

Obesity: Developmental Origins and Environmental Influences

Spring 2004 Symposium

Duke University Integrated Toxicology Program
National Institute of Environmental Health Sciences

Obesity

- Genetic Susceptibility
- Environment (Nutrition, Exercise)
- Time

New Focus : Developmental Basis of Adult Pathophysiology

- **Definition:** In utero and/or neonatal exposure to environmental agents that result in a **functional change (without obvious teratology)** in a tissue/organ that results in increased susceptibility to disease later in life.
- The functional change is due to altered **programming**– a lifelong change resulting from a change in gene expression, due to altered imprinting or chromatin structure during development .

Developmental Basis of Adult Pathophysiology: Background

- **Barker Hypothesis:** Poor nutrition during development alters “programming” leading to low birth weight or thinness at birth.
 - ◆ **Consequences are increased risk for**
 - ◆ hypertension, hyperlipidemia, ischemic heart disease
 - ◆ insulin resistance, type 2 diabetes,
 - ◆ breast and prostate cancer in adult life.

Birthweight and Obesity

- Nutritional conditions experienced *in utero* may have a life-long effect on the propensity to develop obesity.....
 - ◆ Low birth weight
 - ◆ High birth weight

Symposium Goal: Examine The Following Hypothesis

Obesity can be caused or exacerbated by *in utero* exposure to **environmental chemicals** either alone or in concert with nutritional status.

This increased susceptibility to obesity can occur in normal weight newborns.

We Propose That.....

- The fetal basis area should be expanded to include exposure to environmental chemicals in addition to or in concert with altered nutrition.
- The environmental insult can be in utero and/or neonatal.
- The resulting pathophysiology can have a variable latent period from few years to decades.
- The altered programming can be measured using tool of genomics and epigenetics.
- The effects may be small.
- The effects will be difficult to detect in humans due to human genomic variability and SNPs.
- The effect may be due to multiple chemicals with varying sensitivities and half lives—multiple hits.

Focus of Hypothesis

- In utero exposure with measurement of gene expression in adipose tissue.
- Measure onset of obesity or exacerbation of obesity. Measure gene expression in adipose tissue.
- Correlate gene expression changes during development to those in adult adipose tissues.
- Show cause and effect relationship between in utero exposure, altered gene expression and obesity.
- Show mechanism of altered gene expression.

Symposium Program

- Overview and clinical perspective
- Adipocyte development and signaling control
- Birthweight, in utero nutrition and obesity
- Genetic imprinting and obesity
- Effect of in utero exposures to environmental chemicals and obesity
 - ◆ Dioxin, phytoestrogens, environmental estrogens, nicotine