TOXIC STRESS AND THE CHILDHOOD ORIGINS OF LIFELONG HEALTH AND DISEASE

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Early Brain and Child Development
CME Disclosures

- I do **NOT** intend to discuss off-label uses for FDA-approved products
- I do **NOT** have any financial relationships to disclose
My 3 Objectives For Today

• Explain how **toxic stress** mediates the relationship between childhood adversity and poor adult health

• Describe an “**ecobiodevelopmental** framework” and list its advantages

• Discuss the **public health implications** and potentially lifelong consequences of toxic stress
Critical Concept #1

Life-Course Science

Experiences in childhood (both good and bad) are strongly associated with behaviors, health and economic productivity ... ... DECADES LATER!
## 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>
</tr>
<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>
</tr>
<tr>
<td>- Parental Separation or Divorce</td>
<td>24.5%</td>
<td>21.8%</td>
<td>23.3%</td>
</tr>
<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

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

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

Mental Health
- High perceived stress
- Poor Self-Rated Health
- Hallucinations
- Depression
- Sleep Disturbances
- Memory Disturbances
- Anxiety
- Panic Reactions
- Poor Anger Control

Sexual Health
- Teen Paternity
- Fetal Death
- Unintended Pregnancy
- Early Age of First Intercourse
- Sexual Dissatisfaction

Sexually Transmitted Diseases

ACEs

Poor Perceived Health

Difficulty in job performance

Difficulty in job performance

Difficulty in job performance

Difficulty in job performance
Linking **Childhood Experiences** and **Adult Outcomes**

Childhood Adversity → ? → Poor Adult Outcomes
Developing a Model of Human Health and Disease

Early childhood ecology strongly associates with lifelong developmental outcomes.

What are the mechanisms underlying these well-established associations?

How do you begin to define or measure the ecology?
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)
Defining **Adversity** or **Stress**

- **Positive Stress**
  - 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
  - **Social-emotional buffers** allow a 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**
  - Long lasting, frequent, or strong intensity
  - More extreme precipitants of childhood stress (ACEs)
    - Physical, sexual, emotional abuse
    - Physical, emotional neglect
    - Household dysfunction
  - Insufficient social-emotional buffering
    (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)
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 Stable

“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.

Developing a Model of Human Health and Disease
**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**
Two Types of 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 Brain Maturation

Prefrontal Cortex (the “OFF” switch)
- Cold Cognition
  - Judgmental
  - Reflective
  - Calculating
  - Think about it

Amygdala (the “ON” switch)
- Hot Cognition
  - Emotional
  - Reactive
  - Impulsive
  - Just do it

Biological maturity by 24

Biological maturity by 18

Adapted from Ken Winters, Ph.D.
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.
Eco-Bio-Developmental Model of Human Health and Disease

NOT: “What’s WRONG with you?”

BUT: “What’s HAPPENED to you?”

Ecology Becomes biology, development
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 with children to improve education, health, and lifelong productivity.
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 ongoing, re-iterative, and cumulative dance between nurture and nature.

Experience
Protective and Personal (versus Insecure and Impersonal)

Brain Development
Alterations in Brain Structure and Function

Epigenetic Changes
Alterations in the Way the Genetic Program is Read

Behavior
Adaptive or Healthy Coping Skills (vs. Maladaptive or Unhealthy Coping Skills)

Adapted from: Helping Foster and Adoptive Families Cope with Trauma
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/collaboration (Rishi Manchanda)

• Highlights the pivotal role of toxic stress
  – Not just “step on the gas” or enrichment (ed model)
  – But “take off the brake” by treating, mitigating or immunizing against toxic stress (med model; not new!)
# Reinventing the Wheel - All over again?

## Models

<table>
<thead>
<tr>
<th>Needs</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maslow's Hierarchy of Needs</td>
<td>(Theoretical - 1943)</td>
</tr>
<tr>
<td>Self-Actualization</td>
<td>Need to know, explore and understand</td>
</tr>
</tbody>
</table>

## Release the BRAKE ... before stepping on the GAS!
Critical Concept #5

Yin/Yang of Early Childhood:
- Protect the Brain (Med)
- Build New Skills (Ed)

SE Buffers
Toxic Stress
Protect the Brain
Build New Skills
Maladaptive Skills
Adaptive Skills
Linking **Childhood Experiences** and **Adult Outcomes**

- **Childhood Adversity**
- **Toxic Stress**
  - Epigenetic Modifications
  - Disruptions in Brain Architecture
  - Behavioral Allostasis
- **Poor Adult Outcomes**
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 (immunize against?) toxic stress?

- If so, is there a mismatch between:
  - what we **KNOW** ... and ...
  - what we actually **DO**?
Addressing **Toxic** Stress

- **Indicated treatments**
  - Consequences are **Biological Mal-adaptations** ("what’s wrong with you," vs "what’s happened to you")
  - PCIT, CPP, and TF-CBT are evidence-based
  - Efficacy linked to age / chronicity (**brain** plasticity)
  - **REACTIVE** – mal-adaptations are happening!
  - **ACCESS** – interventions must be local
    - More **providers** / better **reimbursement** / advocacy
    - Need a **universal** but **local platform** (Medical homes? Schools?)
    - Better coordination / communication between silos
    - Better identification

[www.aap.org/traumaguide](http://www.aap.org/traumaguide)
Addressing **Toxic** Stress

- **Secondary / Targeted Preventions**
  - Focused, targeted interventions for those deemed to be “at high” or the “highest risk”
  - Home Visiting Programs (NFP, PAT, Child First, etc.)
  - Parenting Programs (PPP, Nurturing Parenting, Legacy)
  - More likely to minimize “biological disruptions” and yield a positive ROI
  - Still issues with stigma; numbers of/access to providers/programs
  - Who is “at high risk?” Requires screening (Not perfect! No ‘OMNI-screen! Child vs Family? Dysfunction vs Risk?)
Addressing **Toxic** Stress

- **Primary / Universal Prevention**
  - Proactive, universal interventions to make stress positive, or tolerable instead of toxic
  - Acknowledges that preventing all childhood adversity is impossible and even undesirable
  - **Actively building resiliency** ("immunizing" through positive parenting, 7Cs, promoting optimism, formalized social-emotional learning)

- **SE Buffers** allow the physiologic stress response to return to baseline
  - **Parenting/Caregiving** skills for younger children
  - **SEL** skills for older children ([www.casel.org](http://www.casel.org))
Critical Concept #6

SOCIAL-EMOTIONAL SKILLS...
(a.k.a – Affect Regulation, Non-Cognitive Skills, Mindfulness)

...Are **learned** (they can be **modeled**, **nurtured**, **taught**, **practiced**, and **reinforced**)

...Effectively **buffer** against **toxic stress**
(by helping to turn **off** the physiologic stress response)

...Increase **test scores**
(an average of **11 points** by meta-analysis!)
Parenting as **Primary Prevention**

- Promoting **PARENTING SKILLS** in the first 1000 days
  - Parenting is personal – makes pediatricians **NERVOUS**!
  - “Positive/Nurturing/Supportive” Parenting
  - A Poor investment?
    - Are parenting skills “**TEACHABLE**?” **YES!!**
    - Is there a “**CEILING EFFECT**” on returns?
  - Or the “**GOLD STANDARD**?”
    - Shouldn’t **SAFE, STABLE, and NURTURING RELATIONSHIPS** be THE reference point (NOT routine, general, or control populations)

- Significant Challenges:
  - Define what the basic, **BIOLOGICAL NEEDS** of children are
  - Utilize a **TWO GENERATION APPROACH** to meet those needs
  - Utilize a **PUBLIC HEALTH APPROACH** to match the **FAMILY’S NEEDS** with the indicated, local services
Universal Primary Preventions
AG “Plus” (ROR / PFR / BF Grid)
Consistent messaging (CTC)
No identification
No stigma
Ceiling effects = Limited evidence base

Targeted Interventions
(for those “at risk”)
Home visiting (NFP/PAT)
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

Social-Emotional Safety Nets
A Public Health Approach to “Toxic Stress”
ALL are necessary – NONE are sufficient!
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?

- If so, is there a mismatch between:
  - what we **KNOW** ... and ...  
  - what we actually **DO**?
Public Health Implications

• What we **DO**:  
  – 95% of the trillions of dollars that we spend on health is on treatment and **NOT prevention**

• What we **KNOW**:  
  – That **70% of early deaths are preventable**, with...
  – The **majority (40% overall)** due to **behavioral patterns** that lead to **chronic disease**.  
  – Is this **Behavioral Allostasis** due to toxic stress?

McGinnis, Williams-Russo and Knickman, 2002
**Proximal Causes of Death: Chronic Disease**

**EXHIBIT 2**
Total Deaths And Age-Adjusted Death Rates (Per 100,000 Population) For The Fifteen Leading Causes Of Death In The Total U.S. Population, 2003

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Number of Deaths (thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseases of heart</td>
<td>232.3</td>
</tr>
<tr>
<td>Malignant neoplasms (cancer)</td>
<td>190.1</td>
</tr>
<tr>
<td>Cerebrovascular diseases (stroke)</td>
<td>53.5</td>
</tr>
<tr>
<td>Chronic lower respiratory diseases</td>
<td>43.3</td>
</tr>
<tr>
<td>Accidents (unintentional injuries)</td>
<td>37.3</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25.3</td>
</tr>
<tr>
<td>Influenza and pneumonia</td>
<td>22.0</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>21.4</td>
</tr>
<tr>
<td>Nephritis, nephrotic syndrome, nephrosis</td>
<td>14.4</td>
</tr>
<tr>
<td>Septicemia</td>
<td>11.6</td>
</tr>
<tr>
<td>Intentional self-harm (suicide)</td>
<td>10.8</td>
</tr>
<tr>
<td>Chronic liver disease and cirrhosis</td>
<td>9.3</td>
</tr>
<tr>
<td>Essential hypertension/hypertensive renal disease</td>
<td>7.4</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>6.2</td>
</tr>
<tr>
<td>Assault (homicide)</td>
<td>6.0</td>
</tr>
</tbody>
</table>


**NOTE:** Numbers in parentheses are age-adjusted death rates per 100,000 population.

*Acute causes of death are the exception, not the rule*
Distal Causes of Death: Unhealthy Lifestyles

If these unhealthy lifestyles are manifestations of behavioral allostasis, a **FUNDAMENTAL** cause of death is **TOXIC STRESS**!
By 2030, **90%** of the morbidity in high income countries will be due to **NCDs (Non-Communicable Diseases)**.

NCDs are related to **unhealthy behaviors** (overeating/inactivity, smoking, alcohol, and substance abuse).
How/When do those automatic processes form in the first place!? 

**How/When do those automatic processes form in the first place!?**
Critical Concept #7

Do we continue to treat disease, the unhealthy lifestyles that lead to disease, or the TOXIC STRESS that leads to the adoption of unhealthy lifestyles??
Developing a Shared “VISION”

Toxic Stress

It’s like a snake!

It’s like a tree trunk!

It’s like a straw fan!
• What is Toxic Stress?
  – A physiologic stress response that is excessive or prolonged (reflects an inability to “turn it off”)
  – Results in potentially permanent changes in:
    • Gene expression (epigenetics)
    • Brain development (neuroscience)
    • Behavior (allostasis)
SUMMARY

- Why should we care?
  - **Toxic stress** is a **MEDIATOR** between early childhood **adversity** and less than optimal outcomes in **learning**, **behavior** and **health**
  - Understanding the **BIOLOGY** underlying these well established associations opens up new opportunities for **primary prevention** and **early intervention**
Linking **Childhood Experiences and Adult Outcomes**

**Toxic Stress**
- Epigenetic Modifications
- Disruptions in Brain Architecture

**Behavioral Allostasis**
- Maladaptive behaviors
- Non-communicable Diseases

Improve caregiver/community capacity to prevent or minimize toxic stress (e.g. – efforts to promote the safe, stable and nurturing relationships that turn off the physiologic stress response)

Improve caregiver/community capacity to promote healthy, adaptive coping skills (e.g. - efforts to encourage rudimentary but foundational SE, language, and cognitive skills)
SUMMARY

- **EDUCATION** – for providers, trainees, families, the general public and business/philanthropic communities (re: science, TS, and EBD frame)

- **MESSAGING** – be a “convener” (ala CTC); develop a shared “vision” locally to support a public health approach towards toxic stress

- **ADVOCACY** – partner with like-minded stakeholders to “incentivize” wellness/relational health, population health, and long-term outcomes

- **RESEARCH** – basic (non-invasive biomarkers, personalized med), clinical (standardized screens – not just for the child, but the family; not just for dysfunction, but those at risk), and translational (medical homes, schools, communities are integrated vertically and horizontally)

- **PRACTICE TRANSFORMATION** – promoting wellness (over chronic/acute care) and supporting families (PPP, Family Safe Zones)
Since there are known, established ways to treat, mitigate and even prevent toxic stress, 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