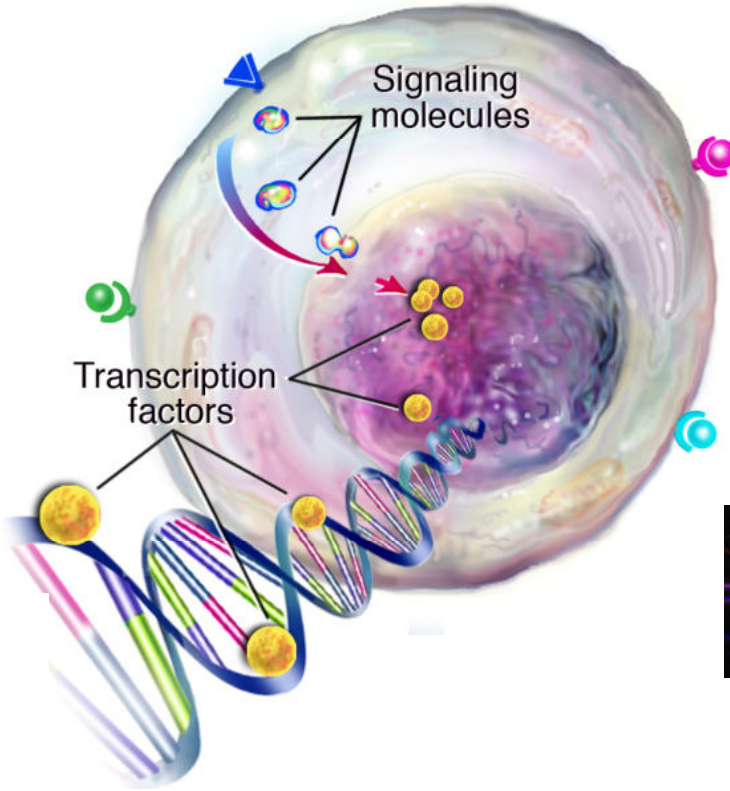


Epigenetics and Gene Activation
for Improved Health and Longevity

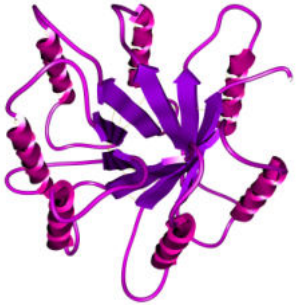
Excercise
- BDNF

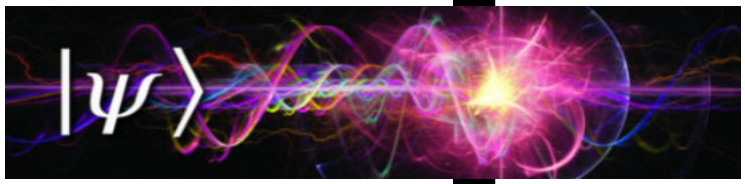


Epigenetics and Gene Activation
for Improved Health and Longevity

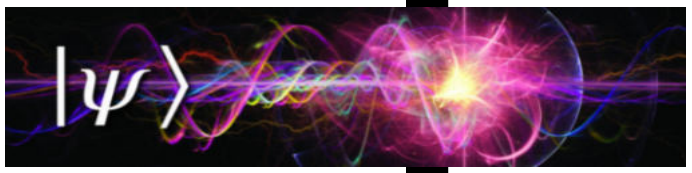


Environment
- Clean air, water and soil
- No smoking





Epigenetics and Gene Activation
for Improved Health and Longevity



Emotional Health
- Religion
- Meditation
- Spirituality

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

FOREWORD 6

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Gene 345 (2005) 91–100

GENE
SECTION
EVOLUTIONARY GENOMICS

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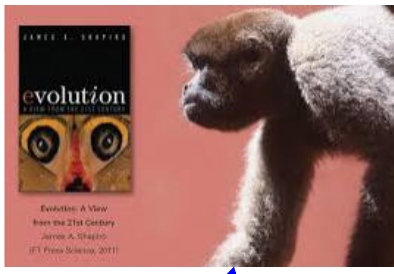
Review

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

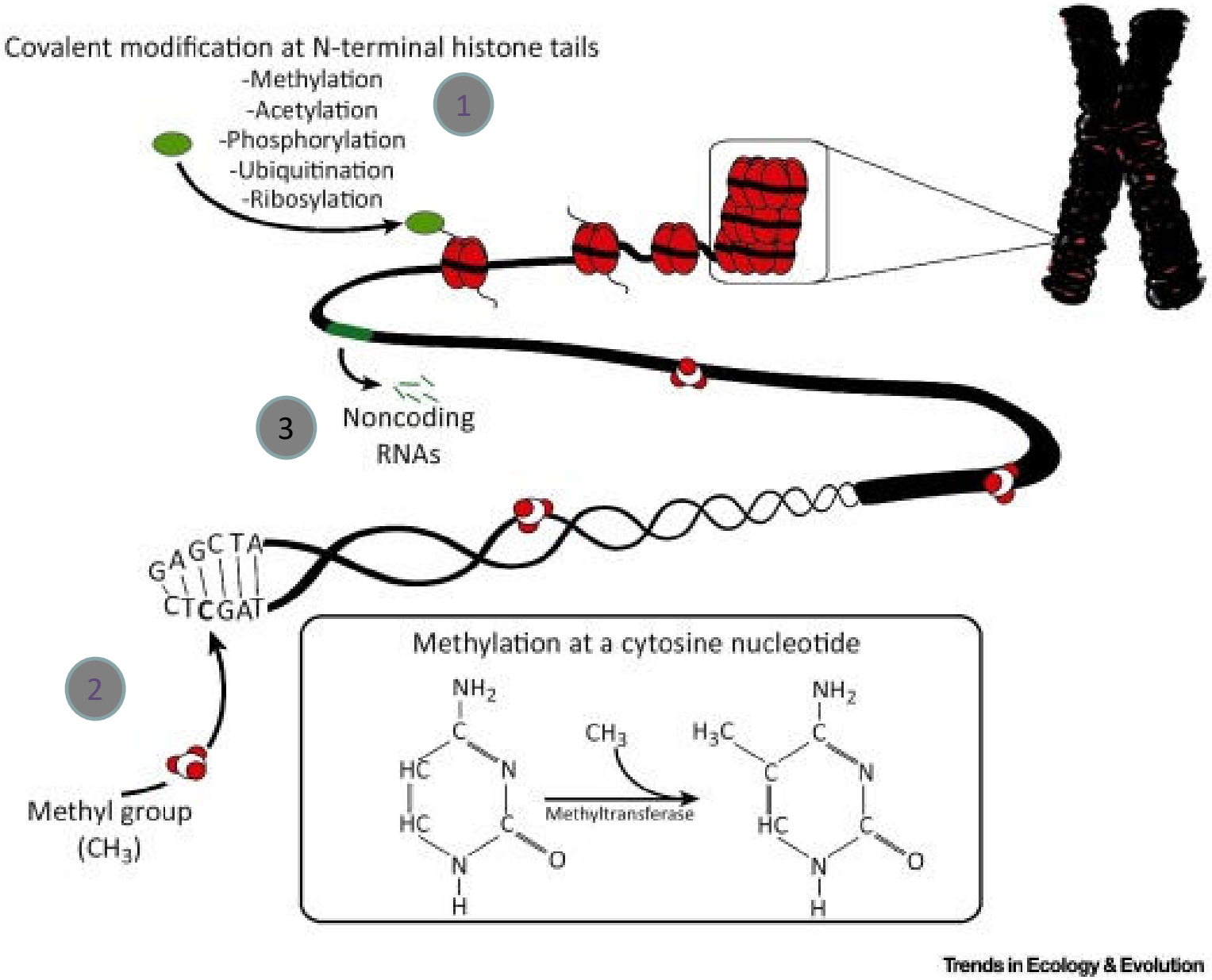
James A. Shapiro

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



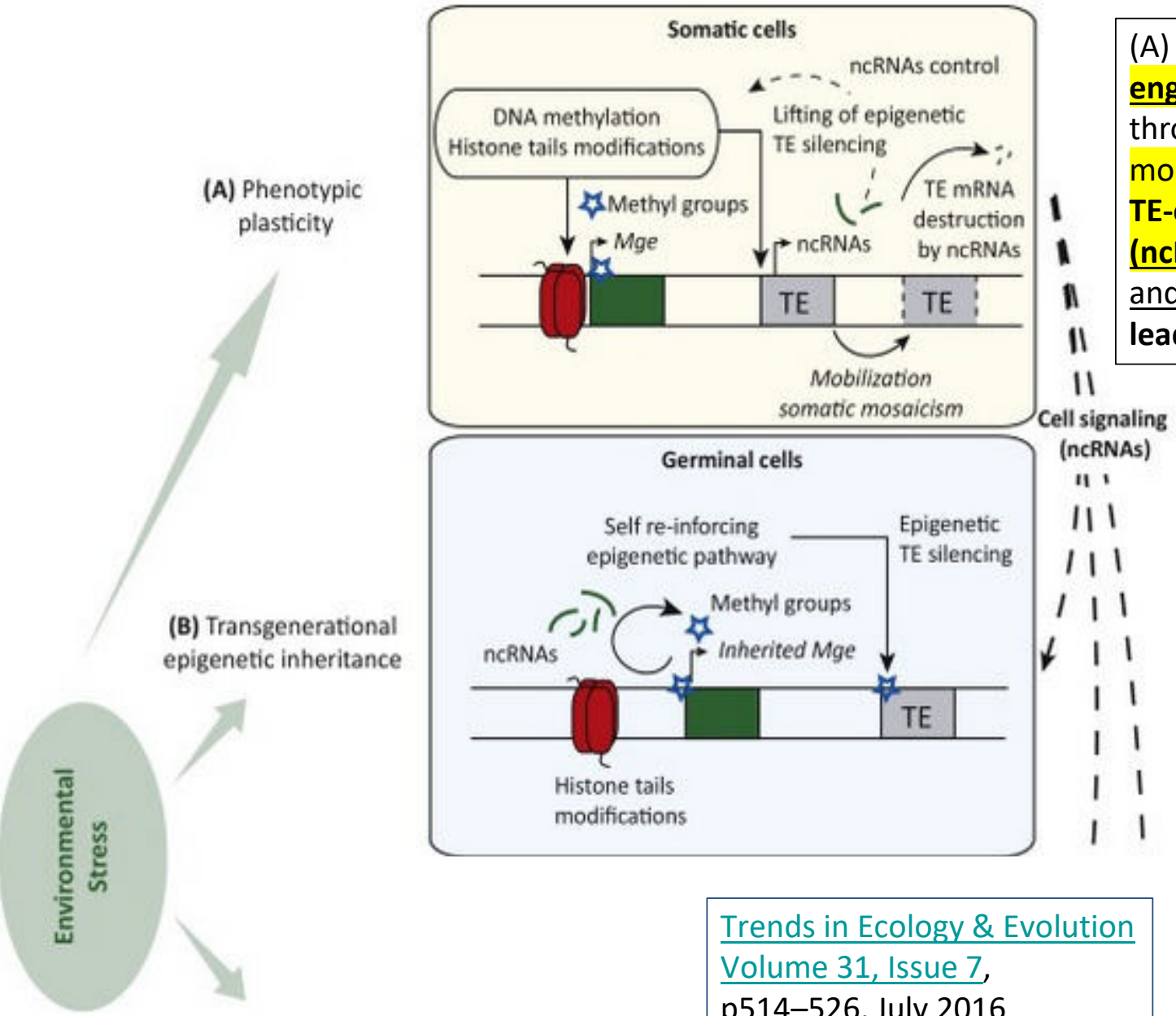
The last 50 years of molecular genetics have produced an abundance of new discoveries and data that make it useful to revisit some basic concepts and assumptions in our thinking about genomes and evolution. Chief among these observations are the complex modularity of genome organization, the biological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

1 2 3 4 5



Adaptation to Global Change: A Transposable Element–Epigenetics Perspective

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



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

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

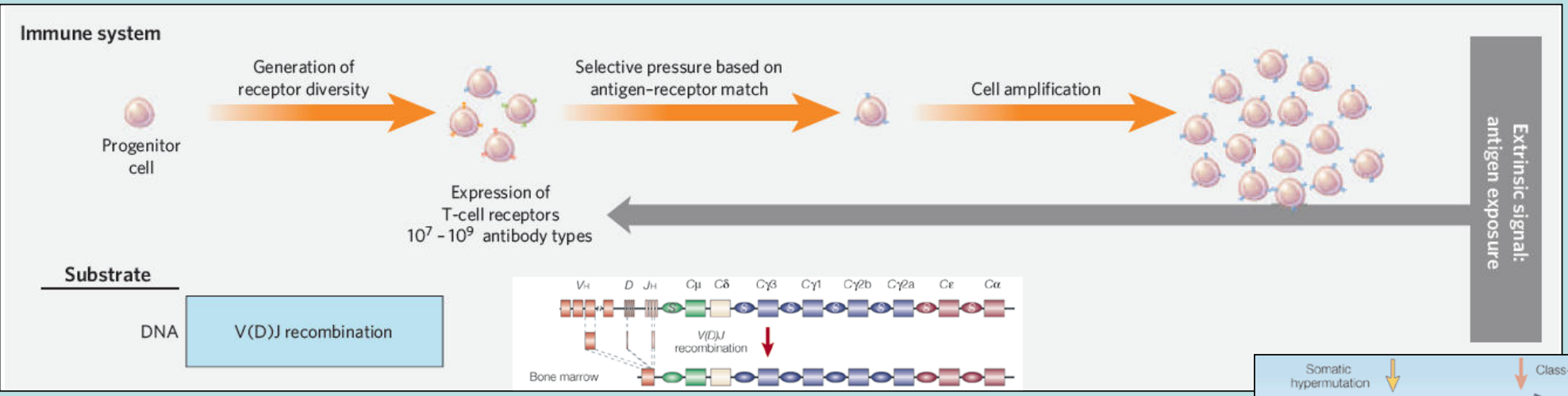
Stress perceived in somatic cells can also induce the **production of circulating ncRNAs that may modify the epigenome of remote germline cells** [dashed arrow from (A) to (B)].

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

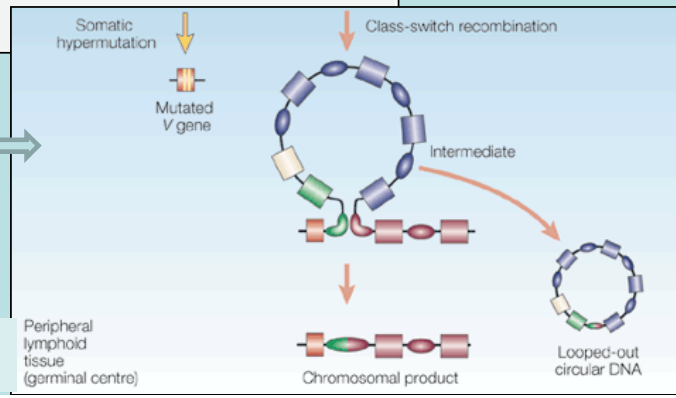
NATURE|Vol 441|29 June 2006|doi:10.1038/nature04959

Generation of neuronal variability and complexity

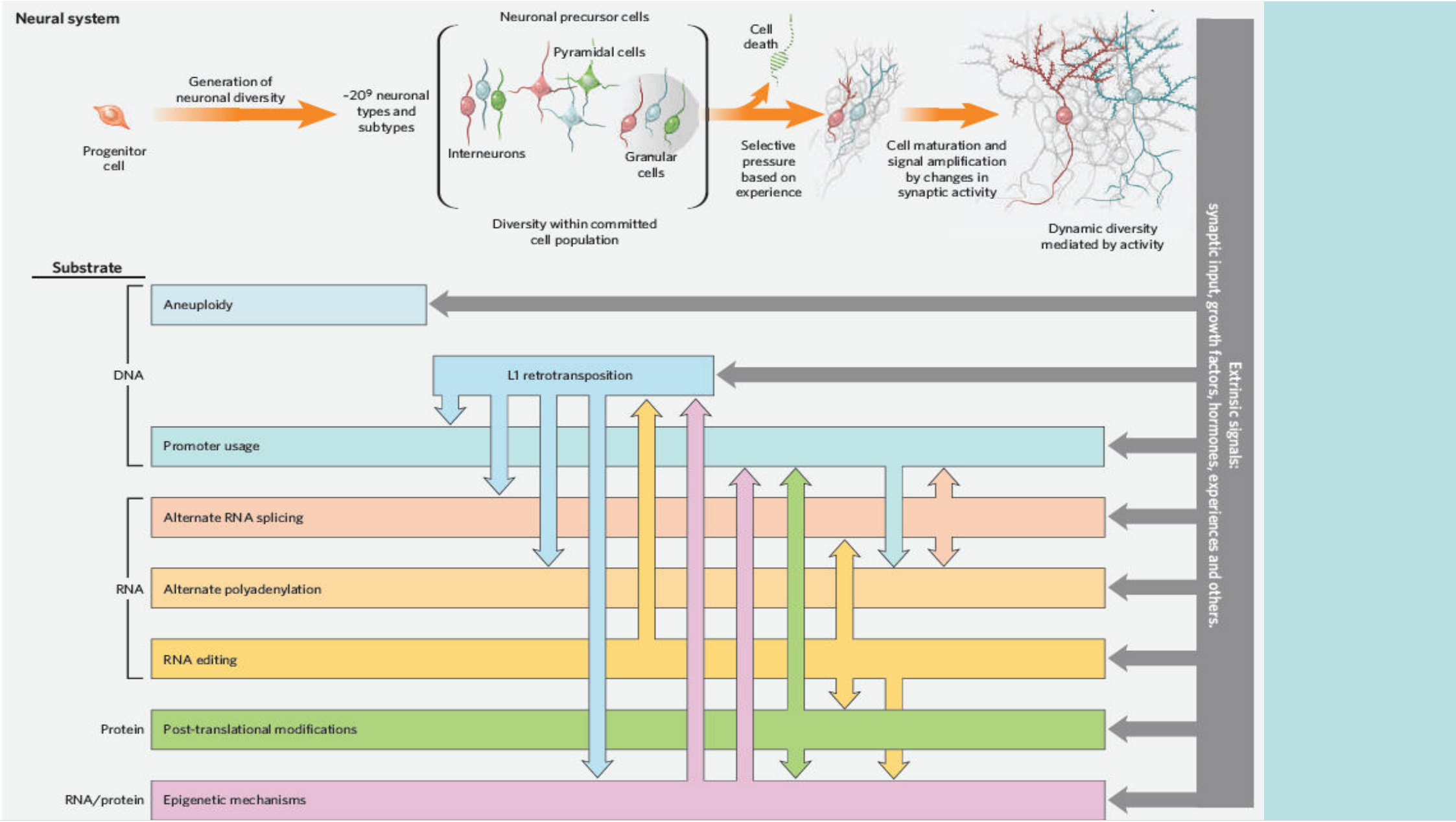
Alysson R. Muotri[1] & Fred H. Gage[1]



+ Somatic Hypermutation !



Kinoshita K., Honjo T. *Linking class-switch recombination with somatic hypermutation*
Nature Reviews Molecular Cell Biology (2001) 2, 493–503


Neural system
Neuronal precursor cells
Pyramidal cells
Cell death
Generation of neuronal diversity
~20^9 neuronal types and subtypes
Progenitor cell
Interneurons
Granular cells
Selective pressure based on experience
Cell maturation and signal amplification by changes in synaptic activity
Diversity within committed cell population
Dynamic diversity mediated by activity
Extrinsic signals: synaptic input, growth factors, hormones, experiences and others.
Substrate
DNA
RNA
Protein
RNA/protein
Aneuploidy
L1 retrotransposition
Promoter usage
Alternate RNA splicing
Alternate polyadenylation
RNA editing
Post-translational modifications
Epigenetic mechanisms

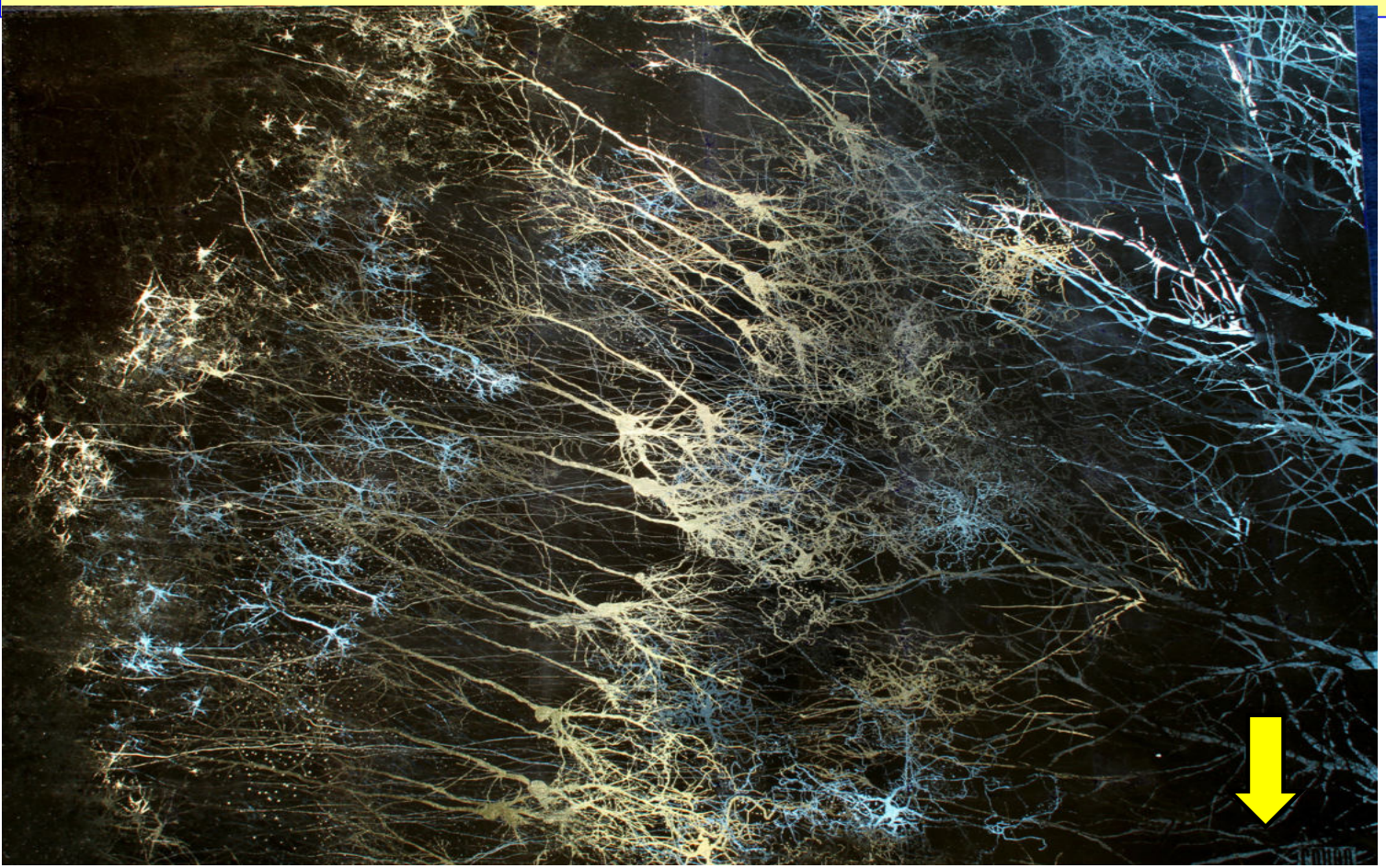
FOREWORD 7

.. *unlike your **genome**, which is **fixed from the moment of conception*** **(…)**
your **connectome* changes throughout your life**.

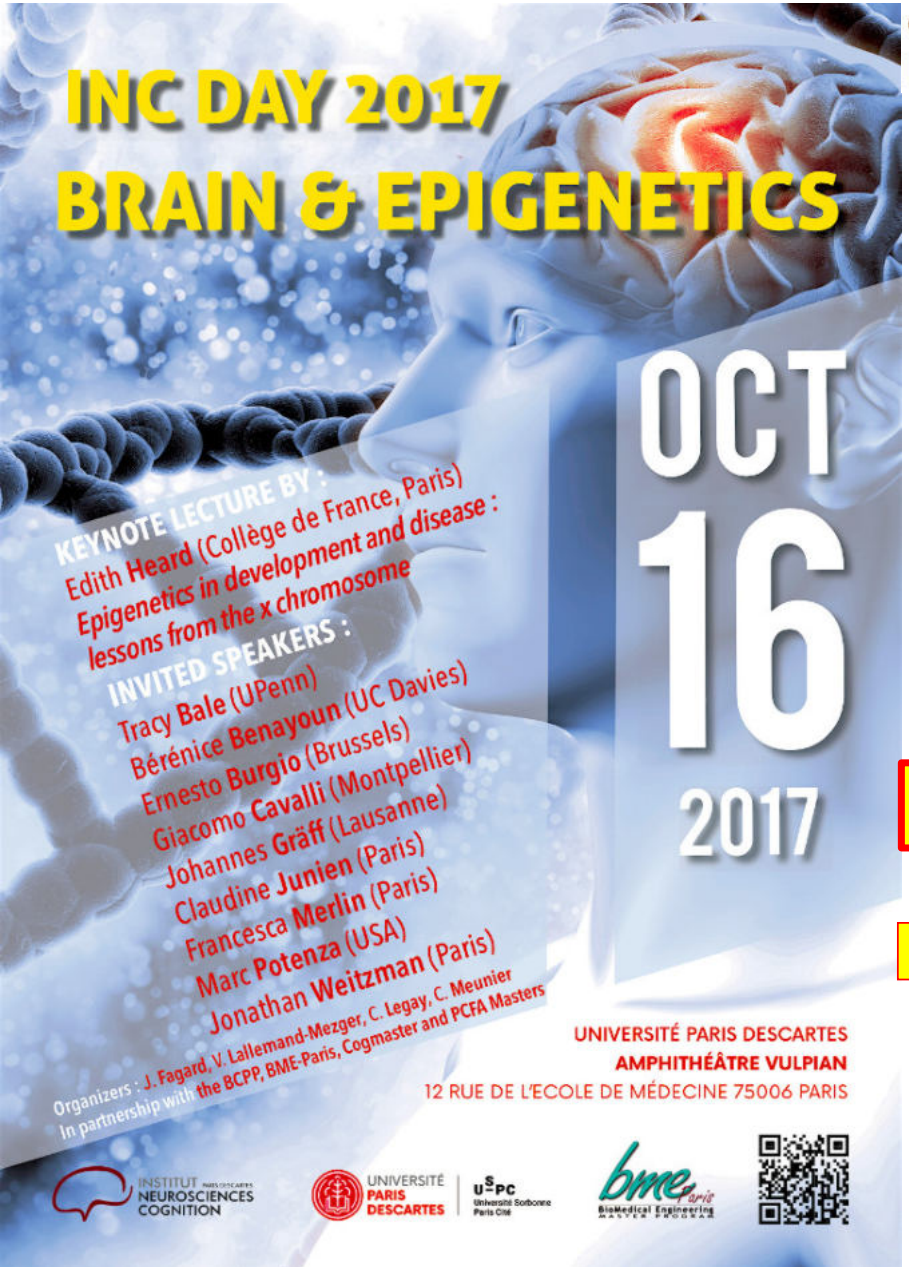
Neurons adjust…their connections (to one another) by ***strengthening*** or ***weakening*** them.

Neurons **reconnect by creating and eliminating synapses**, and **they rewire by growing and retracting branches**.

***You are more than your genes. You are your connectom* (*Sebastian Seung, MIT*).**



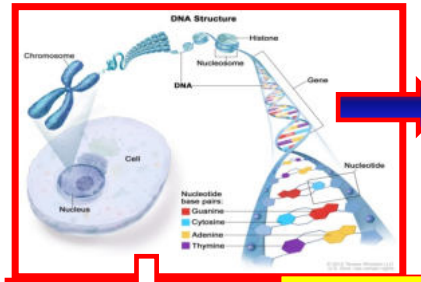
Seung S. ***Connectome: How the brain's wiring makes us who we are*** (2012)

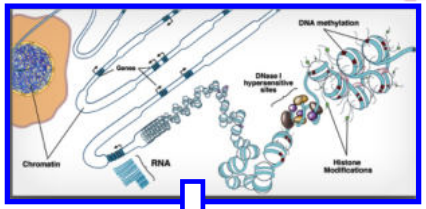


Categories: EVENTS, INC MEETINGS

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

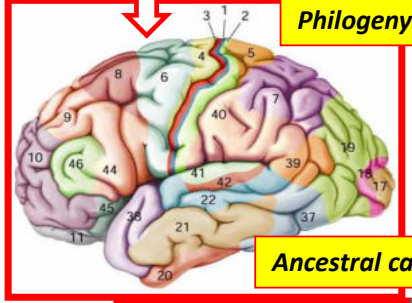
INSTITUT PARIS DESCARTES NEUROSCIENCES COGNITION

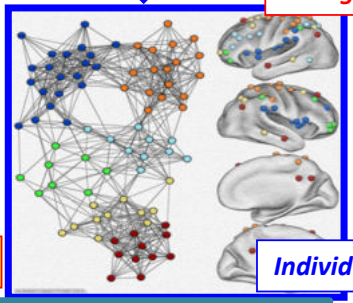




Philogeny

Ontogeny





Ancestral cablage

Individual cablage

Brodmann areas

The human Connectome

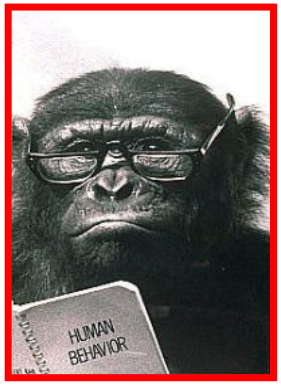
(I) The building of the *hardware* is under *genetic control*

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

Neurodegenerative diseases

Neurodevelopmental disorders

Neuropsychiatric diseases



Brain Evolution and Neurodevelopmental Disorders

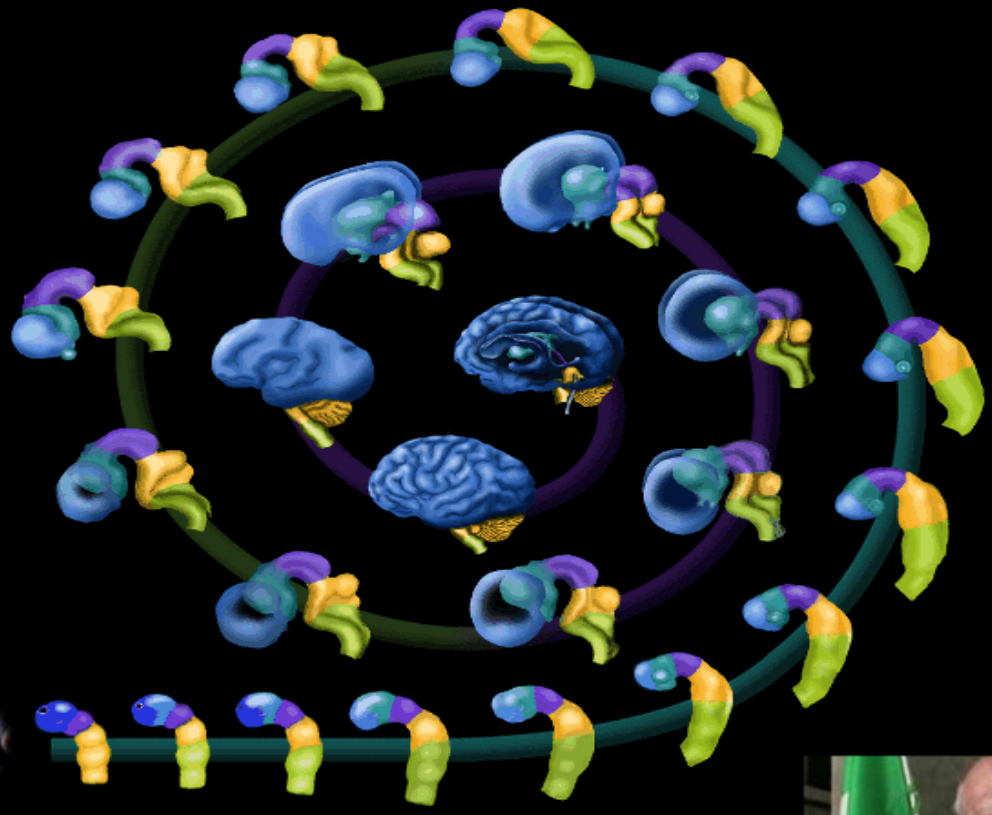
From Genetics to Epigenetics

ECERI
European Cancer and Environment Research Institute

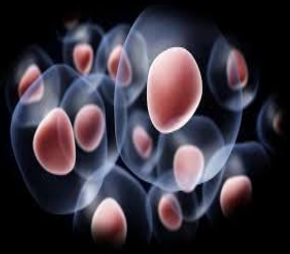
Ernesto Burgio (ECERI, Brussels, Belgium

EPIGENETICS > GENETICS

Neurogenesi



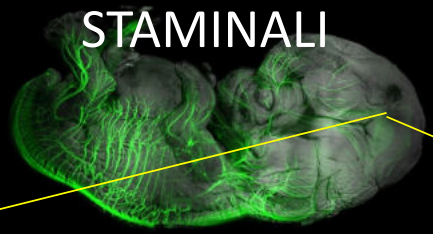
STAMINALI



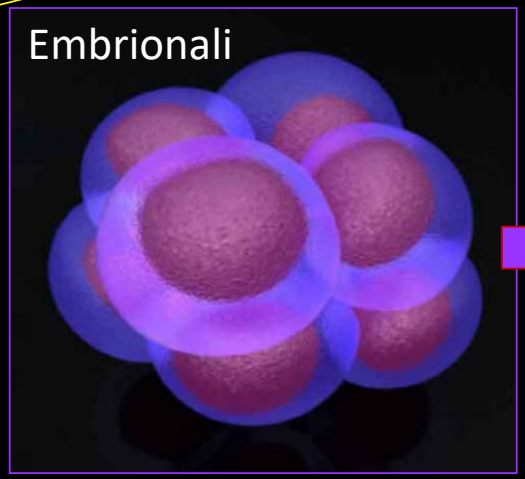
Prof. Gianfranco Tajana
Ordinario di Istologia & Embriologia, Anatomia Umana Normale
Facoltà di Medicina e Chirurgia e Dipartimento Scienze Farmaceutiche
Università di Salerno

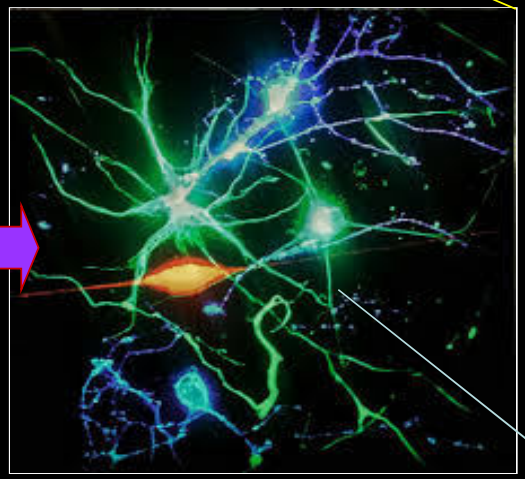
EPIGENETICS > GENETICS

STAMINALI



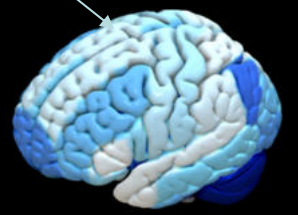
Embrionali





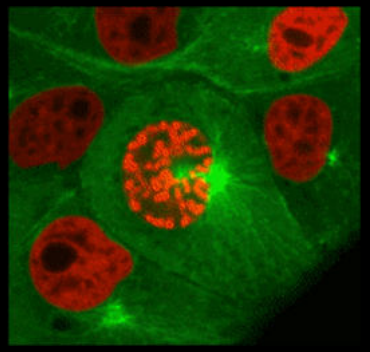
GLIA

NEURONI



EPIGENETICS > GENETICS

NICHE



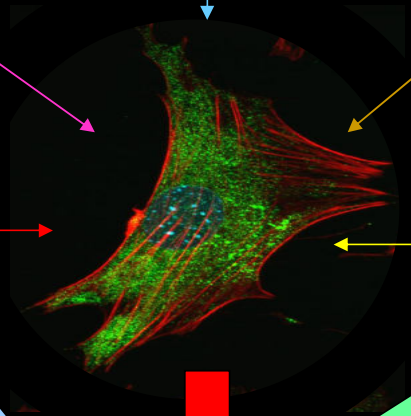
Morfogeni

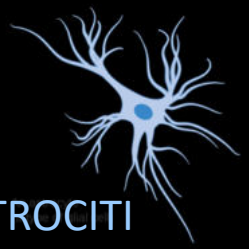
Fattori di crescita

Proteoglicani

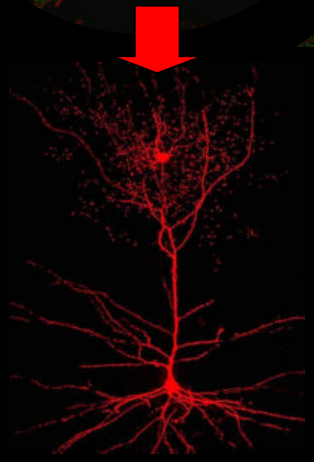
Citochine

Ormoni

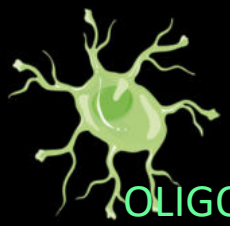




ASTROCITI

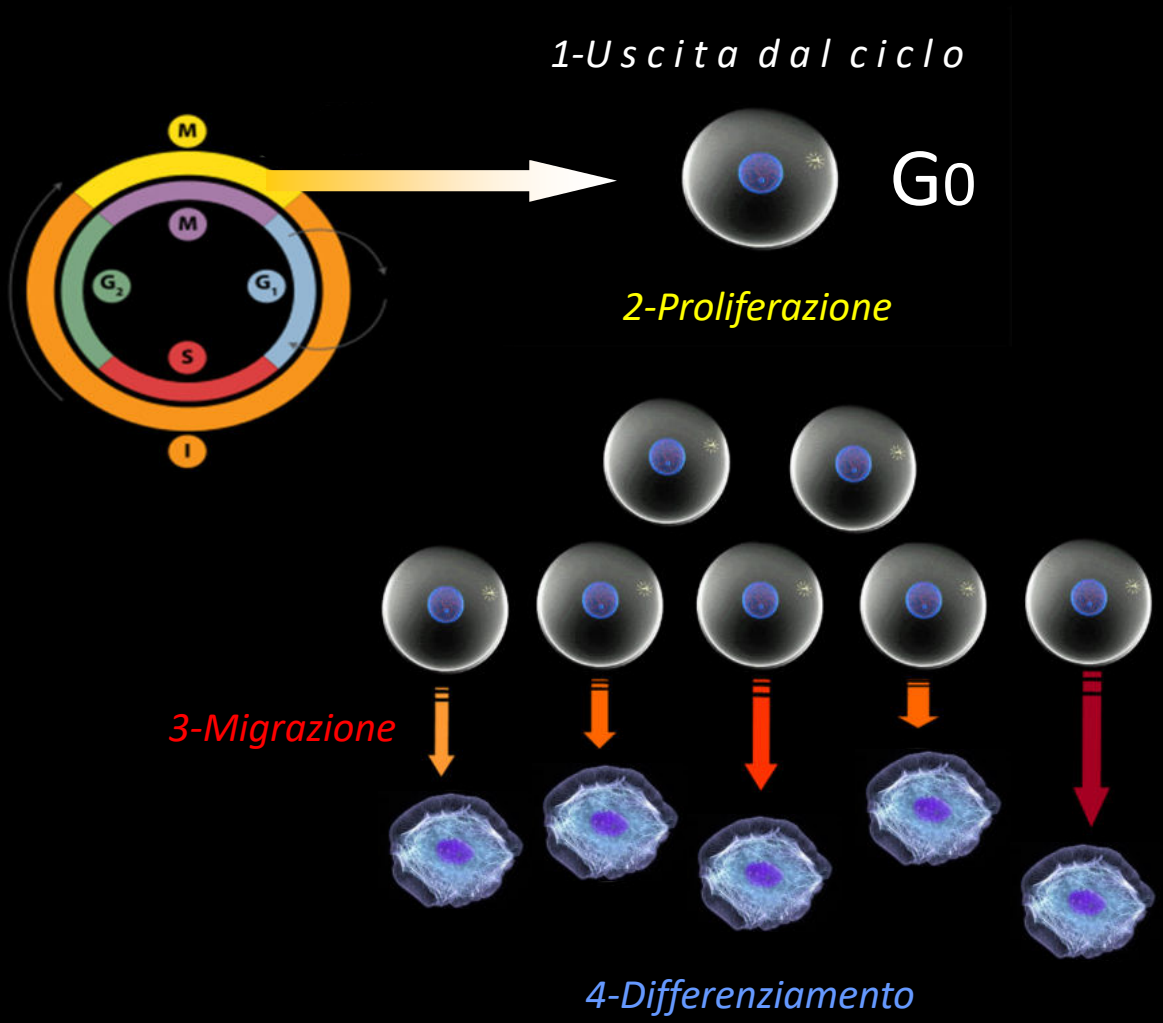


NEURONE



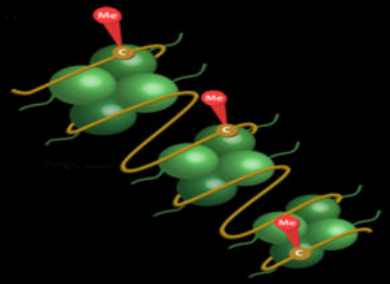
OLIGODENDROCITI

EPIGENETICS > GENETICS

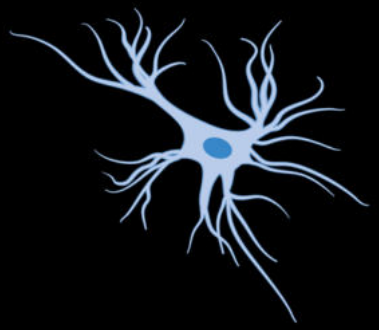


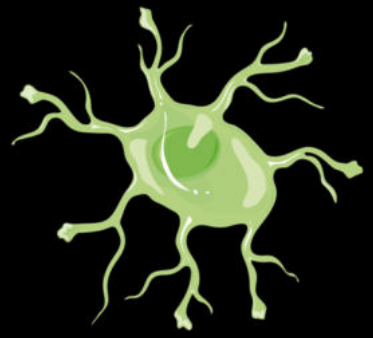
EPIGENETICS > GENETICS

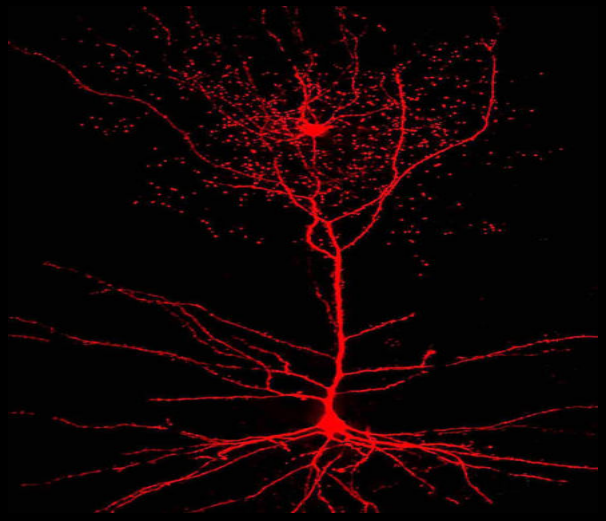
EXPOSOMA



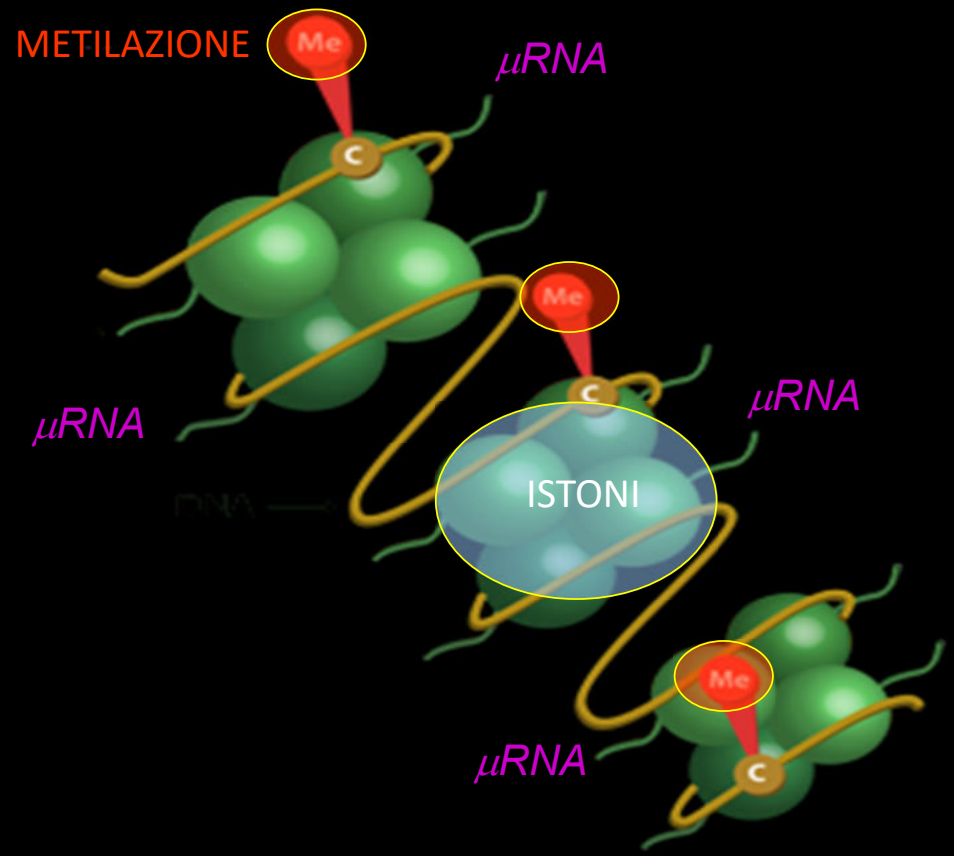
Software Epigenetico







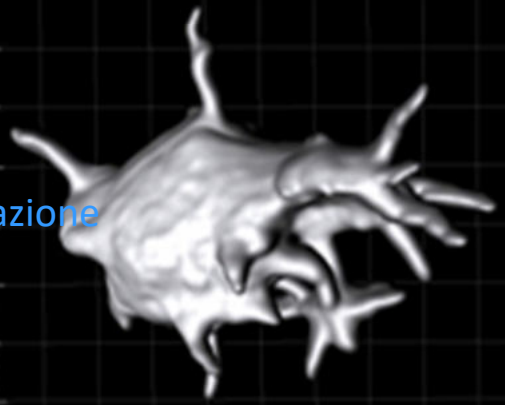
EPIGENETICS > GENETICS



EPIGENETICS > GENETICS

Navigator

Sistema di navigazione



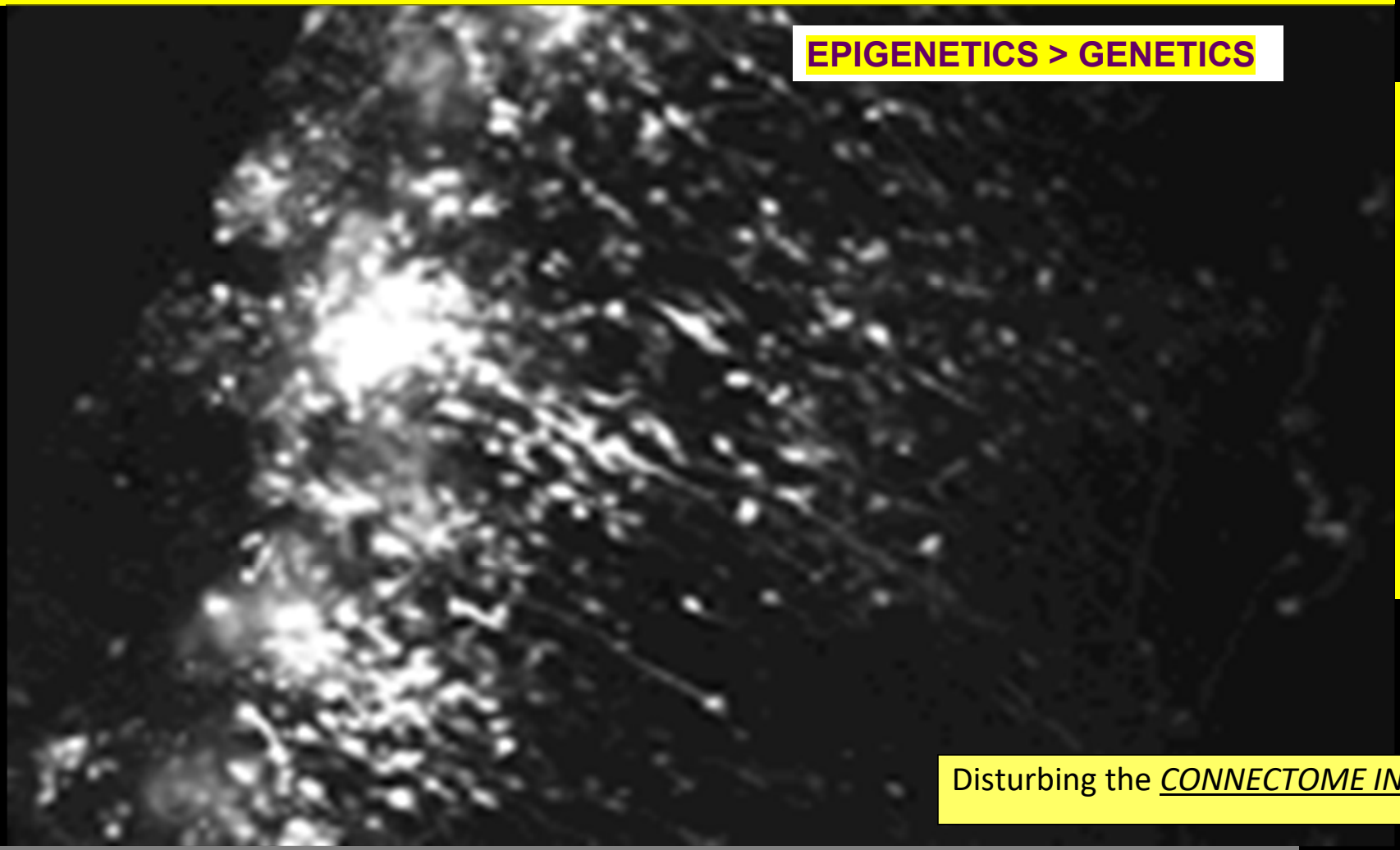
Dove andare ?

A che velocità ?

Secondo quale strategia ?

Brain plasticity and modulation of its structure and its functions

The ***Individual*** wirir



EPIGENETICS > GENETICS

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

Disturbing the *CONNECTOME INSTRUCTION*

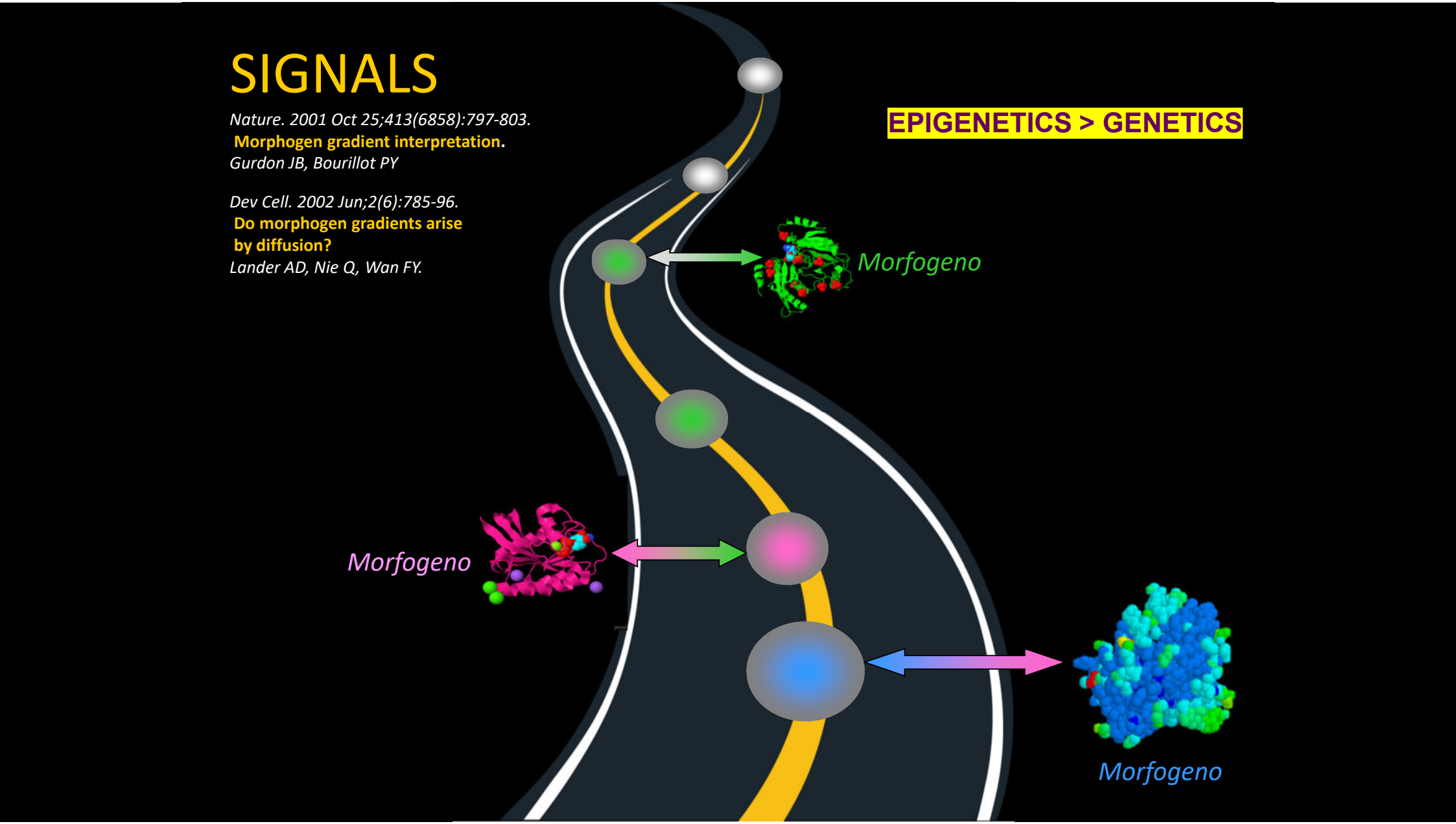
Wingate ***Imagining the brain cell: the neuron in visual culture***. Nature Rev Neuroscience 2006; 7: 745-752.

SIGNALS

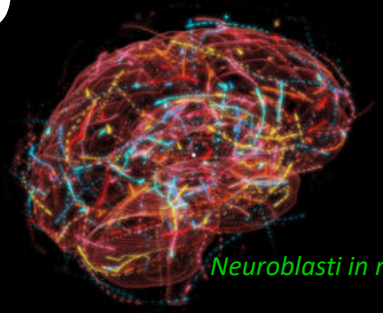
Nature. 2001 Oct 25;413(6858):797-803.
Morphogen gradient interpretation.
Gurdon JB, Bourillot PY

Dev Cell. 2002 Jun;2(6):785-96.
Do morphogen gradients arise by diffusion?
Lander AD, Nie Q, Wan FY.

EPIGENETICS > GENETICS



10^{18}



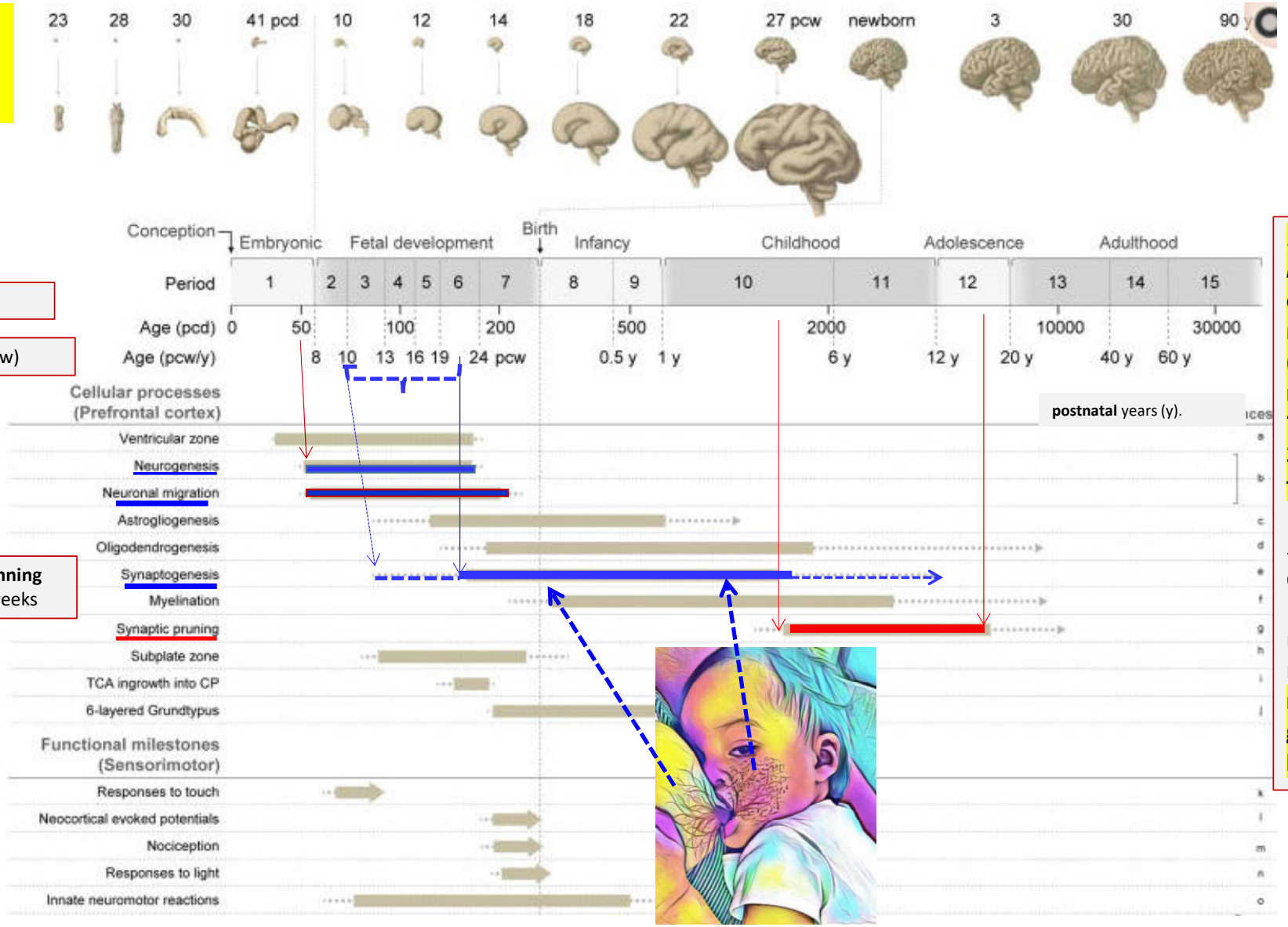
Neuroblasti in migrazione

EPIGENETICS > GENETICS

Un milardo di miliardi

EDCs…
PSEUDOMORFOGENI

Timeline of Key Human Neurodevelopmental Processes and Functional Milestones **



Post-conceptional days (pcd),

Post-**conceptional** weeks (pcw)

postnatal years (y).

Synaptogenesis' beginning between 10 and 20 weeks

Cfr slide 117 **

.. Most of the *neuronogenesis* of the central nervous system (about 86.1 billion neurons) occurs in 781 days, from 32nd to 813th day from conception [234 prenatal + 547 postnatal days: up to the 18th post-natal month] which means **about 4.6 million neurons generated every hour ..**

Silbereis JC, Pochareddy S, Zhu Y, Li M, Sestan N. ***The Cellular and Molecular Landscapes of the Developing Human Central Nervous System***. Neuron. 2016;89(2):248–268. doi:10.1016/j.neuron.2015.12.008

Leading Edge
Previews

Cell 164, February 11, 2016 ª2016 Elsevier Inc. 593

Cell

EPIGENETICS > GENETICS

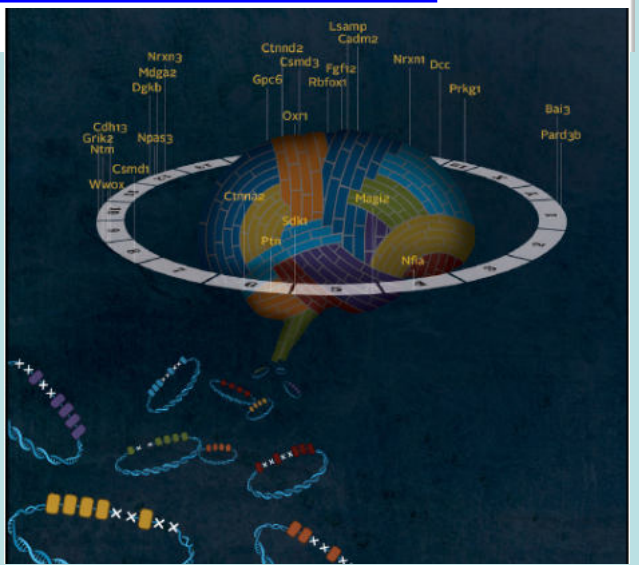
EPI-GENOMICS

A Mechanism for Somatic Brain Mosaicism

Irving L. Weissman[1,*] and Fred H. Gage[2,*]
[1]Institute of Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford University, Palo Alto, CA 94305, USA
[2]The Salk Institute for Biological Studies, Laboratory of Genetics, La Jolla, CA 92037, USA
*Correspondence: irv@stanford.edu (I.L.W.), gage@salk.edu (F.H.G.)
http://dx.doi.org/10.1016/j.cell.2016.01.048

Double-strand break repair is required for neural development, and brain cells contain somatic genomic variations. Now, Wei et al. demonstrate that neural stem and progenitor cells undergo very frequent DNA breaks in a very restricted set of genes involved in neural cell adhesion and synapse function.

Many of the identified genes are **expressed in NSPCs located in the brain regions responsible for higher functions such as short-term learning,** and mutations in these genes in humans are associated with (and maybe predispose to) **psychiatric and neurological disorders manifested in mind functions—autism, manic depressive and depressive disorders, schizophrenia**, and others



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

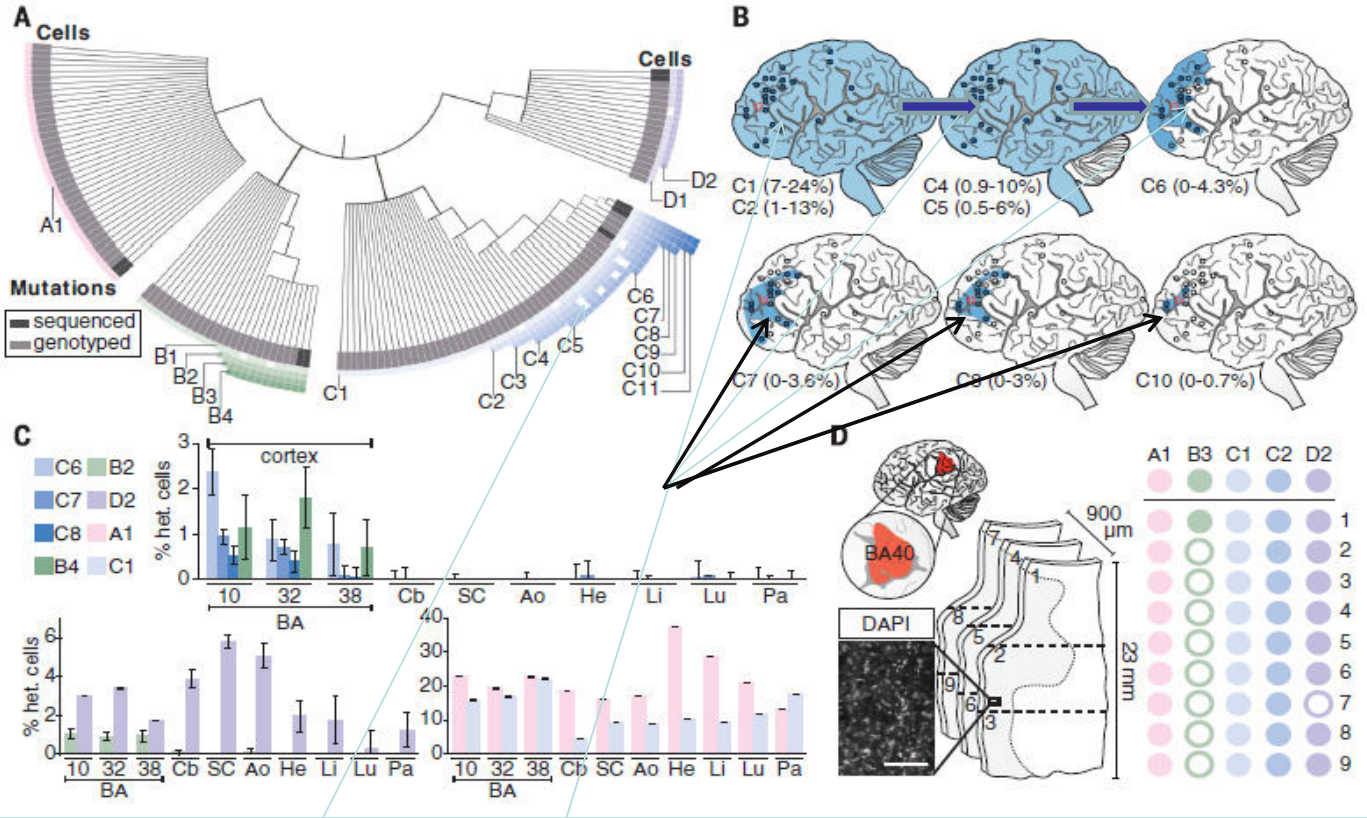
NEURODEVELOPMENT

Somatic mutation in single human neurons tracks developmental and transcriptional history

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

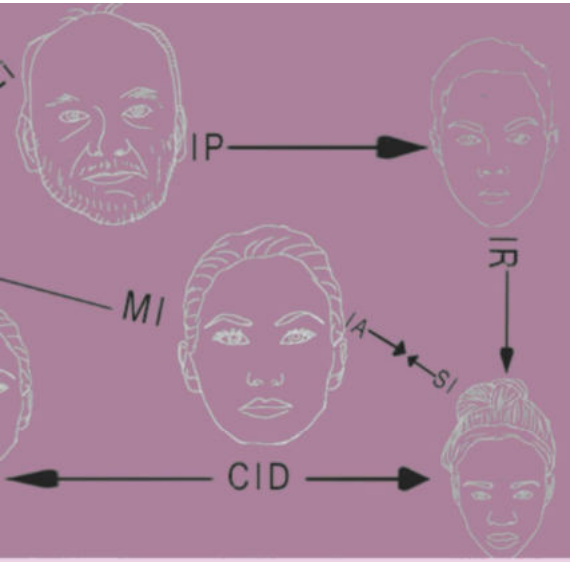
Neurons live for decades in a postmitotic state, their genomes susceptible to DNA damage. Here we survey the landscape of somatic single-nucleotide variants (SNVs) in the human brain. We identified thousands of somatic SNVs by single-cell sequencing of 36 neurons from the cerebral cortex of three normal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

EPI-GENOMICS



EPI-GENOMICS

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



Quantum Psyche 2
Quantum Psychoanalysis

Editors: F.Carminati, G.Galli Carminati, F.Martin
Authors: E.Burgio, F.Bussat, S.Cobianchi, J.Demongeot, E.Facco, M.A.Fernandez Rivas, C.Fouassier, F.Fracas, E.Gonzalez de Mendibil, M.A.Gonzalez Torres, R. Hasler, D.Lucangeli, A.-L.Oberson, L. Perez-Bayas, P.Quagliarella, J.-P.Revol, K.Stanley, S.Tagliagambe, B.Trojaola Zapirain, P.Zizzi

Presentiamo un **modello di mente quantistica** che riconosce sia il **modello di *Hameroff-Penrose*** che il modello della ***Teoria Quantistica dei Campi*** del cervello come complementari e li integra, grazie al ruolo delle **informazioni quantistiche nascoste associate ai biofotoni emessi dal genoma (DNA più epigenoma),** che interagendo con le **tubuline nel citoscheletro**

A Model of Quantum Epigenetics in Neuropsychiatry

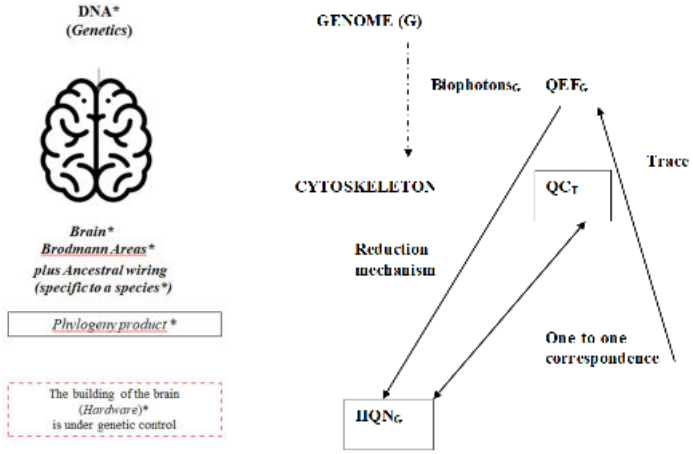
E. Burgio* † D. Lucangeli ** † P. Zizzi* †**
** ECERI, European Cancer and Environment Research Institute*
Square de Meeus 38-40, 1000, Bruxelles
*** Department of Developmental Psychology and Socialization Processes (DPSS)*
Padua University, Via Venezia 8, Padova, Italy
**** Department of Brain and Behavioural Sciences,*
Pavia University, Piazza Botta, 11, 27100 Pavia, Italy
† Science of Consciousness Research Group - Department of General Psychology
Padua University, Via Venezia 8, Padova, Italy

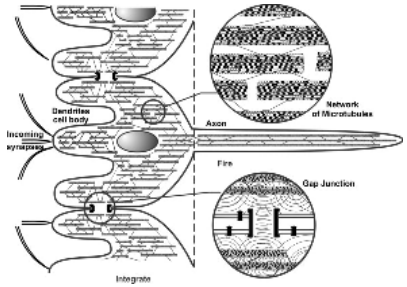
$$\lambda = \frac{h}{p} = \frac{h}{mv}\sqrt{1-\frac{v^2}{c^2}}$$

$$\frac{d\mathbf{Q}_k}{dt}(t) = \frac{\hbar}{m_k}\,\mathrm{Im}\left(\frac{(\psi, D_k\psi)}{(\psi,\psi)}\right)(\mathbf{Q}_1,\ldots,\mathbf{Q}_N,t),$$

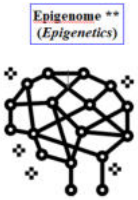
$$i\hbar\frac{\partial}{\partial t}\psi = \left(-\sum_{k=1}^{N}\frac{\hbar^2}{2m_k}D_k^2 + V - \sum_{k=1}^{N}\mu_k\frac{\mathbf{S}_k}{\hbar s_k}\cdot\mathbf{B}(\mathbf{q}_k)\right)\psi,$$

We present a model of the quantum mind which recognizes both the Hameroff-Penrose model and the model of Quantum Field Theory of the brain as complementary and integrates them, thanks to the role of the hidden quantum information associated with the biophotons emitted by the genome (DNA plus epigenome), which, interacting with tubulines in the cytoskeleton modulate their computational activity. It turns out that our approach can define the computational and logical borders between the normal mind and the autistic and schizophrenic mind.





Result: quantum simulation of QEF$_G$ by QC$_T$



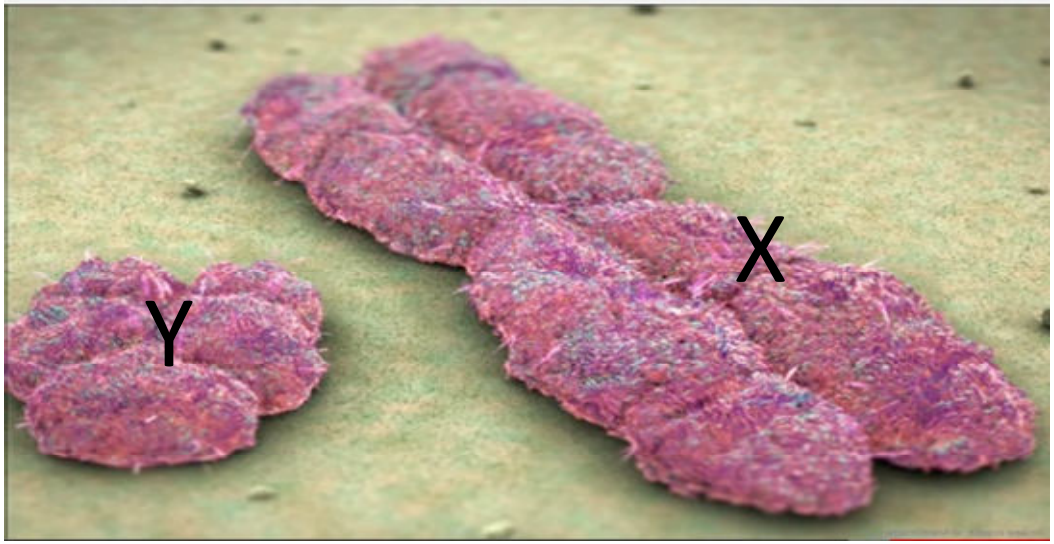
FOREWORD 8

DIMORFISMO SESSUALE

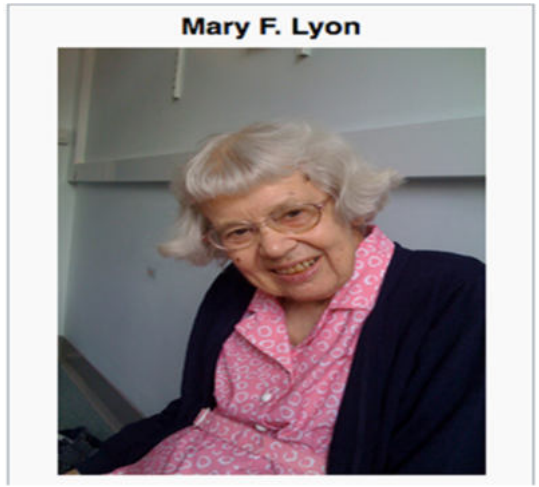
And yet this is not new!
Genetics : XY vs. XX

1861-1912

1905



1961



1921-2014

Sex differences in the structural connectome of the human brain

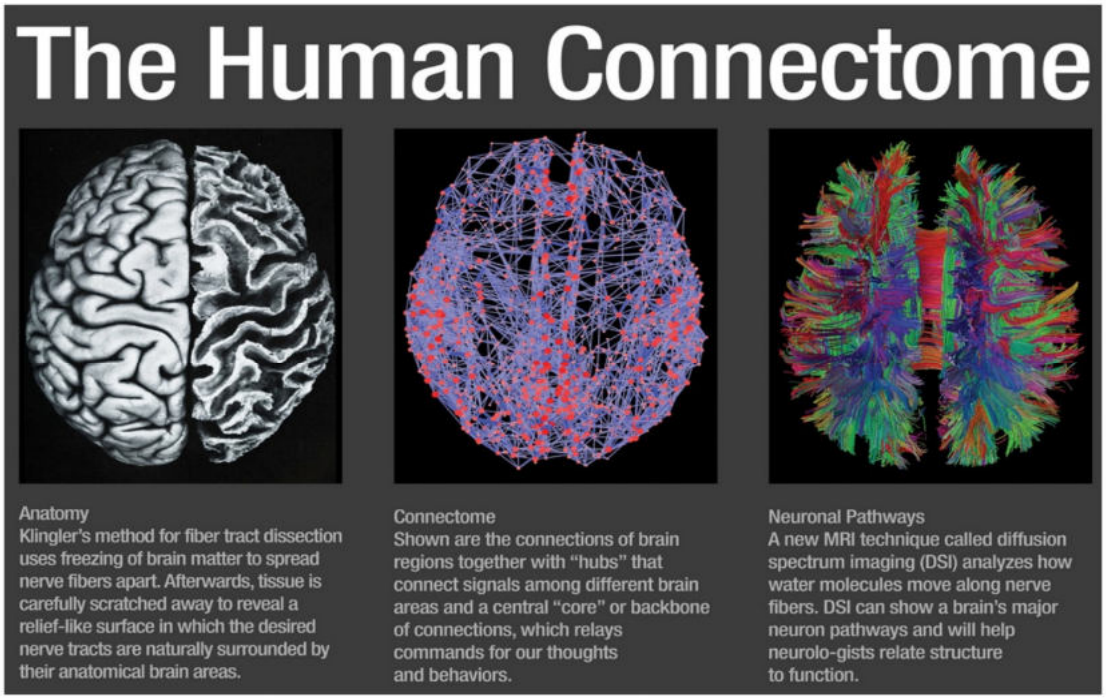
Madhura Ingalhalikar[a,1], Alex Smith[a,1], Drew Parker[a], Theodore D. Satterthwaite[b], Mark A. Elliott[c], Kosha Ruparel[b], Hakon Hakonarson[d], Raquel E. Gur[b], Ruben C. Gur[b], and Ragini Verma[a,2]

Sex differences in human behavior show adaptive complementarity: Males have better motor and spatial abilities, whereas females have superior memory and social cognition skills. Studies also show sex differences in human brains but do not explain this complementarity. In this work, we modeled the structural connectome using diffusion tensor imaging in a sample of 949 youths (aged 8–22 y, 428 males and 521 females) and discovered unique sex differences in brain connectivity during the course of development. Connection-wise statistical analysis, as well as analysis of regional and global network measures, presented a comprehensive description of network characteristics. In all supratentorial regions, males had greater within-hemispheric connectivity, as well as enhanced modularity and transitivity, whereas between-hemispheric connectivity and cross-module participation predominated in females. However, this effect was reversed in the cerebellar connections. Analysis of these changes developmentally demonstrated differences in trajectory between males and females mainly in adolescence and in adulthood. Overall, the results suggest that male brains are structured to facilitate connectivity between perception and coordinated action, whereas female brains are designed to facilitate communication between analytical and intuitive processing modes.

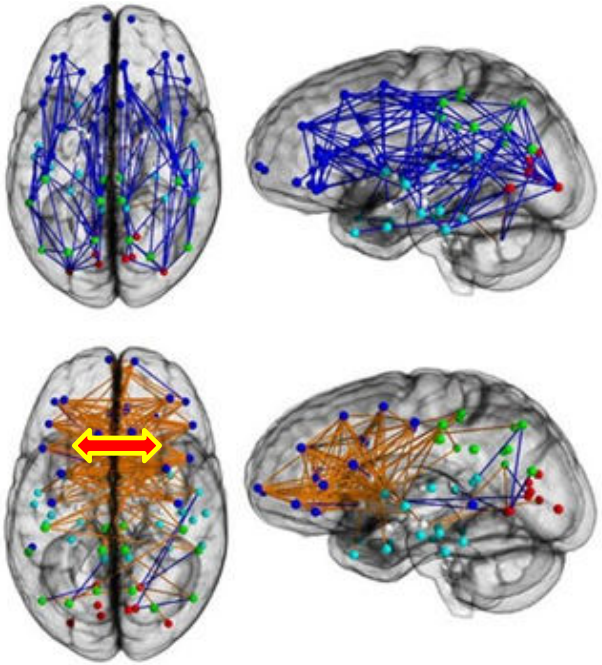
Sex differences are of high scientific and societal interest because of their **prominence in behavior of humans and nonhuman species**. This work is highly significant because it studies **a very large population of 949 youths** (8–22 y, 428 males and 521 females) **using the diffusion-based structural connectome of the brain, identifying novel sex differences**. The results establish that **male brains are optimized for intrahemispheric** and **female brains for interhemispheric communication.**

The developmental trajectories of males and females separate at a young age, demonstrating wide differences during adolescence and **adulthood**. The observations suggest that **male brains are structured to facilitate connectivity between perception and coordinated action**, whereas **female brains are designed to facilitate communication between analytical and intuitive processing modes.**

http://www.humanconnectomeproject.org/



The Human Connectome - Eugen Ludwig, Josef Klingler, Patric Hagmann & Olaf Sporns - 1956, 2008



♂

♀

Male brains during development are structured to facilitate within-lobe and within-hemisphere connectivity, with networks that are transitive, modular, and **discrete** whereas **female brains have greater interhemispheric connectivity and greater cross-hemispheric participation.**

♂

♀

Le ***connectome*** est un **plan complet**
des *connexions neuronales* dans un cerveau

Extraordinary intelligence and the care of infants

Steven T. Piantadosi[a,1] and Celeste Kidd[a,1]

[a]Department of Brain and Cognitive Sciences, University of Rochester, Rochester, NY 14627

Published online before print May 23, 2016, doi: 10.1073/pnas.1506752113 PNAS May 23, 2016

We present evidence that pressures for early childcare may have been one of the driving factors of human evolution. We show through an evolutionary model that runaway selection for high intelligence may occur when (*i*) altricial neonates require intelligent parents, (*ii*) intelligent parents must have large brains, and (*iii*) large brains necessitate having even more altricial offspring. We test a prediction of this account by showing across primate genera that the helplessness of infants is a particularly strong predictor of the adults' intelligence. We discuss related implications, including this account's ability to explain why human-level intelligence evolved specifically in mammals. This theory complements prior hypotheses that link human intelligence to social reasoning and reproductive pressures and explains how human intelligence may have become so distinctive compared with our closest evolutionary relatives.

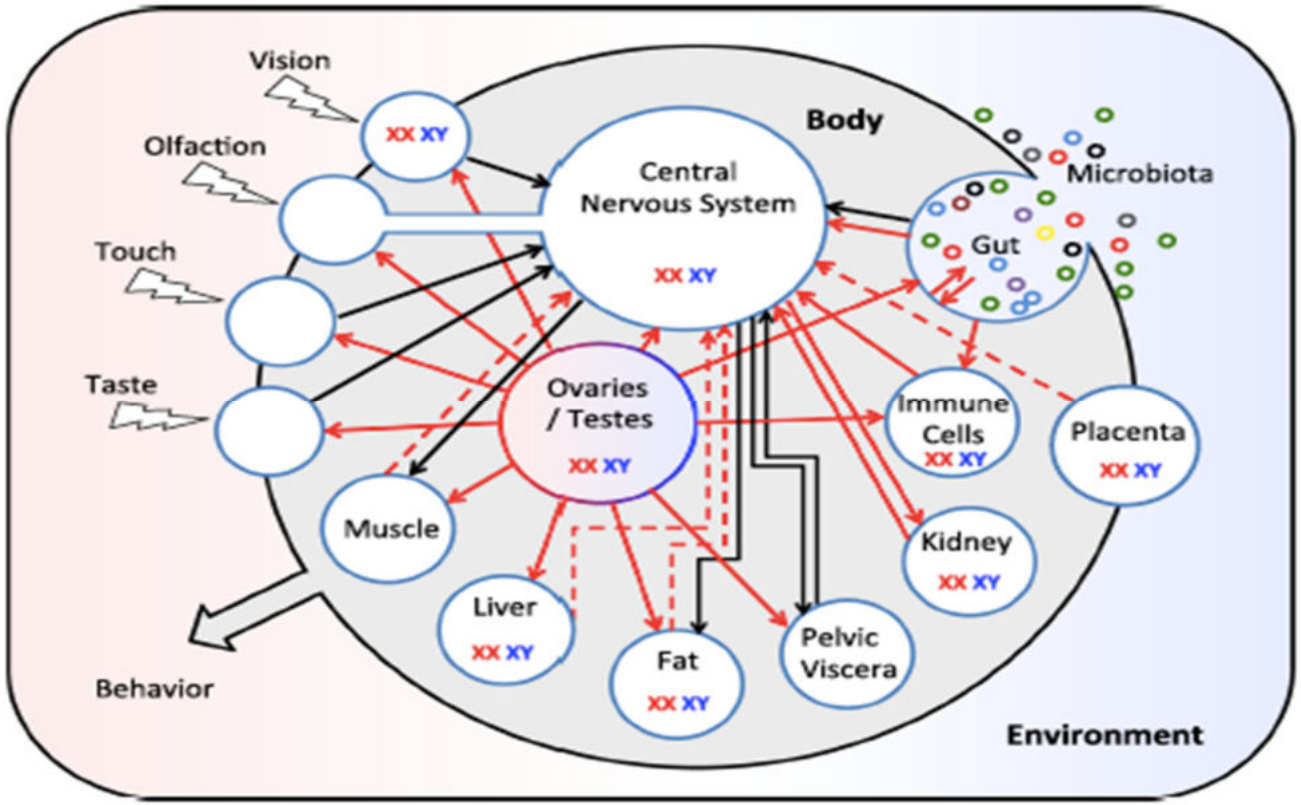
"**Our theory is that there is a kind of self-reinforcing cycle where big brains lead to very premature offspring and premature offspring lead to parents having to have big brains.** What our formal modeling work shows is that those dynamics can result in **runaway pressure for extremely intelligent parents and extremely premature offspring.**"

"**Humans have a unique kind of intelligence**. We are good at social reasoning and something called ***'theory of mind'***--**the ability to anticipate the needs of others, and to recognize that those needs may not be the same as our own**.. This is especially helpful when taking care of an infant who is not able talk for a couple of years."

https://www.sciencedaily.com/releases/2016/05/160523160445.htm

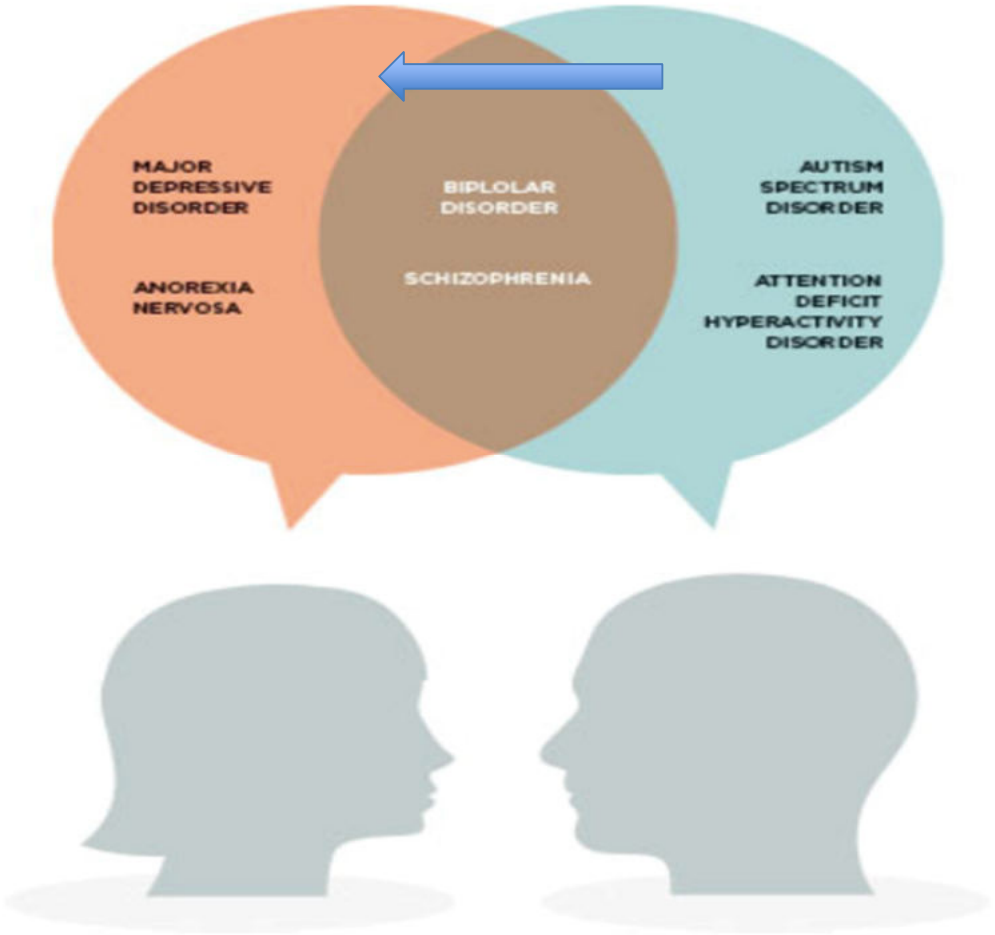

Who is really
nurturing who?

Sex differences in the brain: a whole body perspective



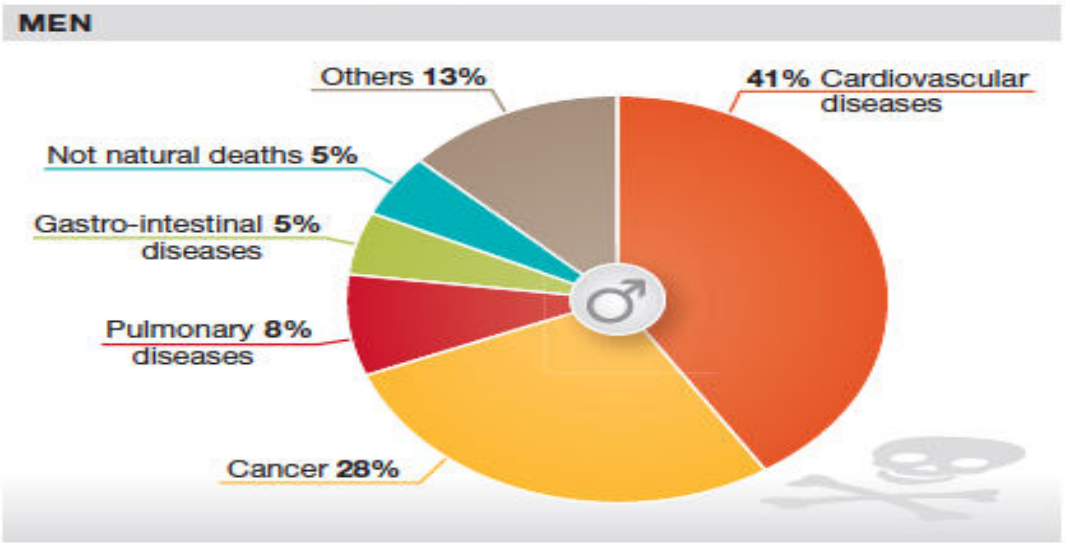
de Vries and Forger Biology of Sex Differences (2015) 6:15

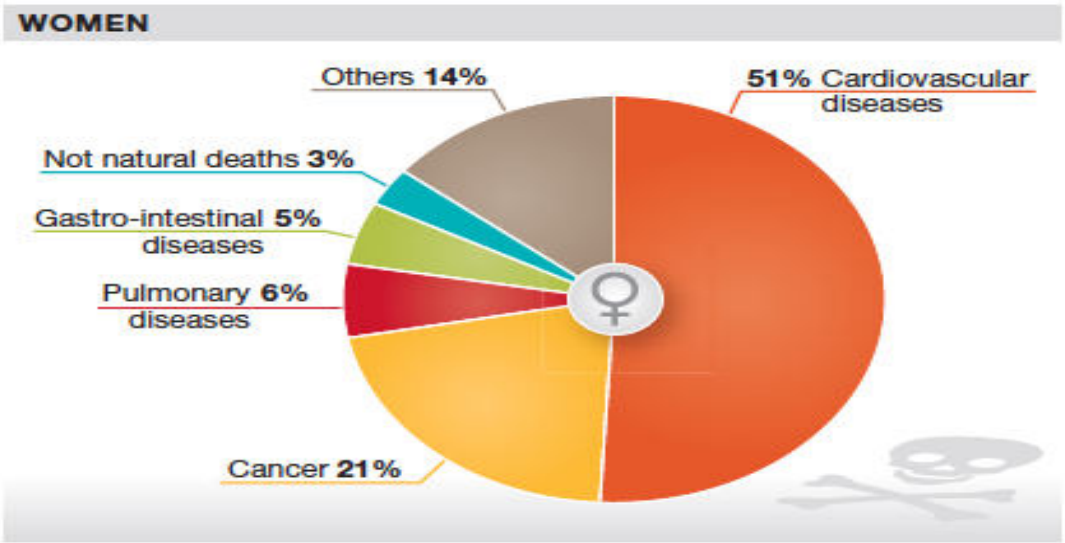
Sex differences in psychiatric diseases



Women and men
Are not equal in terms of health & diseases

Mortality





Vera Regitz Zagrosek
Sex and Gender Differences in Health, Embo Reports 2012

FOREWORD 9

A Symbiotic View Of Life: We Have Never Been Individuals

Scott F. Gilbert
Swarthmore College, sgilber1@swarthmore.edu

J. Sapp

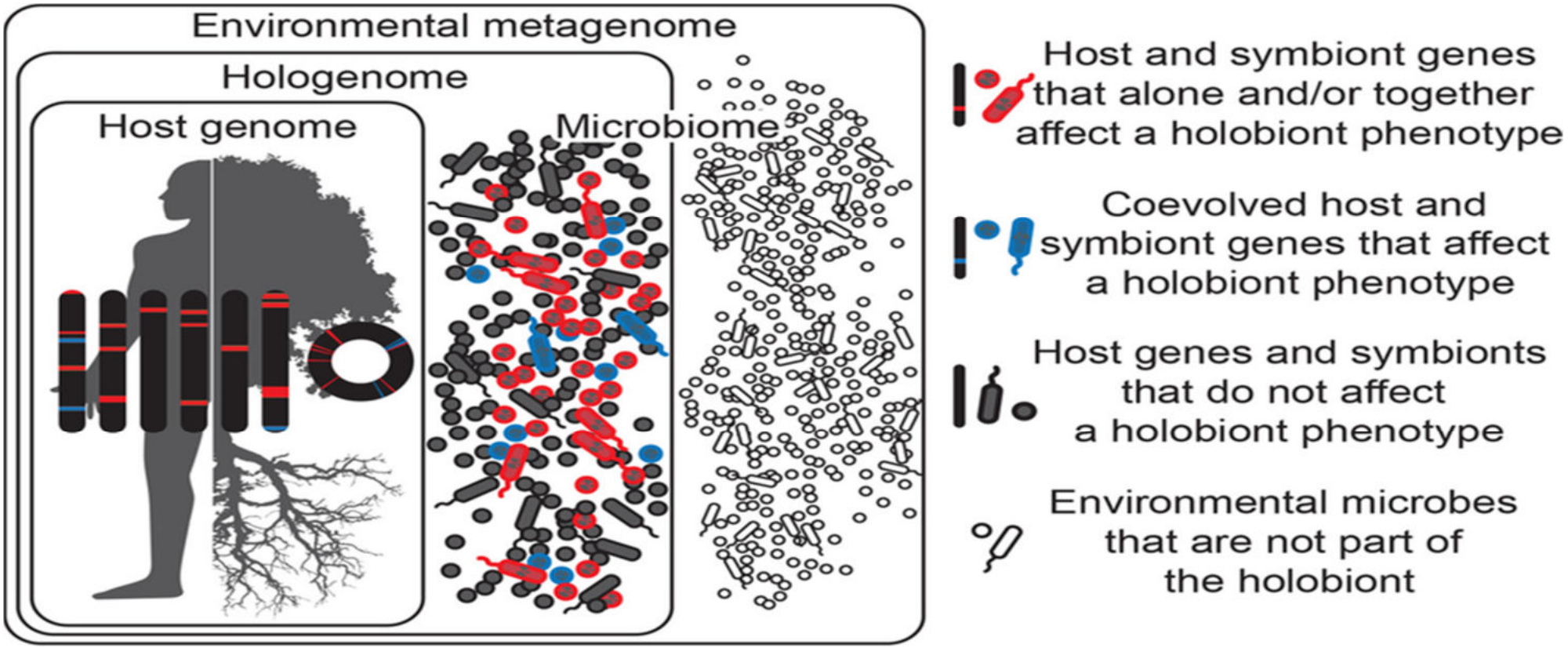
A. I. Tauber

CHICAGO JOURNALS

A Symbiotic View of Life: We Have Never Been Individuals
Author(s): Scott F. Gilbert, Jan Sapp and Alfred I. Tauber
Source: *The Quarterly Review of Biology*, Vol. 87, No. 4 (December 2012), pp. 325-341
Published by: The University of Chicago Press
Stable URL: http://www.jstor.org/stable/10.1086/668166

The notion of the "biological individual" is crucial to studies of genetics, immunology, evolution, development, anatomy, and physiology. Each of these biological subdisciplines has a specific conception of individuality, which has historically provided conceptual contexts for integrating newly acquired data. During the past decade, nucleic acid analysis, especially genomic sequencing and high-throughput RNA techniques, has challenged each of these disciplinary definitions by finding significant interactions of animals and plants with symbiotic microorganisms that disrupt the boundaries that heretofore had characterized the biological individual. Animals cannot be considered individuals by anatomical or physiological criteria because a diversity of symbionts are both present and functional in completing metabolic pathways and serving other physiological functions. Similarly, these new studies have shown that animal development is incomplete without symbionts. Symbionts also constitute a second mode of genetic inheritance, providing selectable genetic variation for natural selection. The immune system also develops, in part, in dialogue with symbionts and thereby functions as a mechanism for integrating microbes into the animal-cell community. Recognizing the "holobiont"-the multicellular eukaryote plus its colonies of persistent symbionts-as a critically important unit of anatomy, development, physiology, immunology, and evolution opens up new investigative avenues and conceptually challenges the ways in which the biological subdisciplines have heretofore characterized living entities.

Una **visione simbiotica della vita: non siamo mai stati «in-dividui»**
La nozione di "individuo biologico" è cruciale per gli studi **di genetica, immunologia, evoluzione, sviluppo, anatomia e fisiologia**... **Durante l'ultimo decennio, il sequenziamento genomico ha sfidato le varie definizioni** trovando **interazioni significative in animali e piante con i microrganismi simbiotici che rompono i confini che prima avevano caratterizzato l'individuo biologico.. lo sviluppo animale è incompleto senza simbionti**...
I simbionti costituiscono una **seconda modalità di ereditarietà genetica.. il sistema immunitario si sviluppa nel dialogo con i simbionti**. **Riconoscere l'olobionte - l'eucariota multicellulare più le sue colonie di simbionti persistenti - come unità di anatomia, sviluppo, fisiologia, immunologia ed evoluzione criticamente importanti** concettualmente **sfida i modi in cui le varie discipline biologiche hanno fino ad ora caratterizzato le entità viventi.**


Environmental metagenome
Hologenome
Host genome
Microbiome
Host and symbiont genes that alone and/or together affect a holobiont phenotype
Coevolved host and symbiont genes that affect a holobiont phenotype
Host genes and symbionts that do not affect a holobiont phenotype
Environmental microbes that are not part of the holobiont

nature REVIEWS GENETICS

Nature Reviews Genetics **18**, 128–142 (2017)

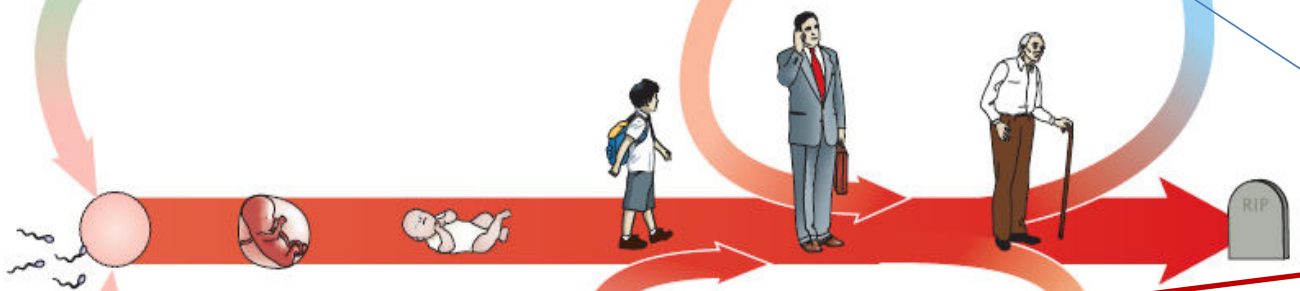
Mosaicism in health and disease – clones picking up speed

An adult human body is likely to contain as many versions of the genome as the number of somatic cells. This is a result of the fact that every cell division is coupled with risk for new mutations.

Germline variation (GV)
- Constitutional and intergenerational; the classic type of genetic variation inherited from germ line to zygote
- Together with DNVs the most frequently studied type of genetic variation in GWAS

Post-zygotic variation (PZV)
- Variants arising at the first division of the zygote or later in different somatic cell lineages
- Variants arise in one soma and typically disappear from the population with the death of its carrier
- PZV is a possible driver in many disease processes but is often an ignored source of variation

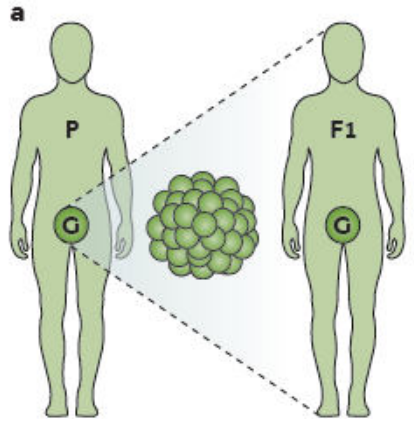
Cellular depletion (CD)
- Reduction of mosaicism by age-associated cell death

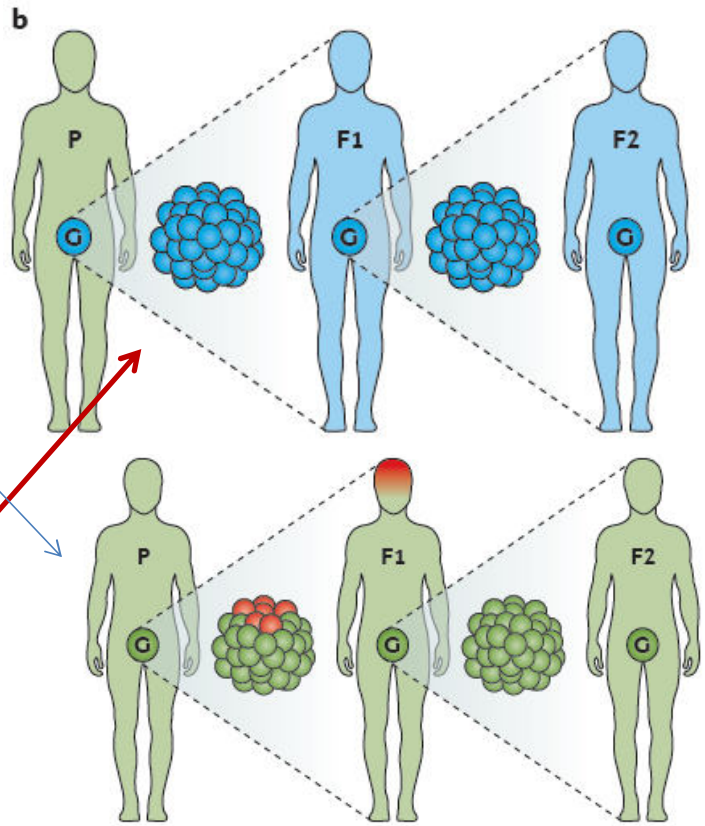


***De novo* variants (DNVs)**
- Arise in cells of the germ line in parental generation and are present in the next generation
- Also encompass variants arising by gonadal mosaicism

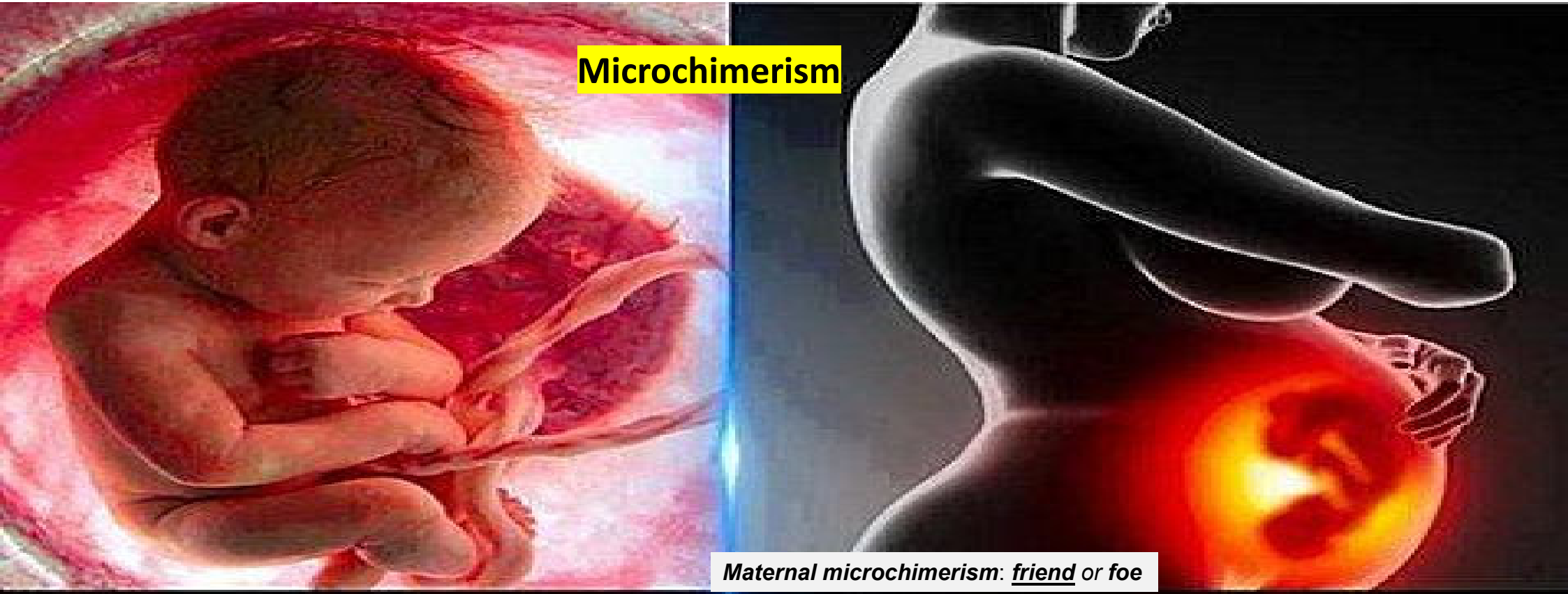
Microchimerism (MC)
- The presence of cells from another subject in the soma of a host individual

Revertant mosaicism (RM)
- Reduction of total variation of the soma by back mutations





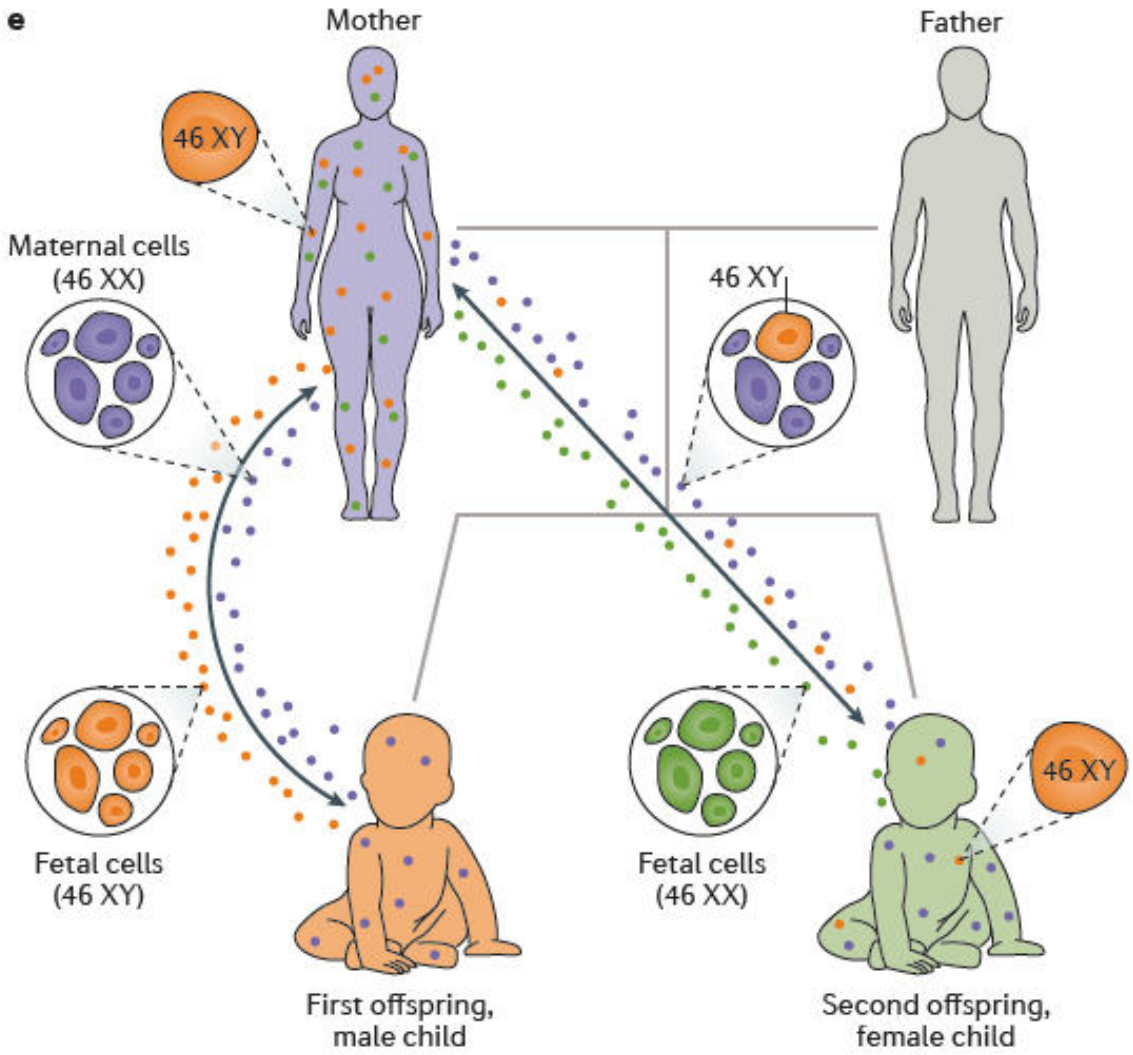
Microchimerism

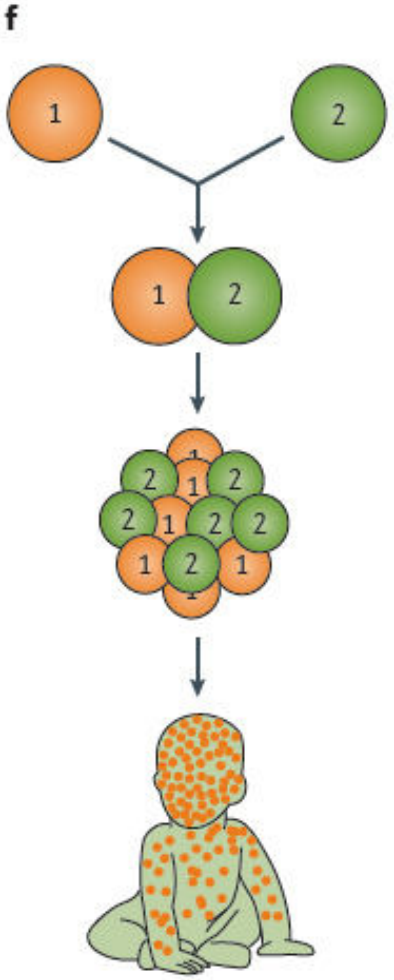


Maternal microchimerism: ***friend*** *or* ***foe***

In the womb, the fetus receives blood proteins from his mother through the placenta which protects him against various diseases for the rest of his life.

When the mother suffers organ damage such as heart attack, the fetus sends stem cells through the placenta to repair the damaged organ.





Microchimerism

Classical chimerism is a rarely observed phenomenon that occurs when **an embryo is formed from two independently conceived zygotes**.
It results in a fetus with a **mixture of cells with genotypes derived from different germ cells**

FOREWORD 10

EPIGENETICS > GENETICS

Cosa è la "MALATTIA" ?

G. Fanconi " ***Non*** *vi sono* ***malattie nuove****.. nuovo è il modo di interpretarle*"
(Burgio-Notarangelo
Malattie Maestre**,** 2002
pag. 170)

- **M. Grmek**: da ***Vesalio*** e ***Sydenham*** → ***malattia come quadro sintomatologico ben definito = nuova ontologia***

Viruses ←→

PATHOCENOSIS *(cfr.* ***biocenosis****)*

Microbes **TLRs** → ***Natural Immunity***

"changing environment"

Gut Ecosystem

Immuno-systems

Biosphere

tolerance

Adaptive Immunity

Hypersensitivity

type I

type II

type III

type IV

type 0

Fluid Genosphere

Genetic background

Microbioma.. Epigenetics

Systemic (micro)vascular phlogosis

Kawasaki Disease
(*systemic* endothelitis)

Atherosclerosis
(**systemic** endothelitis)

Coeliac Disease

Autism (?)

"Neurodegenerative" diseases

Eventually, during the last years, the ***fetal programming mismatch theory*** has been transformed **from a theory essentially useful to explain the pathogenic mechanisms causing certain diseases of adulthood, into the key-model theory of the embryo-fetal origins of adult diseases (DOHA-Developmental Origins of Health and Diseases)**

Obesogens

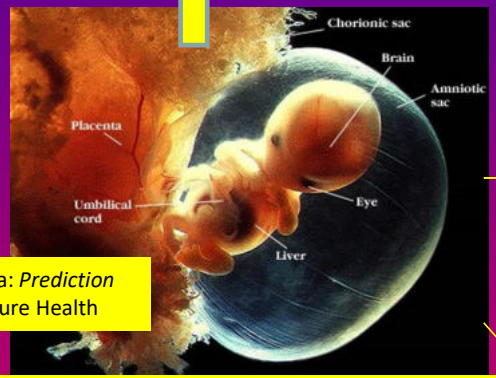
Multiorgan Effects of Endocrine Disruptors

Pesticides

In Vitro Fertilization

Materno Fetal Stress

Obesity/Metabolic Syndrome/Diabetes 2



Placenta: *Prediction* of Future Health

Developmental Time Windows of Vulnerability

Cardiovascular Diseases

Ipertension

Asthma and allergies

Lung Development

Reproductive Diseases/Dysfunctions

Semen Abnormalities

CANCER

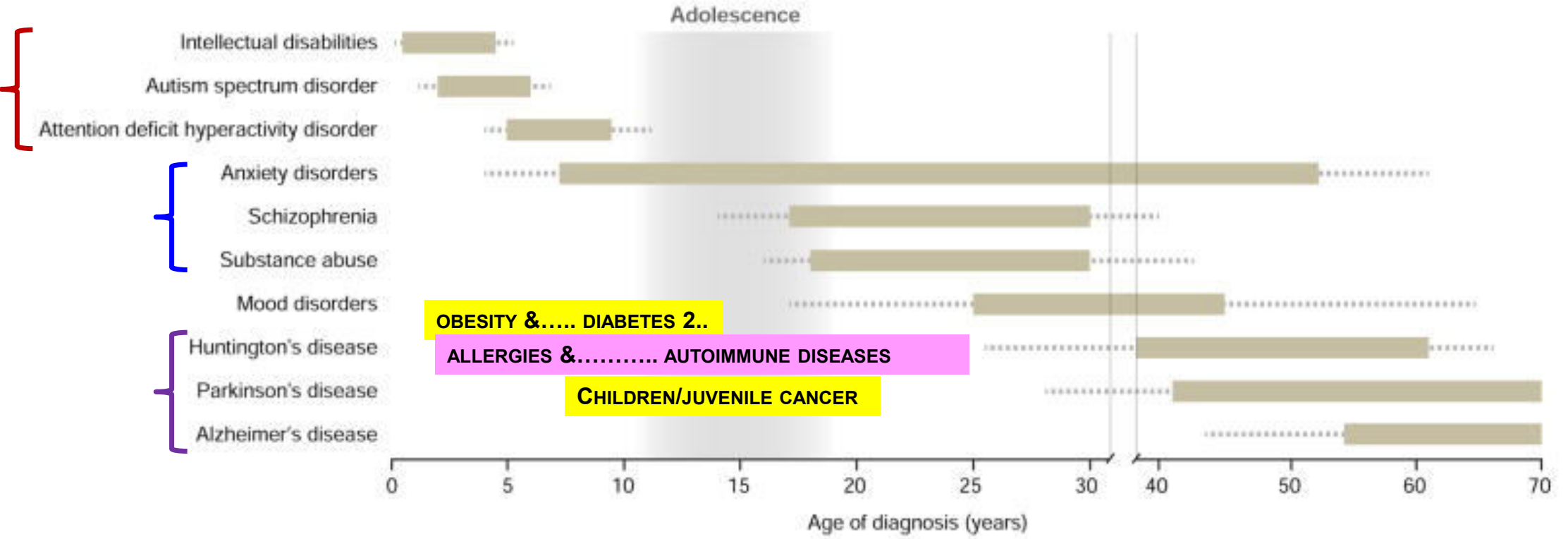
DOHAD

Neurobehavioral Deficits and Diseases

Psychiatric Diseases

Psychiatric and Neurological disorders Have Discrete Ages of Onset (but represent a *continuum*)..
the most interesting and mysterious aspect of the DOHaD model is that their origin is during the fetal-embryo period (*fetal programming*) as for all other chronic diseases that are dramatically increasing in the world (Obesity & Diabetes 2.. Allergies & Autoimmune diseases.. Cancer..) ... which means: *EPIGENETICS > GENETICS*

….it's almost like a time bomb ..



Silbereis JC, Pochareddy S, Zhu Y, Li M, Sestan N. ***The Cellular and Molecular Landscapes of the Developing Human Central Nervous System***. Neuron. 2016;89(2):248–268. doi:10.1016/j.neuron.2015.12.008

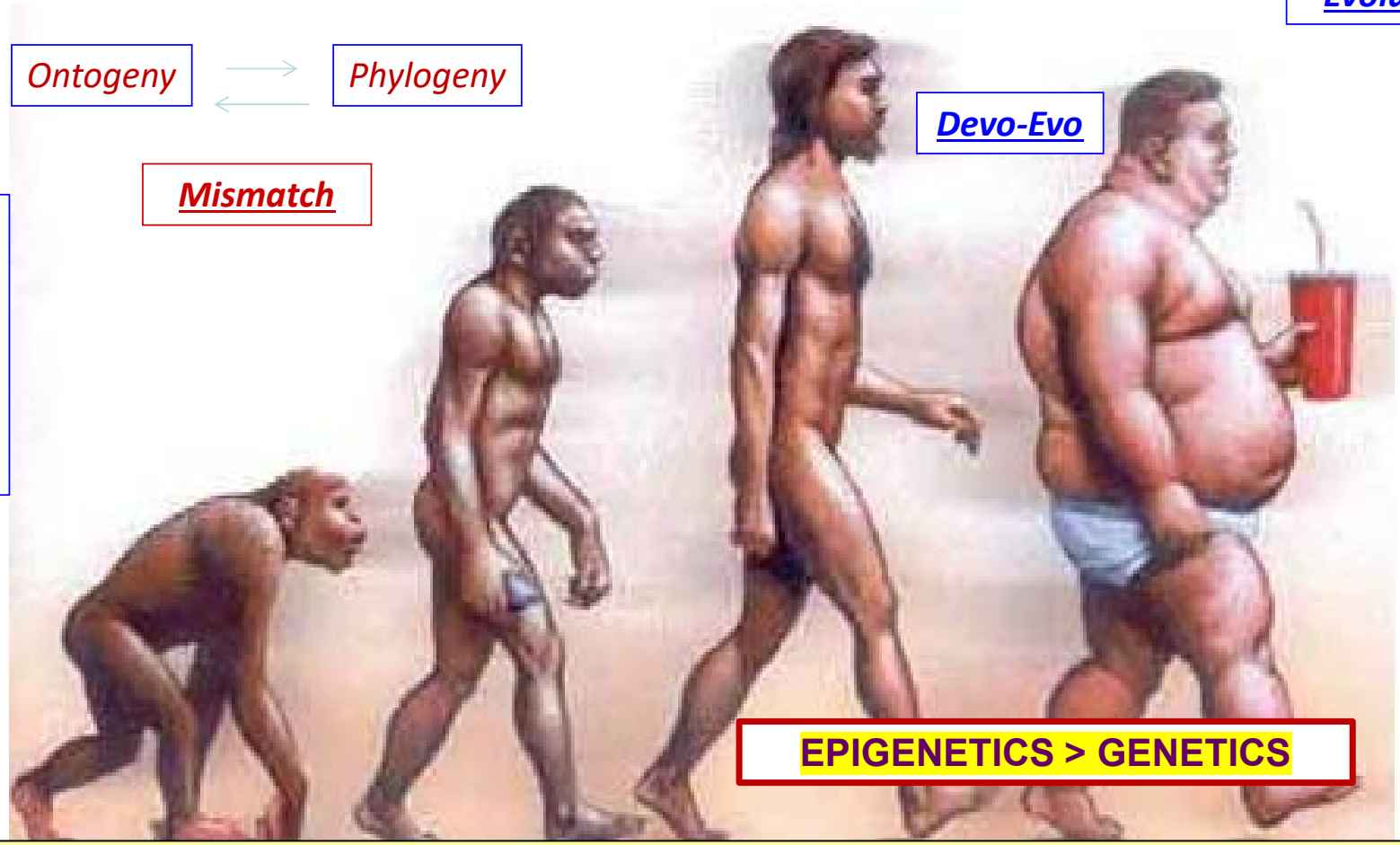
Evolutionary Medicine

Ontogeny ⇄ *Phylogeny*

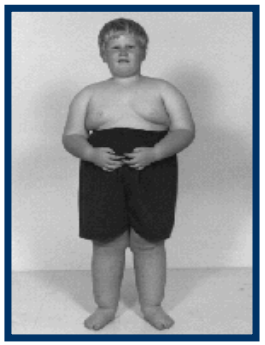
Devo-Evo

Mismatch

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



EPIGENETICS > GENETICS



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

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

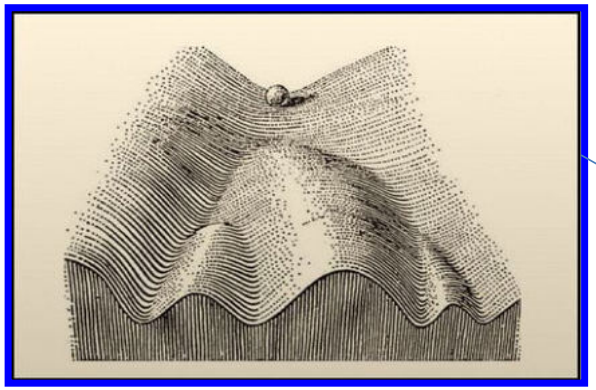
Relative frequency of articles with *epigenetic* or *epigenetics* in their title

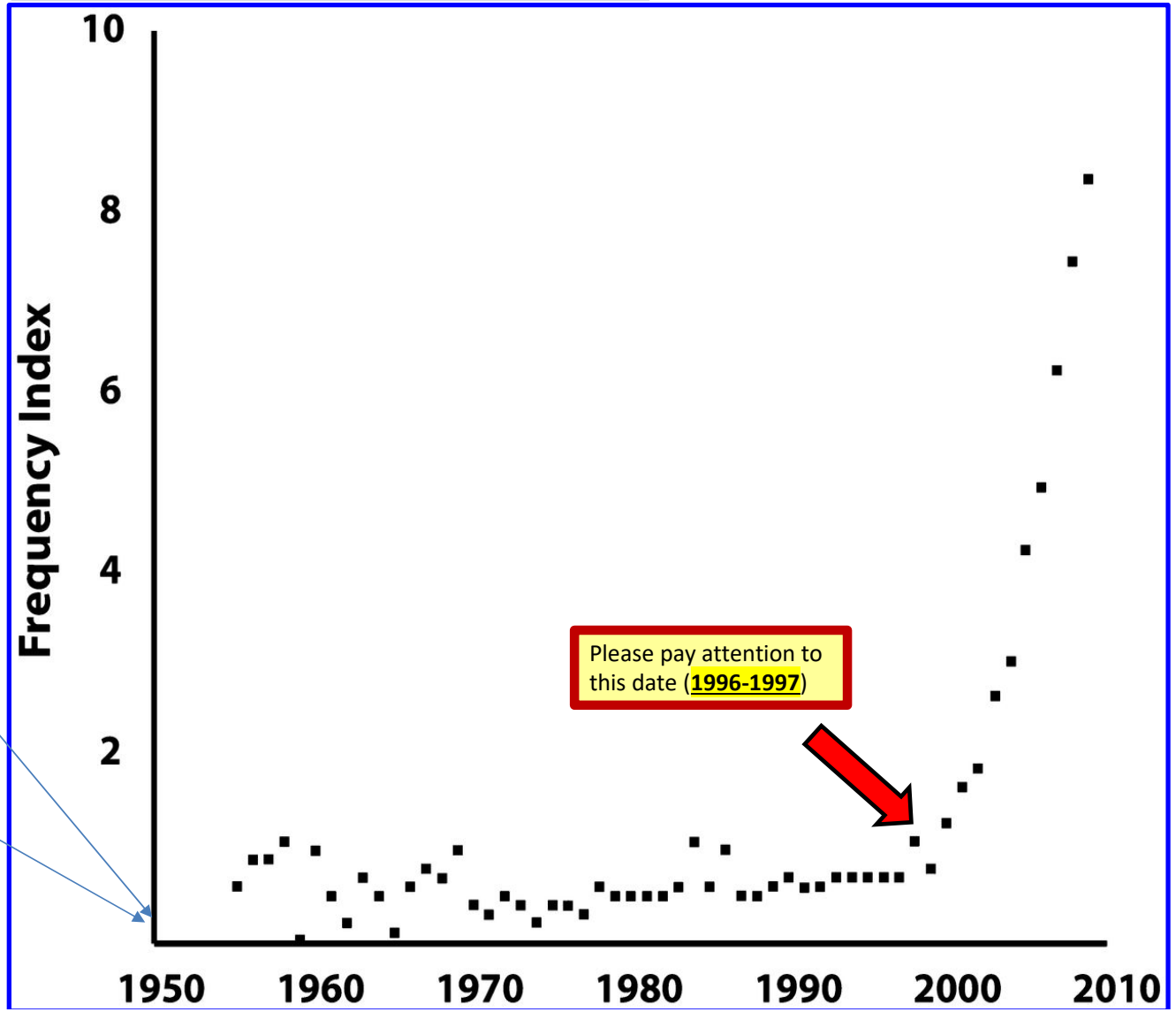
David Haig Int. J. Epidemiol. 2012;41:13-16

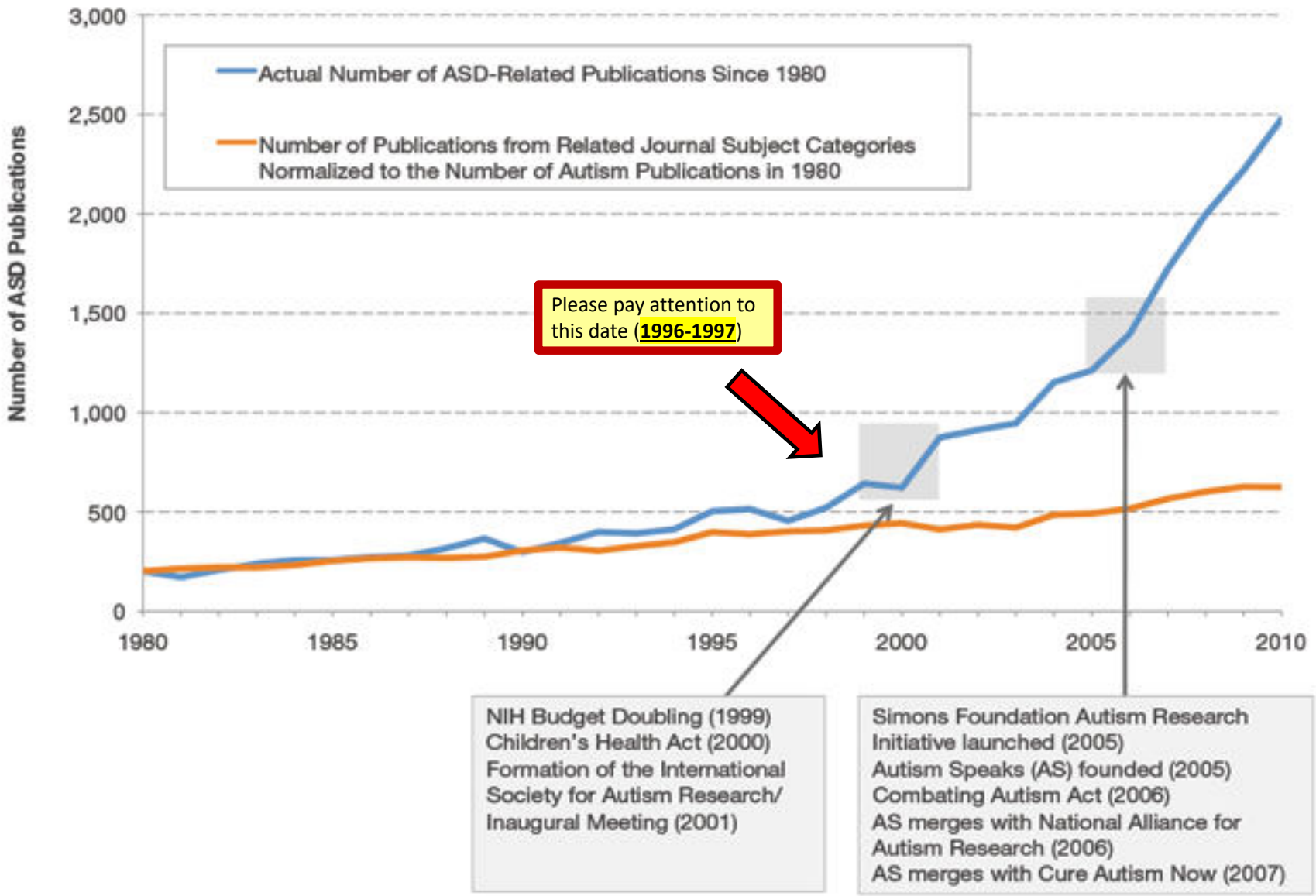
International Journal of Epidemiology

THE AUTHOR

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

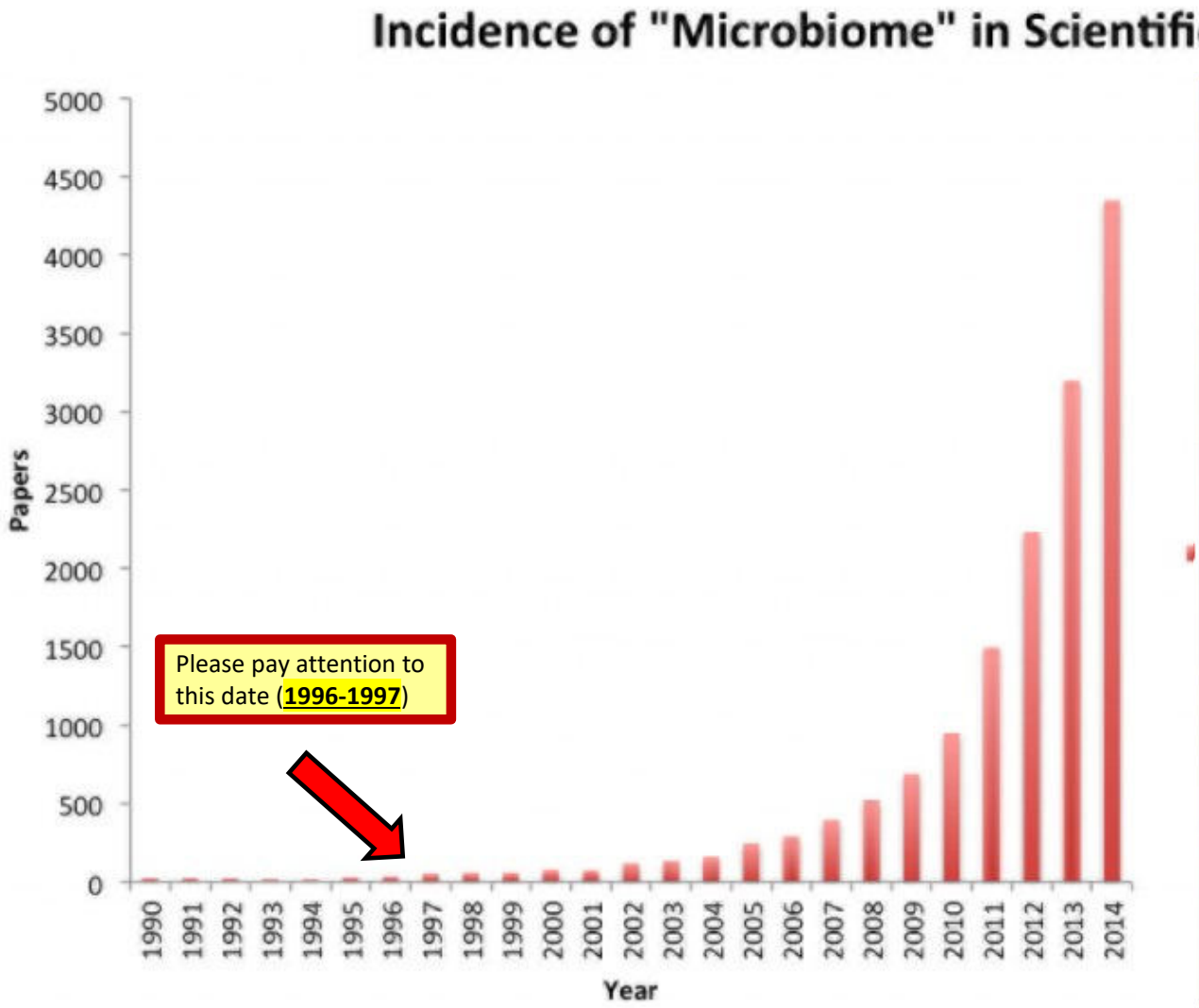


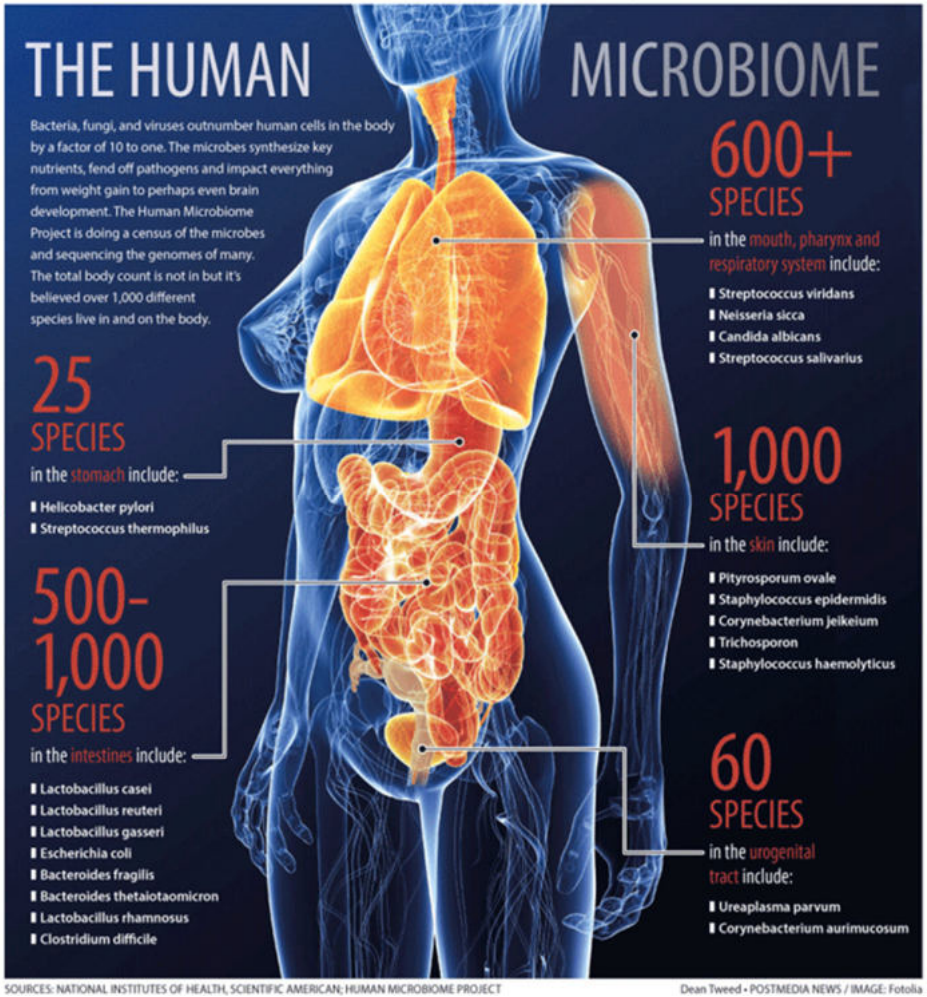



Number of ASD Publications
3,000
2,500
2,000
1,500
1,000
500
0
1980
1985
1990
1995
2000
2005
2010
Actual Number of ASD-Related Publications Since 1980
Number of Publications from Related Journal Subject Categories Normalized to the Number of Autism Publications in 1980
Please pay attention to this date (1996-1997)
NIH Budget Doubling (1999)
Children's Health Act (2000)
Formation of the International Society for Autism Research/ Inaugural Meeting (2001)
Simons Foundation Autism Research Initiative launched (2005)
Autism Speaks (AS) founded (2005)
Combating Autism Act (2006)
AS merges with National Alliance for Autism Research (2006)
AS merges with Cure Autism Now (2007)

The microbiome is the most powerful "epigenetic internal modulator" of early childhood

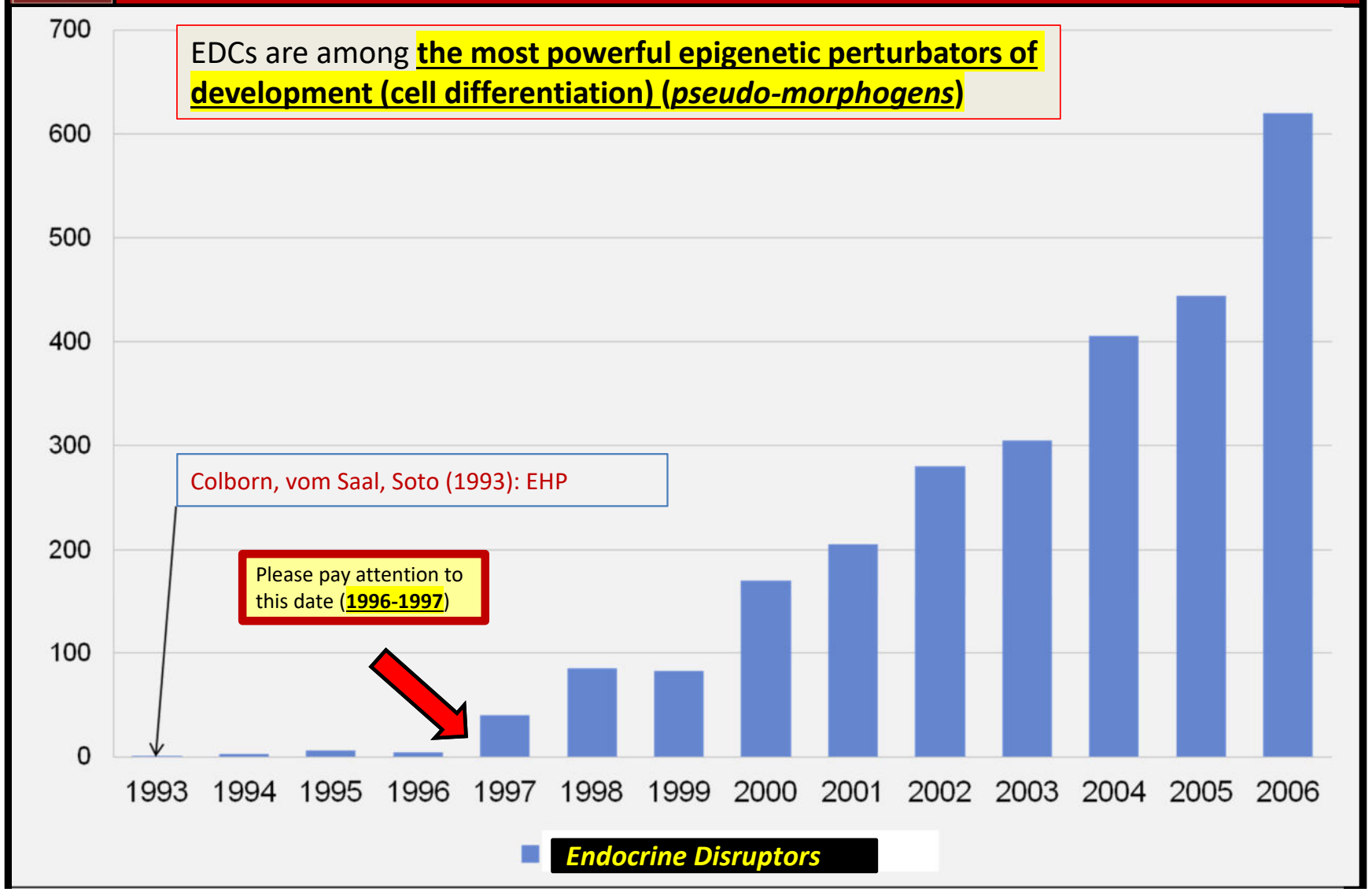
*A quick search for "**Microbiome**" in **scientific journals online** demonstrates how significantly this field of research has been **growing over the past ten years***





ACADEMY FOR ENVIRONMENTAL MEDICINE

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



We have to hope that **this famous quote by Max Planck will be overcome**

A **new scientific truth** does not triumph by **convincing its opponents** and making them see the light,
<u>but rather because its opponents eventually die, and a new generation grows up</u> that is familiar with it.

Max Planck (1858 - 1947)