PEERING INSIDE THE BLACK BOX: The Biology Linking Childhood Adversity and Poor Adult Outcomes

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Disclosures

• I do **NOT** intend to discuss any unapproved or investigational uses for commercial products or devices

• I do **NOT** have any financial relationships with any commercial entities to disclose
Learning Objectives

• Briefly explain recent advances in the basic science of development

• Reframe vague concepts like “adversity” and “resilience” within the context of the physiologic stress response

• Describe the advantages of an EcoBioDevelopmental framework

• Discuss some of the innumerable implications for primary care pediatrics
Critical Concept #1

Life-Course Science

Experiences in childhood (both good and bad) are strongly associated with behaviors, health and economic productivity ...

... DECADES LATER!
Linking **Childhood Experiences** and **Adult Outcomes**

- **Childhood Experiences**
  - ACEs
  - Poverty
  - Violence
- **Parent Engagement**
- **Quality Childcare**
- **Play**

**Childhood Experience** → **Adult Outcomes**

- **Healthy Lifestyles**
- **Academic Success**
- **Economic Stability**

- **Poor Health**
- **Academic Failure**
- **Economic Hardship**
## ACE Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Women (n=9,367)</th>
<th>Men (n=7,970)</th>
<th>Total (17,337)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abuse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Emotional</td>
<td>13.1%</td>
<td>7.6%</td>
<td>10.6%</td>
</tr>
<tr>
<td>- Physical</td>
<td>27.0%</td>
<td>29.9%</td>
<td>28.3%</td>
</tr>
<tr>
<td>- Sexual</td>
<td>24.7%</td>
<td>16.0%</td>
<td>20.7%</td>
</tr>
<tr>
<td><strong>Household Dysfunction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mother Treated Violently</td>
<td>13.7%</td>
<td>11.5%</td>
<td>12.7%</td>
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<tr>
<td>- Household Substance Abuse</td>
<td>29.5%</td>
<td>23.8%</td>
<td>26.9%</td>
</tr>
<tr>
<td>- Household Mental Illness</td>
<td>23.3%</td>
<td>14.8%</td>
<td>19.4%</td>
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<tr>
<td>- Parental Separation or Divorce</td>
<td>24.5%</td>
<td>21.8%</td>
<td>23.3%</td>
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<tr>
<td>- Incarcerated Household Member</td>
<td>5.2%</td>
<td>4.1%</td>
<td>4.7%</td>
</tr>
<tr>
<td><strong>Neglect</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Emotional</td>
<td>16.7%</td>
<td>12.4%</td>
<td>14.8%</td>
</tr>
<tr>
<td>- Physical</td>
<td>9.2%</td>
<td>10.7%</td>
<td>9.9%</td>
</tr>
</tbody>
</table>

*Wave 2 data only (n=8,667)

Data from [www.cdc.gov/nccdphp/ace/demographics](http://www.cdc.gov/nccdphp/ace/demographics)
ACEs Impact Multiple Outcomes

Risk Factors for Common Diseases:
- Smoking
- Alcoholism
- Promiscuity
- High Perceived Risk of HIV
- Obesity
- Illicit Drugs
- IV Drugs
- Multiple Somatic Symptoms
- Poor Perceived Health

Prevalent Diseases:
- Cancer
- Liver Disease
- Chronic Lung Disease
- Ischemic Heart Disease
- Skeletal Fractures
- Sexually Transmitted Diseases

General Health and Social Functioning:
- Relationship Problems
- High perceived stress
- Married to an Alcoholic
- Difficulty in job performance

Mental Health:
- Depression
- Anxiety
- Panic Reactions
- Memory Disturbances
- Poor Anger Control

Sexual Health:
- Teen Paternity
- Teen Pregnancy
- Unintended Pregnancy
- Fetal Death
- Sexual Dissatisfaction

Sexually Transmitted Diseases

Early Age of First Intercourse

Hallucinations

Poor Self-Rated Health

Difficulty in job performance

Depression

Anxiety

Panic Reactions

Memory Disturbances

Poor Anger Control

Teen Paternity

Unintended Pregnancy

Fetal Death

Sexual Dissatisfaction

Early Age of First Intercourse
Developing a Model of Human Health and Disease

Early childhood ecology strongly associates with lifelong developmental outcomes.

How do you begin to define or measure the ecology?

What are the mechanisms underlying these well-established associations?
Defining **Adversity or Stress**

- How do you define/measure adversity?

  - Huge **individual variability**
    - **Perception** of adversity or stress (subjective)
    - **Reaction** to adversity or stress (objective)

- National Scientific Council on the Developing Child (Dr. Jack Shonkoff and colleagues)
  - **Positive** Stress
  - **Tolerable** Stress
  - **Toxic** Stress

Based on the **REACTION** (objective physiologic responses)
Physiologic Stress Response

- **Amygdala** – threat recognition -> hypothalamus

**HPA Axis:**
- Hypothalamic paraventricular nucleus (CRH) ->
- Anterior lobe of the Pituitary (ACTH) ->
- Adrenal Cortex (cortisol)

**SAM Pathway:**
- Hypothalamospinal tract -> sympathetic NS ->
- Adrenal Medulla (epinephrine, nor epinephrine)

**Critical Regulators:**
- PFC/Hippocampus (amygdala); cortisol (Hypo + Pit);
- parasympathetic/vagal nerve (sympathetic NS)
Defining **Adversity or Stress**

- **Positive Stress Response**
  - Brief, infrequent, mild to moderate intensity
  - Most normative childhood stress
    - Inability of the 15 month old to express their desires
    - The 2 year old who stumbles while running
    - Beginning school or childcare
    - The big project in middle school
  - Safe, Stable and Nurturing Relationships (**SSNRs**) allow for a prompt return to **baseline**
    - (responding to non-verbal clues, consolation, reassurance, assistance in planning)
  - **Builds motivation and resiliency**
  - “Positive Stress” is **NOT** the **ABSENCE** of stress
Defining **Adversity or Stress**

- **Toxic** Stress Response
  
  - Long lasting, frequent, or strong intensity
  
  - More extreme precipitants of childhood stress (**ACEs**)
    - Physical, sexual, emotional abuse
    - Physical, emotional neglect
    - Household dysfunction

  - **SSNRs are insufficient to buffer the stress response**
    (Deficient levels of emotion coaching, re-processing, reassurance and support)

  - Potentially permanent changes and long-term effects
    - **Epigenetics** (there are life long / intergenerational changes in how the genetic program is turned **ON** or **OFF**)
    - **Brain architecture** (the mediators of stress impact upon the mechanisms of brain development / **connectivity**)

- Toxic Stress Response

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Critical Concept #2

EPIGENETICS

• “Above the genome”

• Change in gene expression/no change in DNA sequence

• Larger revolution in genomic science
  • OLD VIEW = STATIC; NEW VIEW = PLASTIC (environ. input)

• Complex set of SWITCHES
  • Some are: Master; Dynamic; Programmed Early and Stabile

“Genes load the gun; the environment pulls the trigger”

“Epigenetics: NOT your parents’ genome!”
Impact of Early Stress

MATERNAL STRESS

NEWBORN HPA reactivity and salivary cortisol levels

methylation of the FETAL glucocorticoid (GC) receptor gene

brain expression of the GC receptor
Through epigenetic mechanisms, the early childhood ecology becomes biologically embedded, influencing how/which genes are used.
Critical Concept #3

Developmental Neuroscience

• **Brain Architecture** is experience dependent
  (individual connections or “synapses” and complex circuits of connections or “pathways” are both dependent upon activity)

• **Ecology** (environment/experience) influences how brain architecture is **formed** and **remodeled** (plasticity)

• **Diminishing cellular plasticity** limits remediation

• **Differential Maturation + Significant Adversity** -> **Vicious Cycle of Stress**

• **Early Experiences** create potentially permanent alterations in brain architecture and functioning
Impact of Early Stress

CHILDHOOD STRESS

Hyper-responsive stress response; calm/coping

Chronic “fight or flight;” ↑ cortisol / norepinephrine

Changes in Brain Architecture
Declining plasticity in the developing brain results in potentially permanent alterations in brain functioning and development.
Critical Concept #4

Toxic Stress: Many End-Organs

- **Genome** – changes in telomerase, base-pair mismatch repair, etc.

- **Brain** – changes in the structure/function of the PFC, hippocampus, and amygdala, etc.

- **Endocrine** – changes in acute “stress reactivity” & chronic “basal levels;” altered metabolism

- **Immune system** – changes in immune regulation & surveillance (associations with asthma, dementia, diabetes, cancer, rheumatologic dz)

- **Cardiovascular system** - changes in risk AFTER adjusting for “behavioral allostasis”
Eco-Bio-Developmental Model of Human Health and Disease

NOT: “What’s WRONG with you?

BUT: “What’s HAPPENED to you?

Ecology Becomes biology, and together they drive development across the lifespan.
The critical challenge now is to translate game-changing advances in developmental science into effective policies and practices for families w/ children to improve education, health and lifelong productivity.
“You never change things by fighting the existing reality.

To change something, build a new model that makes the existing model obsolete.”

- R. Buckminster Fuller
I. **Biomedical Model of Disease**
- mid 19th century
- embraced biological reductionism 
  (disease is due to a single, organic etiology)
- embraced mind-body dualism 
  (psychosocial vs. organic etiologies) 
  ("problems of living" versus "problems of life")
- the practice of medicine demands a knowledge 
  of human biology and the physical sciences
- health is simply the absence of disease
II. **Biopsychosocial Model of Health**

- 1977
- grounded in social-cognitive theory; refuted mind-body dualism; embraced a broader vision of health
- the practice of medicine demands an understanding of the nexus between human biology, psychology and sociology
- health is the product of many factors and more than the absence of an objective disease state
III. **Ecobiodevelopmental Model of Disease & Wellness**

- 2012

- driven by advances in basic developmental science, replaces mind/body dualism with adaptive vs maladaptive responses to experience, and acknowledges the developmental origins of both disease and wellness

- the practice of medicine demands an understanding of how the ecology (e.g., the physical, nutritional and psychosocial milieu) and biology (e.g., the genome, the brain) interact in a dynamic and cumulative manner over time

- health is a dynamic continuum between disease & wellness, and early experiences play a pivotal role because the foundations for both disease and wellness are built over time
Advantages of an **EBD** Framework

- Though grounded in **developmental science**, the **simplicity** of the EBD framework may promote understanding as well as **support for translation** (early investments are the right thing to do **biologically**)

- Psychosocial stressors and other salient features of the **ecology** are every bit as **biological** as nutrition or lead (**no** distinction between mental and physical health, just healthy vs. unhealthy **development**)

- Emphasizes the dimension of **time** – to reflect the **ongoing, cumulative** nature of benefits and threats to health, educational success, and economic productivity
Development results from an on-going, re-iterative, and cumulative dance between nurture and nature.
Epigenetics
Neuroscience

ECOLOGY
Physical, nutritional and psychosocial milieu

BIOLOGY
Genomic function, physiology, and brain function

Cumulative Changes Over Time:
- Changes at the molecular, cellular, & behavioral levels
- Changes are either adaptive or maladaptive, depending upon the context

DEVELOPMENT
Risks / benefits to health, academic success & economic productivity
Advantages of an EBD Framework

• Underscores the need to improve the early childhood ecology in order to:
  – Mitigate the biological underpinnings for educational, health and economic disparities
  – Improve developmental/life-course trajectories
    • Changing the early childhood ecology will require a PUBLIC HEALTH approach ... and collaboration!!

• Highlights the pivotal role of toxic stress
  – Not just “step on the gas” / enrichment (ed model)
  – But “take off the brake” by treating, mitigating or immunizing against toxic stress (med model)
Release the **BRAKE** before stepping on the **GAS**!!

**Models**

**Maslow’s Hierarchy of Needs**
(Theoretical - 1943)

**Needs**

- **Self-Actualization**
  - Need to know, explore and understand

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Unmet **NEEDS** are potential triggers of **TOXIC STRESS**!
Critical Concept #6

Unmet Needs in childhood are potential precipitants of Toxic Stress

Unmet Needs in childhood are potential barriers to Relational Health
Adversity & Resilience

- **Adversity** leads to physiologic stress
  - Positive (if buffered by SSNRs)
  - Toxic (if unmitigated by SSNRs)

- **Resilience** is the ability to handle adversity in a healthy manner
  - In the absence of SSNRs, toxic stress leads to maladaptive responses
  - In the presence of SSNRs, positive stress builds motivation & resilience

- *It’s all about SSNRs & “relational health”*
Childhood Experience

Toxic Stress

Epigenetic Modifications
Disruptions in Brain Architecture
Behavioral Allostasis

Safe, Stable and Nurturing Relationships
Social-Emotional Learning
Healthy Adaptations

Parent Engagement
Quality Childcare
Play

ACEs
Poverty
Violence

Healthy Lifestyles
Academic Success
Economic Stability

Adult Outcomes

Poor Health
Academic Failure
Economic Hardship

Parent Engagement
Quality Childcare
Play

Healthy Lifestyles
Academic Success
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Parent Engagement
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Play

Healthy Lifestyles
Academic Success
Economic Stability

Adult Outcomes

Poor Health
Academic Failure
Economic Hardship
The **BIG** Questions are...

Since **TOXIC STRESS** mediates the association between **ACE exposure** and **poor adult outcomes**, it raises the following **BIG** questions:

- Are there ways to:
  - **Treat**,  
  - **Mitigate**, and/or  
  - **Prevent** toxic stress?

But the corollary for primary care pediatrics is ...
The **BIG** Questions are...

Since **Relational Health** and **SSNRs** are the antidote to **toxic stress**, it raises the following **BIG** questions:

- Are there ways to:
  - Repair,
  - Eliminate barriers to, and/or
  - Promote **SSNRs** and relational health?

- If so:
  - Why are we not actually **DOING** them?!
Social-Emotional Safety Nets
A Public Health Approach to “Toxic Stress”

Universal Primary Preventions
Social supports, AG-Plus, Consistent messaging (CTC)
No identification
No stigma
Ceiling effects = Limited evidence base

Targeted Interventions
(for those “at risk”)
Nursing home visits (NFP)
Parenting programs (Legacy/PPP)
Early Intervention (Ideally!)
Less ceiling=More evidence
Requires screening
Issues with stigma

Evidence-Based Treatments
(for the symptomatic)
PCIT; TB-CBT; Pharmacotx
Treatment works!
Screening / stigma / access

ALL are NECESSARY, NONE are SUFFICIENT
A Broader Vision for Pediatrics?

NOT just about children ...  
But about their families and communities

NOT just about physical health ...  
But about social-emotional or relational health

NOT just about child development ...  
But about life course trajectories

NOT just about acute or chronic care ...  
But about proactively building WELLNESS ...  
... NOT a new idea!!
Will it be “BACK TO THE FUTURE?”

“The study of psychopathology and the management of disturbed children is a legitimate and socially necessary function. But pediatricians are concerned primarily with the developmental process and prevention, which I submit is a quite different frame of reference ...”

JULIUS RICHMOND, receiving the AAP’s Aldrich Award, October 23, 1966
Will it be “BACK TO THE FUTURE?”

“I refer to the dynamic development of individual differences in behavior patterns, the observation of child rearing practices and their consequences, the emergence of curiosity, learning patterns, coping behavior, and personality, and the capacities of children and families to master adversity.”

JULIUS RICHMOND, receiving the AAP’s Aldrich Award, October 23, 1966
<table>
<thead>
<tr>
<th><strong>Type of Prevention</strong></th>
<th><strong>Chronic Care</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Tertiary</td>
</tr>
<tr>
<td><strong>Primary Objective</strong></td>
<td>Indicated (those who are diagnosed)</td>
</tr>
<tr>
<td></td>
<td>To reduce negative impact of known disease by restoring function and reducing disease-related complications</td>
</tr>
<tr>
<td><strong>Essential Elements</strong></td>
<td></td>
</tr>
<tr>
<td>• On-going disease education and management</td>
<td></td>
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<tr>
<td>• Minimizing disease progression</td>
<td></td>
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<tr>
<td><strong>Example Resources</strong></td>
<td>Health Supervision for Tri-21, Asthma, DM</td>
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<tr>
<td><strong>Possible Venues</strong></td>
<td></td>
</tr>
<tr>
<td>• Medical Homes</td>
<td></td>
</tr>
<tr>
<td>• Specialty Care Clinics</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Wellness Care</strong></td>
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<tr>
<td>--------------------------</td>
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<tr>
<td><strong>Type of Prevention</strong></td>
<td>Primary</td>
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<tr>
<td><strong>Population</strong></td>
<td>Universal</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary Objective</strong></td>
<td>To avoid the occurrence of disease</td>
</tr>
<tr>
<td><strong>Importance of Continuity</strong> (Therapeutic Partnership)</td>
<td>Extrememly Important</td>
</tr>
<tr>
<td><strong>Importance of Context</strong> (Social + Family Histories)</td>
<td>Extrememly Important</td>
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<tr>
<td><strong>Amenable to Algorithms</strong></td>
<td>Somewhat Amenable</td>
</tr>
<tr>
<td><strong>Addressed in Training</strong></td>
<td>Limited Training</td>
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<tr>
<td><strong>Incentivized Through Reimbursements</strong></td>
<td>Minimal Incentives (bundling; low pt. volumes)</td>
</tr>
<tr>
<td><strong>Long Term Returns on the Initial Investment</strong></td>
<td>Large (e.g., immunizations)</td>
</tr>
</tbody>
</table>
A Pivotal Point for Pediatrics:

“Back to the Future?” ... or “Oh, Canada!”

Pediatrics:
1) Reclaims “wellness care”
2) Embraces a broader vision
3) Collaborates and even coordinates local efforts to proactively build wellness

Pediatrics:
1) Is relegated to consult care
2) Surrenders “wellness care”
3) Remains “sil-o-ed” – with little connection to social and educational services
A Broader Mission for Pediatrics?

To support and empower parents, caregivers and communities as they nurture their children’s development

This mission will require:

• A nested/layered/tiered/’public health’ approach

• A “train the trainer” or 2GEN approach

(it’s all about relationships!)

• A grass-roots, community-based, team approach
Since there are known, established ways to treat, mitigate & prevent toxic stress / to repair, eliminate barriers to & promote relational health,

WHY ARE WE NOT DOING THEM?!

- “They cost too much” or “TS is not my concern”
  When kids don’t fulfill their potential, we ALL lose

- “Defensiveness” (“It’s not MY fault” or “It’s THEM!”)
  Toxic stress is not restricted by race, wealth, zip code

- “Too complicated”
  The biology suggests that it is all about relationships

- “Too hard”
  1) understand the science, 2) advocate for a public health approach, 3) develop a shared language/vision
CONCLUSION:

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

Frederick Douglass