Developmental Origins of Chronic Disease

You Are What Your Mother & Grandmother Ate: Transgenerational Influences

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Biology of Developmental Programming

OUTLINE

- What is “Developmental Origins of Health & Disease”?
- The Origins of Developmental Origins: A Paradox
- Evolving History: Lessons from Cohort Studies
- Biological Pathways of Disease Vulnerability
  - change in organ structure
  - change in homeostatic system setpoints
  - interactions of prenatal and postnatal exposures
- Transgenerational Transmission of Disease Risk
- Obesity Programs Obesity: A crisis in progress
We Are What We Eat -
And so are our kids & grand-kids!

Nutritional Life of the Egg is Trans-Generational
What is ‘Developmental Origins of Health and Disease’?

- **Concept:** biologic capacity of normal *developing* organisms to be *durably* changed by environmental exposures without change in the inherited genome

- **Process:** ‘developmental programming’

- **Exposures:** nutrients, O₂, chemicals, toxins

- **Mechanisms:** substrate deficits; epigenetic changes

- **Pathways:** Δ organ structure (permanent)
  Δ cell/organ function (± reversible)
  Δ regulatory system setpoints

- **Impact:** **Vulnerability** to development of chronic disease in later life
"Double Burden" of Malnutrition

Nutritional Adversity

Undernutrition
- Low Prot
- Low Calorie

HiCal Malnutrition
- Obesity/HiFat
- Gest’l DM

Abnormal ↓ Fetal Growth (slow/asymmetric)
Abnormal ↑ Fetal Growth (fast/asymmetric)

Vulnerability

Environmental Stressors

Chronic Diseases in Children and Adults
- CardioRenalMetabolic
- Behavioral/Mental
Death from Coronary Heart Disease
England & Wales 1968-1978

High

Low

The Origins of Developmental Origins
Socioeconomic Health Disparity

Red areas:
• poor land
• sparse food
• Urban poverty

Green areas:
• rich land
• abundant food
• Non-$ wealth

Neonatal Mortality in early 1900’s has identical pattern

Everyone ‘knew’ that Coronary Artery Disease was a disease of societal affluence.

How then can Coronary Mortality be tracking with socioeconomic disadvantage?

**Answer:** Babies developing in adverse conditions are uniquely susceptible to negative impacts of affluence (hi animal protein, fat, calories)
A Link to Health Disparity

Developmental Programming

- First recognized because it led to socioeconomic-based health disparity
- Is a major mechanism by which:
  - SE/psychosocial stressors become biologically embedded within a population
  - Developmentally-based health disparities can be transmitted to future generations
The Barker Hypothesis
Developmental Origins of Disease

Lessons from Cohort Studies

The British Cohorts
- Small English villages
- Two time points: Birth and 50+ yrs

Poor Fetal Growth Increases Risk of Chronic Disease in Later Life
The Effect of Term Birthweight on Mortality

Barker et al., 1989

Women: 5585 (1923-30)
Men: 10,141 (1911-30)
Poor Fetal growth → Increased Risk of Disease

**Hypertension**

Jarvelin – HTN 2004
n = 5960 offspring

**Coronary Disease & Stroke**

Am Nurses Study
BMJ 1997
Mean ± 95% CL

**Risk of Glu Intol or Diabetes**

Hales 1991
370 men
Age 64 yrs

Birth Weight (lbs)

-5.5 6.5 7.5 8.5 9.5 >9.5

Gestat’l DM

Birth Weight (gm)

<2500 -2999 -3499 -3999 -4499 >4500

Sys BP (mmHg)

130 128 126 124 122

Relative Risk

0.50 0.75 1.00 1.25 1.50

Mean ± 95% CL
Birth Weight is Crude Surrogate for Fetal Growth

Asymmetric Growth Restriction

- Thin (↓ Wt:Ht ratio)
- Fetal blood flow redistribution ↓ kidney, liver, pancreas ↓ abdom’l girth
  Heart/brain ‘sparing’
- Low arm circumference (↓ muscle mass)

May Occur with Normal Birth Weight!
Developmental Origins of Chronic Disease

In Utero
- Fetal Under-Nutrition

Birth
- Altered Birth Phenotype

Childhood
- MODIFIERS
- COFACTORS

Adulthood
- Metabolic/Cardiovascular Disease
  - HTN
  - Renal Disease
  - Abd’I Obesity
  - Diabetes
  - ↑TG/↓HDL
  - Cor Art Dis

Vulnerability
What is the link?
Developmental Origins of Chronic Disease

Hypertension
Kidney Disease
Obesity
Type II Diabetes
Dyslipidemia
Ischemic Heart Disease
Osteoporosis
Asthma/Allergies
Depression, Anxiety
ADHD, Schizophrenia
Breast, Ovarian, & Lung Cancers
Developmental Origins of Disease
Pathways of Nutritional Programming

- Altered organ structure/function
- Altered homeostatic system setpoints
- Adverse interactions of prenatal vulnerabilities with postnatal stressors
Pathways of Nutritional Programming

Altered Organ Structure/Function

“Critical Windows” of Organ Development

- Brain
- Placenta
- Pancreas (insulin)
- Kidney (filtering units)
- Early Heart
- Heart cell maturation

Embryo → Fetus → Birth

Time from Conception
# Pathways of Nutritional Programming

**Structural Deficits → ↓ # Functional Units**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Effect 1</th>
<th>Effect 2</th>
<th>Effect 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>↓ Nephron #</td>
<td>HTN, renal risk</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>↓ Islet β cell #</td>
<td>Δ Insulin secretion</td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>↓ muscle mass</td>
<td>↓ Basal met rate</td>
<td>↓ Exercise capacity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Insulin sensitivity</td>
</tr>
<tr>
<td>Heart</td>
<td>↓ myocyte #</td>
<td></td>
<td>↑ Risk CHF</td>
</tr>
<tr>
<td>Liver</td>
<td>↓ lobule, cell #</td>
<td>Δ lipid/protein metab.</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>↓ microvasc dens</td>
<td>↑ vasc resistance</td>
<td>↑ ischemia risk</td>
</tr>
</tbody>
</table>
Time Course of Renal Development

Human

Rat or Pig

Gestation

Birth

# Nephrons (% Max)

0

100

100

0

5 - 35 wks

1 2 3 4 Weeks
New Nephrons Form in Concentric Layers during Gestation

Condensing Mesenchyme

Comma Shaped Bodies

Outer Nephrogenic Layer

Branching Morphogenesis $\rightarrow$ Nephrogenesis
Reduced Glomerular # in Human IUGR

Developmental Origins of HTN
Pathways of Nutritional Programming

- Altered Organ Structure $\rightarrow$ $\Delta$ Function
  
  Kidney: ↓ nephron number

- Altered Homeostatic Setpoints
  
  Energy Balance: “thrifty phenotype”

- Interactions of prenatal vulnerabilities with postnatal stressors
Altered Homeostatic System Setpoints in Programmed Offspring

Enhanced Response to Postnatal Environment

- Sympathetic nervous system hyperactivity
- Renin/AngII system hyperactivity
- Stress hyperreactivity: HPA Axis
- Oxidative Stress/Inflammatory responses
- Immune hyperactivity (asthma, allergies)
- Energy homeostasis: Fat, glucose/insulin metabolism, appetite regulation
Altered Homeostatic System Setpoints in Programmed Offspring

Hyperreactive Cardiovascular Responses in Normotensive Low-Birth Wt Children

- ↑ Cold Pressor Test\(^1\)
- ↑ Psychological stress responses\(^2,3\)
  - mental arithmetic
  - public speaking
- ↓ Flow-dependent vasodilation\(^4\)

Stress Hyperactivity Predicts Later Hypertension

\(^1\) Nichols 2005; \(^2\) Matthews 2004; \(^3\) Ward 2004; \(^4\) Leeson 1997
Altered Energy Homeostasis in Programmed Offspring

“The Thrifty Phenotype”

- The fetus adapts to nutrient deficit by permanently
  - ↑’g energy utilization efficiency
  - ↑’g appetite-promoting circuits
  - promoting survival in utero

- These permanent adaptations:
  - enhance postnatal tolerance to famine
  - impair ability to handle nutrient excess

- Example: “Rural-to-Urban Transition”

Hales & Barker, 2001
“The Thrifty Phenotype”
Asymmetric Growth Restriction

△ Energy Homeostasis

“Thrifty Phenotype”
↑ Appetite
↑ Energy Efficiency
↓ Locomotor Activity

+ FOOD

Accelerated Growth

↑ BODY MASS

Crossing Centiles
What is the Impact of Thrifty Phenotype?

Lessons from Cohort Studies

The Helsinki Cohorts

- Finnish public health records
- Annual child growth data: birth-15 yrs
- Adult Outcomes: med Rx, hospital records

Accelerated Postnatal Growth Enhances Risk of Chronic Disease in Later Life
Early Growth Patterns Predict Adult HTN

Growth Patterns in 1404 Children who later developed Hypertension

Rapid Childhood Growth Predicts HTN

Helsinki Cohort

Cumulative % HTN: BWt vs Δ BMI over 3-11 Yrs

Rapid Childhood Growth Predicts HTN & Enhances BirthWeight Effect

Helsinki Cohort: Random Sample

Avg Age 62 yrs
n = 2003

Early Growth Patterns Predict Adult HTN

Growth Patterns in 1404 Children who later developed Hypertension

- --- BMI
- ○ Weight
- ⋄ Height

not obese as children

Cohort Average (n=8760)

Developmental Origins of CVascular Disease

In Utero

Fetal Under-Nutrition

Altered Birth Phenotype

Birth

Vulnerability

Food

COFACTORS

↑ Postnatal Growth

Childhood

Cardio/Renal/Metabolic Disease

↓ Postnatal Growth

Adulthood

HTN
Renal Disease
Diabetes
Cor Art Dis

What is the link?
Developmental Origins of HTN
Pathways of Nutritional Programming

- Altered Organ Structure $\rightarrow \Delta$ Function
  - Kidney: $\downarrow$ nephron number

- Altered Homeostatic Setpoints
  - Energy Balance: “thrifty phenotype”

- Adverse interactions of prenatal vulnerabilities with postnatal stressors
What Conveys Risk of HTN-Renal Disease in Lower Birth-weight Offspring?

Low Nephron Number?

Nephron Dosing

Risk of HTN & Renal Disease

Brenner Hypothesis

1 Am J HTN 1988 1:335-47;
2 Am J Kid Dis 1994 23: 171
Programming Pathways: Mismatch

Early Asymmetric Growth Restriction

△ Energy Homeostasis
- “Thrifty Phenotype”
- Hyperphagia
- ↓ Locomotor Activity
- ↑ Energy Utiliz’n Effic’y

△ Renal Development
- ↓ # Nephrons
- FIXED LOW Excretory Capacity

FOOD

Accelerated Growth

↓ # Nephrons

HTN & Renal Risk

BODY MASS
Nephron Response to Excretory Overload

Increase glomerular capillary pressure ($P_{GC}$)

Increase single-nephron GFR
Mismatch

BODY MASS

↓ # Nephrons

Focal Glomerular Sclerosis (FSGS)

END STAGE RENAL DISEASE (ESRD)
Dialysis or Transplant

High Cardiovascular Risk

Chronic Kidney Disease (CKD)
Reduced GFR (late stage)

HTN

Progressive nephron loss;
Fewer and fewer functional nephrons
Poor Fetal Growth Affects ESRD Risk

<table>
<thead>
<tr>
<th>Birth Weight (kg)</th>
<th>Cause of ESRD</th>
<th>Odds Ratio for Renal Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.5</td>
<td>Diabetes</td>
<td>2.5</td>
</tr>
<tr>
<td>2.5-2.9</td>
<td>HTN</td>
<td>2.01</td>
</tr>
<tr>
<td>3.0-3.49</td>
<td>Other</td>
<td>1.5</td>
</tr>
<tr>
<td>3.5-3.9</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>≥ 4.0</td>
<td></td>
<td>0.5</td>
</tr>
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Adapted from: Lackland D et al. Arch Intern Med, 2000
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Transgenerational Transmission of Programmed Changes

Nutritional Life of the Egg is Trans-Generational
Transgenerational Transmission

More Lessons from Cohort Studies

The Helsinki Cohorts

- Finnish public health records
- Maternal pelvic dimensions
- Annual growth data from birth-15 yrs
- Adult Outcomes: random sampling of cohort members at avg age 62 yrs

Programmed abnormalities can be transmitted to the next generation
Maternal Anterior-Posterior Pelvic Dimension Reflects Mom’s Early-Life Nutrition

- Set in infancy
- Reflects fetal/infant nutrition (Vit D)
- Flatter pelvis indicates fetal/neonatal undernutrition
Mother’s Early-Life Nutrition Affects *Future* Offspring Disease Risk

**Mother’s Pelvis**

- Flatter ant-posterior Pelvic diameter
- $\cong$ fetal/neonatal undernutrition

**Daughter’s Outcome**

- Short at birth
- Slow growth as child
- Overweight as adult
- Late-onset HTN

Barker et al. Hypertension 50: December 2008
Transgenerational Transmission of Disease Risk

**OUTCOMES at 62 yrs**
- HTN
- Obesity

**Adult Pelvic A-P Diam**

**Poor Nutrition Conceptn -2 yrs**

**Short at Birth**

**Poor Growth 3-15 yrs**

**GrandMother**

**Mother**

**Daughter**
Transgenerational Transmission

Mother's Pelvis
Wide, rounded (? Hi estrogens)

Daughter's Outcome
Breast, Ovarian Cancer

Hi maternal estrogen acts on developing fetal breast cells in utero?

Mom’s delayed puberty prolongs estrogen exposure of oocytes?
Mom’s Body Status Alters Future Fetal Nutrition

PrePregnancy

Pathways of Transgenerational Transmission

Mom’s adult body status:
- non-fat body mass (visceral)
- Protein turnover rate
- Amino acid oxidation capacity

FETAL IMPACTS
△ AA delivery
△ Fetal Growth
△ Birthweight

GrandMother
Mother
Daughter
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Nutritional Adversity

Undernutrition
- Low Prot
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HiCal Malnutrition
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Abnormal ↓ Fetal Growth (slow/asymmetric)

Abnormal ↑ Fetal Growth (fast/asymmetric)

Vulnerability

Environmental Stressors

Chronic Diseases in Children and Adults
- Cardio/Renal/Metabolic
- Behavioral/Mental
Obesity Risk in Offspring following Fetal Overnutrition

Maternal Obesity/High Energy Diet

Eriksson J et al Internat J Obesity 2001
Maternal Hi Fat Diet/Obesity Programming Effects in Monkey Offspring

- **Fetal/Neonatal Liver:**
  - Lipotoxicity, inflammation, oxidative stress
  - Non-alcoholic fatty liver disease (neonate)

- **Fetal Brain:**
  - Inflammation
  - Δ neural appetite circuits, reward centers

- **Postnatal Behaviors:**
  - Hyperphagia
  - Preference for hi fat/sweet/salty food
  - Rapid infant growth rate
  - Early excess adiposity (age 6 mo)
  - Early onset puberty
  - ↑ Anxiety (females)/Aggression (males)

Grove K et al: Non-human primate model (ONPRC)
Fetal Liver Fat Accumulation/Lipotoxicity in Offspring of Monkey Mom’s on Chronic High Fat Diet

McCurdy et al, J Clin Investigation, 2009
Rising Prevalence of Maternal Obesity

Impact of Neighborhood Socio-Economic Status

Sellstrom E et al, BMC Pregnancy and Childbirth, Sweden, 2009

Accelerating rate of increase
Projected for 2010: 22% obesity
OHSU 2010: 40%

Percentage Obesity


Poor
Mid Level
Affluent
Maternal Obesity & Risk of Behavioral Dysfunction

Children's ADHD and Executive Function Scores Based on Mother's Body Mass Index

Buss C et al. PLoS One, June 2012
Chronic Hi-Fat Diet Monkey Model
Partial Improvement by HiFat Diet Reversal despite Persistent Maternal Obesity

Fetal Liver Triglyceride Content

- Offspring of Chronic HiFat Diet Moms
- Offspring of HiFat Moms after Diet Reversal

Other Features Improved
- Liver inflammation
- Brain Inflammation
- Melanocortin Fxn

McCurdy et al, J Clin Investigation, 2009
“Double Burden” of Malnutrition

In Utero

- Undernutrition
  - Low Prot
  - Low Calorie
- HiCal Malnutrition
  - Obesity/HiFat
  - Gest’l DM

Birth

- Lower BirthWeight
- Asymmetric IUGR/ESRD
- Higher BirthWeight
- Macrosomia

Childhood

- Rapid Childhood Growth
- Rapid Infant Growth

Adulthood

- Adult-onset
  - Obesity/HTN/Diabetes
  - CKD/ESRD
  - ↓ Nephron #/Body Mass
- Childhood-onset
  - Obesity/HTN/Diabetes
  - CKD/ESRD
  - ↓ Nephron #/Body Mass
  - CKD/ESRD
What Do We DO About All This??

Think Trans-generational

A girl is a mother from the time of her own mother’s conception.

A mother is the biological bridge to the health of future generations.
What Do We Do About All This??

Act Now: Nutrition

- Focus on girls, mothers and mothers-to-be
- Community-based research to define safe & effective interventions
- Harness the village:
  - change our food culture
  - change our school culture
  - change our corporate Agric. and food processing cultures
THE BOB & CHARLEE MOORE INSTITUTE for NUTRITION & WELLNESS

MISSION

To reduce the prevalence of chronic diseases across the lifespan

❖ in current and future generations

❖ via promoting healthy, nutrient-rich whole-food diets in early life

  - before conception
  - during pregnancy and lactation
  - in infancy and early childhood

The Power of Partnership
A CONVERSATION

DOHaD: Implications for Practice

Harnessing the Power of the Science

I. Patient/Client Education (life stage-specific)
II. Professional Training (multi-level)
III. Public Policy Advocacy
Developmental Origins of Chronic Disease

You Are What Your Mother & Grandmother Ate: Transgenerational Influences

Pediatric Nutrition Symposium
March 2013

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