The First 1000 Days:
Do YOU see what WE see?

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Our Agenda:

**Epigenetics Overview** (10min)

**Brain Basics** (10min)

**Case Study** (15min)

**Discussion** (25min)
Epigenetics Vocabulary

- DNA methylation
- Evolutionary capacitance
- GenomePlex
- Histone code
- Nutriepigenomics
- Preformationism
- Synthetic genetic array
Fetal Transcriptome Trisomy 21

• Three #21 Chromosomes
• Each Chromosome by itself is normal
• Changes in gene expression:
  – 311 genes are up- or down-regulated
    (when compared to euploid)
• Only 5 genes on the 21 Chromosome!
• MANY downstream effects!

Diana Bianchi, AAP NCE, 2012
Slonim et al., 2009. PNAS 106:9425-9
Twins
Percent of twin pairs who share the trait

- Height
- Reading Disability
- Autism
- Alzheimer's
- Schizophrenia
- Alcoholism
- Bipolar Disorder
- Hypertension
- Diabetes
- Multiple Sclerosis
- Breast Cancer
- Crohn's disease
- Stroke
- Rheumatoid Arthritis

Legend:
- Greater genetic influence
- Greater environmental influence

Identical Twins

Fraternal Twins
Chromosome 3 Pairs

3-year old twins vs. 50-year-old twins

3-year-old twins

Yellow shows where the twins have epigenetic tags in the same place.

50-year-old twins

Red and green show where the twins have epigenetic tags in different places.
Neonatal Diabetes

- IUGR
- Severe diabetes - regresses 3 months
- May relapse with stress
- Paternally expressed, maternally hypomethylated
  - Upd(6)pat – 40%
  - Dup(6q24)pat – 32%
  - Maternal hypomethylation of TNDM1 – 28%
Tobacco Exposure in utero

Suter et al. Epigenetic 2011;6:1284
Asthma

Inherited genotype

Effects may depend on functional genetic polymorphisms

Environmental exposures modify gene expression

Viruses  Bacteria  n-3PUFA  Antioxidants  Prebiotics  Folate  Allergens  Pollutants

Tissue effects

At birth: emerging differences in immune

Immune effects

ANTENATAL EFFECTS

POSTNATAL EFFECTS

Evolving phenotype / Trans-generational effects?

David Martino and Susan Prescott

Chest 2011;139:640-647
DOI 10.1378/chest.10-1800

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Obesity

Eric Snyder et al.

The Human Obesity Gene Map: 2003 Update
Obesity Research 12(3): 369-439, March ’04
710 references, special populations
41 syndromes, fat distribution
Insulin, diabetes, growth hormone, lipin, leptin, leptin receptor, cholecystokinin receptor
450 genes, markers, chromosomal regions
23 chromosomes affected
Summary

**EPIGENETICS:**
Not your parents’ genome!
Brain Basics

Three Cellular Mechanisms

• Neurogenesis / Cell death
  (Redundancy / Efficiency Motif)
  (On-going in some areas of the brain)

• Synaptogenesis / Pruning
  (0-18mo / 18-36mo)
  (Repeats again in early adolescence)

• Myelination
  (From “dial-up” to “broadband”)
#1. Experience-Dependent

- Experience / Activity influence the cellular mechanisms of development
  - Stress dec. neurogenesis/inc. cell death
  - “Fire together = wire together” (synaptogenesis)
  - “Don’t use it, you lose it” (pruning)

- Brain structures are like muscles
- Which parts of the brain are being strengthened?
#2. Cumulative

• Architecture is built from the bottom up
  - Is the foundation sturdy or weak?
• Synapses $\rightarrow$ circuits $\rightarrow$ pathways $\rightarrow$ behaviors and skills
• Early experiences are foundational
• Skills beget skills
  (and deficits beget deficits)
• Gaps/disparities appear early
  (Hart and Risley, 1995)
#3. PLASTIC

- **PLASTICITY** refers to the brain’s unique ability to literally “rewire” itself in response to experience.

- Experience influences not only the foundational architecture, but the on-going connectivity and functionality.

- Two different types of plasticity.
PLASTICITY

• **Synaptic Plasticity** –
  – Variation in the **STRENGTH** of individual connections
  – “from a whisper to a shout”
  – Lifelong (how old dogs learn new tricks)

• **Cellular Plasticity** –
  – Variations in the **NUMBER (or COUNT)** of connections
  – “from one person shouting to a stadium shouting”
  – Declines dramatically with age (**waning by age 5**)
Asynchronous/Differential Maturation

Brain Stem & Cranial Nerves:
Vital functions
Swallowing

Cerebellum:
Smooth movements
Coordination

Occipital Lobe:
Visual processing

Parietal Lobe:
Integration of sensory data and movement

Temporal lobe (outside):
Processing sound and language

Limbic System (inside):
Emotions and impulsivity
+ The Gas Pedal +
Amygdala

Frontal lobes:
Abstract thought, reasoning, judgment, planning, impulse and affect regulation, consequences

-PFC (with some hippocampal help)
- The Brake – PFC

Brain Stem & Cranial Nerves:
Vital functions
Swallowing

+ The Gas Pedal +
Amygdala

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Out of Balance?

**Prefrontal Cortex**
- Cold Cognition
- Judgmental
- Reflective
- Calculating
- Think about it

**Amygdala**
- Hot Cognition
- Emotional
- Reactive
- Impulsive
- Just do it

Biological maturity by **24**

Biological maturity by **18**

Adapted from Ken Winters, Ph.D.
Early Stress

CHILDHOOD STRESS

Hyper-responsive stress response; calm/coping

Changes in Brain Architecture

Chronic “fight or flight;” ↑ cortisol / norepinephrine
Development results from an on-going, re-iterative, and cumulative dance between nurture and nature.
Case Study

Background

- 3 year old female presents for WCC
- This is her first visit to see you
- Recently placed in foster care with one of your established families
- Foster mother has some limited history provided to her by CPS
Past Medical History

• 19 year old mother with poor prenatal care
• 36 and 6/7 weeks gestation; SGA (2kg)
• In the NICU for a few days
• Admitted to PICU at 9 months with bronchiolitis; again last year for asthma
• Immunizations are up to date
Family History

• Mother had severe seasonal allergies and eczema as a child
• Mother had “ADHD” as a child; “anxiety” as a teenager
• Mother was smoking at 12, drinking at 14
• Mother had severe postpartum depression
Case Study

Social History

- Mother was placed in foster care at 12 yo (abused by her step father)
- Mother dropped out of school at 16 yo
- Mother and patient spent several months in a shelter for women and children
- Patient placed in foster care when found by police running in the street at 2AM
Case Study

Physical Exam

**Wt:** 40# (>95%tile)  **Ht:** 39” (75%tile)  **BMI:** 18.5 (>95%tile)

**GEN:** sullen, shy toddler, clinging to foster mom

**HEENT:** NC; PERRL; MMMP; Left TM scarred, right w/pus, red

**CHEST:** rare end expiratory wheezing, no WOB, no rales

**COR:** S1, S2, RRR, no murmur audible

**ABD:** +BS, soft, non-tender, non-distended

**SKIN:** rough, red, dry patches inside of both elbows
Each table to discuss 4 questions; present their answer to 1 question

1) What other information would you like to have ... and why?

2) What risks to her health and well-being have you identified and why are they risks?

3) What opportunities to promote wellness and development have already been missed?

4) What are your priorities moving forward?
Take Home Messages

First **1000** days are not so much about what to **DO** ...

- Not ordering a specific methylation test
- Not giving a specific standardized screen
- Not referring to a specific resource
  (although all of these may be appropriate)

...More about what to **SEE**!
Take Home Messages

Change the LENS we use to PRIORITIZE how we use our limited time w/ families:
- Use an ecobiodevelopmental framework
- Understand life-course theory and developmental trajectories
- Know the biological threats to healthy life courses
- Identify/address environmental risks early
- Whenever possible, proactively build wellness
Take Home Messages

It is easier to **build strong children** than to **repair broken men**.

Frederick Douglass