

**HYPOTH – Gene Environment Obesity April 15, 2002**  
**Initial Proposal for Core Hypothesis\Question**  
**Please limit your response to 2 to 5 pages**

- I. Proposed Core Hypothesis\Question – include what is the primary outcome associated with this hypothesis:

**What are the genetic determinants of obesity in childhood, specifically which factors influence adipocyte proliferation and growth in children, and how are they modified by environmental factors such as quality and quantity of nutrition and physical activity? (These ideas can be extended to include mechanisms for insulin resistance, lipid metabolism, and cardiovascular disease risk).**

- II. Workgroup: **Gene-environment, (others?)**
- III. Contact Person for Proposed Core Hypothesis\Question (include phone and email):  
**Molly Bray, 713-500-9891, molly.s.bray@uth.tmc.edu**
- IV. Public Health Significance - please address the following issues to the extent possible for both the exposure and outcome:

**While much attention has been given to the increasing prevalence of obesity among U.S. adults, one of the fastest growing obese populations is that of children and adolescents. According to the latest NHANES survey, 13 percent of children age 6-11 years and 14 percent of adolescents age 12-19 had a body mass index (BMI) greater than the 95<sup>th</sup> percentile of sex-specific BMI growth charts. These statistics are particularly alarming given the wealth of evidence suggesting that adult comorbidities associated with obesity such as cardiovascular disease, insulin resistance, hypertension, and type 2 diabetes mellitus may have their origins in youth (McGill et al. 1995; McGill et al. 1997). Further studies suggest that adults who were obese as adolescents constitute a large proportion of the heaviest adults and that obesity in childhood has strong predictive power for severe obesity in adulthood (CDC, 2001). According to data from the latest National Health and Nutrition Examination Survey (NHANES III), overweight adults aged 20 to 34 years had greater relative risks for development of hypertension, diabetes mellitus, and hypercholesterolemia than overweight adults aged 45 to 70 years. Obesity, once established in adolescence, becomes almost intractable, and children may constitute a key population in which intervention may be most effective for preventing the onset of obesity in later life.**

**Along with the many serious health implications, childhood obesity also appears to have devastating impact on overall quality of life. During childhood and adolescence, obesity has a direct negative effect on both self-esteem and the ability to socialize (Bar-Or, 1987). The rejection of the obese child by others often leads to lower general self-concept, lower self-concept concerning physical appearance, and greater depression than non-obese children (Strauss et al., 1985). In addition,**

aerobic fitness, defined by maximum oxygen uptake (VO<sub>2</sub>max), is negatively correlated to BMI, and obesity has been associated with low fitness. Such low fitness levels initiate a cycle of low activity and further decrease in fitness that may prevent the obese child from physically participating in activities designed to provide both social and physiological benefits.

Obesity is linked to increased risk for insulin resistance, hypertension, type 2 diabetes mellitus, gallbladder disease, and dislipidemia and is well-established as a risk factor for cardiovascular disease (Pi-Sunyer, 1993). Abdominal obesity, in particular, is associated with insulin resistance and an atherogenic phenotype characterized by hypertension, hyperlipidemia, hyperglycemia, and a prothrombotic state (Reaven, 1996). Obesity is associated with alterations in lipid metabolism and in blood pressure, and it is estimated that up to 75% of hypertension can be directly attributed to obesity (Krauss et al., 1998). Almost \$100 billion is spent annually to cover both the health costs of illnesses associated with obesity and indirect costs due to lost productivity, exemplifying the tremendous economic liability posed by this disease (Wolf et al., 1998). Between 20 and 40 percent of adult Americans are trying to lose weight at any given time,<sup>7</sup> and an estimated \$30 to \$50 billion is spent yearly on unsuccessful efforts to lose weight, illustrating the fact that obesity is both difficult to alleviate and, even today, not well understood.

Though obesity has been attributed to psychological, behavioral, nutritional, and socioeconomic influences, numerous studies of related and unrelated individuals have provided support for the role of genes in the determination/regulation of body size and mass. This is particularly true in the case of morbidly obese children, in whom a genetic susceptibility for obesity very likely precedes or exacerbates the effects of overeating or lack of physical activity often found in these individuals. Though the number of genetic factors that may be related to body mass and composition is substantial, at least three mechanisms may contribute to an individual's susceptibility for obesity in childhood: 1) increased resistance to factors that influence satiety, 2) increased propensity for the formation and growth of adipose tissue, and/or 3) decreased capability for muscle cell growth or maintenance. The National Children Study provides a unique and powerful opportunity to investigate genetic factors that may influence physical maturation, health throughout childhood, and early development of disease. Importantly, the wealth of behavioral, family, emotional/attitudinal, and physical environmental data that will be amassed during the course of the study will provide an unparalleled chance to investigate the interaction between genetic variation and environmental factors in determining growth and health. Much research has demonstrated that the common, chronic diseases that currently present the greatest burden on public health, such as cardiovascular disease, obesity, diabetes, and hypertension, have their origins in childhood. Prevention programs designed to reduce the risk and occurrence of chronic disease in adults commonly focus on modifiable environments and behaviors such as diet and physical activity, with varied results among

**individuals. This heterogeneity in response to disease interventions is at least in part of genetic origin. Although a number of candidate genes have been identified that appear to influence the development of common, chronic disease, little is known about how these genetic effects may vary within demographic (e.g., race and gender), environmental, and behavioral (e.g., diet and exercise) contexts. Particularly important is the tracking of factors that influence early development and increase risk for later onset of disease. Detection of these effects in adults is often difficult due to the number of mediating factors that influence the health of the individual throughout the course of a lifetime. The analysis of genetic data in children provides a rare opportunity to investigate the effects of the gene-environment interactions that influence childhood development and health. Analyses of gene-environment interaction would address the effects of genetic variation within the contexts of environments such as quality and quantity of dietary intake, physical activity, and family environment, for example.**

V. Justification for a large, prospective, longitudinal study

**While obesity, even in children, is becoming increasingly prevalent, it is a complex disease with a multifactorial etiology, and its genetic underpinnings are likely to be heterogeneous. Large samples are necessary to have adequate power for the investigation of gene-gene and gene-environment interactions and to enable stratification by distinguishing components of the disease such as body fat distribution, age of onset, physical activity level, etc.**

VI. Scientific Merit - please address the following issues to the extent possible:

- Limits of our current understanding
- How will answering this hypothesis/question advance our understanding

**Though much progress has been made in our understanding of the etiology of obesity, it is not clear how our changing environment (i.e., increasing fat content of the diet and lack of opportunity for exercise) may be exacerbating a genetic susceptibility to fat formation, particularly in children. Research evidence suggests that high intake of fat, particularly in early life, may stimulate the formation of adipocytes and the proliferation of adipose tissue but these hypotheses have not yet been tested in humans. Sophisticated quantification of body fat during growth may serve to answer such questions.**

VII. Potential for innovative research

**New devices are being developed to measure body composition non-invasively (e.g., lipometer), and the use of such instrumentation in children would be innovative.**

VIII. Feasibility - please address the following issues to the extent possible:

- Critical period for exposure and outcomes

- 1) Very early onset obesity may be indicative of rare/recessive mutation – we do not know how prevalent these types of genetic mutations may be;
- 2) Onset of obesity prior to age 10 may be indicative of genetic susceptibility that is more common or less severe and may be a function of early childhood nutritional habits;
- 3) Onset of obesity during puberty may be indicative of sex effects, along with cultural or behavioral change;
- 4) Onset of obesity post-puberty may bring into play more the effect of changing physical activity behaviors and eating habits that interact with genetic susceptibility

- Sampling needs: targeted groups or settings, special strategies, sample size, special subgroups of interest, etc

**No special group needs to be targeted for these analyses, as long as the sample is multi-racial and each race group is sufficiently powered to detect effects**

- Contact – if more than one contact is needed, frequency and timing of the recontact

**Yearly or semi-annual measures of height/weight, body composition (by DXA or other sophisticated measures), and fat distribution**

- Nature of measurement (biologic – blood, tissue, etc, interview – is there a standardized questionnaire?, educational\psychologic testing – does a standardized instrument exist?, etc.)

**A blood draw at baseline, collecting in a manner suitable for cryopreservation, would be sufficient for DNA analyses; habitual physical activity and food intake should be taken at least semi-annually; additional blood draws for the analysis of blood lipids, insulin and glucose (at the minimum) would add to the study**

- Burden on the participant and family

**Moderate burden on family, depending on the frequency of contact**

- Ethical considerations

**Consent for the use of DNA**