Health Implications of Prenatal/Early Childhood Exposures

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JOHNS HOPKINS

BIRTH DEFECTS ARE THE RESULT OF A GENE - ENVIRONMENT INTERACTION

GENE ENVIRONMENT

Cystic Fibrosis – a Gene Defect

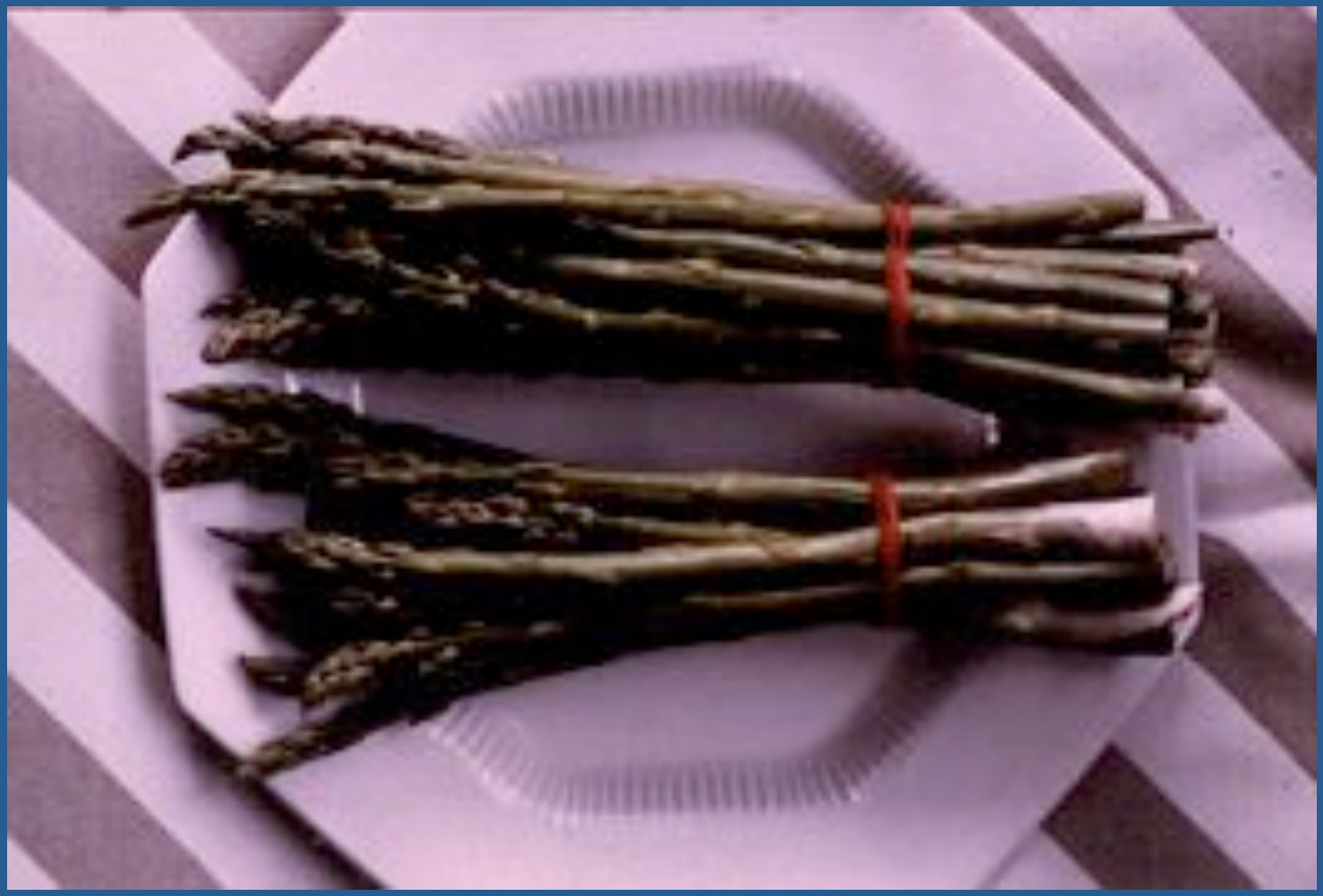
- Autosomal recessive
- 1 in 2000 Caucasians are carriers, 1 in 19 in Ireland
- Mutation in the gene for the cystic fibrosis transmembrane conductance regulator (CFTR) – a chloride channel important in forming sweat, digestive juices and mucus.

Frederic Chopin, 1838

Flashback: Dissident's poisoning

The poison ricin, which has been found by the British police at an address in London, was famously used to murder Bulgarian dissident Georgi Markov in 1978. Markov, a BBC World Service journalist and a strong critic of the communist regime, was killed in London when he was injected with ricin while he waited at a bus stop.

A Gene-Environment Interaction
Asparagus



Genetic Polymorphism vs. Genetic Mutation

- Extremely common vs. extremely rare
- Change in the sequence of DNA
- Heritable

Thalidomide

- 1950 -1960
- Rare birth defect, so increase in numbers noticed.
- Overturned current medical thought
- Exposure in a critical window (GD 28 – 35)
- Increased risk of autism if exposed GD 20 – 25)

15% of exposed infants affected

So What is Epigenetics?

- If thalidomide was taken intermittently, why didn't the arms and legs continue to grow?

Why are Identical Twins not exactly the same?

- Have the same DNA sequence
- Chemical modifications to the histones or to the DNA itself cause changes in gene expression (epigenetic changes)
- The epigenetic differences in

Fetal Origins of Adult Health

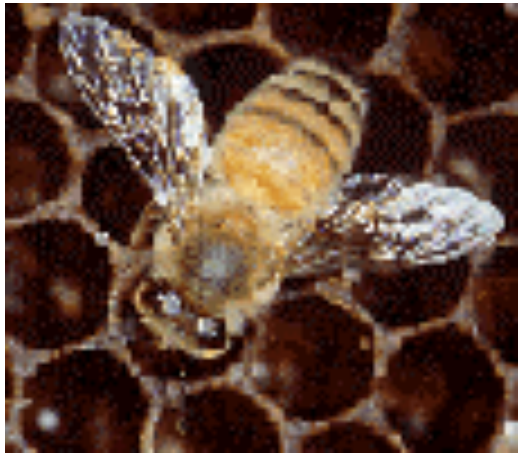
Honeybee - Queen

Nurture
(Environment)

Honeybee - Worker

Nature
(Genes)

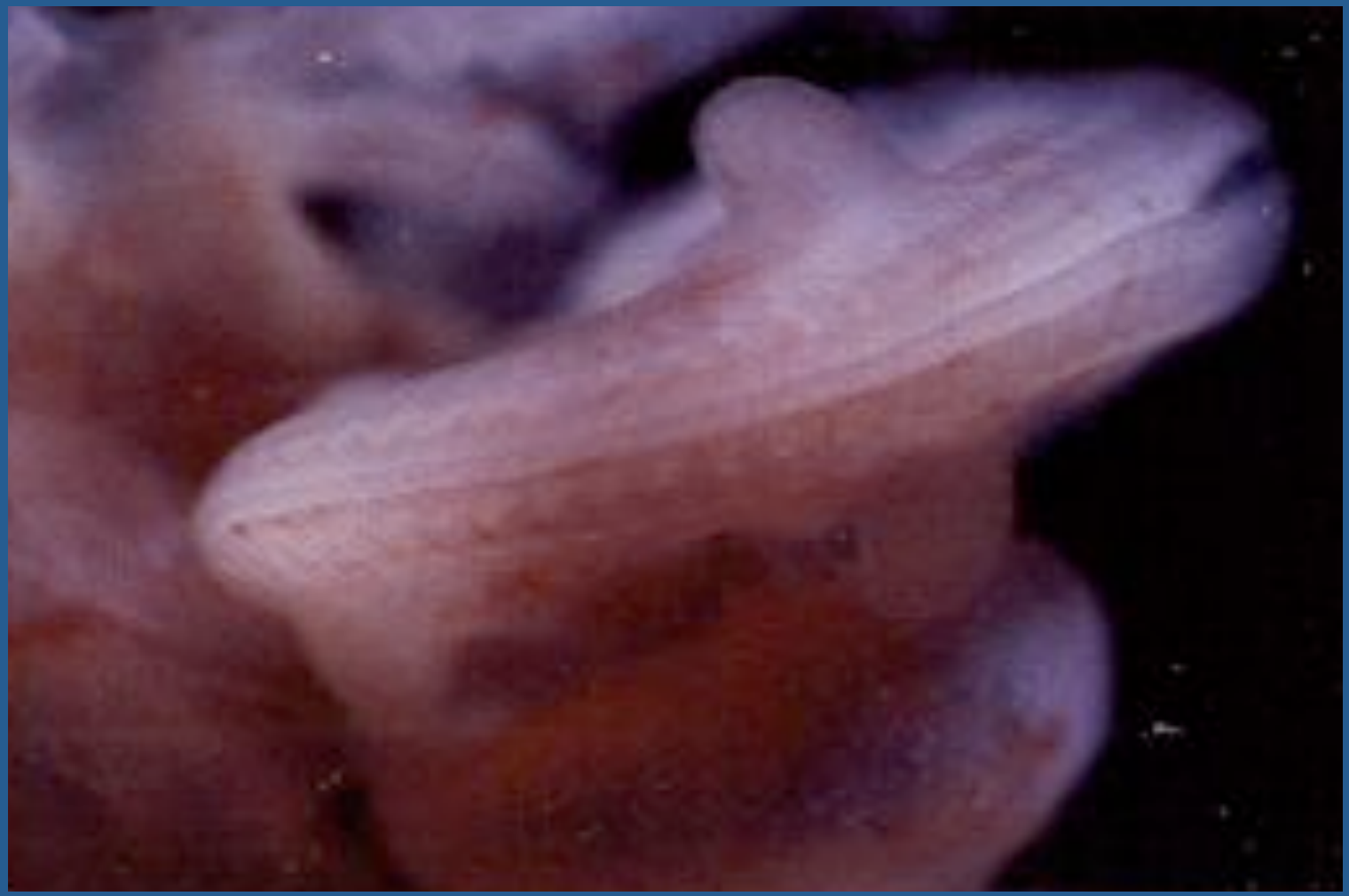
Africanized bee - Worker



Barker's Hypothesis

- Named after David J. P. Barker, a researcher at the University of Southampton
- Published in 1997
- Fetal growth is strongly associated with a number of chronic conditions later in life.
- Increased susceptibility results from adaptations made by the fetus in an environment limited in its supply of nutrients

Neural Tube Closure



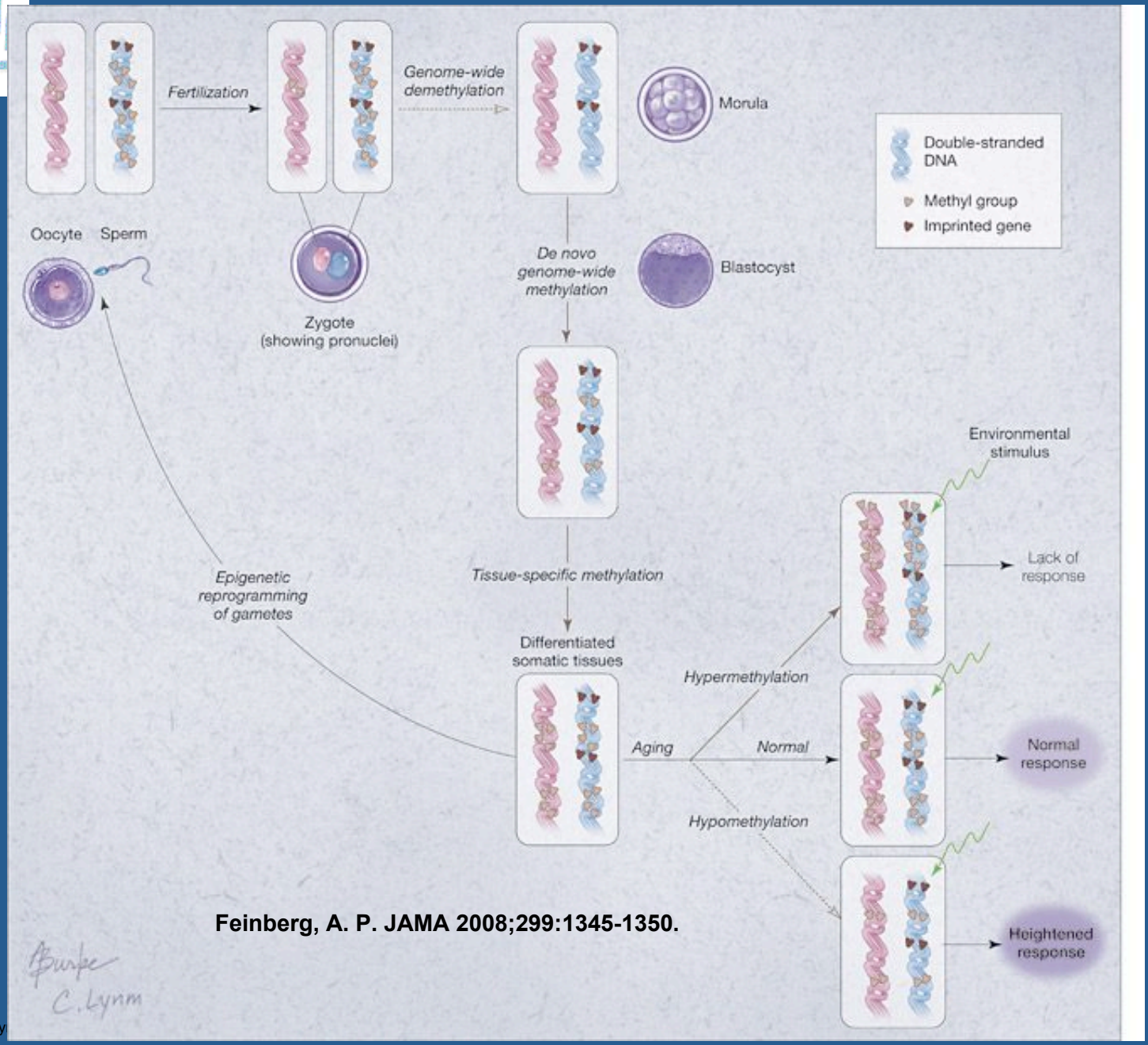
Spina Bifida
(Neural Tube Defect - NTD)

- Reduced with folic acid supplements
- Folic acid is methyl doner
- Epigenetics at work?

Types of Epigenetic Information and Epigenetic Inheritance

1. Modification of chromatin structure
2. Chromatin factors
3. Histone Modification
    1. Methylation
    2. Acetylation
    3. Ubiquitinylation
    4. Phosphorylation
4. Methylation of DNA

Life Cycle of the Epi-genome



Feinberg, A. P. JAMA 2008;299:1345-1350.

Genomic Imprinting

- A form of gene regulation in which epigenetic chromosomal modifications drive differential gene expression in a parent of origin manner.
- Once set in the embryo, stable over the lifespan.

Prader Willi – Genomic Imprinting

- Lack of paternal segment of chromosome 15 either by deletion or by maternal uniparental disomy
- Associated with paternal occupational exposure to hydrocarbons

Angelman Syndrome

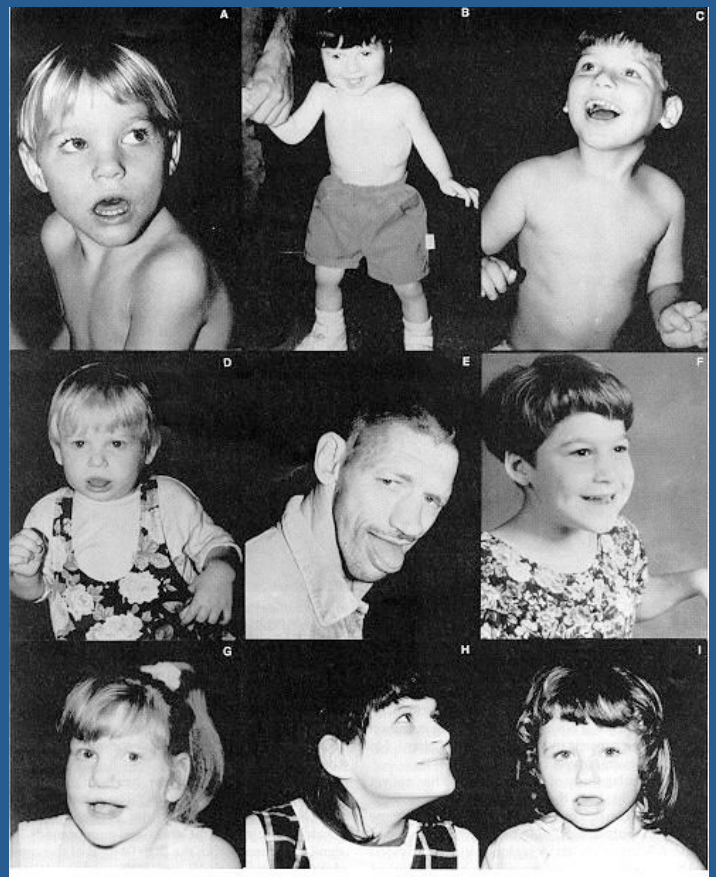
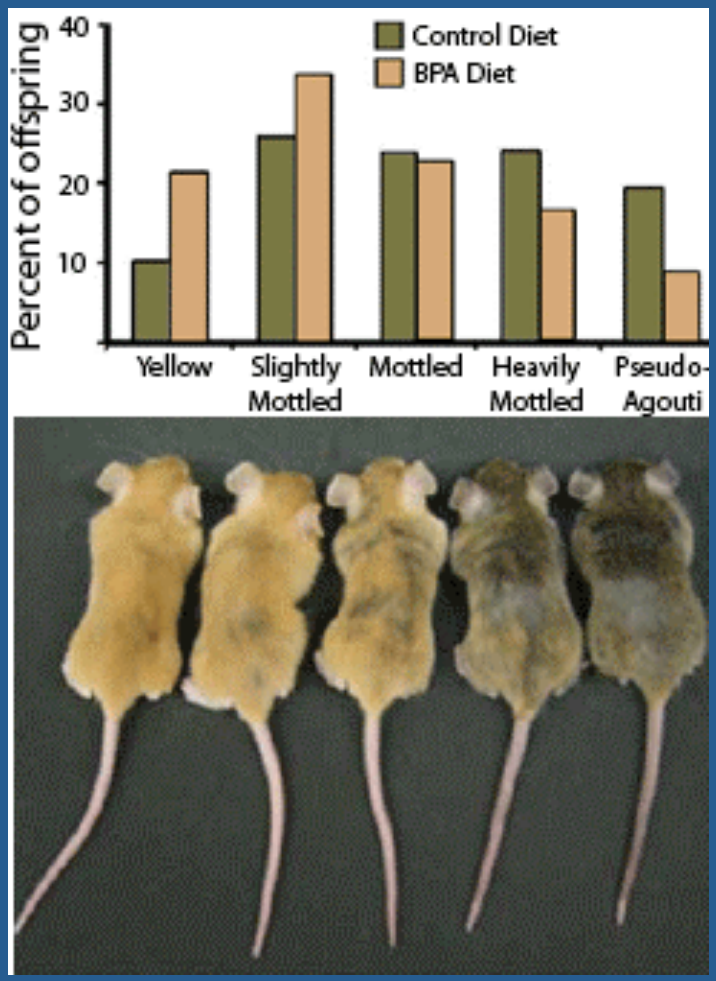


FIGURE 1. Composite of unrelated individuals with AS illustrating some typical behavioral and facial appearances. All individuals except C have typical large deletions of 15q11-13. Individual C has no abnormality yet detected of his chromosomes 15. See text for details.

- **Lack of maternal expression of region of chromosome 15**
- **Demonstrates importance of parent of origin**

Metastable Epialleles

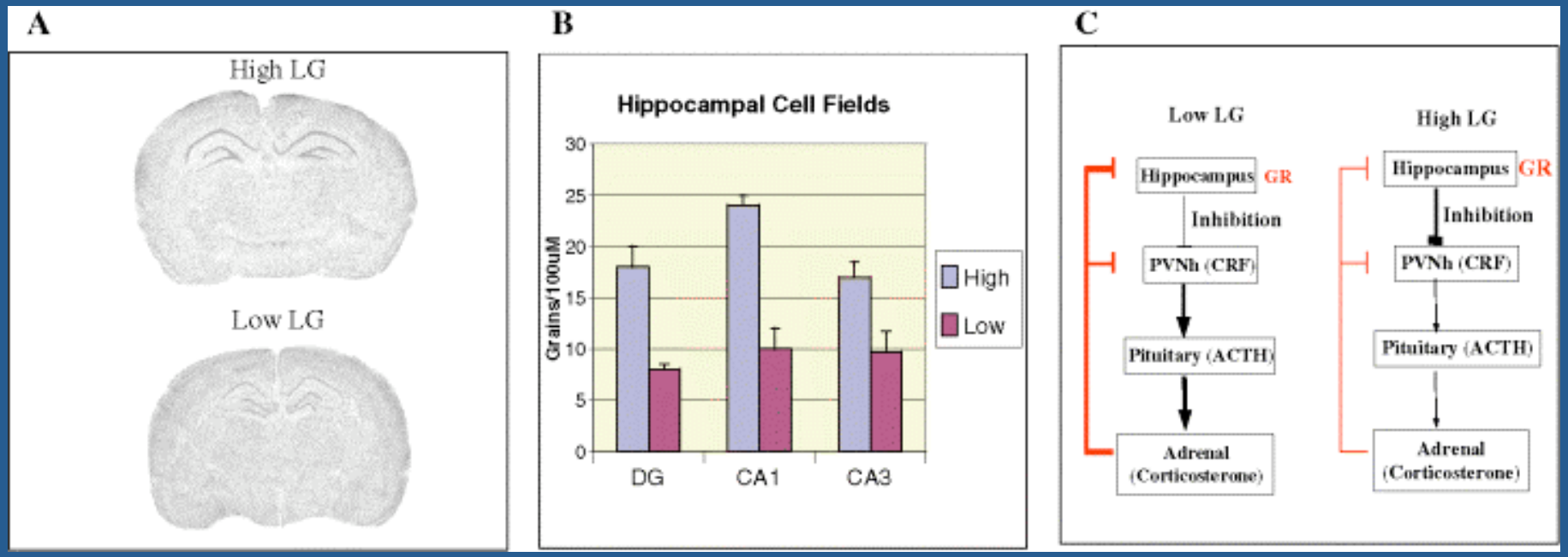
- Dynamic changes in the epigenetics of certain genes
- Ex. Yellow agouti color is dependent on DNA methylation
- Bisphenol A decreased the methylation
- Supplementing the diet with methyl donors (folate, choline) returned coat color to normal



The Nurture of Things

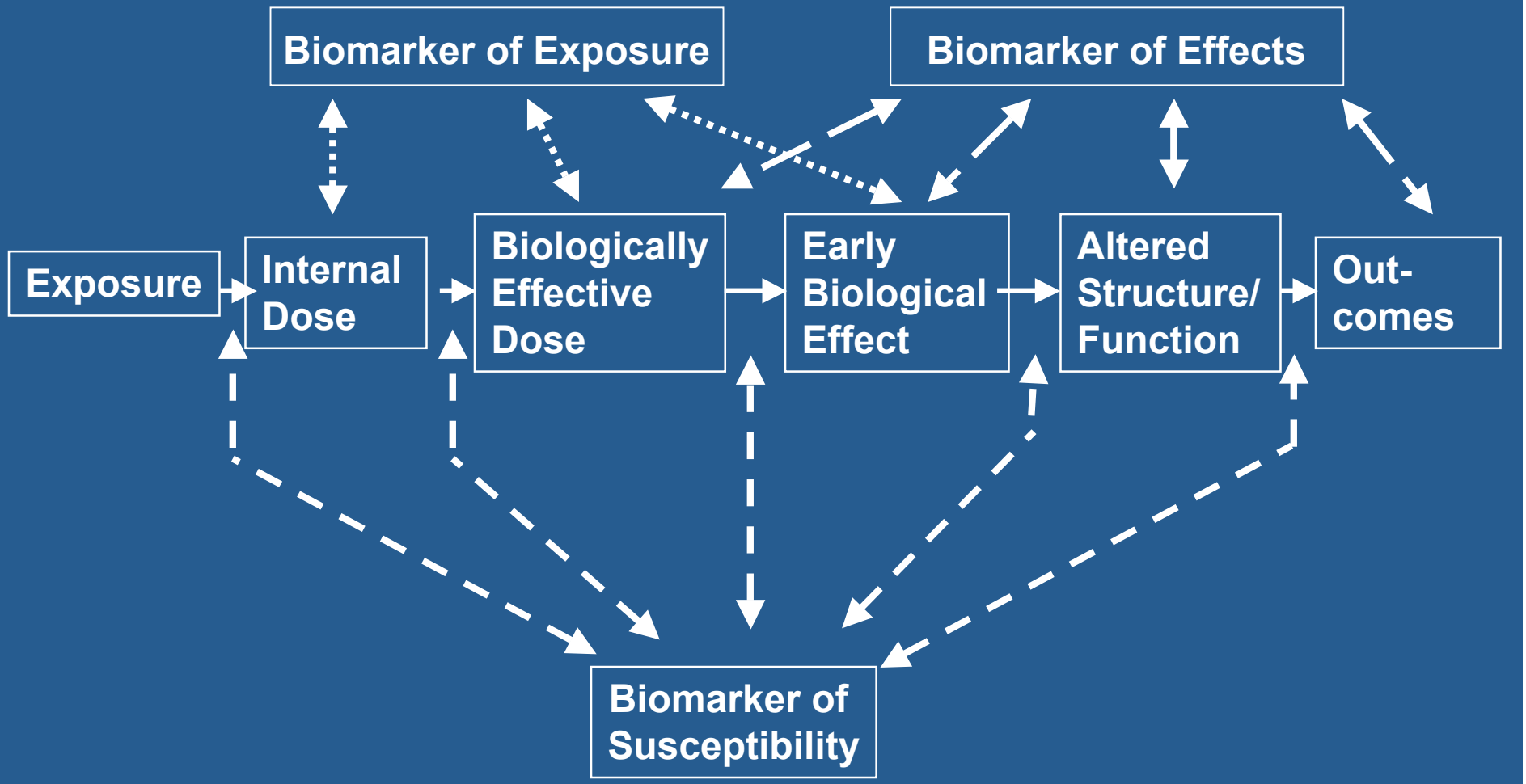
Like the rodents shown here, rats that are good moms can permanently change the way the genes of their offspring act, causing the pups to be calmer throughout adulthood, professors Moshe Szyf and Michael Meaney found. The epigenetics pioneers were the first to prove that nurture can in fact trump nature.

Maternal licking/grooming during critical period determines adult behavior phenotype

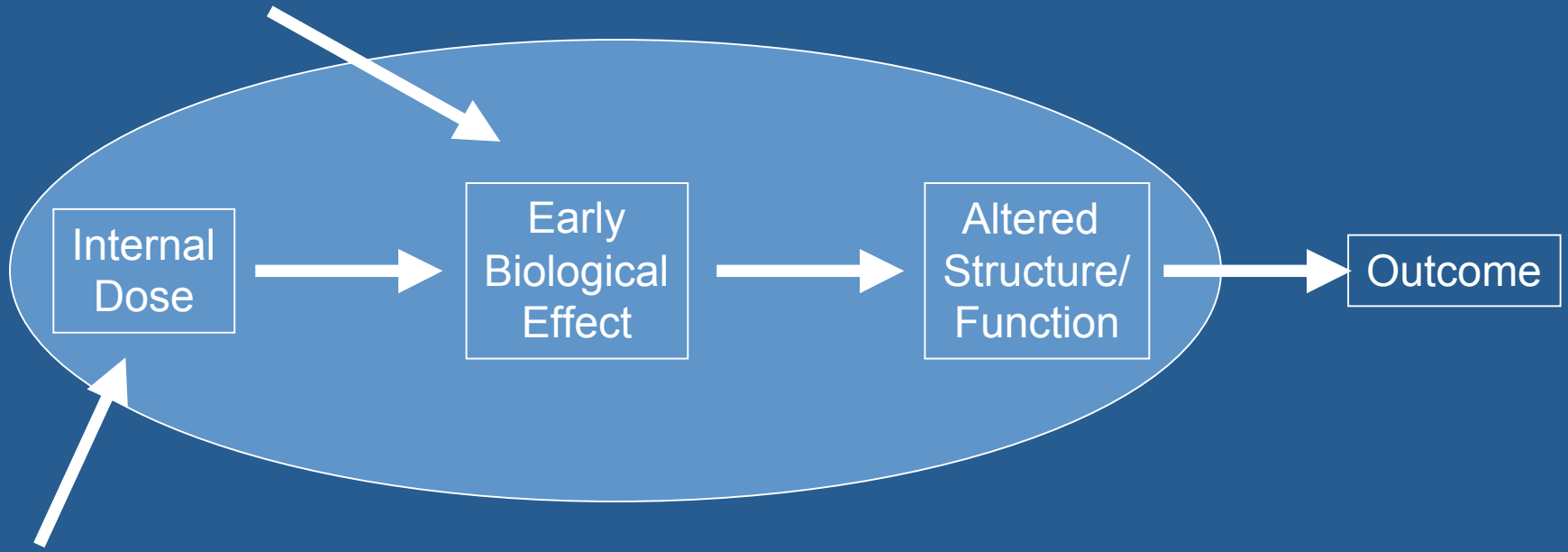


Glucocorticoid Receptor expression

Biomarkers


Biomarker of Exposure
Biomarker of Effects
Exposure
Internal Dose
Biologically Effective Dose
Early Biological Effect
Altered Structure/ Function
Out-comes
Biomarker of Susceptibility

An Influence that is not taken up by the body, e.g. witnessing violence, family relationships, experiencing wilderness, playing music



Influences that can be introduced Into the body, e.g. diet, lead, Bacterial toxins

Outcomes to Avoid!!

MUSIC

Dancing with Cats

Language

- Different parts of the brain from vocalizations/gestures
- Incredible speech acquisition of young infants/children
- Poetry
  - To make a prairie, it takes a clover and one bee,--
  - One clover, and a bee,
  - And revery.
  - The revery alone will do
  - If bees are few.
    - Emily Dickinson

Leadership

Everybody wants their

kid to be President!!!

Human Beings

Human Beings

Epigenetics?

Thank you!
Questions?