The Barker Hypothesis

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Overview

- History
- Adult disease
- Current understanding of mechanisms
- Implications for clinical care
- Summary

Terminology

- Barker Hypothesis
- Fetal origins of adult disease
- Developmental origins of adult disease
- Developmental origins of health and disease (DOHaD)
  - Now an international research society

Dutch Famine 1944-45

- Ravelli 1976: male adult obesity related to timing of perinatal famine exposure
Infant mortality and heart disease

- Neonatal mortality (1st month of life) correlated with heart disease
  - Decreasing neonatal mortality rates with increasing heart disease mortality -> "increased prosperity" during lifetime
- Post-neonatal mortality (> 1 month of life) correlated with stomach cancer, bronchitis, and rheumatic heart disease
  - Diseases associated with poor socioeconomic conditions

Birthweight and heart disease

- Barker 1989: "Weight in infancy and death from ischaemic heart disease"
- 5654 men from Hertfordshire born 1911-1930
  - Weights in infancy were recorded
  - 92.4% breastfed

Table III - SMRs for ischaemic heart disease according to birthweight and weight at one year in men who were breast fed

<table>
<thead>
<tr>
<th>Weight at one year (pounds)</th>
<th>Below average (≤7)</th>
<th>Average 7-8.5</th>
<th>Above average (≥9)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below average (≤21)</td>
<td>100 (80)</td>
<td>100 (77)</td>
<td>58 (17)</td>
<td>93 (174)</td>
</tr>
<tr>
<td>Average (22-23)</td>
<td>86 (34)</td>
<td>87 (67)</td>
<td>80 (29)</td>
<td>85 (130)</td>
</tr>
<tr>
<td>Above average (≥24)</td>
<td>53 (14)</td>
<td>65 (42)</td>
<td>59 (32)</td>
<td>60 (88)</td>
</tr>
<tr>
<td>Total</td>
<td>88 (128)</td>
<td>85 (186)</td>
<td>65 (78)</td>
<td>81 (392)</td>
</tr>
</tbody>
</table>

Barker 1989
Placental size and hypertension

- Barker, August 1990, BMJ
- BW and placental wt. stronger influences than BMI and EtOH -> discordance in fetal growth

Barker Hypothesis

- Barker, November 1990, BMJ
  - Research article: “The fetal and infant origins of adult disease”
  - Subtitle: “The womb may be more important than the home”
- Paneth and Susser, 1995, BMJ editorial
  - Early origin of coronary heart disease (the “Barker hypothesis”)

Evolution and “thrift”

- Genetic variation and environmental adaptability <-> “plasticity”
  - Not strict genetic “selection” process
  - Gene-environment interactions
    - Twin studies
  - “thrifty genotype”
  - “thrifty phenotype”
  - “predictive adaptive response”

Adult Disease

- Metabolic
  - Obesity
  - Hypertension
  - Type II diabetes (metabolic syndrome)
  - Cardiovascular disease
- Non-metabolic
  - Cancer (e.g. DES exposure)
  - Psychological disorders (e.g. Susser 1992)
Ongoing cohort studies

- Southhampton Women’s Survey
  - 12,500 young females pre-pregnancy
  - Eventually 3000 live births
- National Children’s Study
  - Enrollment of ~750,000 pre- and early pregnant women with target 100,000 children enrolled across 105 centers in USA
  - 7 Vanguard Centers conducting initial field test

Basic Mechanisms

- Variations in organ structure
- Alterations in cell number
- Clonal selection of cell populations
- Apoptotic remodeling
- Metabolic differentiation
- Hormonal imprinting

Epigenetic gene regulation

- Heritable changes in gene expression without change in DNA sequence
- “Permanent” alterations in control of gene expression
  - DNA methylation
  - Histone modification
  - RNA interference

DNA methylation

- DNA methyltransferases
  - $\text{DNA methyltransferases}$
  - $5'\text{GpG-3'}$ to $3'\text{GpG-5'}$
- Methylated DNA
  - $\text{Methylated DNA}$
  - $\text{Unmethylated}$
  - $\text{Acetylation}$
  - $\text{Transcription}$

http://www.cellscience.com/reviews/07/Cancer_DNA_methylation.html
Chromatin structure

Epigenetics and inheritance

Epigenetic dietary modification

Implications for clinical care

- Dolly 2007: maternal rats fed BPA showed coat changes related to DNA methylation at specific sites
- Methyl donor (folate, B12, betaine, choline) or genistein diet supplementation (along with BPA) resulted in normal coat distribution

- sex-specific, male-line trans-generational effect in humans (Kaati 2007, Bygren 2001)

- Prenatal care and counseling
- Neonatal care
- Pediatric care
- Societal
Maternal Diet and Health

- Nutrition: protein intake, ratio to carbohydrates, weight gain
- Maternal smoking cessation
- Glucose control
- Blood pressure control
- Folate supplementation
- Consideration of Rx medications
- Environmental exposures (e.g. BPA)

Neonatal and Pediatric care

- Counseling for parents of SGA infants
- Feeding of SGA infants
- Nutrition during “critical” periods
  - Initial years of life (0-2)
  - “Slow growth period” before pre-pubertal growth spurt
    - 8-11 females
    - 9-12 males

Societal implications

- Public health education
  - Preventative measures include prenatal/perinatal education
  - Parental actions affect child health not just through environment, but through epigenetic effects
- Nutritional supplementation
- Environmental exposures

Summary

- Developmental timeline starts preconception and continues throughout life.
- Intergenerational effects can be modulated through epigenetic phenomena
- Future techniques may be available to improve both health and disease starting prenatally