Understanding & accelerating Progress in Children’s Nutrition:
Is there a way forward

Prof. MK Bhan
National Science Professor
Indian Institute of Technology, Delhi
Progress in India so far

• **Severe forms of malnutrition, single nutrient deficiencies reduced**

• **Persistent problems:**
  ◦ Low birth weight
  ◦ Stunting
  ◦ Under weight
  ◦ Subclinical nutrient deficiencies
  ◦ Geographic variation
Comparison of under nutrition indices as per WHO growth reference in India

### Attained lengths and increments of infants at different ages in the intervention and control groups\(^1,2\)

<table>
<thead>
<tr>
<th>Attained lengths, cm</th>
<th>Food supplement</th>
<th>Nutritional counselling</th>
<th>No intervention</th>
<th>Visitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 26 wk</td>
<td>n= 96</td>
<td>n = 95</td>
<td>n = 100</td>
<td>n = 96</td>
</tr>
<tr>
<td></td>
<td>62.5 ± 2.8</td>
<td>62.7 ± 2.9</td>
<td>62.2 ± 2.9</td>
<td>62.5 ± 2.4</td>
</tr>
<tr>
<td>At 38 wk</td>
<td>n= 88</td>
<td>n= 89</td>
<td>n= 93</td>
<td>n= 95</td>
</tr>
<tr>
<td></td>
<td>65.7 ± 2.5</td>
<td>65.8 ± 3.0</td>
<td>65.5 ± 2.8</td>
<td>65.5 ± 2.6</td>
</tr>
<tr>
<td>At 52 wk</td>
<td>n= 87</td>
<td>n= 97</td>
<td>n= 93</td>
<td>n= 91</td>
</tr>
<tr>
<td></td>
<td>68.4 ± 2.6</td>
<td>68.6 ± 2.9</td>
<td>68.3 ± 2.7</td>
<td>68.4 ± 2.4</td>
</tr>
</tbody>
</table>

\(^1\) All values are mean ± SD except those indicated n (%)

\(^2\) All comparisons not significant (P > 0.05)

Evidence from interventional trials in India show 0.25 SD or lesser shift in weight and linear growth during infancy or childhood.

Conflicting views on importance of stunting among economists, planners and even nutrition scientists.

Wait for usual development process or accelerate to reduce stunting, improve linear growth.
Key Issues

• Are there consequences of under nutrition in critical 1000 day window (-9 months to end of 24 mo)
  ▫ Later life health and development
  ▫ Economic development

• Intergenerational correlation in health & nutrition
  ▫ What are the underlying mechanisms?

• What are appropriate strategies to improve status at birth, and realise potential for growth in first 2 years of life
Lessons from major long term birth cohorts

Early life origins of adult disease

Nutrition insults during fetal life have surprising, long lasting implications for health and development

Linear growth and stunting

Fundamental, persistent problems
Height at 2 years is a predictor of adult life disease, and economic development

Intergenerational effects

Prenatal and possibly postnatal 2 years are the critical window when lack of resources may leave a long term, intergenerational imprint

Maternal and child under nutrition, Lancet series, 2008
Adult height is positively associated with birth weight and length. A 1 cm increase in birth length is associated with 0.7-1 cm increase in adult height.
Forest plot for effect of height-for-age at 2 years on attained schooling

Birth weight rose by 29 g per 100 g increase in mother’s birth weight, and birth length rose by 0·2 cm for every 1 cm in increase in mother’s birth length.

Effect of height-for-age at 2 years on offspring birth weight (females only)

Maternal and child under nutrition: 2, Lancet series, 2008
Income and Assets

Adult height is positively associated with income, even in urban settings and even after adjustment for education.


One additional year of schooling is associated with 12–14% increased lifetime earnings.

Victora CG, Acta Paediatr 2005
Psacharopoulos G et. Al. Educ Econ 2004

1 Z score increase in H/A in men was associated with an 8% increase in income in Brazil (p<0·0001) and Guatemala (p=0·07), as well as with an increase of 0·27 household assets in India (p<0·0001).

Maternal and Child undernutrition:2, Lancet Series
Effect of height-for-age at 2 years on Obesity and associated co-morbidities

Maternal and child under nutrition:2, Lancet series, 2008
Event Study Estimates of the Impact of FSP Exposure on Metabolic Syndrome Index High Impact Sample
Key mechanisms underlying limited progress

- Intergenerational programming
- Reductionism; undernutrition is more than a nutritional disorder
- Most constraint in growth could be periconceptual, prenatal or very early in life (?)
- Discordant twins in Africa have differential risks of Kwashiorkor in same environment. Role of gut microbiome in malnutrition
- Indian gut is chronically inflamed
  Immune activation rather than immune suppression
Stunting is more than a nutritional disorder

Pre- and Peri-conceptual factors

Pregnancy related factors

Feeding quality and quantity

Care practices

Inflammation and infection
Epigenetics as basis of programming of linear growth

Cause

Nutrition
Stress
Depression
Mother infant bonding

Critical Window

Periconception?
Late pregnancy?
Infancy?
Disturbed energy balance; a combination of Genetics, Epigenetics & Environmental Factors

Epigenetic Mechanism and Regulation of Transcription

Heritable changes in gene expression without altering gene sequence

DNA Methylation

Histone Methylation

Micro RNA

Hypo → Transcriptional activation

Hyper → Transcriptional suppression
Maternal Diet And Altered Genetic Regulation

• A nutritional challenge in early pregnancy or early post natal life can result in DNA methylation, which is detectable 60 years later.

• Overfeeding in post natal life can alter methylation of genes critical for appetite control.

• Changes in gene expression are heritable over few generations.
Depression in Pregnancy, Low Birth Weight and DNA methylation of Imprinted Regulatory Genes

Methylation at MEG3 for infants of women with severe and no depressed mood
Malawi – Kwashiorkar and Microbes

- Discordant twins differ in rate of acquiring severe acute malnutrition
- Germ free mice receiving bacteria from kwashiorkor children develops kwashiorkor like symptoms, but not from non-kwashiorkor children
- Significant affect on metabolism
  Less able to process amino-acids containing sulphur
Environmental Enteropathy

is very common in Indian young children; is gut microbiome a modulator?

- Reduced villous height
- Increase IEL, LP T cells, TH1 predominance
- Impaired barrier integrity – lactulose – mannitol uptake
- ↑ Anti endotoxin levels in stunted, not wasted
Fecal markers of intestinal inflammation and permeability are associated with subsequent acquisition of linear growth deficiency in infants

Fecal neopterin (TH1-Activation Markers)

Alpha -1 antitrypsin (Serum, protein, proteolysis resistant)

Myeloperoxidase (neutrophil activity)

Is microbiome a mediator of chronic gut, systemic inflammation?

Infant feeding, the microbiota, immunity and inflammation

Has the Microbiota Played a Critical Role in the Evolution of the Adaptive Immune System?
The infant and his/her flora: a vital two-way interaction

• Colonising bacteria programme the baby

• Interactions with immune system that affect immune development and immune responses, inflammation

• Metabolites that affect:
  Absorption, lipid metabolism, detoxification, stress response, endogenous nutrient production, inflammation

• HPA axis
The Gut’s Clostridium Cocktail
Michael J. Barnes and Fiona Powrie        Science Vol 331 21 January 2011

Different bacteria have different effects on inflammatory and acute phase protein responses
GI flora and infant weight gain

- Increased fecal staph aureus and decreased bifidobacteria at 6 and 12 months age in infants associated with children being overweight or obese at age 7


- High dose erythromycin in <32 wk preterm increased weight gain
  - 12.8 vs 9.2 g/day

  Mansi Y et al, Neonatology 2011
Long term dietary patterns linked with gut microbial enterotypes-human trial

<table>
<thead>
<tr>
<th>Diet</th>
<th>Enterotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>Bacteroides</td>
</tr>
<tr>
<td>Animal fat</td>
<td></td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>Prevotella</td>
</tr>
</tbody>
</table>
Intestinal microbiota can cause metabolic disease in mice independent of genetic factors

Sanitation & linear growth

Water, sanitation, hygiene have far greater potential for linear growth.

Pathways:
  - Diarrhea
  - Enteropathy
Open Defecation Explains Cross-Country Differences in Child Height
Sanitation and Stunting

Open defecation

- Explains 54% of international variation in child growth
- Can statistically account for India-Africa gap in height
The causes and consequences of undernutrition cut across sectors and so do the solutions.

**Direct interventions**
- Infant feeding
- Micronutrients
- Hygiene/health

**Indirect Interventions**
- Agriculture
- Social protection
- Women Education, Empowerment

**Structural interventions**
- Economic growth
- Poverty reduction
- Institutions Governance

**CHILD NUTRITION**

**Food/Nutrient Intake** ↔ **Health**

**Immediate causes**
- Access to Food
- Maternal & Child Care
- Water, Sanitation & Health services

**Underlying causes**
- Environment, Technology & People

**Basic causes**
- Institutions
- Political and Ideological Frameworks
- Economic Structure

**Nutrition specific interventions**

**Nutrition sensitive interventions**

UNICEF 1990 and Black et al 2008
Mother and infant bonding and effective care of child

An recognized crises

Young age of mothers, lack of education, gender insensitivity of our community
Children who have a healthy start in life kick off a virtuous cycle of development