Getting to the Roots: The Benefits of Early Life Intervention

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“As human beings we belong to an extremely resilient species. Since time immemorial we have rebounded from our relentless wars, countless disasters (both natural and man-made), and the violence and betrayal in our own lives. But traumatic experiences do leave traces, whether on a large scale (on our histories and cultures) or close to home, on our families, with dark secrets being imperceptibly passed down through generations. They also leave traces on our minds and emotions, on our capacity for joy and intimacy, and even on our biology and immune systems.”

_The Body Keeps the Score: Brain, Mind, and Body in the Healing of Trauma_, p. 1
Bessel van der Kolk, 2014
An all-too-common story:

“Mary”

- **Pre-conception**
  - Mother’s grandparents went to boarding school, parents have had trouble with alcohol; most of them developed diabetes
  - Family income below poverty line, buy food at reservation store

- **Pregnancy and Birth**
  - Single 15 year old, won’t say who FOB is
  - Intermittent prenatal care
  - WIC foods have to be shared with family
  - Stopped using drugs when found out she was pregnant, cut down but continued smoking and got drunk “just a few times”
  - Mostly kept going to high school thru pregnancy
  - Mary born slightly SGA at 35 weeks gestation, spent 2 wks in hosp.
**“Mary”**

- **Early Life**
  - Grandmother already overwhelmed caring for other grandchildren, but agreed to watch Mary while mother tried to stay in school
    - Mary often sitting in front of TV most of day
  - Then put into tribal child care
    - High staff turnover, minimal teacher-student ratio
  - Family got by on commodities and WIC foods
  - Mary gained weight rapidly in 1\textsuperscript{st} yr, then stayed $>95$\textsuperscript{th} % ile
  - Mother’s boyfriend moved in
    - Intermittently employed, binged on alcohol and drugs, sometimes hit mother in front of Mary
  - Mary held back to repeat 2\textsuperscript{nd} grade as reading difficulties
  - Mary left school after 10\textsuperscript{th} grade
- Now Mary becomes pregnant...
700 New Neural Connections per Second

NEWBORN  |  6 MONTHS  |  2 YEARS

Center on the Developing Child at Harvard website

18 Months: Age at which disparities in vocabulary begin to appear

CORE CONCEPTS IN THE SCIENCE OF EARLY CHILDHOOD DEVELOPMENT

The Ability to Change Brains and Behavior Decreases Over Time

Graph Source: P. Levitt (2009)

Center on the Developing Child website  www.developingchild.harvard.edu
International Diabetes Federation

Conference on Type 2 Diabetes Etiologies

2002

1. Genetics
2. Fetal Origins
3. Lifestyle
4. Stress
1. Genetics

**Genes Inherited**
- It does matter what genes we inherit
  - But proportion of predisposition explained for type 2 DM (5-10%) is fairly small
  - And genes which are associated with ↑ diabetes risk are as common in non-minority as in minority people

**Only 15% of genes in cells “turned on” at any one time**

**Genes Expressed**
- “Epigenetics”: the “on/off switches” for genes
  - Reaction to the environment
  - Not always reversible if at key developmental stage of life
  - Heritable—some are passed to next generation
    - How the experiences of one generation help prepare the next
  - We know the body’s “on/off switches”: DNA methylation, histone acetylation, microRNA

*NEJM 2010;363:2339-50*  
*Diabetes Care 2012;35:193-195*  
*JAMA 2005;294:2221-4 and NEJM 2008;359:61-73*
Epigenetics: Experiences “Programmed In”

- Rat pups raised by nurturing mothers
  - Gene which codes for stress hormone receptors “turned on”
    - Grow up to be stress resilient
  - Opposite is true in rat pups raised by neglectful mothers
  - Same process occurs in humans
    (Nat Neurosci 2009;12:342-348)

- Experiences of one generation transmitted epigenetically to subsequent generations
  - Mice trained to fear an odor→methylation change in Olfr 151→F1 & F2 generations exhibit startle response to same odor
    (Nat Neurosci 2014;17: 89-96 and 2-4)

- First demonstration of transmission of pre-conception stress effects resulting in epigenetic changes in both the exposed parents (Holocaust) and their offspring in humans--associated with stress response
  (Biological Psychiatry http://dx.doi.org/10.1016/j.biopsych.2015.08.005)
Epigenetics and Diabetes Predisposition

- Methylation of gene involved with fat storage at age 5yrs predicted greater likelihood of obesity at age 14
  \( Diabetes\ 2014;\text{doi:10.2337/db13-0671} \)

- “…epigenetic changes occurring during gestation, possibly maternal nutrition-mediated, appear to influence adiposity and related metabolic phenotypes.”
  \( Diabetes\ 2011;60:1859-60 \)

- Genome-wide survey: clear-cut diabetes-predisposing DNA methylation signature in patients with vs. without diabetes

  - Prospective study: different methylation patterns in young people who later developed diabetes vs. those who did not
  \( Hum\ Mol\ Genet\ 2012;21:371-383 \)
2. Fetal Origins

- Alcohol/Drugs
- Nutrition
- Smoking
- Maternal Diabetes
- Toxic/Infectious Exposures
- Maternal Low Birth Weight
- Maternal Stress/Mental Health
  - Mother’s own Childhood
  - Current/Prenatal
Low Birth Weight (SGA) and Preterm

- Babies can be either/both SGA and Preterm
  - they both are strongly associated with that baby’s later risk for chronic disease \textit{Diabetes} 2009;58:523-526
  - Inverse assoc between gest age and insulin levels at birth and early childhood \textit{JAMA} 2014;311:587-596
  - Maternal stressful life events during 1\textsuperscript{st} trimester ↑ risk of preterm birth (OR 2.4) and SGA

\textit{Am J Obstet Gynecol} 2010;203:34.e1-8
FIG. 7. The physiological mechanisms underlying the programming of the separate and combined elements of the metabolic syndrome

In utero Risks for Later Type 2 Diabetes

- Fetuses of obese mothers develop insulin resistance in utero. 
  *Diabetes Care* 2009;32:1076-1080

- Maternal diet during pregnancy:
  - Epigenetically affects child’s adiposity at age 9 yrs. 
    *Diabetes* 2011;60:1528-1534
    “Our findings suggest a substantial component of metabolic disease risk has a prenatal developmental basis.”
  - Affects adipose tissue development leading to insulin resistance 
    *Cell Death Diff* 2012;doi:10.1038/cdd.2011.183

- Inverse relationship between birth weight and risk of diabetes 
  *JAMA* 2008;300:2886-2897

- Rapid weight gain in first 3 months of life associated with ↑CVD and diabetes risk factors by early adulthood 
  *JAMA* 2009;301:2234-2242

- Low birth weight is related to nephron number and future risk of kidney disease 
  *Kidney Int* 2005;68:S68-S77
“Fetal Programming of Type 2 Diabetes”

“It is important to understand that the story is not about birth weight but about fetal programming, and that intergenerational prevention of type 2 diabetes (primordial prevention) will need to target maternal nutrition and metabolism. …Prevention of fetal programming of diabetes will need to concentrate on the health of young girls.”

*Diabetes Care* 2010;33:1146-8
3. Lifestyle

Overeating as an *Adaptive* Response

- **Food Insecurity:**
  - Prevalence of overweight in women ↑’s as food insecurity ↑
    - *Journal of Nutrition.* 2001;131:1738-1745
  - Pregnancy: food insecurity assoc with pregravid obesity, ↑
    gest wt gain, and gest diabetes
    - *J Am Diet Assoc* 2010;110:692-701
  - 42% of households below poverty level are food insecure,
    21% of all households with children
    - *NEJM* 2010;363:6-9
  - Independent risk factor for poor glycemic control
    - *Diabetes Care* 2012;35:233-238

- **Carbohydrates affect brain serotonin levels**

- **“Comfort Foods” ↓ HPA axis stress response**
  - *Proc Natl Acad Sci* 2003;100:11696-11701
4. Stress

- Chronic exposure to Intimate Partner Violence almost doubles (OR 1.8) risk of obesity at age 5 years
  
  *Arch Pediatr Adolesc Med* 2010;164:540-546

- Early life adversity assoc with ↑leptin/irisin and ↓adiponectin in midlife adults
  
  *J Clin Endocrinol Metab* 2014;doi:10.1210/jc.2013-3669

- “...reducing toxic stress can target the common physiologic pathway implicated in an enormous array of health outcomes from asthma to cardiovascular disease.”
  
  *Pediatrics* 2013;131:319-327
Adverse Childhood Experiences (ACE)

- Physical, emotional, sexual abuse; mentally ill, substance abusing, incarcerated family member; seeing mother beaten; parents divorced/separated

--Overall Exposure: 86% (among 7 tribes)

<table>
<thead>
<tr>
<th></th>
<th>Non-Native</th>
<th>Native</th>
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<tbody>
<tr>
<td>Physical Abuse-M</td>
<td>30%</td>
<td>40%</td>
</tr>
<tr>
<td>Physical Abuse-F</td>
<td>27</td>
<td>42</td>
</tr>
<tr>
<td>Sexual Abuse-M</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>Sexual Abuse-F</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>Emotional Abuse</td>
<td>11</td>
<td>30</td>
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<tr>
<td>Household alcohol</td>
<td>27</td>
<td>65</td>
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<tr>
<td>Four or More ACEs</td>
<td>6</td>
<td>33</td>
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ACEs and Adult Health

- ACE Score ≥4
  - 4-12 x risk for alcoholism, drug abuse, depression and suicide attempt
  - 2-4 x risk for smoking, teen pregnancy, STDs, multiple sexual partners
  - 1.4-1.6 x risk for severe obesity
  - Strong graded relationship at all levels of ACEs for almost all outcomes, including heart disease


- Across 10 countries, adults who experienced ≥3 childhood adversities
  - Hazard ratios 1.59 for diabetes, 2.19 for heart disease
  - Risk similar to the association between cholesterol and heart disease

  *Arch Gen Psychiatry* 2011;68:838-844
90-100% chance of developmental delays when children experience 6-7 risk factors

Source: Barth, et al. (2008)
Stress in Children

- **Positive**
  - Normal/necessary part of healthy development
    - First day with new caregiver; immunization
  - Brief increases in heart rate and stress hormones

- **Tolerable**
  - More severe, longer lasting stressor
    - Loss of a loved one, natural disaster, injury
  - If buffered by relationship with supportive adult(s), brain and body can recover

- **Toxic**
  - Strong, frequent, prolonged adversity
    - Abuse, neglect, caregiver mental illness, poverty
  - If no adult support, can disrupt brain and organ development long-term

Center on the Developing Child at Harvard Univ.
### Domains of Impairment in Children Exposed to Complex Trauma

<table>
<thead>
<tr>
<th>I. Attachment</th>
<th>IV. Dissociation</th>
<th>VI. Cognition</th>
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</thead>
<tbody>
<tr>
<td>Problems with boundaries</td>
<td>Distinct alterations in states of consciousness</td>
<td>Difficulties in attention regulation and executive functioning</td>
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<tr>
<td>Distrust and suspiciousness</td>
<td>Amnesia</td>
<td>Lack of sustained curiosity</td>
</tr>
<tr>
<td>Social isolation</td>
<td>Depersonalization and derealization</td>
<td>Problems with processing novel information</td>
</tr>
<tr>
<td>Interpersonal difficulties</td>
<td>Two or more distinct states of consciousness</td>
<td>Problems focusing on and completing tasks</td>
</tr>
<tr>
<td>Difficulty attuning to other people's emotional states</td>
<td>Impaired memory for state-based events</td>
<td>Problems with object constancy</td>
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<tr>
<td>Difficulty with perspective taking</td>
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<td>Difficulty planning and anticipating</td>
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<thead>
<tr>
<th>II. Biology</th>
<th>V. Behavioral control</th>
<th>VII. Self-concept</th>
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<tbody>
<tr>
<td>Sensorimotor developmental problems</td>
<td>Poor modulation of impulses</td>
<td>Lack of a continuous, predictable sense of self</td>
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<tr>
<td>Analgesia</td>
<td>Self-destructive behavior</td>
<td>Poor sense of separateness</td>
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<tr>
<td>Problems with coordination, balance, body tone</td>
<td>Aggression toward others</td>
<td>Disturbances of body image</td>
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<tr>
<td>Somatization</td>
<td>Pathological self-soothing behaviors</td>
<td>Low self-esteem</td>
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<tr>
<td>Increased medical problems across a wide span (e.g., pelvic pain, asthma, skin problems, autoimmune disorders, pseudoseizures)</td>
<td>Sleep disturbances</td>
<td>Shame and guilt</td>
</tr>
<tr>
<td></td>
<td>Eating disorders</td>
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</table>
Stress of Racism

“The lifelong accumulated experiences of racial discrimination by African American women constitute an independent risk factor for preterm delivery.”

- Odds ratio of 2.6
- Independent of maternal sociodemographic, biomedical, and behavioral characteristics.

*Am J Public Health* 2004; 94:2132–2138
In utero exposures to stress/adversity, environmental chemicals

Child Abuse/Neglect

Quality of Early Life Relationships/Learning

Prenatal/Early Life Nutrition

Poverty

Epi/Genetics

Physiologic/Behavioral Ability to Respond to Life Stressors

Diabetes

Obesity

Heart Disease

Addiction

Liver Disease, HIV

Drug Abuse

Alcohol Use

Emotional Responses

Overeating

Violence

Traumatized Parenting

Depression

Seeds planted for the next generation
“We ...know that sound maternal and fetal nutrition, combined with positive social-emotional support of children through their family and community environments, will reduce the likelihood of negative epigenetic modifications that increase the risk of later physical and mental health impairments.”

Center on the Developing Child at Harvard University
Working Paper 10, 2010
Stronger Parents Raise Stronger Children

- Prenatal/Early Life Home Visiting
  - Evidence-based interventions proven to improve the life trajectories of low income women and children
  - Positive effects now shown up to age 19 yrs

Family Spirit Impact: Pregnancy to Age 3

Parenting
- Increased maternal knowledge 1,2,3,4
- Increased parent self-efficacy 3,4
- Reduced parent stress 2,4
- Improved home safety attitudes 3

Mothers’ Outcomes
- Decreased depression. 1,2,4
- Decreased substance use 4
- Fewer risky behaviors 3,4

Child Outcomes
- Fewer social, emotional and behavior problems through age 3. 2, 3, 4
- Lower clinical risk of behavior problems over life course 4

Decreased Externalizing, Internalizing and Dysregulation

ITSEA Problem Domains and Subscales within Domains

Externalizing
- Aggression/Defiance
- Peer Aggression
- Activity/Impulsivity

Internalizing
- General Anxiety
- Depression/Withdrawal
- Separation Distress
- Inhibition to Novelty

Dysregulation
- Negative Emotionality
- Eating
- Sleep
- Sensory Sensitivities
Parenting and Early Childhood Behavior Problems Associated with Obesity

- Negative parenting (inconsistent discipline; restrictive, coercive parenting) associated with increased obesity risk in children.
  - Trends Endocrinol Metab. 2013 Apr 19 E-pub

- Externalizing behaviors at 24 mos associated with higher BMI at 24 months and thru age 12
  - BMC Pediatr. 2010 Jul 14;10:49

- Obese children have higher rates of externalizing and internalizing disorders.
  - Acad Pediatr. 2013 Jan-Feb;13(1):6-13
“Home visits are an important mechanism for improving the capacity of caregivers to (1) promote the safe, stable, and nurturing relationships that buffer toxic stress, and (2) encourage the rudimentary but foundational social-emotional, language, and cognitive skills that promote resiliency and the adoption of healthy, adaptive coping skills.”

“Home Visiting and the Biology of Toxic Stress: Opportunities to Address Early Childhood Adversity”

*Pediatrics* 2013;132:S65-S73
$4-$9 in returns for every dollar invested in early childhood programs

Center on the Developing Child at Harvard website
Sources: Masse, L. and Barnett, W.S., A Benefit Cost Analysis of the Abecedarian Early Childhood Intervention (2002); Karoly et al., Early Childhood Interventions: Proven Results, Future Promise (2005); Heckman et al., The Effect of the Perry Preschool Program on the Cognitive and Non-Cognitive Skills of its Participants (2009)
“Early Life Investments Substantially Boost Adult Health”

- Carolina Abecedarian Project
  - 4 cohorts of disadvantaged children born 1972-77
    - Intervention provided from birth to age 5 years
  - Intervention:
    - Devel of language, emotional regulation, cognitive skills
    - Caregiving/supervised play
    - Nutrition: 2 meals and a snack at childcare center
    - Primary pediatric care
  - In their mid-30s: lower prevalence of CVD and metabolic disease risk factors including BP, A1C, obesity, HDL

*Science* 2014;343:1478-1485
The Path We *Could* Take

Rewind: “Mary’s” life

- As soon as mother’s pregnancy diagnosed:
  - Matched with a home visitor/case manager
    - Weekly/biweekly visits focusing on developing a mentoring-type relationship, building on mother’s strengths, helping her to set goals, teaching her new skills
    - All services needed were offered and tailored to her needs
    - WIC foods supplemented so mother had enough good food even though shared with family
    - Mother rewarded for participation in each component
  - Mother went to 90% of her prenatal appointments
    - All but first urine drug screen negative and most cotinine screens
  - Mary born at 39 wks gest, normal weight for gestation
Rewind: “Mary”

- Visits from home visitor continued until Mary was 2 yrs old.

- Mother set/achieved goals: became a CNA through health occupations class and graduated from high school.
  - Mary cared for during day by excellent tribal child care program: bonding, learning, good food, social skills, active play, tribal language all emphasized.

- Mother attended parenting classes.
  - Praised and hugged Mary, appropriately disciplined her.
  - Ate dinner together and read to Mary most evenings.
  - Left her boyfriend when he wouldn’t stop drinking.

- Mary’s weight stayed around the 90th % ile.

- Mary graduated from high school, went to tribal college, got a good job, married a guy she met at college.

- Now Mary becomes pregnant…
Isn’t this among the most important work we can do?

“The medicine is already within the pain and suffering. You just have to look deeply and quietly. Then you realize it has been there the whole time.” Duran, 2006