Gene-environment interplay and the biology of misfortune

The Jill Joseph Lecture
Children’s National Medical Center

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Biomedical/psychiatric morbidities & Health care utilization

= 80-85%  = 15-20%
• A life of almost shameful good fortune
• A gratifying and productive professional career
• Stable 43-year marriage
• Two thriving children, two grandchildren
• Few or no disturbances of health
• A life of almost shameful good fortune
• A gratifying and productive professional career
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• Two thriving children, two grandchildren
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• A life of disappointment and affliction
• Disabling chronic disease at age 11
• Diagnosis of schizophrenia by age 20
• Unplanned pregnancy; delivery of a disabled child
• Suicide at 53 years of age
Why some get sick and others do not?

The origins of our differences?
• Why some get sick and others do not?
• The origins of our differences?

TWIN HUMAN MYSTERIES
A STORY IN THREE PARTS:
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1. Early, socially stratified exposures to adversity become biologically embedded over time, affecting developmental and disease risk over the entire life course.
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2. Such risk is highly variable from child to child and is influenced by even the most proximate, immediate experiences of social subordination.
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2. Such risk is highly variable from child to child and is influenced by even the most proximate, immediate experiences of social subordination.

3. Genes and social environments operate together to produce these powerful developmental effects.
Social partitioning of child health and development

(Chen et al, 2002)
Social partitioning of child health and development

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(CDC, MMWR; May 6, 2011)
Poorer children sustain higher rates of acute and chronic, physical and mental disorders, school failure and delinquency.

Not simply an effect of poverty.

Graded, linear association, with higher rates of disorder at every step of the SES gradient.

SES is the single most powerful determinant of health outcomes.

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- Poorer children sustain higher rates of acute and chronic, physical and mental disorders, school failure and delinquency.
- Not simply an effect of poverty.
- Graded, linear association, with higher rates of disorder at every step of the SES gradient.
- SES is the single most powerful determinant of health outcomes.
• Toxins
• Diet
• Health care
• Housing
• Violence
• Parenting
• Adversity and stress
Socioeconomic partitioning of stressors and adversities

Evans & English, 2002
Socioeconomic partitioning of stressors and adversities

Evans & English, 2002

Diagram showing the comparison of stressors and adversities in poverty and middle-income groups. The x-axis represents different stressors and adversities: Density, Housing problems, Noise, Family turmoil, Violence. The y-axis represents the level of these stressors and adversities, ranging from 0 to 75.
Socioeconomic partitioning of stressors and adversities

Evans & English, 2002

- Poverty
- Middle Income

Stressors and Adversities:
- Density
- Housing problems
- Noise
- Family turmoil
- Violence
Childhood maltreatment predicts adult inflammation (Danese et al: PNAS, 2007)
Childhood experiences of adversity/trauma predict leading causes of adult mortality (Felitti et al, 1998)
Population attributable risk for psychiatric disorders by exposures to childhood adversities (N=6,483)
(McLaughlin et al: Arch Gen Psychiatry, 2012)
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\[
\text{Population attributable risk} = I_e - I_u
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i.e., the reduction in incidence that would be observed if the population were entirely unexposed, compared with its current (actual) exposure pattern
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nearly 30% of adolescent psychopathology attributable to childhood adversities
Pervasive differences in the experiences of everyday life
Program for International Student Assessment (PISA)
Stressful, disadvantaged environments have highly variable effects on developmental and health outcomes.
Variability in developmental outcomes by adversity and SES

Noise?
Variability in developmental outcomes by adversity and SES

Noise? or music?
Hypothalamic-pituitary-adrenocortical system
Hypothalamic-pituitary-adrenocortical system

Locus coeruleus-autonomic system
• Adrenocortical and autonomic reactivity to standardized laboratory stressors
• Salivary cortisol response
• Impedance cardiography: fight or flight response
• Broad and reliable individual variability in magnitude and patterns of response
INTERACTIVE EFFECTS OF ANS REACTIVITY AND FAMILY CONFLICT

OBRADOVIĆ J, BOYCE WT ET AL: DEV PSYCHOPATHOL, 2011
Interactive effects of ANS reactivity and family conflict

OBRADOVIĆ J, BOYCE WT ET AL: DEV PSYCHOPATHOL, 2011
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OBRADOVIĆ J, BOYCE WT ET AL: DEV PSYCHOPATHOL, 2011
Presyndromal psychopathology

Neophobic, shy, and reactive children with sensory sensitivities

-0.4
-0.3
-0.2
-0.1
0
0.1
0.2
0.3
0.4

Low ANS Reactivity
High ANS Reactivity

Family Conflict

Low ANS Reactivity
High ANS Reactivity

Maskrosbarn (Sw): dandelion child
Orkidebarn: orchid child

OBRADOVIĆ J, BOYCE WT ET AL: DEV PSYCHOPATHOL, 2011
Neophobic, shy, and reactive children with sensory sensitivities

Differential neurobiological susceptibility to social context

OBRADOVIĆ J, BOYCE WT ET AL: DEV PSYCHOPATHOL, 2011
Boyce & Suomi, 1998

Violent injuries (per 100K subject-hours)

Low stress year

- High reactivity
- Low reactivity

Confinement year

- 12
- 9
- 6
- 3
- 0
Violent injuries (per 100K subject-hours)

Low stress year

Confinement year

High reactivity

Low reactivity

Boyce & Suomi, 1998
Boyce & Suomi, 1998

Violent injuries (per 100K subject-hours)

- High reactivity
- Low reactivity

Low stress year  Confinement year
Bush, Adler & Boyce, 2012

BDNF Val66Met polymorphism

- Family Income
- Fall Chronic Daily Cortisol Level (Std)

-1 SD

BDNF Met carrier
BDNF Val/Val

+1 SD
Bush, Adler & Boyce, 2012

BDNF Val66Met polymorphism

Fall Chronic Daily Cortisol Level (Std)

Family Income

-1 SD

+1 SD

BDNF Met carrier

BDNF Val/Val
Ellis, Essex & Boyce, 2011

- Low warmth, low SNS reactivity
- High warmth, low SNS reactivity
- Low warmth, high SNS reactivity
- High warmth, high SNS reactivity
Low warmth, low SNS reactivity
High warmth, low SNS reactivity
Low warmth, high SNS reactivity
High warmth, high SNS reactivity

Ellis, Essex & Boyce, 2011
Ellis, Essex & Boyce, 2011

- Blue line: Low warmth, low SNS reactivity
- Green line: High warmth, low SNS reactivity
- Pink line: Low warmth, high SNS reactivity
- Purple line: High warmth, high SNS reactivity
Ellis, Essex & Boyce, 2011

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DIFFERENTIAL NEUROBIOLOGICAL SUSCEPTIBILITY TO SOCIAL CONTEXT
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SES, stress and oral health

- Dental caries = single most common chronic disease of childhood
- Strong SES and racial disparities
- Known etiologic factors: lead exposure, tobacco smoke, diet, and access to fluoridated water
- Oral bacteria Strep mutans and Lactobacillus acidophilus
- Leading account of disparities: neglect of children’s dental hygiene by low SES parents
BLOOD CORTISOL LEVELS OVER 24 HOURS

**SLEEPING**

**WAKING**

[Graph showing blood cortisol levels with marked times T1, T2, T3]
Deciduous teeth as a stress biomarker in young children?
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Sociobiological effects on childhood dental caries
(Boyce et al, 2010)
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SES → Cariogenic bacteria → Dental caries
Sociobiological effects on childhood dental caries
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Oral health disparities related to two interacting pathways:
• Earlier and more intensive exposure to an agent of disease among low SES children
• More family adversity resulting in greater HPA activation, cortisol secretion, and microanatomic vulnerability
Beyond the visible, surface forces driving socioeconomic health disparities...
Beyond the visible, surface forces driving socioeconomic health disparities...

- Toxins
- Diet
- Health care
- Housing
- Violence
- Parenting
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Might there be deeper, less visible currents of social inequality?
• African cichlid fish maintain severe hierarchical organization in which only dominant males have reproductive access to females
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• Rats in subordination paradigm show pro-inflammatory shifts in cytokine signaling pathways.
• Primate species form stable, linearly transitive social hierarchies
• Subordinate positions: upregulated adrenocortical function, impaired immune competence, decreased resistance to disease

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• Young children form social orders within weeks of entering new social groups

• Are subordinate positions in early peer hierarchies associated with greater stress, exaggerated reactivity, and excessive, stress-related morbidity?

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Powerful, stress-related effects of social subordination and marginality, at both the societal and small group level.
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Effects that can be mitigated by more egalitarian, empathic policies and practices.
Developmental calibration of neurobiological circuitry: How does it happen?
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- Same species of buckeye butterfly
- Polyphenism driven by temperature and length of daylight
- A conditional adaptation involving differential epigenetic regulation of genes determining wing coloration and pattern
DNA methylation

DNA double helix

Histones

Nucleosome

Histone tails

Open chromatin

Closed chromatin

Epigenetic factor

23 pairs of chromosomes packed into the nucleus
Environmental exposures

DNA methylation

DNA double helix

Histones

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Open chromatin

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23 pairs of chromosomes packed into the nucleus

Epigenetic factor
Environmental exposures
Epigenetic marks as the physical nexus between genes and environments
Wisconsin Study of Families and Work

N = 570

Parental stressors

Infancy  Preschool

N = 109

Epigenetic profiling of buccal epithelial cells
• Epigenetic vestiges of early parental stressors

Essex, Boyce et al: Child Dev, 2013
Epigenetic vestiges of early parental stressors

Mothers’ stressors in infancy more related to differences in methylation for both girls and boys

Essex, Boyce et al: *Child Dev*, 2013
Epigenetic vestiges of early parental stressors

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- Fathers’ stressors in preschool associated with demethylation differences, primarily for girls

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• Epigenetic vestiges of early parental stressors
• Mothers’ stressors in infancy more related to differences in methylation for both girls and boys
• Fathers’ stressors in preschool associated with demethylation differences, primarily for girls
• Pattern of association consistent with known developmental time course of parental influence

Essex, Boyce et al: Child Dev, 2013
“So, how do you want to play this? Nature, nurture, or a bit of both?”
Adaptive phenotype

Maladaptive phenotype
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Why?  How?
Why? How?

- Unshared family environment; i.e., raised in “different families”
- Sibling differences in genomic risk
- Birth order or gender
- Complex, epigenetic interaction between allelic variation and family environment
8 year old patient with chronic abdominal pain
"I am sick of this messy life. Always the same. Everyone makes fun of me. No one recognizes my potential. I am serious."
— Tim Kreschmer, secondary school student
Posted on the internet the night prior to a shooting rampage that killed 15 people

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• Subordination
• Stress and adversity
• Inequality in life chances
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• “A selfish and boundless thirst for power and material prosperity” (Pope Francis, in address to U.N. General Assembly)
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Social relationships are important!
• Social stratification
• Subordination
• Stress and adversity
• Inequality in life chances
• “A selfish and boundless thirst for power and material prosperity” (Pope Francis, in address to U.N. General Assembly)
Nancy Adler, Abbey Alkon, Ron Barr, Loïc Belingard, Pam Den Besten, Nicki Bush, Nicole Catherine, Bruce Ellis, Tanya Erb, Marilyn Essex, John Featherstone, Clyde Hertzman, Young Shin Kim, Mark Kishiyama, Mike Kobor, Stephanie Lam, Amani Nuru-Jeter, Tim Oberlander, Doug Jutte, Amani Nuru-Jeter, Jelena Obradović, Khaled Sarsour, Margaret Sheridan, Juliet Stamper, Anat Zaidman, the MacArthur Foundation Research Network on Psychopathology and Development, the National Institute of Mental Health, the National Institute of Child Health and Human Development, the WT Grant Foundation, the Robert Wood Johnson Foundation Health & Society Scholars Program, the University of British Columbia, the UBC Human Early Learning Partnership, and the Experience-Based Brain and Biological Development Program of the Canadian Institute For Advanced Research, and the Child and Family Research Institute.
...she has to be able to connect your voice to your touch

DUPREE M: LEADERSHIP IS AN ART, 1989