Nutrigenomics and Epigenetics: Public Health Perspective

Introduction

Greater understanding of the molecular basis of environmental and genetic interactions

Strengthened scientific base in support of the view that development is not the consequence of “nature or nurture,” but of both

And, in a broader sense that phenotypes are the consequences of Darwinian selection and order imposed “spontaneously” by the properties of metabolic networks and the environment, e.g. of food availability and accessibility (modifications) climate interactions with other replicating “life” forms
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Introduction: Three questions

What is the evidence for the public health relevance of this new knowledge?

If it is relevant, are developmental/metabolic effects of early genetic and environmental interactions reversible?

Whether reversible or not, are such effects single or multi-generational?
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Four additional questions to help assess public health relevance:

What is the nature of the targeted benefit or hazard?

What is the prevalence, actual or potential, of the outcome(s) of interest?

Are there means to prevent, control, and/or reverse the hazard(s) or achieve the benefit(s)?

And are these “means” socially acceptable, e.g. financially, culturally, etc.?.
Phenotypic Engineering

The predictable determination of specific phenotypes by identifiable nutritional treatments or experiences enabled by genetic endowment.

Empirical evidence for Phenotypic Engineering:

McCay’s early animal studies
Migration studies of populations with stable genotypes
Longitudinal studies of populations with stable genotypes
Human epidemiological data

There is substantial evidence that birth weight is linked to adult BMI, cardiovascular disease, blood pressure, and/or glucose tolerance, but less agreement on the magnitude of those effects.

There also is evidence that early infant growth rates and patterns may also influence risk to various chronic diseases.

Recognition of the inherent weaknesses of the long-term retrospective nature of studies that have made those links.

Thus, available epidemiologic data clearly are limited by their inability to refute competing hypotheses or to ascribe causative relationships between perinatal nutritional experiences and disease outcomes of adult onset, e.g. underlying genetic endowment and continuity of social circumstances.
Perinatal nutrition: Driver for Phenotypic Engineering

Animal models

Generally support the view that early nutrition causes “permanent” changes in metabolic responses.

Ability to control potentially confounding factors adds significantly to the biologic plausibility of epidemiologic studies.

Specific relationships between nutritional treatments and adult outcomes in animal models are not always concordant with expectations extrapolated from the epidemiologic literature.

But most models are based on rodents; differences in metabolic ontogeny dampens concerns raised by the lack of total overlap.

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Phenotypic variation in isogenic Avy/a mice correlates with IAP methylation

Morgan et al., *Nature Genetics* 1999;23:314

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IMPRINTING

may occur only during “a narrowly defined period in an individual’s life”, and the imprinted behavior “cannot be ‘forgotten’!”.

Konrad Lorenz, 1970
Metabolic Imprinting

Adaptive responses to specific nutritional conditions early in life. Characterized by

1) susceptibility limited to a “critical window”
2) persistent effect lasting into adulthood
3) specific and measurable outcome
4) dose-response or threshold relationship

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Potential mechanisms of metabolic imprinting

Organ structure
Cell number
    hepatocyte polyploidization
    myocyte multinucleation
Clonal selection
Metabolic differentiation
Apoptotic remodeling
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Epigenetic mechanisms implicated in maintaining cellular differentiation

Self-perpetuating DNA binding proteins
Methylation of cytosine in DNA
Specified alterations in chromatin structure
Others
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**Two classes of transgenerational effects of transient nutritional exposure**

<table>
<thead>
<tr>
<th>Mode of transmission</th>
<th>Exposure alters maternal reproductive structure or function</th>
<th>Exposure alters development of germ line epigenetically</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered fetal environment leads to effect on birth weight, metabolic differentiation, etc.</td>
<td>Epigenetic alterations pass directly to next generation</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Critical window for primary effect</th>
<th>Likely limited to perinatal period; possibly also sexual maturation</th>
<th>Potentially diverse critical windows encompassing embryonic period to adulthood</th>
</tr>
</thead>
</table>

| Gender specificity | Transmission through females only | Transmission through male or females possible |

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Mean z-scores of healthy breastfed infants relative to the NCHS/WHO reference
CONSEQUENCES OF SHIFTS IN STANDARD DEVIATIONS: RURAL INDIANS
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CONSEQUENCES OF SHIFTING STANDARD DEVIATIONS: US Children

- Weight-for-age
- Length-for-age
- Weight-for-length

![Graphs showing the percentage of total data points above +2 SD for weight-for-age, length-for-age, and weight-for-length over age (mo).]

Legend:
- NCHS-WHO
- Breast-fed set
WHO Child Growth Standard

A growth chart for the 21st century
The WHO Multicentre Growth Reference Study

DESIGNED TO DESCRIBE HOW CHILDREN SHOULD GROW REGARDLESS OF TIME OR PLACE

NOT HOW CHILDREN GROW AT A PARTICULAR TIME OR PLACE
Growth Reference Study
Prescriptive Approach

1. Optimal Nutrition
   - Breastfed infants
   - Appropriate complementary feeding

2. Optimal Environment
   - No microbiological contamination
   - No smoking

3. Optimal Care
   - Immunization
   - Pediatric routines

WHO Multicentre Growth Reference Study

Optimal Growth and perhaps Help Assess Optimal Well-being
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Sample sizes: New Growth Standard

Target for stable outer centiles: 400 both sexes recruited from six sites internationally

Longitudinal sample:

1743 total enrolled
882 (428 boys/454 girls) complied with feeding & non-smoking criteria and completed 24 months follow-up

Cross-sectional sample:

6669 (3450 boys/3219 girls)
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Mean length from birth to 24 months for the six MGRS sites

![Graph showing mean length from birth to 24 months for six MGRS sites: Brazil, Ghana, India, Norway, Oman, USA.](image)

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Concordance between smoothed curves and empirical values: Length-for-age, boys, 0-24 months

Comparison of WHO with CDC 2000 weight-for-age-z-scores for boys
Comparison of WHO with CDC 2000 BMI-for-age z-scores for boys

Mean weight-for-age z-scores of healthy breastfed infants relative to the WHO standards and the CDC 2000 charts
WHO Growth Standards

• Attained growth
  • Weight-for-age
  • Length/height-for-age
  • Weight-for-length/height
  • Body mass index-for-age
  • Mid-upper arm circumference-for-age
  • Triceps skinfold-for-age
  • Subscapular skinfold-for-age
  • Head circumference-for-age

• Growth velocity
  • Weight
  • Length/height
  • Head circumference
  • Arm circumference
  • Body mass index
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Robert Waterland (BCM)

Mercedes de Onis (WHO)
Elainie Borghi (WHO), et al

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Katherine Dewey et al (U California, Davis)
Ali Jaffer et al (Ministry of Health, Oman)
Ana Lartey et al (U of Accra, Ghana)
Kaare Norum et al (U of Oslo, Norway)
C Victoria et al (U Fed, Pelotas, Brazil)

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