Endocrinology, Nutrition, and Growth Branch (ENGB) NICHD

Report to the NACHHD Council June 2009

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Eunice Kennedy Shriver National Institute of Child Health and Human Development

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EXECUTIVE SUMMARY

The Endocrinology, Nutrition, and Growth Branch (ENGB) is pleased to present a summary of its activities to the National Advisory Child Health and Human Development (NACHHD) Council. One of the four Branches of the Center for Research for Mothers and Children (CRMC) at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the ENGB provides a focus for research and research training in pediatric endocrinology and diabetes, pediatric gastroenterology, nutritional science, physical growth and body composition, including bone health and obesity, and the developmental origins of health and disease. Figure 1 illustrates the relative size of the Branch's investment in various topics. Research supported in these areas is directed toward laying the groundwork for future health so that children can achieve their full potential for growth and development.

Since its last report to the NACHHD Council, the Branch's budget increased from $55 million in fiscal year 2004 to $68.7 million in fiscal year 2007, a figure that does not include the additional $5 million the ENGB received from the Congressional Special Statutory Funding Program for Type 1 Diabetes Mellitus (T1DM) Research beyond the funds provided in the National Institutes of Health (NIH) budget. By the end of fiscal year 2007, these funds supported 243 projects. In addition, in 2004, the Pediatric Pharmacology Research Program was transferred to the newly created Obstetric and Pediatric Pharmacology Branch, a move that decreased the ENGB base budget by $8 million beginning in fiscal year 2004 (as shown in Figure 2). The ENGB has a large commitment to training the next generation of pediatric academic scientists, devoting more than one-fifth of its budget to training and career development.

The ENGB has a long-standing interest in preventing chronic disease later in life and has stimulated the field of the developmental origins of health and disease on topics such as the metabolic syndrome and diabetes, bone health and osteoporosis, nutrition and obesity, and other topics. During the past four years, the Branch has expanded its support of projects in the areas of maternal-fetal nutrition, infant nutrition, and childhood obesity, as shown in Figure 3, Figure 4, and Figure 5. The ENGB has also been active in international studies of diabetes, nutritional aspects of HIV, and the effect of iron status on malaria. *Appendix B* provides a complete listing of Branch funding opportunity announcements (FOAs).

The Congressional Special Statutory Funding Program for T1DM Research, which began in fiscal year 1998 and was reauthorized through 2011, enables the support of T1DM research, including three multisite networks involving the ENGB: the Trial to Reduce the Incidence of T1DM in the Genetically at Risk (TRIGR), the Diabetes Research in Children Network (DirecNet), and TrialNet. These projects are described in more detail later in this report.

Outside of the Special Statutory Funding Program, the Branch has also supported other projects on metabolic syndrome and diabetes, including (but not limited to):

- Metabolic Syndrome in Children and Adolescents and the Pediatric Metabolic Syndrome Working Group are major initiatives, led by ENGB, to elucidate the risk factors for the metabolic syndrome in children in relation to clinical outcomes in adolescence and adulthood. (See *Appendix D* and *Appendix E* for publications related to these initiatives).

- Prospective Assessment in Newborns for Diabetes Autoimmunity seeks to detect the earliest changes in gene expression in the pathogenesis of T1DM among 23,000 infants who are at genetic risk for diabetes.
- The Branch continues its efforts to understand Type 2 Diabetes Mellitus (T2DM), including racial and ethnic disparities in its prevalence and the Diabetes Prevention Program, to ascertain genetic variants and their associations to T2DM.

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study of women with Gestational Diabetes Mellitus was completed after the last of 23,000 babies was born in 2006. Outcome data were published in an article in the *New England Journal of Medicine* in May 2008 (see *Appendix H* for more details on the HAPO Study).

The Branch has continued its efforts to understand bone health and the prevention of osteoporosis. The ENGB recently enhanced its bone health program by funding studies on growth factors, signaling molecules, and essential regulators involved in bone growth and fracture healing, in addition to its ongoing studies of the effects of nutrition and physical activity on bone health. The Bone Mineral Density in Children Study includes 2,000 children and adolescents and will provide reference data for monitoring bone density in growing children and assessing the changes of other components of growth during childhood and adolescence. The Branch also plays an active role in initiatives involving vitamin D, within the contexts of both bone health and overall nutrition.

Since the last ENGB report to the NACHHD Council, the Branch has also initiated a program of cross-disciplinary multilevel research on childhood obesity. The Branch has led or co-organized a number of workshops and international conferences on childhood obesity and has been instrumental in the release of funding opportunity announcements on the topic. The NICHD also formally established a "virtual research entity"—the Obesity Research Strategic Core (ORSC)—to coordinate obesity research efforts across the Institute. Led by ENGB staff, the ORSC includes more than 30 members from the NICHD's Branches, Centers, Divisions, Offices, and Laboratories. (*Appendix F* and *Appendix G* provide more information on these topics.)

Partnerships and collaborations such as the ORSC are nothing new for the Branch. To leverage its limited resources and ensure maximum return on investment, the ENGB frequently partners with other NICHD and NIH components, other government agencies, and various non-government organizations, including (but not limited to): Congressional Special Statutory Funding Program for T1DM Research; the Bill and Melinda Gates Foundation; the Juvenile Diabetes Research Foundation; the NIH Office of Dietary Supplements; and the Canadian Institutes of Health Research, to name a few. (*Appendix A* provides a full listing of Branch partnerships and organizations.)

The Branch has continued its studies of the complex nutritional relationships between mother and fetus, the placental transfer of nutrients, and the role of nutrition in infant development. Research on infant nutrient requirements and optimal feeding regimens for very low birth weight and extremely low birth weight infants has also continued with Branch support, with a focus on studies of dietary essential fatty acids and their effects on visual acuity and brain development. The Branch has expanded its work on lactation and the components of human milk to include

studies of the role played by oligosaccharides, lactoferrin, and lactadherin in treating or preventing enteric disease. These compounds hold great potential for the development of a new class of antibiotics that would not induce microbial resistance. Within the nutrition research portfolio, Branch researchers are also examining the roles of various macronutrients and micronutrients on nutrition and overall health. Zinc, vitamin D, and iron are among the nutrients of interest. *Appendix J* and *Appendix K* provide additional information on these topics. Since its last report to the NACHHD Council, the Branch has also expanded its efforts related to global health and nutrition, with a renewed focus on the role of nutrition in the prevention, care, and treatment of HIV/AIDS.

As a complement to its research on nutrition, the Branch also supports basic and clinical studies on the normal development of the infant gastrointestinal system and digestive function, including necrotizing enterocolitis (NEC). In 2006, the Branch organized a workshop on preventing NEC and identifying newborns at high risk for the condition. The Branch also began funding seven projects on NEC in 2008, as a result of a Branch-supported FOA issued in 2007. A related FOA on oligosaccharides for preventing enteric disease was issued in 2008; applications submitted for that opportunity will be reviewed at the NACHHD Council meeting in June 2009.

The ENGB has also enjoyed the honor of having two of its long-term grantees recognized by the NICHD and other organizations. In 2007, the NICHD inducted Dr. Stanley Cohen into its Hall of Honor, which honors scientists for their renowned discoveries, and for the humanity that motivates them to serve others. Dr. Cohen's work on epidermal growth factor earned him the Nobel Prize in Physiology or Medicine in 1986. A summary of his research appears in *Appendix P* of this report.

Similarly, Dr. Maria New was a member of the inaugural NICHD Hall of Honor class in 2003 for her work on steroid metabolism and congenital adrenal hyperplasia. Dr. New, a former member of the NACHHD Council and a member of the Institute of Medicine of the National Academy of Sciences, received NICHD support for her grant, R01HD00072, from 1964 through 2008. A summary of her research is presented in *Appendix Q*.

As part of the NICHD's continued efforts to improve strategic planning for its components, the ENGB sought feedback on its possible future directions from an expert panel, which included two NACHHD Council members and representatives from the U.S. Department of Agriculture's Children's Nutrition Research Center, the International Society for the Developmental Origins of Health and Disease Council, the National Institute of Arthritis and Musculoskeletal and Skin Diseases Advisory Council, and the Robert Wood Johnson Healthy Eating Research Program (see *Appendix T* for a list of panel members). The panel provided extensive review and analysis of current research efforts supported by the Branch, as well as trends in funding and training. Additional information about the panel's discussion and the Branch's plans are included in the *Future Directions for the Branch* section of this report.

OVERVIEW OF THE BRANCH

The Endocrinology, Nutrition, and Growth Branch (ENGB) is pleased to present a summary of its activities to the National Advisory Child Health and Human Development (NACHHD) Council. One of the four Branches of the Center for Research for Mothers and Children (CRMC) at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the ENGB provides a focus for research and research training in pediatric endocrinology and diabetes, pediatric gastroenterology, nutritional science, physical growth and body composition, including bone health and obesity, and the developmental origins of health and disease. Figure 1 illustrates the relative size of the Branch's investment in various topics. Research supported in these areas is directed toward laying the groundwork for future health so that children can achieve their full potential for growth and development.

In the fiscal year ending September 30, 2007, the ENGB supported 243 research projects at a level of $68 million, a figure that does not include an additional $5 million in Congressional Special Statutory Funds for Type 1 Diabetes Mellitus (T1DM) Research. Figure 1 analyzes the research projects supported according to subject matter, and Figure 2 graphically depicts the annual ENGB research budgets from 1992 through 2007. Approximately 30 percent of the Branch budget supports research in obesity, diabetes, and the metabolic syndrome. Another 20 percent supports various aspects of nutritional science including studies of human milk, lactation, and infant feeding. Another 20 percent supports research training programs in pediatric subspecialties and other programs to train pediatricians to apply molecular and basic biological approaches to clinical questions in pediatrics. The remainder of the budget supports research on bone health, the neuroendocrinology of puberty, and growth factors. Currently, 31 of 243 ENGB-supported projects involve studies in a foreign country, but only five grants are held by foreign universities.

At the end of fiscal year 2004, the Obstetric and Pediatric Pharmacology Branch assumed the administration of the Pediatric Pharmacology Research Units Network and related grants in the area of pharmacology, resulting in an $8 million decrease in the ENGB budget. Despite this reduction, the ENGB research budget for the end of the reporting period is $13.8 million greater than the budget at the end of fiscal year 2004, reflecting increased funding for research on maternal and infant nutrition and childhood obesity, as shown in Figure 3, Figure 4, and Figure 5.

Many research projects administered by the Branch also receive significant support from other NICHD and NIH components, other government agencies, and various non-governmental organizations, including (but not limited to): Congressional Special Statutory Funding Program for T1DM Research; the Bill and Melinda Gates Foundation; the Juvenile Diabetes Research Foundation; the NIH Office of Dietary Supplements; and the Canadian Institutes of Health Research, to name a few. (*Appendix A* provides a full listing of Branch partnerships and organizations.)

In one such partnership, initiated in 2006, the leadership and staff from the NICHD and National Institute on Aging (NIA) began a research program on the persistence of juvenile factors in

delaying the onset of aging. After a subsequent workshop, the Institutes issued a Request for Applications (RFA) in 2007, *Studies to Identify Possible Juvenile Protective Factors and Their Effects on Aging*. As a result, four successful applications were funded in 2008. Among the funded projects is one which makes innovative use of the Fels Longitudinal Study database, a project effort long supported by the NICHD, to study the effect of accelerated and delayed physical growth and pubertal maturation on the development of metabolic and cardiovascular disease later in life (see *Appendix L*).

Many of the ENGB's projects involve international partnerships. In fact, for its size and budget, the Branch has a remarkably large global imprint. For example:

- The Trial to Reduce the Incidence of T1DM in the Genetically at Risk (TRIGR) involves 71 sites in 14 foreign countries.
- The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study has 11 sites in eight foreign countries, including Israel, Thailand, China, Singapore, and Barbados.
- The ENGB funds projects on iron requirements during infancy in Costa Rica, Chile, and China, and the Branch recently initiated a project in China to ascertain the genetic and environmental origins of the metabolic syndrome in 2,000 monozygotic and dizygotic twins.
- A recent $10 million contribution from the Bill and Melinda Gates Foundation augmented ENGB research activities in sub-Saharan Africa to study the interactions of iron and malaria.
- ENGB staff represents the NICHD on the External Advisory Board for *Projekt EARNEST*, a study of nutritional programming in humans and animal models funded by the European Commission and private industry in 18 countries.
- ENGB staff also serves as the U.S. Secretariat for two bilateral programs with the government of India, including the Indo-U.S. Program on Maternal and Child Health and Human Development Research.

These studies are described in more detail later in this report.

In addition, researchers supported by the ENGB continue to receive international accolades and recognition for their important work. In 2003, Dr. Maria New—who holds the record for longest support of a single project from the NICHD—was a member of the inaugural class of the NICHD Hall of Honor, which honors scientists who exemplify the science for which they are honored, as much as the common humanity that motivates people to serve others. Dr. New, also a former member of the NACHHD Council and a member of the Institute of Medicine of the National Academy of Sciences, received NICHD support for her grant, R01HD00072, from 1964 through 2008. During this 44-year period, she discovered two defects of steroid metabolism—Apparent Mineralocorticoid Excess, and the Multiple Steroid Resistance Syndrome. She also demonstrated the molecular-genetic basis of the phenotypic variation seen in cases of congenital adrenal hyperplasia. Please see *Appendix Q* for a complete description of Dr. New's many research accomplishments.

In 2007, the NICHD inducted Dr. Stanley Cohen into its Hall of Honor for his work on epidermal growth factor (EGF). Dr. Cohen's R01HD00700 project on EGF received support from the NICHD from 1965 through 1999. Dr. Cohen received the Nobel Prize in Physiology or

Medicine in 1986 for his discovery of EGF and related peptides, for research on how the cellular receptors for this family of growth factors are related to oncogenes, and for work showing that the factors can be used as markers for susceptibility or resistance to cancer chemotherapy. His groundbreaking work illustrated that EGF was anti-inflammatory as well as growth promoting, a finding that paved the way for its use in treatment of burns and corneal abrasions and for its potential use in treating necrotizing enterocolitis (NEC). *Appendix P* provides a description of Dr. Cohen's research accomplishments.

RFAs and other funding opportunity announcements issued by the ENGB since the Branch's last report to the NACHHD are included in *Appendix B*; Branch-supported conferences and workshops, held from 2005 to 2009, are listed in *Appendix C*.

PREVENTING CHRONIC DISEASE

The burdens of obesity, cardiovascular disease, diabetes, and osteoporosis continue to increase in this country and abroad. These chronic conditions are the products of gene-environmental interactions, which have their roots in infancy or childhood and are difficult or impossible to reverse in adulthood. Analyses of high-throughput "-omic" data enable investigators to identify the origins of these diseases, to develop biomarkers that predict disease susceptibility, and to identify targets for interventions. The ENGB encourages research that focuses on detecting the earliest aberrations in molecular and biochemical pathways that lead to disease later in life.

ATHEROSCLEROSIS

Coronary atherosclerosis remains the primary cause of death in the United States. An estimated 1.26 million people in the United States, many younger than 55 years of age, suffer heart attacks each year, one-third of them fatal—amounting to one death per minute. In about 100,000 incident cases per year, sudden death is the first sign of coronary atherosclerosis, yet the early warning signs can be observed in adolescence, as demonstrated by data from the ENGB-funded Fels Longitudinal Study and the Bogalusa Heart Study. The former study has indicated that the onset of low plasma high-density lipoprotein (HDL) cholesterol levels and high plasma triglyceride levels in boys, but not in girls, as early as age 12 years. The latter study showed that the extent of early atherosclerotic lesions correlates with body mass index (BMI), systolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, and serum triglyceride concentrations in the first and second decades of life.

THE METABOLIC SYNDROME AND DIABETES

According to the American Diabetes Association, 23.6 million children and adults—nearly 8 percent of the U.S. population—have diabetes. In addition, the Association estimates that 57 million people in the United States are pre-diabetic, meaning they already show signs of

problems with insulin and blood sugar. The ENGB supports a large research portfolio on diabetes and its associated conditions, including the metabolic syndrome, a group of conditions that put people at risk for heart disease and diabetes.

In addition to its regular funding through Congressional appropriations, the ENGB also benefits from the Congressional Special Statutory Funding Program for T1DM Research, which began in fiscal year 1998 and is reauthorized through 2011. This special funding enables the support of T1DM research, including three multisite networks involving the ENGB: TRIGR, the Diabetes Research in Children Network (DirecNet), and TrialNet. The following section describes these projects and some of the Branch's other efforts related to the metabolic syndrome and diabetes.

Type 1 Diabetes Mellitus (T1DM)

T1DM, sometimes called juvenile diabetes, affects one in 300 people in the United States, accounting for much of the costly retinal, renal, neurologic, and cardiac diseases that are treated every year. Research supported by the ENGB established T1DM as an autoimmune disorder with a strong heritability. The Branch also funded pioneering research on immunogenetic methods of stratifying levels of risk for T1DM. As a result of this research, investigators worldwide are now using immunological markers to establish the risk of T1DM in relatives of index cases.

Successful identification of the pre-diabetic state also presents the prospect of treating high-risk children with antigen-based therapy and other immunomodulatory agents before the onset of clinical disease. This research approach forms the basis of the Diabetes Prevention Trial of T1DM (DPT-1) and TRIGR, which aim to prevent or delay the onset of T1DM in relatives of index cases.

TRIALNET

In 2001, the NICHD joined the National Institute of Allergy and Infectious Diseases (NIAID) and the NIDDK to establish TrialNet, a network of 14 diabetes centers dedicated to testing the ability of biological agents to prevent T1DM in children who are at risk for the disease, or to slow the course of beta-cell destruction in children who are newly diagnosed with the disease. The NICHD has committed $1.5 million every year since then to support this important initiative. TrialNet investigators operate within a paradigm that emphasizes a four-pronged biological approach to mitigating or preventing the autoimmune attack on the beta cells of the pancreas. The paradigm includes:

- Agents, such as anti-interleukin 1, to block the inflammatory component of the autoimmune attack;
- Agents, such as anti-CD 3 and anti-CD 20 (rituximab), to ablate effector populations of T cells and B cells;
- Antigen-based therapy, such as insulin, proinsulin, and glutamic acid decarboxylase (GAD), to tolerize the immune system to beta-cell antigens; and
- Agents, such as glucagon-like peptide-1, to support beta-cell survival or to stimulate beta-cell proliferation.

Biological agents currently under study include: Diamyd™, a new vaccine based on GAD designed to induce immune tolerance and mitigate the autoimmune attack on beta cells in cases of children newly diagnosed with T1DM; rituximab, a monoclonal antibody directed against B cells to block production of antibodies directed against beta-cell antigens; and abatacept, an immunoglobulin that prevents the activation of T cells directed against the insulin-producing beta cells.

TrialNet investigators recently completed a trial of rituximab (Rituxan™) in children and young adults with new onset T1DM with encouraging results. Rituximab is a monoclonal antibody that depletes B lymphocytes of the immune system in order to prevent further autoimmune destruction of beta-cell function. The researchers reported first successful blunting of the autoimmune attack on the beta cells by rituximab. TrialNet investigators showed that exposure to weekly doses of 375 mg/m^2 of rituximab (Rituxan™) over a period of one month prevented further deterioration of beta-cell function in children with new-onset diabetes over the subsequent two years of observation. Further, those children receiving rituximab required 20 percent less insulin than their counterparts who did not receive the medication. Interestingly, rituximab had little or no effect on young adults with new-onset diabetes. This finding indicates a potential window of opportunity in children and suggests that T1DM beginning at age eight years may be a different kind of disease than T1DM with onset at age 18 years or older (Pescovitz et al., in Press).

DIABETES RESEARCH IN CHILDREN NETWORK (DIRECNET)

Establishing the DirecNet, the world's first research network devoted to studying children with T1DM, stands as a notable and significant accomplishment of the ENGB. DirecNet consists of investigators at five diabetes centers who are working together to test non-invasive ways to monitor children with T1DM for episodes of hypoglycemia. The risk of hypoglycemia that attends intensive insulin therapy has become the main obstacle to successful management of diabetic children. During the first funding cycle, DirecNet investigators assessed the accuracy, efficacy, and effectiveness of continuous monitoring devices in children with T1DM. The results of DirecNet studies have stimulated the biotechnology industry to improve the precision and accuracy of glucose-sensing devices. The latest devices provide readings at all levels of glycemia within 11 percent of the actual values as determined in central laboratories. DirecNet was recompeted in 2007, at which time the National Institute of Neurological Disorders and Stroke (NINDS) joined this effort to focus new energies on changes in neurocognitive function at the extremes of glycemia, and on elucidating the cerebral mechanisms involved in nocturnal unawareness of hypoglycemia.

DirecNet investigators are now focusing their attention on the development of an "artificial pancreas"—a combination insulin-delivery and glucose-sensing system that can mimic normal pancreatic beta-cell function. This greatly anticipated research advance could alleviate the burdens of frequent blood glucose testing and multiple daily insulin injections in children with T1DM.

During its first seven years of operation, DirecNet generated numerous abstracts and 32 published peer-reviewed articles about the strengths and weaknesses of non-invasive monitors

for assessing episodes of hypoglycemia and hyperglycemia in children with T1DM. (See *Appendix I* for the DirecNet bibliography.)

Working with staff of the NIDDK, ENGB staff recently formed a partnership between DirecNet and TrialNet to document improvement in glucose metabolism in patients with T1DM who are simultaneously connected to a glucose sensor, an insulin pump, and a computer. This research is moving the diabetes field closer to the development of a closed-loop system, which will permit simultaneous monitoring of plasma glucose and a calibrated delivery of insulin. The results of these projects will change the way T1DM is managed in children, adolescents, and young adults.

TRIAL TO REDUCE TYPE 1 DIABETES IN THE GENETICALLY AT RISK (TRIGR)
TRIGR is the third Branch effort supported by the Congressional Special Statutory Funding Program for T1DM Research. The NICHD is the lead Institute for TRIGR, but the majority of the funding for this large trial emanates from eight additional sources, which greatly leverage the NICHD's contribution. The Mead Johnson Company supplied all of the formula, color-coded the packages, and prepared package inserts in 12 languages.

This trial is the first large effort designed to ascertain if a simple nutritional intervention during infancy can delay or prevent the onset of T1DM in children at high genetic risk for the disease. TRIGR is randomized, controlled clinical trial designed to assess if the onset of T1DM can be delayed or prevented by weaning genetically susceptible infants on to Nutramigen®, a hydrolysate of cow-milk protein, instead of a standard cow-milk-based infant formula. The rationale comes from studies in which hydrolyzed protein diets prevented the onset of T1DM in animal models, presumably by decreasing foreign antigen presentation to macrophages and dendritic cells in the infant intestine.

After four years of recruitment, TRIGR enrolled its last infant at high genetic risk for T1DM in 2006, bringing the total to 2,160 genetically susceptible infants at 71 clinical sites in 15 countries. The primary outcome of TRIGR will be the prevalence of T1DM at age 10 years, and the last infant enrolled will be 10 years old in 2016. Interim analyses of the development of autoantibodies directed against islet-cell antigens are planned for 2011.

PROSPECTIVE ASSESSMENT IN NEWBORNS FOR DIABETES AUTOIMMUNITY (PANDA)
In a partnership with the Juvenile Diabetes Research Foundation, the Branch also supports PANDA, a study to detect the earliest gene-expression changes in the pathogenesis of T1DM among 23,000 infants who are at genetic risk for diabetes. This study has already disclosed an important immunogenetic basis for the autoimmune attack on the insulin-producing beta cells of the pancreas (Guo et al, 2004). PANDA investigators identified a single-nucleotide mutation on a gene which codes for a small ubiquitin-like modifier protein called SUMO-4. SUMO-4 binds to a transcription factor involved in controlling the expression of the pro-inflammatory cytokine, interleukin (IL)-12B; faulty binding by the mutated protein leads to a doubling of the expression of the *IL-12B* gene, thereby initiating or augmenting an autoimmune attack on the beta cells. These findings implicate a new cytokine pathway in the pathogenesis of T1DM that may provide a target for novel therapy.

PANDA investigators are also exploring ways to use genome-wide association studies (GWAS) to discover biomarkers predicting which infants and children are at high risk for T1DM prior to the development of an autoimmune attack on insulin-producing beta cells. Recently, PANDA investigators performed GWAS on more than 2,000 diabetic patients, and on an equal number of control subjects. Their findings implicated that interferon induced with helicase C, domain 1 (IFIH1) as the earliest biomarker of T1DM. This intracellular interferon attacks double-stranded ribonucleic acid (RNA) produced by replicating viruses (Liu et al, 2009). The researchers also found that individuals with the highest levels of IFIH1 were at the greatest risk for T1DM. This finding provides a key molecular link between genetic susceptibility for T1DM, viral infections—particularly infection with Coxsackie B—and the innate immune response, all of which contribute to the earliest pathogenesis of T1DM.

PANDA investigators are now applying the techniques of proteomics to ascertain the presence of evanescent proteins, which may be involved in the earliest autoimmune attacks on the beta cell. This research may reveal new targets and pathways for the development of rational molecular interventions.

Metabolic Risk Factors in Children and Adolescents

Two of the risk factors noted earlier, elevated systolic blood pressure and elevated serum triglycerides, are included in the cluster of metabolic derangements known as the metabolic syndrome. The syndrome is diagnosed in adults who have three or more of the following five risk factors:

- Waist circumference greater than 102 cm in men and 88 cm in women
- Systolic blood pressure equal to or greater than 130 mm Hg and/or diastolic blood pressure equal or greater than 85 mm Hg
- Fasting level of serum triglyceride equal to or greater than 150 mg/dL
- Fasting level of serum HDL cholesterol less than 50 mg/dL in women and less than 40 mg/dL in men
- Fasting plasma glucose equal to or greater than 100 mg/dL

The metabolic syndrome is a precursor of coronary atherosclerosis and Type 2 Diabetes Mellitus (T2DM) and is known to affect 25 percent of U.S. adults. Alarmingly, the components of the syndrome are increasingly being found in children and adolescents. Weiss and colleagues found that obese children as young as four years of age exhibit biomarkers for the metabolic syndrome, including elevated plasma triglycerides, glucose intolerance, and elevated blood pressure (Weiss et al, 2004). These biomarkers are strongly associated with an increased risk of cardiovascular disease later in life.

The ENGB is leading a major initiative to elucidate the risk factors for the metabolic syndrome in children in relation to clinical outcomes in adolescence and adulthood. As part of this initiative, the Branch issued an RFA, *Establishing the Precursors of the Metabolic Syndrome in Childhood*, in 2003 and funded three large ongoing studies: one study focuses on the roots of metabolic syndrome in 600 offspring of Mexican American adults who are enrolled in the San Antonio Family Heart Study; a second study focuses on the interaction between birth weight and

race in terms of generating cardiovascular risk factors; and the third study evaluates the interaction of cardiovascular disease susceptibility genes and the environment in 1,000 pairs of monozygotic and 1,000 pairs of dizygotic twins in their second and third decades of life. These research projects are expected to develop biomarkers for early atherosclerosis as well as new targets for early intervention. Current findings indicate that, in regard to novel biomarkers, low levels of adiponectin predict the early onset of atherogenesis (Bacha, 2004). This observation underscores the role played by adiponectin as an anti-inflammatory agent and as an insulin sensitizer. (*Appendix D* lists publications related to the metabolic syndrome.)

Pediatric Metabolic Syndrome Working Group (PMSWG)

The ENGB, with co-sponsorship from other NIH Institutes, Centers, and Offices invited a national panel of experts to address the possibility of developing pediatric thresholds for each of the five components of the metabolic syndrome. This group became the PMSWG, which was organized to move the science forward rather than to issue consensus guidelines. Members of the PMSWG participated in an initial workshop in July 2006 to evaluate results from a series of ENGB-contracted analyses of existing datasets. These analyses were designed to examine different cutoffs for components of the metabolic syndrome in childhood, as well as adults, in relation to:

- Corresponding adult components
- Adult metabolic syndrome, using the jointly-published definition by the American Heart Association and the National Heart, Lung, and Blood Institute (NHLBI)
- Clinical precursors of disease that were measured precisely in childhood

In January 2008, the PMSWG held a second meeting, following another round of secondary analyses, to: test the stability of the metabolic syndrome and its components over time using serial childhood data; estimate the predictive utility of metabolic syndrome components in childhood for metabolic syndrome and T2DM in adulthood, combining long-term data from the Fels Longitudinal Study, the Princeton-Lipid Research Clinic Cohort Study, and the Muscatine Study; and generate growth curves of waist circumference and lipids using data from the National Health and Nutrition Examination Surveys.

Participants emphasized the need to study clusters of risk factors and to mine data from established cohort studies. For example, data from the Fels Longitudinal study document the onset of low plasma HDL cholesterol levels and high plasma triglyceride levels in boys as early as age 12 years. Both boys and girls in the Fels study show significant correlations between insulin resistance, blood pressure, low HDL cholesterol, and high plasma triglyceride levels. Childhood data from Fels participants, who developed the metabolic syndrome later in life, showed warning levels of HDL cholesterol and plasma triglycerides as early as age 13 years in both boys and girls (Sun et al, 2004). These authors also showed that elevated blood pressure and increased waist circumference in childhood are remarkably accurate predictors of the metabolic syndrome later in life (Sun et al, 2007 & 2008). Preliminary analysis of the Fels serial data also indicates that low HDL cholesterol levels in boys predict an early onset of T2DM in young adulthood. The possible cause-and-effect relationship of this intriguing observation has yet to be elucidated.

As a result of these meetings a collection of six original papers and an editorial were published in the February 2008 issue of *The Journal of Pediatrics*, and an additional seven original research papers, an editorial, and a review paper were accepted for publication in *The Journal of Pediatrics*, due to be released later this year. Findings from these analyses are summarized in *Appendix E*.

Type 2 Diabetes Mellitus (T2DM)

T2DM is a serious metabolic condition that affects roughly 20 million people in the United States. The disorder is closely associated with obesity and, in recent years, has become more prevalent in adolescents as well as adults. Researchers reported that the incidence of T2DM in adolescents increased ten-fold between 1982 and 1994 (Pinhas-Hamiel et al, 1996). Studies funded by the ENGB also disclosed that up to 25 percent of obese children are glucose intolerant. The finding of glucose intolerance in obese children presages the onset of frank diabetes in the second or third decade with attendant eye, kidney, heart, and nerve damage.

T2DM is highly heritable, with concordance in identical twins approaching 100 percent. Recently, ENGB-supported investigators found that a common variant of the gene that codes for transcription factor 7-like 2, which controls expressions of other genes, is associated with T2DM (Florez et al, 2006). The prevalence of a double dose of the variant gene in adults at high risk for T2DM was nearly 10 percent. These homozygous subjects progressed to T2DM nearly twice as fast as the remainder of the subjects, who had either no copy or only one copy of the variant gene. The subjects who were homozygous for the variant gene showed impaired secretion of insulin in response to a glucose challenge. Discovery of a link between the variant gene and impaired insulin secretion will lead to more targeted interventions for prevention and therapy.

Scientists have long suspected that insulin resistance, which precedes nearly all cases of T2DM, is related to inflammation, but the nature of the relationship has been elusive. Because signals from the immune system play critical roles in controlling glucose and lipid metabolism, and because obesity induces a state of chronic inflammation, researchers hypothesize that this inflammation mediates the pathogenesis of obesity-associated health conditions. In obese states, adipose tissue secretes inflammatory cytokines, such as tumor necrosis factor (TNF); adipose tissue macrophages (ATMs) have been identified as the primary source of these factors. These macrophages are believed to alter insulin sensitivity in adipocytes and are required for the development of insulin resistance in animal models.

The ENGB supported investigators examined ATM subtypes and their gene expression in both obese and lean knockout mice (Lumeng, 2007). They found that anti-inflammatory cytokine IL-10, which is overexpressed in ATMs from lean mice, protected adipocytes from TNF-alpha-induced insulin resistance. Thus, diet-induced obesity leads to a shift in the activation state of ATMs from an M2-polarized state in lean animals that may protect adipocytes from inflammation to an M1 pro-inflammatory state that contributes to insulin resistance. This work provides evidence that obesity can be reframed as an inflammatory disease, with macrophages acting at the junction between overnutrition and inflammation. Anti-inflammatory therapies against macrophage activation may provide a new therapeutic approach for T2DM.

DISPARITIES IN EARLY ORIGINS OF T2DM

Several studies have shown that puberty is associated with insulin resistance and altered glucose metabolism. To explore the relationship between puberty and T2DM, Branch-supported researchers modeled changes in insulin sensitivity, acute insulin secretion (initial pancreatic response to glucose stimulation), and pancreatic beta-cell function over the spectrum of pubertal development among African American and Caucasian children (Ball et al, 2005). Results demonstrated that African American children had consistently lower insulin sensitivity and higher insulin secretion during puberty than did Caucasian children, and that beta-cell function diminished during the course of puberty in African American children, but not in Caucasian children. This study revealed a natural, transient dip in insulin sensitivity during puberty and indicated that failure to recover insulin sensitivity at the end of puberty may be a harbinger of T2DM. These observations indicate that there is a physiological basis for health disparities seen between African Americans and Caucasians in the area of insulin resistance and glucose intolerance.

ENGB funding in this area has also led to the discovery of new biomarkers. For example, Branch-funded researchers reported finding an association between retinol-binding protein and insulin resistance in children (Goodman et al, 2008). The physiological basis for this association now needs to be elucidated.

Gestational Diabetes Mellitus (GDM)

GDM occurs in about 3 percent of pregnancies. Affected women have high levels of plasma glucose during their pregnancies; the islet cells of the fetal pancreas respond by producing high levels of insulin, leading to macrosomic babies with birth weights of nine to 14 pounds. Such large babies usually require a caesarian section delivery. In addition, because of their higher levels of insulin, these babies are at risk for neonatal hypoglycemia.

The ENGB continues its support of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, an international study of more than 23,000 pregnant women and their offspring at 15 sites in nine countries. HAPO study researchers are studying the glycemic state of these women in relation to the incidence of macrosomic babies (defined as those above the 95th percentile of birth weight), operative delivery, elevated umbilical cord C-peptide, and the occurrence of hypoglycemia in the newborn offspring. Recruitment for the HAPO study completed in 2006 after the last of 23,000 babies was born.

Major findings from the study were published in the *New England Journal of Medicine* in May 2008. The findings showed that adverse outcomes in mother and baby varied directly, in a straight-line function, over a range of fasting plasma glucose from 75 mg/dL to 105 mg/dL. For example, the prevalence of preeclampsia increased over this range from 3 percent to nearly 15 percent, while the prevalence of macrosomic babies increased from 5 percent to 26 percent. The rate of operative delivery increased from 13 percent to 26 percent over this range as well. These striking data on adverse pregnancy outcomes should lead to improved care of pregnant women who have elevated levels of plasma glucose by reducing both overtreatment and undertreatment of the condition on a worldwide basis.

In addition, the offspring of these carefully monitored pregnancies comprise a valuable international cohort that can be followed into adolescence in order to elucidate the fetal origins of aberrant glucose and fat metabolism later in life. (*Appendix H* includes data findings related to the HAPO study.)

CHILDHOOD OBESITY

The future health of the nation is threatened by an epidemic of obesity that afflicts one in every six children. During the past 25 years, the prevalence of obesity in boys and girls ages six years to 11 years, and in boys ages 12 years to 17 years tripled from 5 percent to 15 percent or more. The situation is particularly alarming among African American girls, ages six to 11 years, whose obesity prevalence quadrupled over the same period of time. Childhood obesity is no longer considered a cosmetic problem, but rather is viewed as a condition that engenders dangerous consequences, including atherosclerosis, insulin resistance associated with metabolic syndrome and T2DM, and serious liver disease beginning in early adolescence.

Infrastructure Activities Related to Obesity

In 2003, the NIH Director began addressing the problem of the obesity epidemic by forming the Trans-NIH Obesity Research Task Force (ORTF). Staff of the ENGB have played a prominent role on this trans-NIH effort since its inception. Additionally, since 2007, ENGB staff have served on a five-member Senior Leadership Group to help set the agenda for the ORTF, and to advise the chairs of the ORTF (the directors of the NIDDK and the NHLBI) on future directions of obesity science and policy.

In 2008, NICHD leadership established the NICHD Obesity Research Strategic Core (ORSC), housed in the NICHD Office of the Director and led by ENGB staff. The ORSC is a virtual center comprising 30 NICHD staff members from across the NICHD. Its mission is to:

- Lead and promote a multilevel, integrative approach to childhood and maternal obesity and related chronic diseases by coalescing obesity research and translation activities across the NICHD;
- Serve as an advisory body to the NICHD on future directions of obesity-related research activities;
- Coordinate and facilitate the implementation of a global multilevel platform to address childhood obesity by engaging and convening interested national and international organizations; and
- Serve as a resource for cross-disciplinary systems research on complex public health issues.

The NICHD, through the ORSC, is co-sponsoring an RFA with the NHLBI to create a Childhood Obesity Prevention and Treatment Consortium. This Consortium will include multi-component, multi-setting interventions to effect changes at the individual, family, primary care, and community levels for preventing or treating childhood obesity. The goal of the Consortium is to examine the synergistic effect of a multi-pronged approach. The NICHD is also participating in another RFA to evaluate a nationally representative selection of community-based programs addressing childhood obesity, including the NIH-sponsored WE CAN! (Ways to

Enhance Children's Activity and Nutrition) Program™. The NICHD program, *Media-Smart Youth: Eat, Think, and Be Active!* ™, falls under the umbrella of WE CAN! (although the program was created and developed outside the purview of WE CAN!). New efforts are also underway to create or improve the capacity for policy-driven obesity research at the local and state levels.

Research Activities Related to Obesity

The ENGB supports a wide range of childhood obesity research, including genetic and molecular mechanisms of obesity, psychosocial risks of obesity, the natural history and clinical pathophysiology of body composition, environmental and policy research in relation to obesity, and preventive and therapeutic interventions for childhood obesity. Brief overviews of these efforts are described below.

ENGB funding has led to several noteworthy findings, including one of the first large GWAS among U.S. children. This study revealed significant associations between single-nucleotide polymorphism variations within the fused toe (*FTO*) gene, and obesity in both Caucasian and African American children (Grant et al, 2008). These investigators also found an association between the melanocortin-4 receptor (*MC4R*) gene and obesity in Caucasian children, but not in African American children. The magnitude of association in Caucasian children in this study was similar to that shown in adults in other studies (Grant et al, 2009).

The ENGB has long been interested in prenatal and early childhood predictors of obesity. In a rodent model of intrauterine growth retardation (IUGR), researchers showed that progressive resistance to anorexigenic agents, such as leptin and sibutramine, increases with age, resulting in hyperphagia and obesity (Desai et al, 2007). The IUGR rats also developed increased levels of hepatic triglyceride content and plasma C-reactive protein (Magee et al, 2008) and exhibited a failure to suppress adipogenic transcription factor PPARγ (Desai et al, 2008). Maternal dietary restriction during pregnancy, coupled with exposure of the offspring to postnatal *ad libitum* diet, heightened the orexigenic effect of ghrelin, leading to increased obesity in adulthood (Jia et al, 2008).

Epigenetic mechanisms of obesity are currently receiving intense scrutiny and, once elucidated, have the potential to help differentiate programmed obesity from diet-induced obesity, or to separate out the additive effects of both. For instance, compared to rats with diet-induced obesity, IUGR rats showed increased hepatic methylation of the *IGF-1* gene, which predisposes the rats to programmed adult obesity (Tosh, 2008). Other Branch-funded researchers reported that animals exposed to prenatal stress showed, postnatally, increased susceptibility to diet-induced obesity (Tamashiro et al, 2009). This study has significant implications for the effects of socio-environmental stressors on the risk of obesity.

Psychosocial and behavioral studies of obesity also make up a significant part of the ENGB portfolio. For example, Branch-supported scientists showed that breastfeeding helped explain racial and socioeconomic status disparities in adolescent adiposity (Woo et al, 2008). Another research group showed that dietary variety, regardless of the energy density of foods, led to increased consumption, suggesting that increasing the variety of low energy-density foods and decreasing the variety of high energy-density foods may exert a great impact on overall energy

intake (Temple et al, 2008). Similarly, researchers addressed the issue that eating occurs in social settings, about which science knows little. This effort showed that overweight children ate substantially more when alone than when with others, and were more likely to choose a healthier snack if the person eating with them selected a healthy snack (Salvy et al, 2008). The findings could augment strategies for improving food selection among adolescents, while also adding to the research foundation on the effects of social networks on obesity (Christakis & Fowler, 2007).

Increased awareness of environmental and policy factors regulating diet and physical activity patterns has also led to increased research on how context affects obesity. One notable study, which examined the effect of price on food purchase behavior among obese and non-obese mothers, found that increasing the price of high energy-density foods increased the purchase of low energy-density foods for non-obese mothers, but not for obese mothers (Epstein et al, 2007). This observation suggests that, to exert a beneficial impact on dietary patterns in the entire population, policy makers may need to advocate decreasing the price of low energy-density foods as well as increasing the price of high energy-density food.

Environmental obesity research has also examined the impact of societal changes in developing countries on the prevalence of obesity in the population. Such research suggests that urbanization may have negative health effects, in terms of physical activity and eating patterns, which engender obesity and poor long-term health. This pattern is especially evident in the health and nutrition outcomes for those living in urban versus rural parts of China. Although urban settings provide improved living conditions, they also account for more than four-fifths of the overall decline in physical activity among the Chinese. When compared to their rural counterparts, urban residents are also more likely to snack and to consume fried food. Now that more than 10 percent of Chinese children are obese, interventions will require far-reaching societal efforts that take into account both economic development and population health (Wang et al, 2008; Ng et al, 2009).

It is currently unknown what impact endocrine disrupters, such as bisphenol A (BPA) and other xenobiotics, in the environment have on obesity. The National Institute of Environmental Health Sciences (NIEHS) is exploring this area of obesity research, but it would also fit well into the Systems-Oriented Multilevel Framework for Obesity Research that the ENGB is developing (see below).

The ENGB is a leader in funding prevention and treatment interventions to combat childhood obesity and has been at the forefront of this field for some time. In a high-profile randomized controlled trial on the maintenance of weight loss in children, Branch-funded researchers showed that social facilitation alone or in combination with behavior modification was critical to sustaining weight loss over a two-year period. In contrast, behavior modification alone was not efficacious, again showing that contextual modifications are essential to the long-term success of obesity interventions (Wilfley et al, 2007). In response to an RFA published in 2004 under Branch leadership, the ENGB funded five R21s and four R01s on the topic of *Prevention and Treatment of Pediatric Obesity in Primary Care Settings*. These studies cover a wide range of ages, types of primary care settings, intervention delivery technologies, and diverse populations and are playing an important role in meeting the goals of the Government Performance and Results Act. The ENGB also serves as the central point of contact for investigators responding

to a series of program announcements on school-based interventions for obesity that have resulted in a significant number of awarded grants across the NIH.

A Systems-Oriented Multilevel Framework for Obesity Research

During the last three years, the ENGB has energized the field of childhood obesity research by emphasizing the need for a systems-oriented multilevel approach, and by developing concrete strategies for implementing new ideas and findings. In 2007, with co-sponsorship from multiple NIH Institutes, Centers, and Offices, the Centers for Disease Control and Prevention (CDC), and the Canadian Institutes of Health Research, the Branch hosted an international conference to begin developing a coherent multilevel research agenda. *Beyond Individual Behavior: Multidimensional Research in Obesity Linking Biology to Society* included three modules: state of the science on cross-level topics, multilevel interventions, and statistical and computational methodologies for the design and analysis of multilevel studies. The conference brought together experts from a diverse range of fields and included an industry panel with representatives from major trans-national companies as a way to begin a dialogue on public-private partnerships, which remains an ongoing initiative. The conference generated ideas for how to implement the systems-oriented multilevel framework to address childhood obesity and resulted in a paper published in *The Journal of the American Medical Association* (Huang & Glass, 2008).

Six key features comprise the systems-oriented multilevel framework:

- Framing obesity as a complex systems problem;
- Emphasizing cross-level and cross-disciplinary hypotheses at the outset of research;
- Increasing efforts in structural or upstream interventions;
- Building capacity for multilevel research, in terms of training and collaborating with partner organizations;
- Investing in complex systems research methodologies; and
- Maintaining a global perspective.

Appendix F delineates ENGB actions that correspond to each of the six key features outlined above. Six module papers, stemming from the conference and further illustrating the features of this framework, will appear in the July 2009 issue of *Preventing Chronic Disease* (see *Appendix G*).

CLINICAL RESEARCH NETWORK IN NON-ALCOHOLIC STEATOHEPATITIS (NASH)

NASH is the most prevalent liver disease among U.S. children between ages 10 years and 18 years, affecting about 20 percent of obese adolescents. NASH is, arguably, the most serious early side effect of childhood obesity. NASH occurs most often in obese children at the time of puberty and, in severe cases, leads to hepatic fibrosis, cirrhosis, and, ultimately, liver transplantation. Little is known of NASH's pathogenesis or treatment, although prevention of obesity in childhood has been shown to prevent NASH later in adolescence.

In 2002, the NICHD, through the ENGB, joined the Clinical Research Network in NASH. Network investigators are currently finishing a randomized three-arm clinical trial of vitamin E and metformin to assess the effect of these agents on NASH in 180 obese children with histologically confirmed fatty liver disease. The rationale for using vitamin E is to reduce the level of oxidant stress engendered by hepatic fat metabolism; the reason for using metformin is to increase hepatic sensitivity to insulin. The results of this trial should be available in 2010. The Network investigators also established a longitudinal database of cases of fatty liver disease for use in future ancillary studies.

Recognizing the importance of the growing problem of NASH in obese adolescents Branch-funded researchers performed a series of studies to define the metabolic phenotype of obese patients who present with NASH (Burgert et al, 2006; Cali et al, 2007). These investigators assessed the relationships between intrahepatic fat accumulation, systemic and hepatic insulin resistance, adiponectin levels, inflammatory markers, and lipoprotein levels in large cohort of obese children and adolescents. The studies clearly showed that NASH during childhood is strongly associated with the triad of insulin resistance, increased visceral fat, and low levels of serum adiponectin.

BONE HEALTH AND OSTEOPOROSIS PREVENTION

More than 43 million Americans have osteoporosis or osteopenia, low bone density that is a marker for risk of fracture. That number is expected to increase to 61 million by 2020. Bone mineral accretion during growth and development in childhood is a critical determinant of the risk for osteoporosis later in life. Failure to achieve optimal bone density during childhood and adolescence results in suboptimal peak bone mass, which contributes to the risk for osteoporosis later in life. Identifying the factors that influence bone mineral accretion during childhood and adolescence is a critical area of research to prevent this common, disabling disorder.

Many children enter adulthood with compromised skeletal systems from poor nutrition, chronic disease, and therapeutic interventions that may have adverse effects on bone accrual. For example, the average adolescent girl consumes about 800 mg of calcium per day, 500 mg less than the current recommended daily allowance and 700 mg less than the amount recommended by the NIH Consensus Conference on Calcium Intake. Small changes in bone mineral content and size early in life may have profound effects on fracture risk later in life.

To better understand the impact of these changes on growth, the ENGB is working with the NIH Office of Medical Applications of Research and the NICHD Public Information and Communications Branch to convene an NIH Consensus Development Conference, *Lactose Intolerance and Health*. The conference will focus on the effects of dairy exclusion diets on bone health and fracture rates in children. This event is currently scheduled for February 22-24, 2010, on the NIH main campus. The ENGB also plays an active role in initiatives involving bone health as a participant in the Federal Working Group on Bone Diseases.

Physical activity is also a vital component in the development of healthy bones, but is also lacking for many children. The ENGB has supported several school-based exercise interventions to test the hypothesis that weight-bearing physical activity is osteotrophic and will elicit positive

adaptations in bone macro-architectural structure in children. An ongoing intervention of 560 elementary school girls in Arizona will assess the effects of weight-bearing physical activity on bone after two years of exercise intervention. This issue is doubly relevant to the ENGB portfolio because physical activity contributes to bone health and obesity prevention.

Another focus for Branch-supported research is the adverse effects of chronic illness and the therapies used to treat diseases of childhood on linear growth. Clinical observations revealed that some pharmaceutical agents can tip the bone balance toward more bone accretion, while others, especially corticosteroids, tip the balance toward bone resorption. To examine the state of the science and develop research directions in this area, the ENGB co-sponsored a research-planning workshop with the American Society of Bone and Mineral Research titled *Effects of Pharmacologic Agents on the Pediatric Skeleton* in April 2005. Participants focused on the effect of corticosteroids and bisphosphonates, such as alendronate and pamidronate, that inhibit the resorptive activity of osteoclasts. The proceedings of the meeting were published in *Pediatrics* online in March 2007, as a supplement (*Pediatrics*, *119*: S125-S174), with the support of Synermed Communications, an Ascend Media Company that produces continuing medical education programs. The articles are available at http://pediatrics.aappublications.org/content/vol119/Supplement_2/index.dtl.

Some Branch-funded researchers are also focusing on the effects of nutritional deprivation and chronic stress on bone accrual and fracture risk, specifically among adolescents with anorexia nervosa (Gordon et al, 2007). Findings indicate that the alterations in cross-sectional variables of bone strength present in this population may have implications for fracture risk. The work also suggests that early osteoporosis and increased fracture risk in this group may stem from increased bone marrow fat and premature conversion of red marrow to yellow marrow. Results from magnetic resonance imaging (MRI) to evaluate bone marrow fat in the knee suggest earlier, more widespread, hematopoietic-to-fatty marrow conversion in this disease.

Fibroblast growth factors (FGFs), important signaling molecules that regulate many stages of endochondral bone development and fracture repair, represent another focus area for Branch-supported research. One of several research areas under study is the mechanism of action of signaling molecules that regulate the healing process. ENGB-funded investigators have shown active roles for FGF signaling during many stages of bone development and during fracture healing, when several features of endochondral bone development are reactivated. To better understand the role of FGFs in skeletal fracture healing, these investigators evaluated the temporal expression patterns of FGFs, FGF receptors, and molecular markers of bone development following long bone fractures in a mouse model (Schmid et al, 2009).

Branch staff anticipate that, because these growth factors are widely expressed in both developing and adult tissues, and because they have a wide variety of functions in organogenesis, tissue repair, and nervous system control, researchers will seek to further develop the area of growth factor signaling in bone. For instance, ENGB-funded researchers have already identified an adaptor protein, Schnurri-3 (Shn3), as another essential regulator of bone formation (Jones et al, 2006; Glimcher et al, 2007). Mice lacking Shn3 displayed an osteosclerotic phenotype with profoundly increased bone mass due to augmented osteoblast activity. Efforts to elucidate the mechanisms by which Shn3 regulates osteoblast function and bone formation are ongoing.

The Bone Mineral Density in Children Study (BMDCS)

Bone mineral density (BMD) during childhood is dependent upon linear growth, sexual and skeletal maturation, physical activity, dietary factors, and heredity. However, the ability to identify disorders of bone density that may accompany chronic illness, or their therapies, has been limited due to the lack of solid, reliably collected reference data. To address this problem, ENGB staff initiated the BMDCS, a population-based longitudinal, observational study of bone accretion in 2,000 healthy children and adolescents ranging from five years to 22 years in age. The BMDCS includes five clinical centers, all adhering to a common protocol that includes dual-energy x-ray absorptiometry (DXA) measurements of the lumbar spine, femur, and radius; bone age x-ray; assessment of pubertal status, stadiometer height, and weight; and information on dietary calcium intake and exercise habits.

The data emanating from the BMDCS will provide BMD reference data for monitoring bone health in growing children. Likewise, the DXA data the study generates enable researchers and health care providers to assess changes of other body-composition components during childhood, puberty, and adolescence. For example, one of the aims of the BMDCS is to establish whether DXA values obtained in early puberty predict BMD at sexual maturity. These normative reference data will provide valuable guidance to children, young adults, their parents and doctors on maintaining bone health.

To date, results of the BMDCS show that bone mineral accretion in childhood occurs at a slow and consistent pace, with a sharp increase associated with the rise in sex steroids during the pubertal growth spurt. After puberty, bone accretion continues gradually until peak bone mass is achieved in early adulthood. Interestingly, the data indicate that BMD continues to rise into early in the third decade, even though an individual reaches peak height several years earlier. BMDCS investigators also observed that boys continue to accrue BMD for several years longer than do girls (Wren et al, 2005; Kalkwarf et al, 2007).

Patterns of bone mineral accretion in childhood during the various stages of linear growth and sexual maturation suggests a separate heritable component distinct from body size as measured by height and weight. To further understand this process and to identify genetic variants associated with BMD and bone mineral accretion, BMDCS investigators are now planning a GWAS of these carefully documented subjects, who have been observed periodically over a period of six years. The investigators anticipate that the GWAS techniques will reveal genetic variants associated with bone mineral accretion and bone mineral status (e.g., bone mineral content or BMD relative to age) and should indicate whether the effects of genetic variants differ in childhood and young adulthood (McCormick et al, 1991; Jakobsson et al, 2008).

MATERNAL-FETAL ORIGINS OF ADULT DISEASE

Observational studies have suggested a link between events that occur during gestation and the subsequent development of disease in adulthood. However, to date the identification of plausible mechanisms to explain how *in utero* events might result in long-term adverse health outcomes has remained elusive. Recent observations on the fetal origins of hypertension and

atherosclerosis have energized the field, specifically within the context of maternal-fetal nutrition. ENGB-supported investigators at the University of Iowa examining the fetal origins of cardiovascular disease hypothesized that fetal exposure to the steroid dexamethasone, a potent glucocorticoid, would lead to cardiovascular dysfunction later in adulthood. Using a sheep model, the researchers demonstrated that fetal exposure to dexamethasone early in gestation is associated with increased coronary reactivity to angiotensin II (Ang II) later in life by enhancing Ang II-stimulated endothelial superoxide production (Roghair et al, 2008). If this programming effect occurs in humans, it may predispose them to progressive coronary endothelial dysfunction and coronary artery disease later in life.

Other findings from this line of research showed an increase in complex I hydrogen peroxide (H2O2) production in intact mitochondria from offspring of the dexamethasone-exposed ewes (Von Bergen et al, 2008). Although the effects were limited to a change in the activity of catalase, an enzyme that destroys H2O2, these findings point to an increase in the release rate of H2O2 from programmed mitochondria despite an increase in catalase activity that would normally be expected to keep H2O2 levels low. These results suggest that greater mitochondrial H2O2 release into the cell may play a role in the development of adult disease following exposure to an adverse intrauterine environment. This effort is one of the first studies to identify a plausible mechanism for explaining the role of the fetal environment in determining subsequent health. Understanding the mechanisms involved in fetal programming will help researchers and health care providers ascertain when and how best to intervene during early development to protect health outcomes later in life.

The Child Health and Development Study (CHDS) of Maternal Exposures during Pregnancy

The CHDS, a study of 20,000 pregnancies and their issue, began in 1959 as a companion to the Perinatal Collaborative Study, both funded by the NINDS. Beginning in 1974, the NICHD assumed responsibility for the ongoing support necessary to maintain the CHDS database and serum collection. Investigators interested in maternal-fetal origins of disease later in life, especially in the long-term effects of exposure to organochlorines, such as dichloro-diphenyl-trichloroethane (DDT), continue to use these important resources.

Recently, Branch-funded researchers analyzed the CHDS serum collection to reveal a striking association between exposure to DDT in childhood and the development of breast cancer before age 50 years (Cohn et al, 2007). The effect varied inversely with the girls' ages of exposure and directly with the amount of exposure (see Figure 6). This phenomenon emphasizes the vulnerability of children to environmental exposures and reinforces the concept of developmental windows of vulnerability. In another analysis, these investigators found that testicular cancers in male offspring of pregnant women who were enrolled in the CHDS indicate a positive association between level of maternal DDT and testicular cancer 40 years to 50 years later (Cohn et al, submitted). Figure 7 illustrates this association.

Using the serum collection database, CHDS investigators have also:

- Uncovered strong associations between *in utero* exposure to inflammatory cytokines and the development of schizoaffective disorders later in life (Brown et al, 2004 & 2005).

- Conducted a nested case-control study on the effect of dormant or remote toxoplasma infection, as reflected by elevated titers of toxoplasma antibodies during pregnancy. Findings suggested that maternal exposure to *Toxoplasma gondii* is a risk factor for schizophrenia in the offspring (Brown et al, 2005).

The unexpected disclosures of the associations between early exposures, either *in utero* or in early childhood, and later disease underscore the value of prospectively and methodically collected and archived serum collections for testing hypotheses of associations that were neither posed nor predicted more than 50 years ago. The CHDS serum collection will continue to provide insights to the field of maternal-fetal origins of adult disease, especially in the area of *in utero* exposure to endocrine disruptors and other xenobiotics.

ENDOCRINOLOGY RESEARCH

NEUROENDOCRINOLOGY AND GROWTH FACTORS

The ENGB funds research on the functions of various growth factors, including epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), nerve growth factor, and brain-derived neurotropic factor (BDNF), and their receptors. This research has led to a greater understanding of post-receptor intracellular events and to clinical applications of growth factors. For instance, researchers are using EGF to prevent NEC in animal models and may soon evaluate heparin-binding EGF for its ability to prevent NEC in preterm infants. EGF receptor activity is also used to plan regimens of chemotherapy for treating breast cancer. Similarly, in animal models, bFGF crosses the blood-brain barrier and has been found to stimulate neurogenesis. Importantly, bFGF also stimulates stem cells of human bone marrow to differentiate into neurons, thus providing a reservoir of cells for treating degenerative neurologic diseases of the brain and spinal cord.

Researchers supported by the ENGB recently reported in *Nature Neuroscience* that an adaptor protein, termed GIPC1, and a motor protein, termed Myo6, form a complex with BDNF and the tyrosine kinase B (TrkB) neuronal cell receptor (Yano et al, 2006). They found that both Myo6 and GIPC1 are essential for BDNF/TrkB-mediated neurotransmitter release in the neurons of the hippocampus, a structure of the brain involved in long-term memory. Importantly, the effects of Myo6 and GIPC1 on long-term potentiation of hippocampal neurons were restricted to a specific developmental window of murine brain development, postnatal days 12 to 13, marking the first time that the unique age-dependent effects of BDNF on hippocampal plasticity were delineated at the molecular level. An important future research direction will be to link BDNF/TrkB signal transduction pathways to the cellular machinery controlling intracellular vesicle movement and neurotransmitter release. These functions are important because they are involved in the development of memory and brain plasticity, and because interruption of their proper function by genetic defects, infection, or other environmental factors may lead to defects in higher-ordered cognitive function and neuropsychiatric disorders. Investigators reported that BDNF exposure induces the neuropeptide nociceptin, which significantly increased neurite length and the number

of neurites per neuron, an important finding because neurites are conduction fibers that project out from neuron cell bodies to make synapses with neurites from other neurons, thus creating a network that forms the neurophysical basis of memory (Ring et al, 2006).

NEUROENDOCRINE CONTROL OF THE ONSET OF PUBERTY

The neuroendocrine control of puberty has been a focus of the ENGB pediatric endocrinology program for several decades. Yet the molecular events that initiate repression of pulse-generating neuron activity of the arcuate nucleus in the hypothalamus soon after birth, as well as the molecular trigger that reawakens these 1,500 or so large hypothalamic neurons early in the second decade of life remain a mystery. In their search for these prime movers, NICHD-funded investigators have uncovered many neuroendocrine mechanisms, which play a contributory role in puberty, and have described new genes contributing to the transcriptional control of sexual maturation (Heger et al, 2007; Roth et al, 2007; Parent et al, 2008).

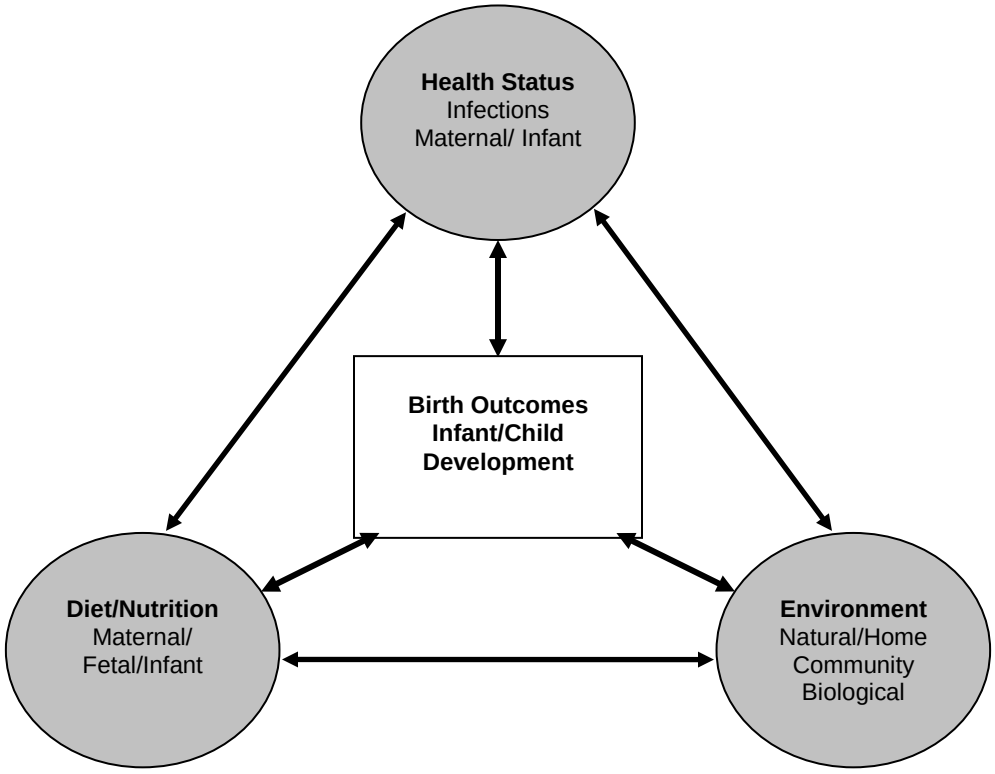
For decades, researchers have known that the increase in pulsatile gonadotropin-releasing hormone (GnRH) triggers the onset of puberty, but what triggers the onset of the increased pulsatility has been elusive until recently. Kisspeptin is now known to play a critical role in eliciting the pubertal resurgence of pulsatile GnRH release. Expression of the kisspeptin G-protein receptor by GnRH neurons indicates a direct action of kisspeptin on the GnRH neuronal network. Recent evidence from ENGB-funded researchers working with rhesus monkeys has demonstrated that kisspeptin signaling at its receptor is critical to the initiation of puberty (Fraser et al, 2005; Terasawa, 2006; Plant, 2008 & 2009). These studies have elucidated the role of kisspeptin in regulating the development and activity of the hypothalamic-pituitary-gonadal axis in the rhesus monkey and in other higher primates.

STUDY NETWORK OF PEDIATRIC ENDOCRINOLOGY (SNOPE)

In the past decade, the ability to identify and understand endocrine disorders on molecular and genetic levels has surpassed the ability to establish effective therapies. Even though the diagnosis and treatment of rare endocrine disorders in children have improved recently, controlled studies to establish therapeutic guidelines are lacking. To address this problem, ENGB staff recently entered into collaboration with the Lawson Wilkins Pediatric Endocrine Society to establish a national network of pediatric endocrinologists who can implement protocols aimed at improving therapeutic options for children with relatively rare endocrine disorders. The initiative is modeled after the Children's Oncology Group Network. SNOPE intends to examine disease management outcomes and to conduct hypothesis-driven multicenter research studies.

NUTRITION RESEARCH

Nutrition is linked to all aspects of human biology and health. The ENGB nutrition research program recognizes the need for a systems approach, which incorporates biological, environmental, and other critical contextual components as integral parts of public health. These relationships are represented in the figure below, showing how diet interacts with the environment to determine the health status of women, infants, and children. This conceptual framework applies to studies ranging from the identification of bioactive components of human milk to the impact of micronutrients on growth and development.



One strength of the ENGB nutrition portfolio is the exploration of nutritional variables in both domestic and international contexts. The ENGB will continue to build on its historical commitment to nutrition by addressing the following core elements: infant feeding and clinical care of low birth weight (LBW) infants; issues involving lactation, such as ontogeny of breastmilk, human milk composition, and identification and characterization of bioactive components in human milk; regulation of food intake; and physical and cognitive/behavioral growth and development. Research efforts and outcomes related to these core areas are described in the following section.

MATERNAL-FETAL NUTRITION

Improving the understanding of maternal-fetal nutrition is critical to developing optimal feeding practices, particularly for LBW and preterm infants. It is also essential to know what the infant ingests and how much food intake is needed to support normal growth and development. Understanding the interaction between the fetal environment and long-term health outcomes has become a major focal point of Branch research activities and requires a better appreciation of the role of the *in utero* nutrient environment, including the impact of maternal nutritional status. To address these issues, and to develop evidence-based guidance for maternal nutrition, the ENGB sponsored the *Maternal Nutrition and Optimal Infant Feeding Practices* workshop, in 2007 in partnership with the U.S. Department of Agriculture (USDA) Children's Nutrition Research Center at Baylor College of Medicine. The conference outlined the current understanding of maternal and newborn nutrition needs and developed a research agenda that has helped to further the ENGB nutrition program (Raiten et al, 2007). (*Appendix J* lists the published proceedings from the workshop.)

The study of how the fetal environment determines long-term health outcomes, including the incidence of obesity, diabetes, and cardiovascular disease in adulthood, continues to serve as a focal point for ENGB activities within the nutrition research program. For example, the ENGB has supported efforts to evaluate the role of essential fatty acids and their metabolites—known as docosahexaenoic acid (DHA) and arachidonic acid (AA)—on fetal and postnatal development. The importance of DHA to maternal and child health was recently reviewed by an ENGB-supported scientist who reported positive associations between low levels of maternal DHA intake and poor neurological outcomes in both mothers, in the form of depression, and their babies, in the form of attention deficit-hyperactivity disorder (Ramakrishnan et al, 2009).

The importance of these relationships was further reinforced by the report of another group of Branch-supported researchers who found a positive association between maternal fish consumption—a proxy for intakes of omega-3 fatty acids, such as DHA—and neurological outcomes in their infants (Oken et al, 2008). However, high fish consumption is not without risk. This same group also reported positive associations between maternal fish consumption and an adverse effect from mercury contamination on cognitive development at age three. These studies highlight the need for evidence-based risk-benefit analyses to support dietary guidance for women during pregnancy.

The mechanisms associated with improvements in infants' development as a consequence of improved maternal nutrition remain a high research priority for the ENGB. Related research seeks to determine the optimal mix of nutrients to ensure healthy births and healthy infant development.

NUTRITION AND FEEDING OF LBW INFANTS

The prevalence of LBW and preterm birth continues to be high in the United States and globally. Preterm birth interrupts the normal supply of nutrients essential for growth and neurological development. A central research topic—not just for the Branch, but also for the field—is how to

overcome the consequences of that interruption. It is imperative to understand the maternal-fetal interface and the fetal nutrient environment. Specific research issues within this context include:

- Determination of normal *in utero* growth and health;
- Determination of the normal *in utero* flux of nutrients between mother and fetus;
- Identification of markers to reflect functional changes in the nutrient flux;
- Development of a model to determine the *in utero* nutrient systems biology; and
- Understanding the role of maternal nutrition in prevention and care of LBW infants.

The placental origin of IUGR is an important, but understudied area of research. The ENGB encourages research on the role of placental nutrient transporters in the net transfer of nutrients to the fetus. One group of Branch-supported researchers is using an over-fed ovine model to study placental vascular physiology during pregnancy. Thus far, the researchers found that high dietary intake during pregnancy impairs cell proliferation and alters expression of angiogenic factors in the placenta (Rensink et al, 2008).

In the United States, about two-thirds of the babies born preterm are appropriate in size for their gestational age. The remaining one-third, or about 100,000 infants per year, is small for gestational age because of IUGR, leaving them at increased risk for long-term morbidity. The associations among IUGR, T2DM, and cardiovascular disease later in life confer a sense of urgency to this field of research. Presumably, genetic defects account for impaired placental transport of nutrients; however, little is known about genetic variation in placental nutrient transporters. This topic represents an important area for future Branch studies.

Maternal pre-pregnancy weight-for-height and maternal weight gain during pregnancy are also known to affect birth weight. Because these factors account for only a portion of the variance in birth weight, investigators are searching for other factors, such as vitamins, polyunsaturated fatty acids, and trans fatty acids, that might be involved in affecting infant outcomes. The aim of these studies is to identify maternal diets that promote optimal fetal growth and infant development, and to ensure a healthy life beyond infancy. The issues associated with maternal body composition and health disparities in reproductive health and birth outcomes were the subject of *Obesity, Women's Health, and Pregnancy: Messages to Ensure Healthy Mothers and Babies*, an ENGB workshop held in 2007. The deliberations resulting from that workshop were used to inform a research agenda for the ENGB and other Branches in the NICHD.

In the context of the nutritional needs for preterm infants, the ENGB supports research on nutrient requirements and optimal feeding regimens for very LBW (VLBW) and extremely LBW (ELBW) infants, who weigh less than 1,500g or less than 1,000g at birth, respectively. It is widely held that the goal of feeding preterm infants is to mimic *in utero* conditions to preserve optimal growth rates for both brain and body. However, some experts believe that practice might not be the best approach, especially in light of metabolic stresses imposed on the preterm infant. Although the resolution of this debate is a high priority for the Branch, to date, it has been an elusive goal for two primary reasons: first, few data exist on the normal fetal nutrient environment; and second, concerns abound about the potential for inducing NEC by early feeding.

Until they can safely accept enteral/oral feeding, VLBW and ELBW infants must rely on total parenteral nutrition (TPN) as their sole source of nutrients. These infants have a large brain-to-body ratio, which increases their glucose demands because glucose is the primary source of energy for the brain. However, research showed that these fragile babies are at risk for hyperglycemia and even death from increases in the glucose concentration of the TPN solution (Hays et al, 2006). Researchers are exploring other options, such as increasing lipid and amino-acid concentrations of the TPN, for feeding these fragile infants.

ENGB-funded investigators are also exploring infants' protein needs and the catabolic response to severe illness that dangerously depletes lean body mass, although previous studies indicated that a delay in protein feeding caused growth restriction with long-term physical and neurological consequences in LBW infants. A recent Branch-supported review of the literature found that, despite some evidence on the short-term safety of early feeding of amino acids while keeping nitrogen to calorie ratios stable, little evidence exists on long-term safety or efficacy (Kashyap, 2008). This quandary remains a high research priority for the ENGB.

An equally important aspect of feeding the preterm infant is the mode in which nutrients are provided. The ENGB has been a leader in supporting research on how best to induce oral feeding in high-risk infants, as evidenced by the recent report comparing a controlled-flow system of feeding to standard bottle feeding (Fucile et al, 2008). Compared to the standard, the controlled-flow system improved feeding without significantly altering the sucking response. This innovative system could, in fact, reduce energy expenditure owing to lower sucking demands. The study also showed that VLBW infants can tolerate faster milk flow than had been presumed. The Branch intends to build upon these findings to elucidate infant nutrient requirements and optimal feeding regimens, especially in regard to dietary essential fatty acids and their effects on visual acuity and brain development.

LACTATION AND MILK COMPOSITION

Surprisingly little is known about how the mammary gland changes from a ductal network to a secretory organ capable of copious milk secretion. The ENGB supports research within this unique context as a way to understand the mechanism(s) by which nutrients become incorporated into human milk. Improved understanding of how human-milk lipids are formed is important because lipids provide most of the calories for the newborn infant and because they seem to determine duration of breastfeeding episodes. This research has made significant contributions to the knowledge base on the physiology of the mammary gland, and to the health of both nursing infants and their mothers (Rudolph et al, 2007).

The ENGB is also acutely interested in identifying the nutrients and bioactive components in human milk. These ingredients may affect the duration of exclusive breastfeeding and the timing of the introduction of complementary foods, which could impact current global recommendations on breastfeeding. Specifically, iron is the nutrient that has received the most attention in this regard. ENGB-supported investigators have been leaders in the effort to understand the adequacy of iron supplied to infants during the course of extended breastfeeding. The Branch currently supports the evaluation of lactoferrin, a novel iron-binding compound in

human breastmilk that may, in part, explain the high bioavailability of iron in human milk. In addition to its role in enhancing iron bioavailability in human milk, lactoferrin may also modulate the natural defense against enteric infections. This fascinating topic is under active investigation by ENGB researchers (Ochoa & Cleary, 2009).

Another group of Branch-funded investigators conducted a randomized open-label trial in which they provided iron to breastfed infants for between four months and nine months (infants were not iron deficient at baseline). Infants received either medicinal iron or cereal fortified with iron, in the form of ferrous sulfate. The researchers observed that iron status (plasma ferritin) improved in both intervention groups (Ziegler et al, in press). However, the medicinal iron group had a statistically significant decrease in length gain and a trend for reduced weight gain at nine months. In addition, 2.3 percent of infants developed iron deficiency anemia before six months in the study; investigators later associated this outcome with low iron endowments at birth. These findings indicate that testing for serum ferritin levels early in life may provide a means for early detection of iron-deficiency anemia.

BIOACTIVE COMPONENTS OF HUMAN MILK

An important feature of human milk is its role in the ontogeny of the gastrointestinal microbiome and the subsequent impact on gastrointestinal immunity. However, the mechanism(s) responsible for these functions are unknown. Due to the importance of the gastrointestinal ecology for human health, this issue is a critical area of research for the Branch.

Knowing about these functions would be extremely useful in combating one of the leading causes of death in children younger than five years of age worldwide: severe diarrhea and its resulting dehydration. Globally, rotavirus is the most common cause of diarrhea in infants and young children; in the United States, rotaviruses cause up to 50 percent of cases of gastroenteritis in infants. The most common cause of bacterial diarrhea in the United States is *Campylobacter jejuni*, a bacterium that initiates disease by binding to intestinal cell surfaces. In this regard, the Branch supports studies of the role played by bioactive, non-nutritive components of human milk called oligosaccharides—short chains of sugar molecules joined together by chemical bonds—in gastrointestinal health. Oligosaccharides play significant roles in natural defenses of breastfed infants specifically by binding to enteric bacteria and viruses, thus preventing these pathogens from binding to the cells that line the infant intestine (Morrow et al, 2004). In a series of landmark studies, Branch-funded investigators found that oligosaccharides inhibited the toxic effects of enteropathogenic *Escherichia coli* and also inhibited infection by *Campylobacter jejuni* (Ruiz-Palacios et al, 2003) and by caliciviruses, which include the Norwalk virus that incapacitates thousands of cruise ship voyagers every year (Jiang et al, 2004).

These investigators also showed that the milk protein lactoferrin significantly decreased the invasiveness of *Shigella flexneri* by degrading bacterial proteins called invasion plasmid antigens. Likewise, another milk glycoprotein, lactadherin, prevented symptomatic rotavirus infection in breastfed infants by binding to rotaviral particles and inhibiting their replication. These results may lead to the use of oligosaccharides, lactoferrin, and lactadherin as antibiotics or as prophylactic agents against intestinal pathogens, either singly or in combination.

Research has also shown that these protective effects might not be limited to mucosal tissue in the intestine. Early consumption of human milk may also reduce the risk of respiratory disease in infants. Investigators found that infants with higher levels of the oligosaccharide lacto-*N*-fucopentaose II had reduced respiratory illnesses at ages six weeks and 12 weeks (Stephans et al, 2006).

This groundbreaking research signals the advent of a new class of antimicrobial agents to prevent and treat bacterial and viral infections. One important advantage of developing synthetic oligosaccharides and glycoproteins in this manner is that, because they block receptor binding rather than interfering with protein synthesis and bacterial replication, they do not induce bacterial resistance (Newburg et al, 2005).

The Branch also supported the first report of adiponectin in human milk (Martin et al, 2006). Although the biological significance of this finding is still under investigation, further research showed that adiponectin plays roles in inflammation, fatty-acid metabolism, and insulin sensitivity. Adiponectin concentrations in milk were lower in Hispanic women, and in mothers whose BMI was higher after pregnancy in this study.

Although human milk is recognized as the gold standard for infant feeding, the public health community still faces the challenge of low rates of exclusive breastfeeding, particularly in certain segments of the U.S. population. Along with the Branch's seminal work on the ontogeny, composition, and role of human milk in infant health and development, the ENGB continues to support efforts to increase the prevalence of exclusive breastfeeding for healthy term and preterm infants.

VITAMIN D AND HEALTH

The ENGB has highlighted the importance of vitamin D not only for its role in bone health, but also as an integral component of many other biological systems. The ENGB has an active research portfolio that addresses the issue of safe and effective interventions to improve the vitamin D statuses of mothers, infants, and adolescents.

As a result of expanding interest and concern about health disparities in the prevalence and impact of vitamin D deficiency in the United States, the Branch funds research on safe and effective levels of vitamin D intake for newborn infants and for women during pregnancy and lactation. For instance, ENGB-funded researchers who assessed the vitamin D status of a cohort of unsupplemented breastfed infants during the winter in Iowa concluded that vitamin D deficiency, including severe deficiency (defined as a level of 25-hydroxyvitamin D < 5 ng/mL) was common among this unsupplemented population and was present in infants with both light and dark skin pigmentation (Ziegler et al, 2006). Although the prevalence of vitamin D deficiency decreased with age, 12 percent of the unsupplemented cohort was still deficient at 15 months of age. Future studies from this same collaborative team seek to determine the relative strengths of different routes of supplementation; for example, they are

trying to determine whether maternal supplementation or direct supplementation of breastfed infants is a better way to improve infant vitamin D status.

The impetus for these studies began in 2002 with ENGB staff involvement in an expert consultation convened by the CDC to explore potential reasons for and strategies to address a rise in the incidence of rickets among African American infants. As a result of that meeting, the NICHD partnered with the NIH Office of Dietary Supplements (ODS) to convene a landmark workshop, *Vitamin D in the 21st Century: Bone and Beyond*, to focus on the adequacy of extant data supporting current vitamin D intake and exposure recommendations. Participants also took part in expanded discussions on biomarkers for vitamin D status and emerging evidence on the role of vitamin D in biological systems beyond bone health (Raiten & Picciano, 2004). Primary outcomes for the workshop included an expanded research agenda targeting high-priority areas in maternal and infant health. The meeting initiated a concerted effort involving the entire federal nutrition research community, headed by the NIH ODS, to explore ways of improving current public policy and guidance in vitamin D. (*Appendix K* lists the published proceedings from the workshop.) The ENGB continues to play an active role in these activities both through its portfolio on vitamin D research, and as a participant in the Interagency Working Group on Vitamin D.

In an additional aspect of ENGB's focus on functional consequences of nutrient status, the Branch will continue to explore better biomarkers for vitamin D exposure, status, and function. Determining functional biomarkers of immunity and inflammation that provide meaning to current vitamin D status indices is a high priority. An additional area of interest, consistent with the ENGB's focus on understanding the maternal-fetal dyad, is the long-term impact of vitamin D insufficiency during pregnancy and/or infancy.

NUTRITION AND GLOBAL HEALTH

The role of dietary nutrition in the prevention, care, and treatment of disease in mothers, infants, and children in the developing world represents another important component of the ENGB nutrition research portfolio. Of particular interest is the importance of nutrition in the context of infectious diseases and biomarker development. Ideally, biomarker identification would include indices of exposure, status, functional utilization, and impact, with an emphasis on micronutrients. The functional domains of immediate interest are immunology and inflammation. Micronutrients of high priority are iron, vitamin D, and zinc.

A recent report from ENGB-funded researchers describes findings from a randomized clinical trial of infants born to mothers who had received supplemental zinc (Iannotti et al, 2008). The infants whose mothers received the supplement showed significant improvements in lean-tissue growth indices compared to infants whose mothers did not receive extra zinc. A corollary of these activities will address potential bi-directional interactions between micronutrients and pharmaceutical agents.

Because of globalization and economic development, the importance of nutrition in non-communicable diseases, such as obesity, diabetes, and the metabolic syndrome, is increasingly

becoming a worldwide health issue. Paradoxically, in many developing countries, populations of undernourished and over-nourished individuals live in startling juxtaposition. The Branch supports efforts and collaborations related to these topics, as described below.

Impact of Micronutrients on Health of Women, Infants, and Children

Because one out of three people in developing countries is affected by vitamin and mineral deficiencies, individuals in these areas are at higher risk for infection, birth defects, and impaired physical and neurocognitive development. Interventions to ameliorate micronutrient insufficiency require a biological evidence base, which takes into account the cultural and demographic context of the population receiving the interventions.

The impetus for exploring issues of individual micronutrients in the developing world is often the general assumption that a given micronutrient is playing a role in the etiology of a major public health problem, such as anemia or blindness. To design a relevant intervention, research evidence needs to establish the deficiency at a population-wide level and the impact of the micronutrient on health. ENGB-supported investigators continue to lead in advancing the research base on the functional relevance of micronutrient insufficiency. Among these efforts are several clinical trials to assess the effectiveness of nutritional interventions in resource-limited settings. Findings from these trials and other related efforts will help improve nutrition outcomes in developing countries and in resource-poor areas of the United States.

Gastrointestinal Development and Health

The gastrointestinal tract is the gateway to the body for nutrients and other bioactive components; of equal importance is the role it plays as a barrier to protect the body from invasion by pathogenic organisms. ENGB-supported scientists are exploring the ontogeny of the gastrointestinal tract and the mechanisms that serve this barrier function. One group of Branch-funded researchers is studying the interface of malnutrition, enteric disease, and long-term development. Their review found evidence that not only do intestinal infections lead to malnutrition, but also that malnutrition worsens intestinal infections (Guerrant et al, 2008). Another group of researchers reported that vitamin A mitigates the danger of *Clostridium difficile* toxin, the most common anaerobic pathogen-borne toxin involved in the pathogenesis of diarrhea and pseudomembranous colitis (Maciel et al, 2007). This finding adds to the understanding of the functional role of vitamin A in maintaining the integrity of endothelial tissues in the barrier mechanism. These observations could lead to more effective prevention and treatment strategies for intestinal infections and for pathogen-induced diarrhea.

Iron and Iron Deficiency

Despite the fact that factors contributing to risk for iron deficiency in the U.S. population have already been identified, iron deficiency affects more than two billion of the world's people, including those in the United States.

The ENGB continues to support investigator-initiated projects on the role played by iron in the developing nervous system. Much of this seminal work has expanded knowledge of not only short-term effects, but also long-term and, in many instances, irreversible effects of iron deficiency during infancy (Lozoff et al, 2006). As an important corollary to this work, Branch-supported investigators are developing models to identify plausible sites for and mechanisms to

explain the impact of iron deficiency on neurological outcomes (Carlson et al, 2007) and are studying the underlying cognitive and behavioral effects of iron deficiency (Schmidt et al, 2007).

Other important areas of research include global strategies and interventions to prevent and treat iron deficiency. ENGB-supported researchers are currently conducting a randomized control trial in China to examine the potential protective effects of the timing and duration of iron supplementation on neurocognitive function. The study will assess the effects of supplementation during the prenatal and postnatal periods. This study takes advantage of a unique opportunity to add to a preexisting cohort in an ongoing CDC-sponsored study of iron and folic acid supplementation.

Iron and Malaria

Iron deficiency ranks ninth among 26 risk factors included in the World Health Organization (WHO) *Global Burden of Disease 2000 Overview* and accounts for 840,000 deaths and 35 million disability-adjusted life-years lost. Africa and parts of Asia bear 71 percent of this global mortality burden and 65 percent of the disability-adjusted life years lost. According to the United Nations Children's Fund (UNICEF), more than 1,000 maternal deaths per week in developing countries can be attributed to iron deficiency. To address the burden of iron deficiency, many universal health programs are implemented worldwide, and most intervention strategies rely on iron supplements.

Despite the importance of iron intervention programs in the modern era, concerns about the interaction between iron and malaria date back to the work of Armand Trousseau in the 1850s. A recent finding that universal early childhood iron-folic acid supplementation was associated with increased rates of death or hospitalization for an adverse event revived interest in this topic. In a sub-study, investigators observed that iron-deficient children were at greater risk for adverse events than iron-replete children, and that iron-folic acid supplementation in the deficient sub-group substantially reduced the rate of adverse events (Sazawal, 2006). These findings have raised questions regarding the relationship between iron interventions and health, especially in areas of the world rife with cases of malaria.

Because anemia of infection is a well-described clinical condition, researchers can posit a teleological explanation for this phenomenon—anemia confers protection by preventing invading infectious organisms from acquiring iron. Recent studies have described iron deprivation as a component of an innate immune response (Wander et al, 2008).

The fundamental biological question is whether, in the context of endemic infectious diseases such as malaria, it is beneficial to the host to be nutritionally iron-deficient to limit the availability of this essential nutrient to infectious organisms. The corollary to this question is whether providing iron has a detrimental effect on the host by increasing availability of iron to infectious organisms. To elucidate this issue, the Bill and Melinda Gates Foundation awarded the NICHD $10 million to study the potential adverse effects of iron supplements in the context of infectious disease. The NICHD, with input from the global nutrition community, has designed a two-track project on the topic that includes research and policy arms.

The research arm includes an agenda developed at a workshop entitled *Iron and Malaria-Interactions and Interventions: Where are we now and where do we go from here?* sponsored by the Branch. The agenda seeks to address three fundamental issues:

- Identifying the plausible mechanism(s) for how iron interventions may negatively impact health in the context of infectious diseases, particularly malaria;
- Determining the most appropriate biomarkers to be used in clinical care, research, and evaluation of iron status; and
- Evaluating iron interventions for relative safety and effectiveness in regions with a high malaria burden.

To support research in these core areas, the NICHD issued an RFA, *Considerations for the Safe and Effective Use of Iron Interventions in Areas of High Malaria Burden*, and used a cooperative agreement (U01) mechanism to encourage a close interaction among investigators, NICHD program staff, and partners involved in the initiative. To leverage the initial Gates Foundation award, the NIH ODS provided an additional $500,000 to the effort. In response to the RFA, the NICHD awarded five new projects designed to address key questions regarding the safety of interventions in pregnant women and children, and to examine potential mechanisms by which the administration of different forms of iron might impact host response to malaria infection. The RFA was reissued in April 2009 to address additional unanswered questions.

The track for this project is to translate science into practice though a partnership with the WHO. Researchers, including a 10-member international technical working group, drafted a state-of-the-science technical report on the three core areas of mechanisms, biomarkers, and interventions (Raiten & Namaste, 2009) that the WHO will use to develop evidence-based guidelines. The report is considered to be a "working document," meaning it will be updated as data from the newly funded projects become available. The next phase of this collaboration will include a WHO consultation with members of the pubic health community from areas with high malaria/iron deficiency prevalence.

The ENGB anticipates that this unique global project will serve as a model for other efforts to translate research findings into public health policy and practice through active engagement with the WHO. Other partner agencies in this project include relevant Institutes, Centers, and Offices of the NIH, UNICEF, and the International Atomic Energy Association.

NUTRITION AND HIV/AIDS

One other area of high priority for the global community is how to feed infants exposed to HIV infection. Current policies call for early exclusive breastfeeding followed by rapid weaning to limit exposure to HIV. A significant challenge is how to accomplish the weaning process safely while insuring adequate nutrition, particularly in resource-constrained settings. ENGB-supported investigators have developed a method to reduce transmission by heat-treating expressed milk. The process produced minimal changes in breastmilk composition and was successfully implemented in rural settings where HIV prevalence is high (Israel-Ballard et al,

2008). This work represents the importance of translational science in providing infants with a safe source of nutrition.

The Branch's expertise in both nutrition and child development makes research on nutrition and HIV/AIDS a natural fit. ENGB staff has helped lead the effort to enhance the Institute's research agenda on nutrition and HIV/AIDS and to provide evidence for recommendations on this topic for the global community. Other Branch efforts in this area are described below.

ENGB staff have participated on the WHO Technical Advisory Committee on Nutrition and HIV/AIDS since 2003. For the 2005 WHO Regional Consultation on Nutrition and HIV, held in Durban, South Africa, Branch staff served as the primary point of contact between the Technical Advisory Committee and the NIH/DHHS community. Participants at the Consultation included Ministry of Health representatives from 21 countries in sub-Saharan Africa. The Participants' Statement resulting from the Consultation formed the basis for a resolution, passed unanimously by the World Health Assembly in 2005, codifying the importance of fully integrating food and nutrition into all aspects of prevention, care, and treatment of HIV-infected and affected persons.

In addition, Branch staff was involved in a Southeast Asia Regional Consultation on Nutrition and HIV in Bangkok, Thailand, in 2007. Participants at this consultation included Ministry of Health representatives from all 14 countries in the WHO Southeast Asia Region, as well as China, Laos, Vietnam, and Cambodia. The consultation addressed regional issues about the role of nutrition and HIV and included updated versions of the WHO technical reports. In 2008, Branch staff and staff from the NIH Office of AIDS Research (OAR) also helped support a Regional Consultation on Nutrition and HIV in West/Central Africa, held in Burkina Faso. A draft of the final Participants' Statement was presented to the WHO Executive Board in January 2009; a review of the entire WHO effort in the area of nutrition and HIV occurred in May 2009.

In 2006 and 2007, the NICHD published RFAs focused on nutrition and HIV to address outstanding gaps in knowledge, based on input from the 2005 Consultation and from interactions with the global community. As a result, the Institute funded eight R01 and four R03 projects addressing issues related to feeding HIV-exposed infants, the impact of diet on disease progression, relative benefits of protein on health of HIV-infected women, impact of nutritional status on pharmacology of available treatments, and impact of food insecurity on health and HIV risk.

In October 2008, the ENGB, in partnership with the NIAID Division of AIDS Research and the OAR, organized a workshop on nutrition in clinical management of HIV infection. This meeting represented a watershed event in the nutrition and HIV research agenda because it was the first time that the full breadth of the NIH-funded clinical trials community came together to discuss how to integrate this nutrition research into ongoing HIV/AIDS activities. Workshop participants identified five priorities for this research:

- Impact of nutrition on disease progression;
- Interaction between infant feeding practices and susceptibility to HIV infection (the role of human milk, ontogeny of human microbiome, gut integrity and probiotics);

- Impact of nutrition on HIV drug metabolism and vice versa, as well as on clinical management of side effects of highly active anti-retroviral therapy;
- Interactions among nutrition, HIV, and susceptibility to and treatment for co-morbidities (e.g., tuberculosis, malaria, etc.); and
- Best practices for feeding infants born to HIV-infected mothers, with a focus on nutrition instead of viral transmission.

Following the workshop, ENGB began serving as an *ad hoc* member of the OAR Advisory Council (OARAC). The OARAC supports the need to expand the nutrition research agenda into the priority areas identified and suggests both domestic and international foci. The OAR director endorsed both the submission of supplemental applications to support the integration of nutrition into the network system and the acceptability of a new funding opportunity announcement for the 2010 planning process.

The first global recommendations on nutritional care for people living with HIV/AIDS, released in 2003, remain the only such guidance published to date and form the basis of current programs addressing food and nutrition by the President's Emergency Plan for AIDS Relief (PEPFAR), the United Nations World Food Programme, the Joint United Nations Programme on HIV/AIDS, and the Global Funds for Tuberculosis, Malaria, and HIV. A comprehensive review of the interactions between nutrition and antiretroviral drugs, published in 2005, is one of a series of comprehensive reviews produced for the WHO; topics for these reviews include macronutrients, micronutrients, infant feeding and prevention of maternal-to-child transmission, nutritional needs in the context of pregnancy and lactation in HIV-infected women, and infant and young child nutrition. These reports served as the focal point for a series of WHO Regional Consultations intended to begin the process of integrating food and nutrition programs at community, country, and regional levels. In 2006, PEPFAR released its *Report on Food and Nutrition for People with HIV/AIDS*, a document that was based on the WHO recommendations and that acknowledged the role of the Technical Advisory Committee as the lead technical authority. Researchers in the field also convened a workshop in 2006 to develop guidelines for the nutritional care of HIV-infected infants and children. The process for developing these guidelines, which are built on existing platforms designed for use in primary care in resource-constrained settings, included field-testing in several countries in sub-Saharan Africa in addition to the workshop. Meeting outcomes and publications have been broadly disseminated; please visit http://www.who.int/nutrition/topics/hivaids/en/index.html and http://www.who.int/nutrition/publications/hivaids/en/index.html for more information.

NECROTIZING ENTEROCOLITIS (NEC)

NEC is a devastating gastrointestinal disease that strikes about one in 10 preterm infants born weighing less than 1,500 grams. About one in three affected infants succumbs to this disease. Those infants who escape death are left with morbid sequelae, such as intestinal strictures, a short intestine, and resulting malabsorption. The etiology of NEC remains unclear, but two commonly reported risk factors are preterm birth and enteral feeding. Elevated serum levels of factors involved in the inflammatory process may also play a role in the morphological changes seen in NEC.

Despite advances in the care of preterm infants and new surgical approaches to NEC, morbidity and mortality figures for NEC have remained unchanged during the past 40 years. Traditionally, attempts at curing cases of perforated colon in NEC involve surgical resection of the necrotic colon. Severe cases of perforated NEC in preterm infants who seem too fragile to survive colectomy are traditionally treated with a temporizing measure, the insertion of surgical drains in the abdomen to provide an outlet for infected peritoneal fluid. The latter method has had unexpected success for severe cases of perforated NEC.

To compare the two surgical interventions, a group of pediatric surgeons at 15 centers in the United States and Canada randomized 117 similar cases to either colectomy or drainage. The surgeons reported their results in *The New England Journal of Medicine* (Moss et al, 2006). They found that survival, length of hospitalization, and reliance on TPN were not significantly different between the infants assigned to either intervention. These results imply that future research on NEC should focus on improved identification of infants at risk for developing perforated NEC, rather than on improving details of the operative interventions. The study also showed that critical questions about surgical interventions in children could be answered by randomized controlled trials if the interventions are in equipoise.

In July 2006, at the ENGB research workshop, *New Approaches to the Treatment and Prevention of NEC*, participants agreed that research should focus on prevention of NEC in high-risk infants rather than on treatment. Participants also emphasized that when NEC is observed in an infant in the morning, the baby is usually on the operating table by the afternoon, illustrating that the disease advances so swiftly there is almost no time for therapeutic interventions to work. Following the workshop, the Branch issued an RFA directed at the twin goals of identifying high-risk infants and preventing the disease. As a result of the RFA, ENGB funded seven new grants with specific aims to identify at-risk infants and to develop preventive strategies. Preventive strategies proposed include the use of prebiotics and probiotics, which show promise in altering bacterial populations in the infant intestine by replacing aggressive organisms, such as *E. coli* and *Clostridia spp*, with more quiescent commensal organisms, such as *Bifidobacter spp*.

A related RFA, *Antimicrobial and Prebiotic Activity of Oligosaccharides*, was issued in 2008; applications received in response to this RFA were reviewed at the NACHHD Council meeting in June 2009.

GROWTH RESEARCH AND OTHER BRANCH ACTIVITIES

THE FELS LONGITUDINAL STUDY (FLS) OF PHYSICAL GROWTH AND DEVELOPMENT

The FLS is the largest and oldest longitudinal study of growth and development in the world, having followed more than 1,500 individuals from birth beginning in 1929. Arthur Morgan, a civil engineer, and then president of Antioch College, inaugurated the FLS by persuading Samuel Fels and the Fels Foundation to provide funds for a longitudinal study to find out why people differ. The NICHD began funding the FLS in 1976 when Fels Foundation support for the project dwindled. Since then, the FLS has had a series of internationally recognized principal investigators, including Drs. Frank Falkner, Stanley Garn, and Alex Roche.

The FLS has also contributed greatly to knowledge about pubertal changes in body composition and to awareness of the early appearance of cardiovascular risk factors in children and adolescents. The FLS provided growth data for the North American Standard Tables of Height, Weight and Head Circumference, as well as for the Roche-Wainer-Thissen *Atlas of Bone Age and Skeletal Development*. These standards remain in widespread use in the United States and abroad.

More recently, researchers have been exploiting the FLS database to ascertain the origins of the metabolic syndrome in childhood. One major effort involves examining retrospective childhood data on adults who currently have the metabolic syndrome (Sun et al, 2008; Schubert et al, in press). In an interesting new ancillary study, the ENGB is supporting researchers who are using data from the FLS to examine the effects of rapid and slow attainment rates of pubertal milestones on body composition and metabolic and cardiovascular risk decades later. *Appendix L* provides graphical information on important findings that have emanated from the FLS.

The perennial productivity of its investigators has enabled the FLS to compete successfully for support six times since the initial period of NICHD funding ended in 1981. Reviewers and experts in the field often refer to the FLS as a "national resource." The FLS and the Tennessee Valley Authority, a showcase of the Franklin Delano Roosevelt Administration, both remain as enduring legacies of Arthur Morgan.

PEDIATRIC AND OBSTETRIC PHARMACOLOGY

In 1994, the ENGB initiated the Pediatric Pharmacology Research Units (PPRU) Network to address the problem of the dearth of drugs approved by the U.S. Food and Drug Administration (FDA) for pediatric indications, and to demonstrate that pediatric drug studies could be ethically and efficiently performed in children. In the ensuing five years, the Network performed more than 100 studies in newborns, children, and adolescents. In 2001, the Joint Conference Committee of the House and Senate recognized the PPRU Network as a "national resource" in its deliberations on the Best Pharmaceuticals for Children Act (BPCA), which passed in 2002.

The PPRU Network grew from seven sites to 13 sites, after recompetitions in 1998 and 2003. Its success led the ENGB to establish a similar network, focused on obstetric pharmacology, in 2003. Increased Congressional interest in pediatric and obstetric pharmacology research and a desire to emphasize the importance of these activities within the Institute led the NICHD to transfer this portfolio to a new Branch, resulting in the birth of the Obstetric and Pediatric Pharmacology Branch (OPPB) in 2004. Despite the organizational separation, the ENGB and the OPPB have maintained close cooperation on issues related to pediatric and obstetric pharmacology. Some examples of this cooperation include the following:

- The two Branches jointly sponsored the *Pharmacologic Agents and Their Effects on the Pediatric Skeleton* meeting in 2005 (described in the *Bone Health and Osteoporosis Prevention* Section of this report). Proceedings of this meeting were published in 2007 as a supplement to *Pediatrics* (*119*, S125-S174).
- The OPPB has provided the NICHD's annual support of TrialNet since 2008 because of TrialNet's focus on developing new antigen-based and immunomodulatory therapies for children with new-onset T1DM. The ENGB staff presented a synopsis of the new biological agents being studied by TrialNet investigators at the congressionally mandated annual meeting of the Drug Prioritization Committee in July 2008.
- The two Branches will work together to develop oligosaccharides as a new class of antimicrobial agents directed against enteric infections.
- The two Branches are planning a conference in conjunction with the Children's Nutrition Research Center in Houston on the interaction of drugs and nutrients that will be held in 2010.

The ENGB will continue to work with the OPPB and with other entities within the NICHD to support research on pediatric and obstetric pharmacology.

TRAINING AND CAREER DEVELOPMENT

Among the ENGB's principal objectives is training future generations of clinical scientists and promoting interdisciplinary training opportunities through career (K) awards and through individual and institutional National Research Service Awards (NRSAs). One-fifth of the ENGB budget supports the training of investigators at various stages in their careers. A description of some of the Branch's efforts in training and career development are included below.

BRANCH-SUPPORTED CAREER (K) AWARDS

The largest of the ENGB training programs is the congressionally mandated Child Health Research Career Development Award (CHRCDA) program. Initiated in 1990, the CHRCDA represents a major development in U.S. pediatric science and is a vital part of the Institute's response to the growing need to expand basic science and translational research training for pediatricians. Now in its 19th year, the CHRCDA Program has developed a cadre of highly

skilled physician-scientists, who have successfully competed for NIH funding. This Program expands basic science and translational research training for pediatricians who are within four years of completing their subspecialty training by providing support for an ideal environment for learning, while also nurturing the scientists in the pediatric research field. At each funded Center, established mentor-investigators offer their expertise and laboratory facilities to junior investigators (scholars), so that the latter can hone their research skills. This experience also enables the CHRCDA scholars to generate preliminary data, which can be included in grant applications for independent funding. The Program currently funds 20 Centers, which receive five-year K12 awards for new research projects by nascent pediatric investigators as well as support for laboratory resources. Throughout its existence, the CHRCDA Program has supported 32 pediatric departments in the United States. *Appendix N* lists past CHRCDA recipients; Figure 9 displays current CHRCDA sites.

Over nearly two decades, this Program has developed a total of 640 highly skilled pediatric physician-scientists, who have successfully competed for NIH funding in 15 subspecialties. Overall, 67 percent of Program scholars apply for NIH funding, and 72 percent are successful. One-half of all Program scholars have applied for R01 funding and, of those, 60 percent were successful. Program-funded scholars have also risen to the top of their fields to assume leadership positions; for instance, 40 past scholars have reached the level of full professor, and 130 have reached the level of associate professor. The Program has had a large impact both locally and nationally as the Branch trains the future leaders in pediatric medicine.

The Branch also uses the K12 mechanism to support the Pediatric Scientist Development Program (PSDP). The PSDP is also a long-standing program, currently in its 21st year of funding. Although it is considerably smaller than the CHRCDA Program, the PSDP boasts graduates with a similar record and level of distinguished accomplishments. Participants in the PSDP are listed in *Appendix M*; Figure 8 displays current PSDP sites.

NATIONAL RESEARCH SERVICE AWARD (NRSA) TRAINING PROGRAM

The NICHD also supports the training of junior investigators and promotes interdisciplinary training opportunities through individual postdoctoral fellowships and institutional training grants. The Branch uses the NRSA Training Program to enhance postdoctoral pediatric research training in both basic and clinical research. The Branch awards individual postdoctoral fellowships (F32s) to newly trained young scientists for up to three years, enabling them to work full-time with a qualified mentor to develop expertise in research. The Branch relies on institutional training grants (T32s) to establish or maintain an exceptional environment for research training of pediatric physician scientists at outstanding institutions. The Institute initiated a new institutional T32 program in September 2001, in response to the Children's Health Act of 2000. This new program encourages the initiation of subspecialty programs at qualified institutions to train pediatricians. When the program began in 2002, it supported six centers; by 2003, the program had more than doubled in size to 13 centers. *Appendix O* lists participants in the Branch's NRSA Training Programs; Figure 8 displays NRSA site locations.

FUTURE DIRECTIONS FOR THE BRANCH

On January 23, 2009, in accordance with the NICHD process for improving transparency of and enhancing input toward strategic planning, the ENGB convened a panel of experts to review and discuss Branch activities and possible future research directions. The expert panel included two NACHHD Council members and representatives from the USDA Children's Nutrition Research Center, the International Society for the Developmental Origins of Health and Disease Council, the National Institute of Arthritis and Musculoskeletal and Skin Diseases Advisory Council, and the Robert Wood Johnson Healthy Eating Research Program. (See *Appendix T* for a list of panel members.)

The panel appreciated the Branch's emphasis on pediatric endocrinology, nutritional science, pediatric gastroenterology, physical growth and body composition, the prevention of chronic conditions, such as diabetes, obesity, and osteoporosis, and the developmental origins of health and disease. They agreed that training the next generation of pediatric investigators should remain one of the Branch's highest priorities. The discussion highlighted critical, unanswered questions related to the clinical care of infants and children and framed the implications of these questions in the context of the onset of chronic diseases later in life. Other topics included the value of major longitudinal databases supported by the Branch, systems science, and multilevel modeling of the complex factors that contribute to childhood obesity and nutrient deficiencies. The panel's insights assisted the Branch in identifying public health priorities and research opportunities. A full summary of the panel's discussion is available on the ENGB Web site at http://www.nichd.nih.gov/about/org/crmc/eng/index.cfm; the Branch's possible future research directions are included below.

RISK FACTORS, BIOMARKERS, AND EPIGENETICS

The panel discussed the Branch's broad portfolio on issues related to preventing chronic diseases and emphasized a continued need for research on childhood biomarkers for disease later in life and steps which can be taken during childhood to mitigate or prevent conditions, such as atherosclerosis, metabolic syndrome, diabetes, obesity, and osteoporosis. For example, the panel noted that atherosclerosis remains the major lethal disease in the United States, adding that decision science may be useful in translating evidence-based information about childhood risk factors for the disease into clinical practice and public health interventions.

In the context of discussing the developmental origins of health and chronic disease, the panel also noted that epigenetics is an area of research that will advance the ENGB interest in the molecular biology of growth and development. Epigenetic changes serve as markers of longitudinal changes during growth and development and of exposure to nutrients, stress, and xenobiotics in the environment. Panel members explained that gaining a better understanding of epigenetic processes could also inform an understanding of the developmental origins of health and disease. The panel emphasized that the relationship between epigenetics and the origins of health and disease is so complex that it becomes a problem of systems biology. Given the rapid

development of the epigenetics field the panel indicated that investigator-initiated research would be the most appropriate mechanism to support this line of scientific inquiry.

Within the context of the panel's discussion, the ENGB may consider the following research activities:

- Continue support of efforts to discover genetic or biochemical biomarkers in childhood to predict future disease; this research could include efforts to ascertain the effects of low-frequency genetic polymorphisms.
- Support research to more accurately define levels of risk that attend various levels of HDL or BMI outside of absolute cut-off points in continuously distributed variables.
- Partner with various professional and advocacy organizations to support research that accurately assesses food intake because current measures are inaccurate and inconsistent and yet may be important in defining risk for future chronic disease.
- Consider using the techniques of decision science to develop applicable biomarkers, especially as a means of translating findings into clinical practice.
- Support research related to the field of epigenetics and the mechanisms of disease.
- Explore ways to understand how mediators of cardiovascular health affect the developing brain. For example, studies could address the long-term outcomes of chronic exposure to cortisol, which truncates dendrites in the hippocampus and reduces hippocampal volume. Studies are also needed on the effects of pro-inflammatory cytokines, such as interleukin-8, on oligodendrocytes and myelination, processes that appear to increase the likelihood of developing schizoaffective disorders later in life.
- Encourage workshops on epigenetics and the mechanisms of disease, including discussions of the roles played by nuclear receptors in determining how genes and the environment interact during development and the regulatory controls of development and metabolism. For example, epigenetic effects driven by methylation of cytosine nucleotides and acetylation of histones can modify expression of genes not only through the lifespan, but also across generations.

OBESITY AND ITS ORIGINS

The panel discussed the issue of how origins of childhood obesity result from the interaction of biological systems with societal systems. Panel members agreed that the best approach to developing hypotheses concerning causality would be multifactorial modeling on levels ranging from epigenetic control of tissue-specific gene expression to agricultural policy and society's efforts to control environmental pollution. Because rapid weight gain in infancy predicts obesity later in life, the panelists emphasized the need to learn more about the predictors of infant weight gain, such as growth factors and cord blood leptin, in addition to food intake.

The panelists endorsed the Branch's analytical approaches to the problem of childhood obesity and encouraged ENGB staff to continue to develop the systems-oriented multilevel framework for obesity research. In contrast to current obesity initiatives, which focus on one or two factors, usually within one level, the panel supported the goals of the multilevel framework: to generate plausible hypotheses that can be tested empirically, and to elucidate the "cause of the causes" of

the epidemic of childhood obesity. Panel members felt that this new approach would prove more fruitful than current approaches.

Within the context of the panel's discussion, the ENGB may consider the following research activities:

- Support efforts to assess how early macrolevel and microlevel factors act at different points along growth and developmental pathways, especially during critical windows when development is more vulnerable to environmental factors, such as endocrine disruptor chemicals.
- Examine circumstances of both macronutrient restriction and micronutrient restriction in relation to later development of the cardiovascular system and to obesity, specifically in the context of critical windows during which environmental nutrient supply influences gene "sculpting."
- Explore ways to incorporate studies of the microbiome in relationship to obesity, as well as studies of how to assess accurately adiposity in pregnant women and infants.
- Encourage studies that use various models of catch-up growth in VLBW infants born preterm and in term infants with IUGR to elucidate the underpinnings of the later development of obesity and the metabolic syndrome.
- Foster initiatives to understand the mechanisms of impaired linear growth in children with chronic illness, with particular attention to the effect of chronic inflammation on the function of the cartilaginous growth plates at the ends of the long bones of the appendicular skeleton; such work could also address issues related to the therapeutic effects of growth-promoting therapies—both established and evolving—in children whose growth is retarded by chronic illness.
- Address issues related to health disparities and incorporate measures of disparities in both mechanistic and intervention studies, including disparate exposure to environmental contamination.
- Consider comparative studies in the country of origin of specific U.S. population groups to evaluate the relative importance of innate biological factors and environmental influences acting on the biological substrate.
- Develop research efforts that cut across multiple fields and disciplines and explore ways to involve non-traditional partners in obesity research and intervention.
- Establish a Web site portal to both Branch- and Institute-supported efforts on obesity research, including data-sharing capability and information related to recruitment into clinical research.

NUTRITIONAL RESEARCH AND NUTRITIONAL COGNITIVE NEUROSCIENCE

The panelists engaged ENGB staff in a discussion about essential nutrient requirements during infancy and childhood. Panel members were concerned about the lack of evidence base in this area and noted a significant dearth of information related to nutrition for preterm infants and for those with IUGR. Currently, many neonatologists treat preterm infants by trying to achieve a rate of growth comparable to the rate *in utero* for the same gestational age, despite little scientific evidence to support the concept. This nutritional therapy in the neonatal intensive care unit

might increase the risk of NEC and could lead to cardiovascular and metabolic consequences later in life.

The panelists also noted that disparate nutritional insults, such as deficiencies or surfeits of iron, zinc and copper—and even obesity— during development lead to frontal lobe dysfunction. The reasons for the special vulnerability of the frontal lobes are unclear. Fortunately, new techniques are available, such as functional MRI (fMRI) and positron emission tomography (PET), to address such questions and possibly to identify a common pathway of impaired frontal lobe development. Members of the panel noted that children afflicted with frontal-lobe malfunction are at risk for an exponential increase in learning difficulty as they grow older; this malfunction, in turn, poses a threat to their cardiovascular and metabolic health because this area of the brain is critical for determining adherence to healthy lifestyle behaviors.

The panelists expressed enthusiastic support for the Branch's recent forays into global health and nutrition, noting the importance and relevance of the study of nutrition and HIV and iron deficiency anemia in malarial regions of the globe. Panel members also noted that the Branch's collaboration with the Bill and Melinda Gates Foundation could provide a model for further international studies and were enthusiastic about the contributions of the NIH ODS to leveraging the funds supplied by the Gates Foundation.

Within the context of the panel's discussion, the ENGB may consider the following research activities:

- Support efforts to understand the effects of hyperglycemia and hypoglycemia on brain function in newborns. Activities could include studies of the following:
  - Effects of micronutrient and macronutrient supply to the brain during the vulnerable period of cerebral maturation, especially in preterm infants, among whom such periods are often undetected and untreated, and integrating these effects across multiple levels of regional brain assessment, including the genome, epigenetic effects, cell signaling, brain structure, cerebral physiology, and behavior
  - Effects of diabetes or other problems of plasma glucose regulation on cerebral metabolism, brain function, and behavioral outcomes in infants and children
  - Identification of biomarkers, such as hypoglycemia, for cardiovascular disease later in life, and balancing cardiovascular and neurocognitive risks during early development
  - Effects of breastfeeding on hypoglycemia in infancy
  - Development of non-invasive sensors to monitor and treat hypoglycemia and to accurately measure levels of plasma glucose in newborns, especially those born to mothers with T1DM or GDM, and in VLBW infants who have unstable plasma glucose
  - Identification of genetic mechanisms and polymorphisms activated by perturbations in glucose, especially those affecting nutrient availability, absorption, and metabolism and influencing nutrient requirements
  - Effects of disease, stress, and non-septic inflammation on nutrient accretion and nutrient traffic through the body, in states of both nutrient deficiency and surfeit
- Support research to ascertain optimal maternal nutrition prior to and during pregnancy, which could reduce or prevent preterm birth, VLBW, and IUGR.

- Encourage studies of infant feeding and infant body composition in different locations throughout the world.
- Further efforts to develop more fine-grained biomarkers of nutrient intake, status, and function rather than relying on relatively coarse anthropometric measurements to support decisions about the impact of nutrition on the health and development of infants and children.
- Extend efforts to define the impact of nutrition on health and disease with a specific emphasis on gastrointestinal development, immunocompetence, and neurological function.
- Support efforts to understand the development of taste receptors for amino acids and fatty acids in the gastrointestinal system beyond the oropharynx; support attempts to comprehend how the function of these receptors, as well as exposure to various types and amounts of nutrients early in life, influence food preferences later in life.
- Encourage partnerships and collaborations to explore the interrelationships among nutrition and pharmacokinetics and pharmacodynamics, such as the ongoing collaboration with the USDA Children's Nutrition Research Center on agenda-setting workshops and the additional activities with the NICHD's OPPB.
- Consider expanding collaborations and partnerships to further initiatives related to global health and nutrition and to incorporate a systems perspective within this field of research.

FOLLOW-UP OF BRANCH-SUPPORTED DATABASES AND COHORTS

The panel appreciated the value of the CHDS database and the FLS database, given their contributions to understanding children's growth and development. Both studies have entered productive new phases with a shift in focus toward ascertaining developmental origins of health and disease.

The panel reviewed the history and findings of the BMDCS, which uses serial DXA measurements to generate longitudinal reference data on BMD that can then be used to estimate fracture risk and to identify children at risk for developing osteoporosis later in life. Panelists lauded the BMDCS for its many contributions to the field, especially in that it allows researchers to visualize abnormal skeletal changes during growth and development. They also noted the potential of this new longitudinal database for answering additional research questions, calling the database a "gold mine of data" and admitting it had uses that "none of us can imagine" because of its meticulous serial documentation of pubertal status and the density of bone, muscle, and fat compartments of the body, in addition to its wealth of information about nutrient intake and physical activity.

Similarly, the panel noted that the HAPO study, which examined the offspring of 23,000 women to ascertain the relationship among maternal glycemia during the second trimester of pregnancy and infant outcome measures, such as macrosomia and neonatal hypoglycemia, offered a great deal of untapped potential. For instance, the panel noted that information from this cohort could confirm whether metabolism of the offspring is programmed by level of glycemia during pregnancy.

In the context of these discussions, the Branch may consider the following research activities:

- Support efforts to use Branch-supported datasets to study outcomes and long-term health of participants. For example:
  - Because nearly all other longitudinal datasets rely on the coarse measurement of BMI rather than precise DXA to estimate total body fat, the BMDCS dataset is especially valuable for research on the onset and progression of obesity in the first two decades of life.
  - The BMDCS database could also be used for tracking surrogates of cardiovascular risk and for delineating risk of bone fracture according to BMI, diet, vitamin D status, age, race, and ethnicity.
  - The HAPO study database could also yield important metabolic data about the cohort of 23,000 infants as they mature.
- Encourage efforts to mine data from these and other Branch-supported databases/cohorts for the study of other conditions. Important and well-collected data, such as the tracking of the age of entry into each of the stages of puberty, the progression through puberty, and the onset of obesity in different racial and ethnic groups could provide additional clues to risks and biomarkers of chronic or acute diseases. Similarly, these data could offer unique insights into the origins of effects on bone of other chronic conditions, such as anorexia nervosa.
- Consider support of supplemental data collection for these databases, such as collecting samples *in utero* to determine the role of maternal vitamin D and calcium status in the earliest phases of bone matrix establishment.
- Encourage the use BMDCS data to establish BMD correction factors for severely short children with metabolic bone disease as a means to develop therapeutic options and to understand outcomes of treatment for disorders of bone accrual in childhood.
- Publicize the availability of Branch-supported databases so that investigators are aware of these valuable opportunities for further research and analysis.

TRAINING THE NEXT GENERATION OF PEDIATRIC RESEARCHERS

The panel discussed the Branch's current and historical support for training activities. The panelists praised the congressionally mandated CHRCDA Program, noting that it enables department chairs to direct the best young pediatricians for this important expanding scientific area. They also noted the value of the NRSA Program, for subspecialties in pediatrics, and the PSDP, which is designed to give fellows two years to three years to immerse themselves in a field of research, usually in molecular biology with potential clinical applicability. Panelists suggested that the ENGB continue its support of these and other mechanisms for training pediatric investigators because the number of academic pediatricians actively involved in research continues to dwindle in size.

In the context of the panel's discussion, the ENGB may consider the following activities related to training:

- Maintain the allocation of 20 percent of the Branch's overall budget to training pediatric scientists.
- Expand the number of slots in various training programs for clinical and population scientists.
- Encourage training in transdisciplinary research on topics relevant to the Branch; such training should include substantive aspects of a systems approach to health that transcends basic, clinical, and population sciences and methodological advances for dealing with such complexities.
- Seek out opportunities to train or assist in the training of young investigators in systems science and multilevel modeling, especially in the area of obesity research.

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FIGURES AND TABLES

Please Note: The numbers and amounts presented in these figures and tables represent unofficial figures prepared by the NICHD Referral and Program Analysis Branch. Some of the amounts may differ from those reported by the NIH Research, Condition, Disease, and Categorization Process, which provides the only official amounts for the NIH. Please visit http://report.nih.gov/rcdc to view official numbers and amounts for specific disease categories.

FIGURE 1: BRANCH RESEARCH PORTFOLIO BY TOPIC, FISCAL YEAR 2007

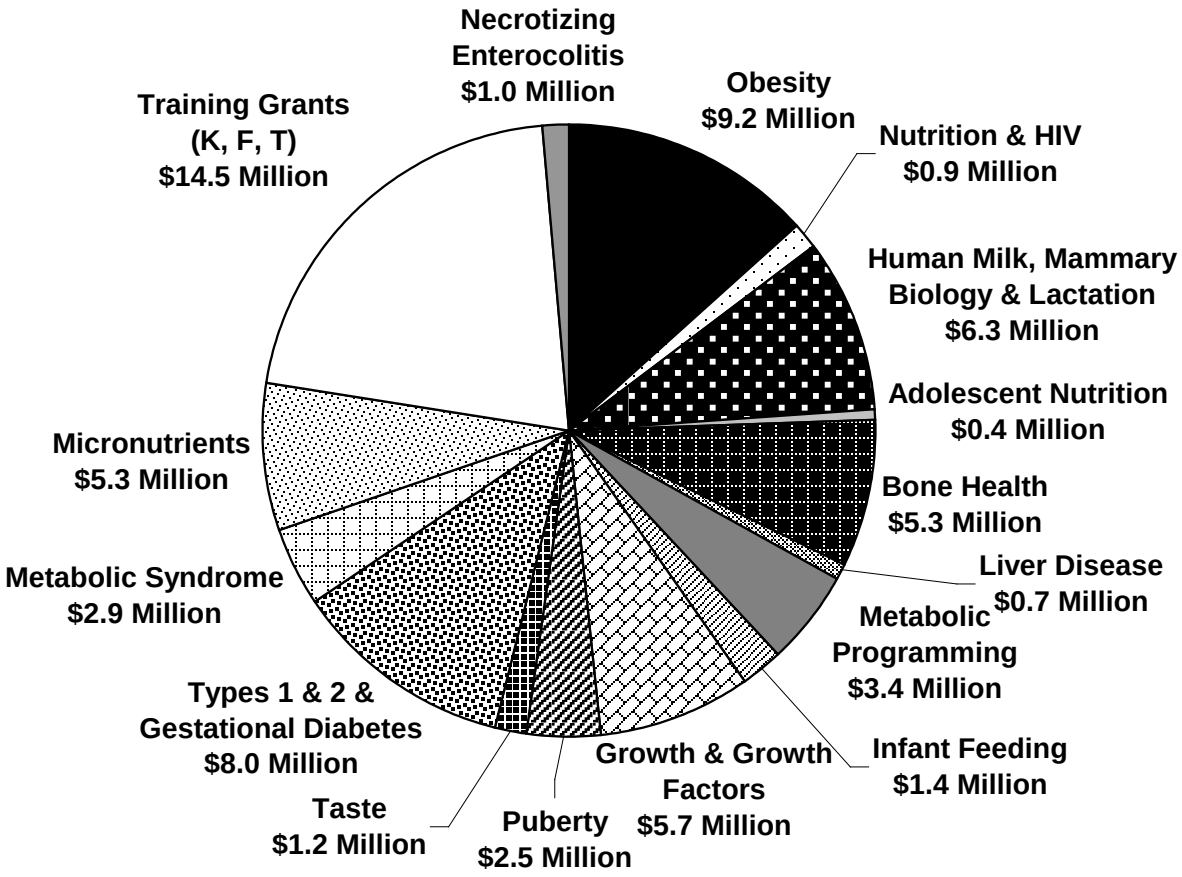


FIGURE 2: BRANCH FUNDS IN CURRENT AND CONSTANT DOLLARS, FISCAL YEAR 1992 THROUGH FISCAL YEAR 2007

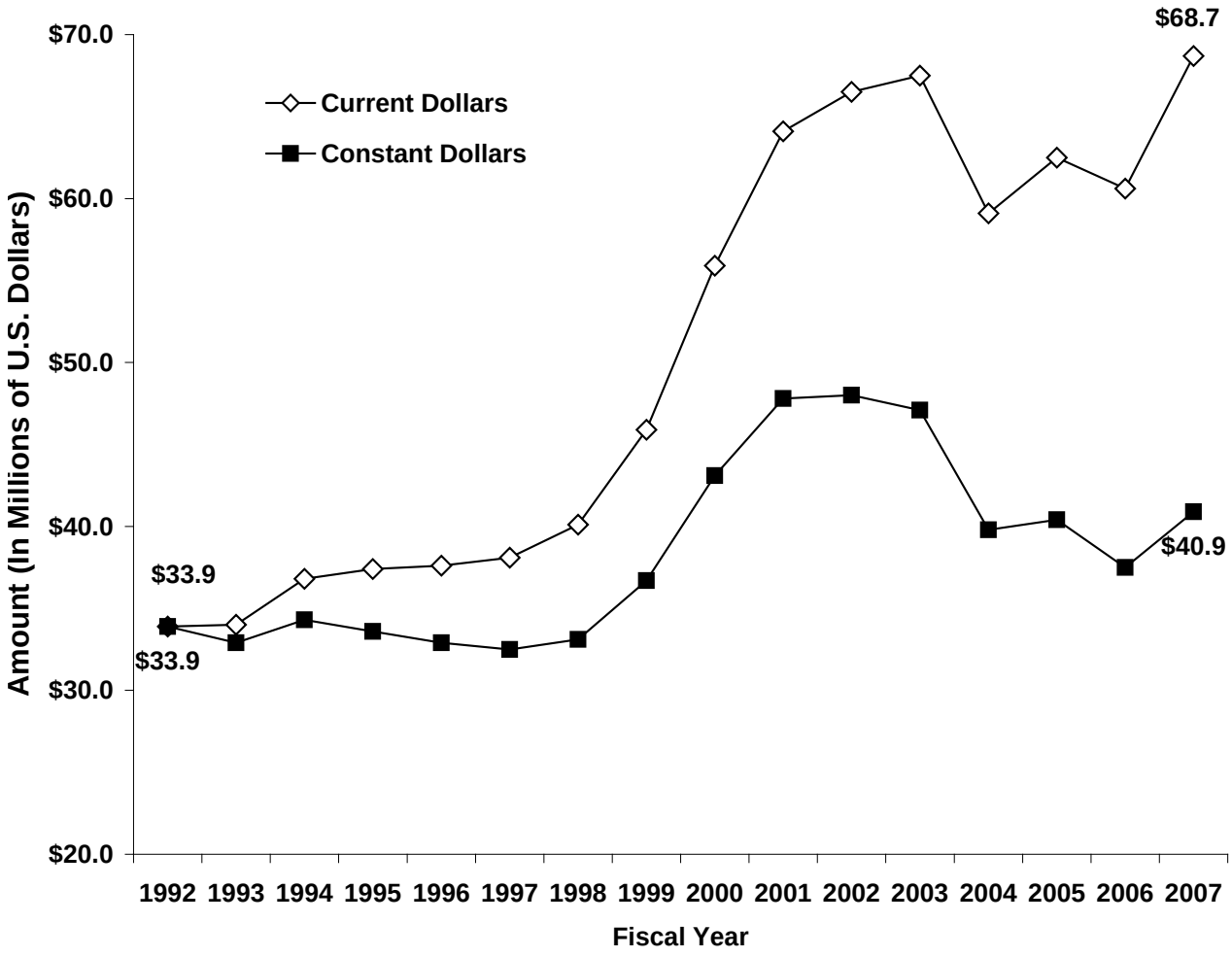


FIGURE 3: BRANCH FUNDING FOR MATERNAL-FETAL NUTRITION RESEARCH, FISCAL YEAR 2004 THROUGH FISCAL YEAR 2007

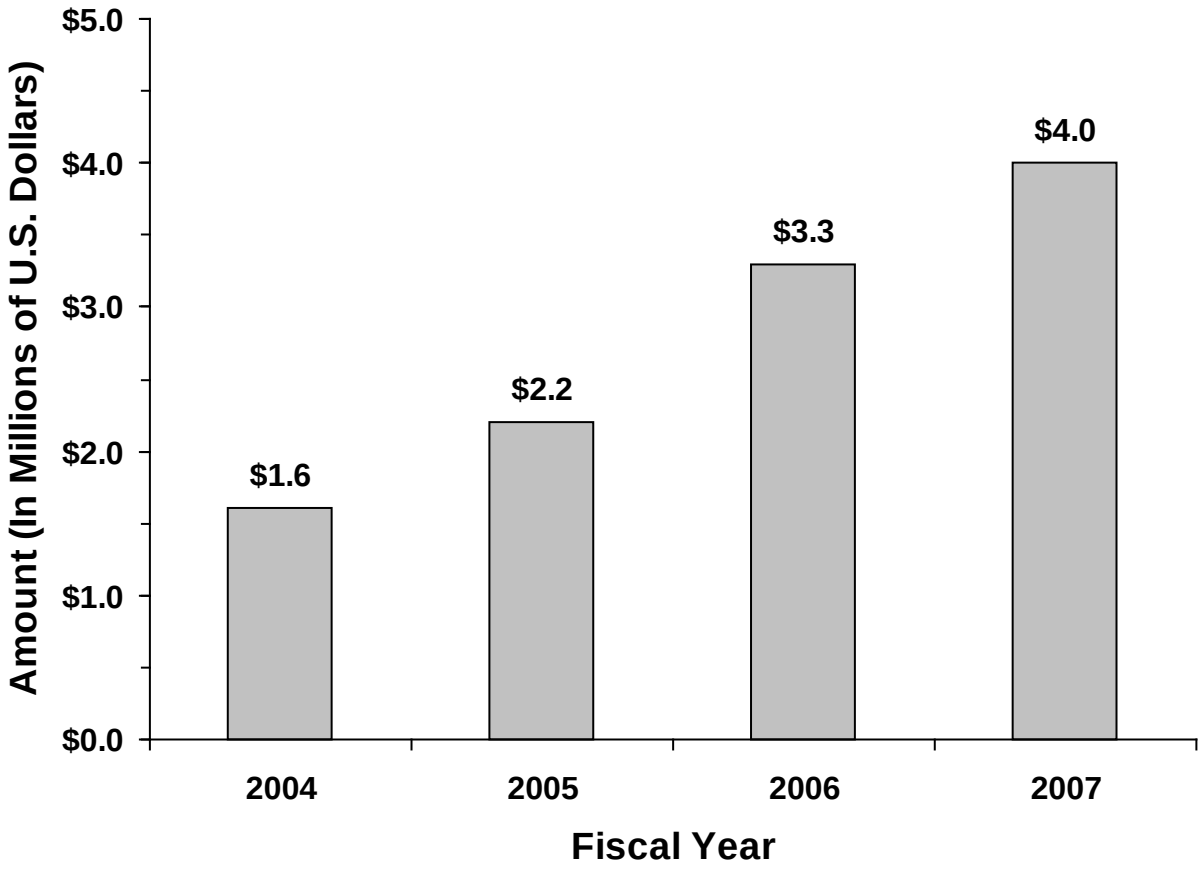


FIGURE 4: BRANCH FUNDING FOR INFANT NUTRITION RESEARCH, FISCAL YEAR 2004 THROUGH FISCAL YEAR 2007

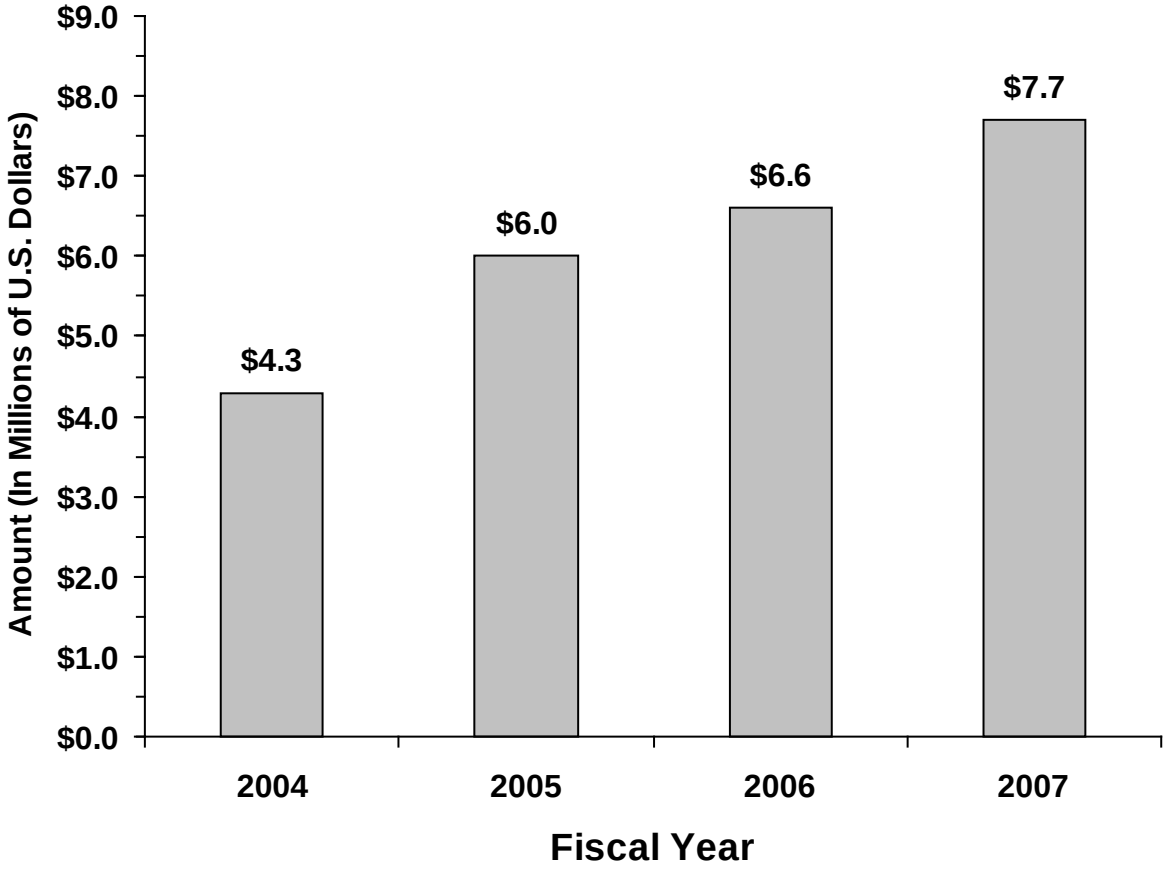


FIGURE 5: BRANCH FUNDING FOR RESEARCH ON OBESITY AND ANTECEDENTS OF ADULT DISEASES, FISCAL YEAR 2004 THROUGH FISCAL YEAR 2007

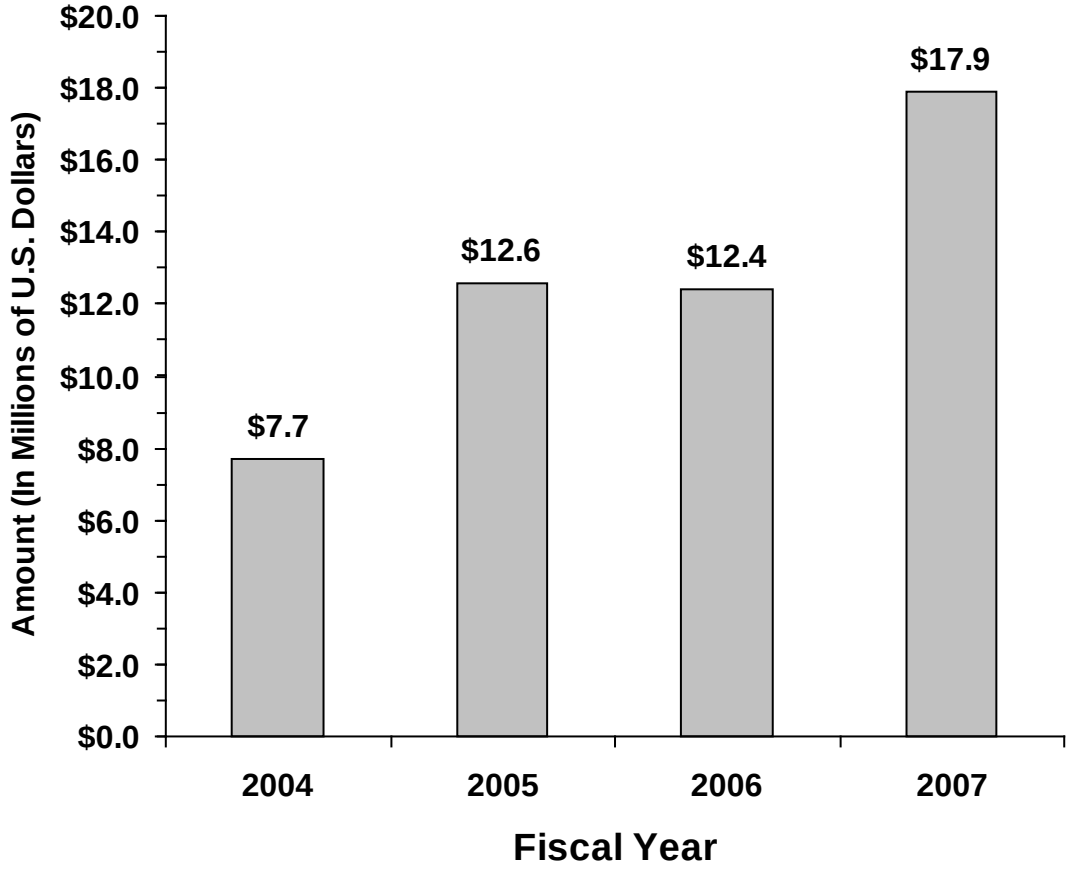


FIGURE 6: CHILD HEALTH AND DEVELOPMENT STUDY (CHDS) OF MATERNAL EXPOSURES DURING PREGNANCY: DICHLORO-DIPHENYL-TRICHLOROETHANE (DDT) EXPOSURE AND BREAST CANCER BEFORE AGE 50 YEARS

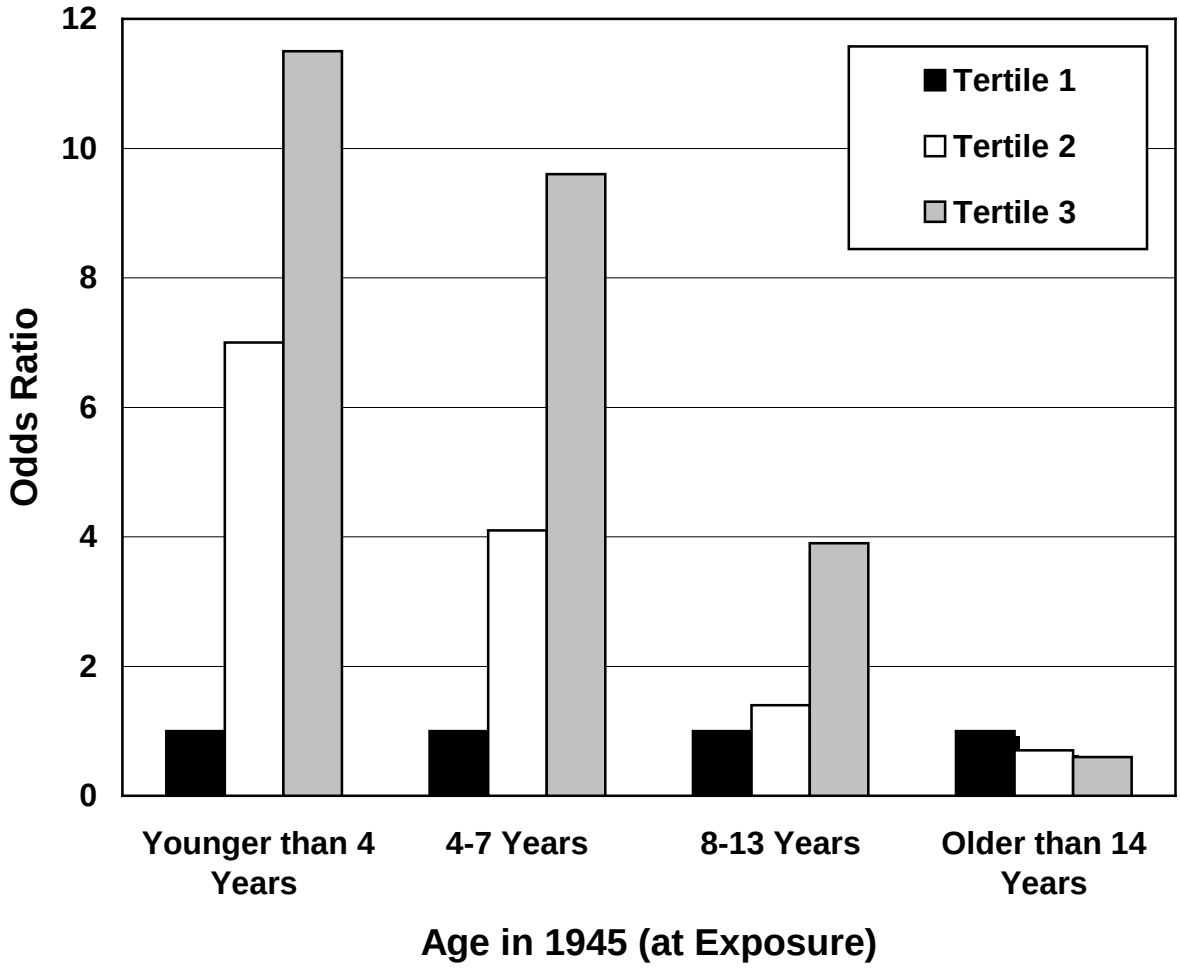
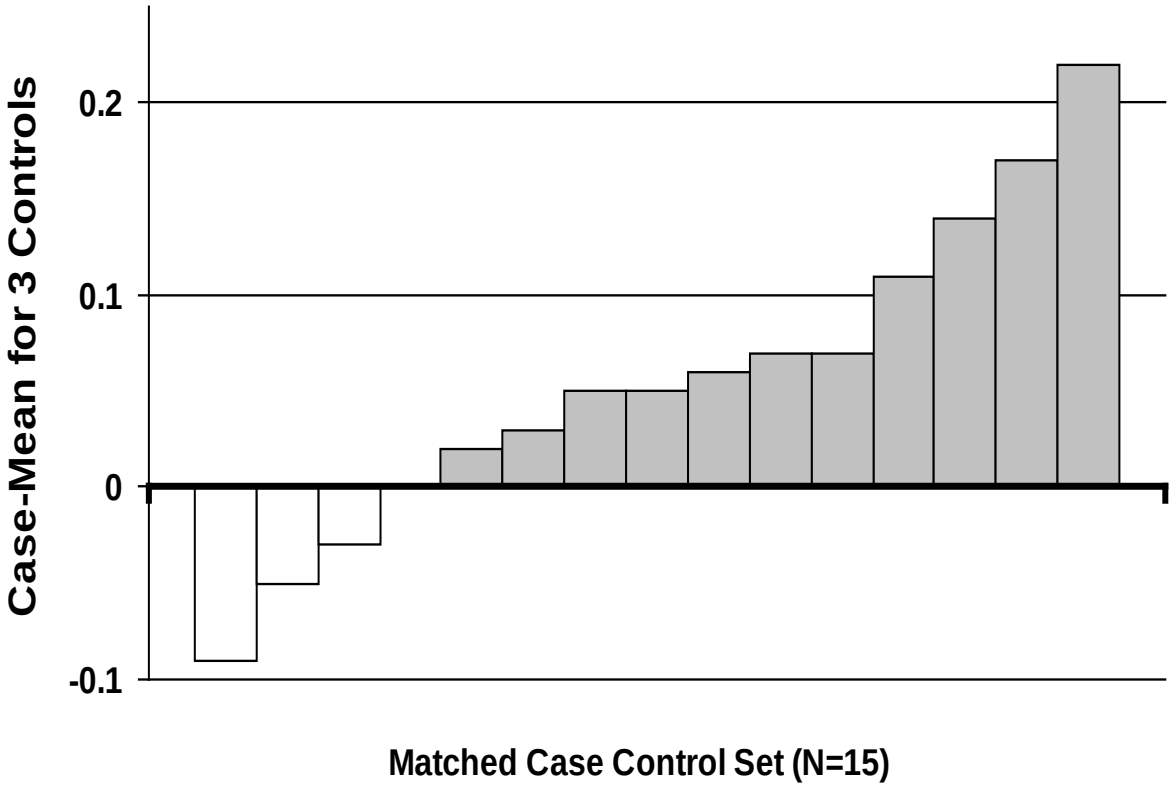
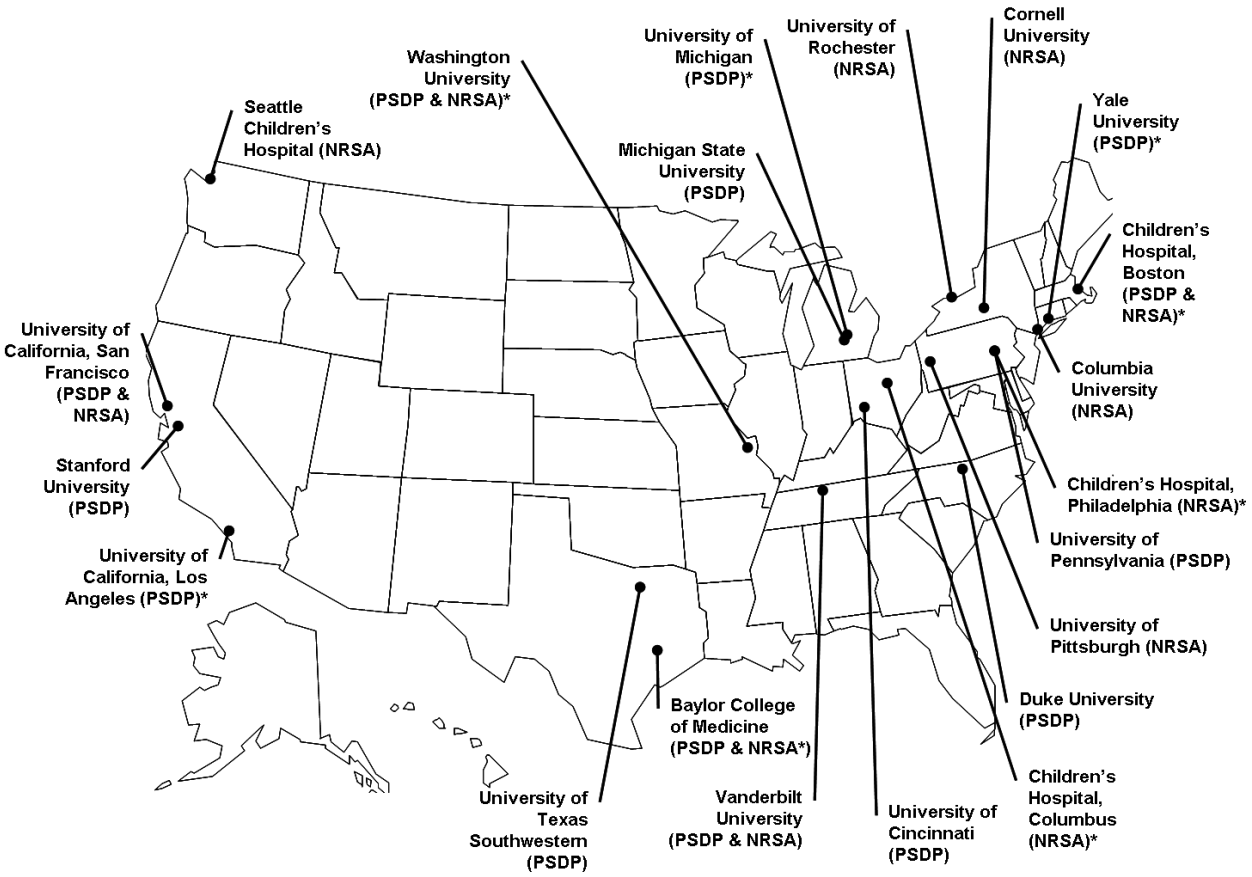


FIGURE 7: CHILD HEALTH AND DEVELOPMENT STUDY (CHDS) OF MATERNAL EXPOSURES DURING PREGNANCY: MATERNAL EXPOSURE TO DICHLORO-DIPHENYL-TRICHLOROETHANE (DDT) AND TESTICULAR CANCER



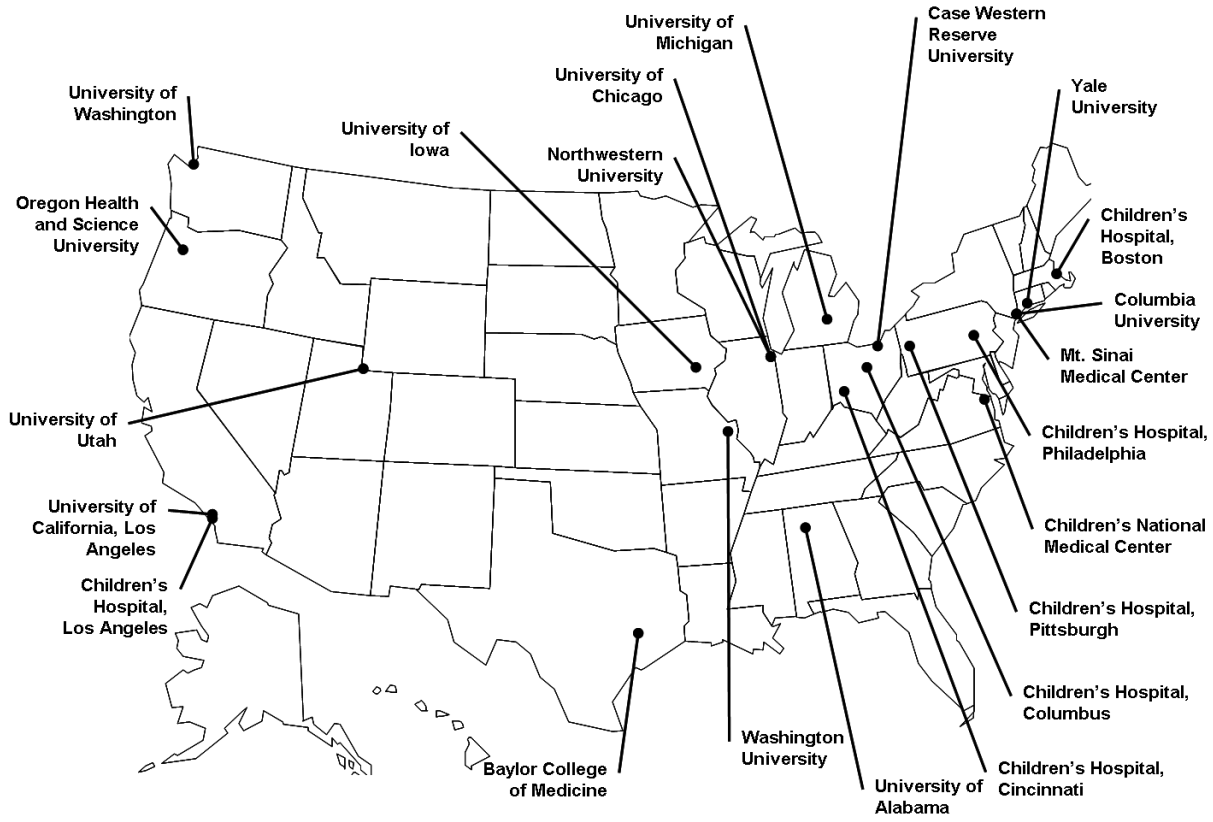
Note: For the above graph, $p < 0.03$.

FIGURE 8: BRANCH-SUPPORTED TRAINING AWARDS: PEDIATRIC SCIENTIST DEVELOPMENT PROGRAM (PSDP) AND NATIONAL RESEARCH SERVICE AWARDS (NRSA) INSTITUTIONAL TRAINING GRANTS



* = Denotes locations that are also Child Health Research Career Development Award (CHRCDA) Program sites; see Figure 9.

FIGURE 9: BRANCH-SUPPORTED TRAINING AWARDS: CHILD HEALTH RESEARCH CAREER DEVELOPMENT AWARD (CHRCDA) PROGRAM SITES, FISCAL YEAR 2006 THROUGH FISCAL YEAR 2012



For a listing of sites back to fiscal year 1990, please see *Appendix N*.

APPENDIX A: BRANCH PARTNERS IN RESEARCH FUNDING

(In descending order of co-funding)

- Congressional Special Statutory Funding Program for Type 1 Diabetes Mellitus Research
- Bill and Melinda Gates Foundation
- Office of Dietary Supplements, National Institutes of Health (NIH)
- Juvenile Diabetes Research Foundation
- European Commission
- European Foundation for the Study of Diabetes
- Canadian Institutes of Health Research
- World Health Organization
- Office of Rare Diseases, NIH
- Robert Wood Johnson Foundation
- Office of AIDS Research, NIH
- National Institute of Allergy and Infectious Diseases, NIH
- National Institute of Diabetes and Digestive and Kidney Diseases, NIH
- National Heart, Lung, and Blood Institute, NIH
- National Cancer Institute, NIH
- National Institute on Aging, NIH
- National Institute of Environmental Health Sciences, NIH
- St. Jude’s Hospital Foundation
- Centers for Disease Control and Prevention, U.S. Department of Health and Human Services

APPENDIX B: BRANCH REQUESTS FOR APPLICATIONS (RFAS), FISCAL YEAR 2004 THROUGH FISCAL YEAR 2008

- HD 04-020: *Prevention and Treatment of Childhood Obesity in Primary Care Settings*
- ES 04-003: *Obesity and the Built Environment* (National Institute of Environmental Health Sciences primary)
- HD 05-027: *Child Health Research Career Development Awards (CHRCDA)*
- HD 06-011: *CHRCDA*
- HD 06-012: *Nutrition and Prevention, Care, and Treatment of HIV/AIDS* (R01)
- HD 06-020: *Diabetes Research in Children Network* Recompetition
- HD 07-001: *Integration of Food and Nutrition into Prevention, Care, and Treatment of HIV Infection and AIDS* (R03)
- HD 07-010: *CHRCDA*
- HD 07-018: *New Approaches to the Prevention and Treatment of Necrotizing Enterocolitis*
- HD 07-022: *Nutrition and Prevention, Care, and Treatment of HIV/AIDS* (R01)
- HD 07-023: *Integration of Food and Nutrition into Prevention, Care, and Treatment of HIV Infection and AIDS* (R03)
- HD 08-004: *Studies of Antimicrobial and Prebiotic Activity of Oligosaccharides*
- HD 08-020: *Considerations for the Safe and Effective Use of Iron Interventions in Areas of High Malaria Burden* (U01)
- AG 08-003: *Studies to Identify Possible Juvenile Protective Factors and Their Effects on Aging* (National Institute on Aging primary)
- HD 08-023: *Innovative Statistical and Computational Methodologies for the Design and Analysis of Multilevel Studies on Childhood Obesity*
- DK 08-505: Limited Competition: *Continuation of the Non-Alcoholic Steatohepatitis Clinical Research Network* (U01) (National Institute of Diabetes and Digestive and Kidney Diseases primary)
- HD 08-029: *Considerations For the Safe and Effective Use of Iron Interventions in Context of Malaria and Its Co-morbidities* (U01)

APPENDIX C: BRANCH-SPONSORED AND CO-SPONSORED CONFERENCES AND WORKSHOPS

(Note: Resulting publication citation included, where applicable)

- *Pharmacologic Agents and Their Effects on the Pediatric Skeleton*; April 2005; *Pediatrics, Mar;119*(Supp.), 2007.
- *Maternal Nutrition and Optimal Infant Feeding Practices* workshop, February 23-24, 2006
- *Workshop on Factors in Youth that Protect Against Aging Processes*, March 22-24, 2006
- *New Therapies and Preventive Approaches for Necrotizing Enterocolitis*; July 10-11, 2006; *Pediatr Res, Oct;62*(4), 510-514, 2007.
- *Pediatric Metabolic Syndrome Working Group (PMSWG): Round 1 Meeting*; July 17-18, 2006; *J Pediatr, Feb;152*(2), 185-190, 2008.
- *Obesity, Women's Health, and Pregnancy: Messages to Ensure Healthy Mothers and Babies*; June 12-13, 2006
- *Prevention and Treatment of Pediatric Obesity in Primary Care Settings: Investigators' Meeting*; April 26, 2007
- *Regional Consultation on Nutrition and HIV/AIDS: Evidence, Lessons, and Recommendations for Action*; October 8-12, 2007
- *Beyond Individual Behavior: Multidimensional Research in Obesity Linking Biology to Society*; October 10-12, 2007; *Prev Chronic Dis*, In Press.
- *Measures of the Food and Built Environment: Enhancing Research Relevant to Policy on Diet, Physical Activity, and Weight*; November 1-2, 2007; *American Journal of Preventive Medicine, Apr;36*(4 Supp. 1), 2009.
- *McGill Health Challenge Think Tank: Changing the Global Dietary Environment*; November 7-10, 2007
- *PMSWG: Round 2 Meeting*; January 31-February 1, 2008; *J Pediatr*, In Press.
- *Iron and Malaria—Interactions and Interventions: Where Are We Now and Where Do We Go from Here?* April 24-25, 2008
- *Environmental Systems in Public Health*; September 26, 2008
- *McGill Health Challenge Think Tank: Active Living and Energy Balance*; November 5-7, 2008
- *Workshop on Building Trust to Address the Obesity Epidemic*; November 12-14, 2008
- *Considerations for the Safe and Effective Use of Iron Interventions in Areas of Malaria Burden*; March 13, 2009

APPENDIX D: PUBLICATIONS ON THE METABOLIC SYNDROME IN CHILDREN

(Branch staff names appear in **bold**.)

Burns TL, Letuchy EM, Paulos R, & Witt J. (2009). Childhood predictors of the metabolic syndrome in middle-aged adults: The Muscatine study. *J Pediatr, Sep;155*(3), S5.e17-S5.e26.

Cook S, Auinger P, Li C, & Ford ES. (2008). Metabolic syndrome rates in United States adolescents, from the National Health and Nutrition Examination Survey, 1999-2002. *J Pediatr, 152*, 165-170.

Cook S, Auinger P, & **Huang TT**. (2009). Growth curves for cardiometabolic risk factors in children and adolescents. *J Pediatr, Sep;155*(3), S6.e15-S6.e26.

Ford ES, Li C. (2008). Defining the metabolic syndrome in children and adolescents: Will the real definition please stand up? *J Pediatr, 152*, 160-164.

Goodman E, Li CY, Tu YK, Ford E, Sun S, & **Huang TT**. (2009). Stability of the factor structure of the metabolic syndrome across pubertal development: Confirmatory factor analyses of three alternative models. *J Pediatr, Sep;155*(3), S5.e1-S5.e8.

Huang TT. (2008). Finding thresholds of risk for components of the pediatric metabolic syndrome. *J Pediatr, 152*, 158-159.

Huang TT, Nansel TR, Belsheim AR, & Morrison JA. (2008). Sensitivity, specificity, and predictive values of pediatric metabolic syndrome components in relation to adult metabolic syndrome: The Princeton LRC Follow-Up Study. *J Pediatr, 152*, 185-190.

Huang TT, Sun SS, & Daniel SD. (2009). Understanding the nature of metabolic syndrome components in children and what they can and cannot do to predict adult disease. *J Pediatr, Sep;155*(3), e13-e14.

Lee S, Bacha F, Gungor N, & Arslanian S. (2008). Comparison of different definitions of pediatric metabolic syndrome: Relation to abdominal adiposity, insulin resistance, adiponectin, and inflammatory biomarkers. *J Pediatr, 152*, 177-184.

Li CY, Ford ES, **Huang TT**, Sun S, & Goodman E. (2009). Patterns of change in cardiometabolic risk factors associated with the metabolic syndrome from childhood to adolescence in a 10-year follow-up: The Fels Longitudinal Study. *J Pediatr, Sep;155*(3), S5.e9-S5.e16.

Schubert CM, Sun S, Burns T, Morrison J, & **Huang TT**. (2009). Predictive ability of childhood metabolic components for adult metabolic syndrome and type 2 diabetes. *J Pediatr, Sep;155*(3), S6.e1-S6.e7.

Schubert CM, Cook S, Sun SS, & **Huang TT**. (2009). Additive utility of family history and waist circumference to body mass index in childhood for predictions of metabolic syndrome in adulthood. *J Pediatr, Sep;155*(3), S6.e9-S6.e13.

Shaibi GQ, & Goran MI. (2008). Examining metabolic syndrome definitions in overweight Hispanic youth: A focus on insulin resistance. *J Pediatr, 152*, 171-176.

Sumner AE. (2009). Ethnic differences in TG and HDL lead to under diagnosis of the metabolic syndrome in black children and adults. *J Pediatr, Sep;155*(3), S7.e7-S7.e11.

Sun SS, Liang R, **Huang TT**, Daniels SR, Arslanian SS, Liu K, Siervogel RM, & **Grave GD**. (2008). Childhood obesity predicts adult metabolic syndrome: The Fels Longitudinal Study. *J Pediatr, 152*, 191-200.

Sun SS, & Schubert CM. (2009). Prolonged juvenile states and delay of cardiovascular and metabolic risk factors: The Fels Longitudinal Study. *J Pediatr, Sep;155*(3), S7.e1-S7.e6.

APPENDIX E: SUMMARIES OF ARTICLES BY MEMBERS OF THE PEDIATRIC METABOLIC SYNDROME WORKING GROUP (PMSWG)

The articles listed in this Appendix either have appeared or will appear in *The Journal of Pediatrics*.

The *PMSWG: Round 1 Meeting*, held July 17-18, 2006, resulted in six papers, which reviewed existing pediatric metabolic syndrome definitions and their variable impact on prevalence estimates (Ford et al, 2008; Cook et al, 2008), and the predictive utility of each risk component at a given cutoff value in relation to clinical precursors of disease in childhood (Shaibi et al, 2008; Lee et al, 2008), or adult metabolic syndrome (Huang et al, 2008; Sun et al, 2008). In general, childhood components showed better sensitivity for predicting clinical precursors of disease in adolescence rather than the metabolic syndrome in adulthood. However, despite low sensitivity levels, childhood metabolic components showed high specificity with regard to adult metabolic syndrome. In addition, combinations of childhood components were identified that had moderately high positive predictive values in addition to high specificity.

PMSWG: Round 2 Meeting, held January 31-February 1, 2008, meeting resulted in seven papers. Two papers showed that, although the metabolic syndrome seemed to be unstable across different stages of sexual maturation (Goodman et al, In Press), individual components were relatively stable over time on a population level (Li et al, In Press). In addition, because data from the Muscatine Study was not included in prior PMSWG work, one paper examined the predictive utility of metabolic risk components in childhood in relation to adult outcomes, including atherosclerosis (Burns et al, In Press). Combining data from three longitudinal studies, one paper estimated the predictive statistics of childhood metabolic components in relation to both adult metabolic syndrome and Type 2 Diabetes Mellitus (T2DM). This study confirmed prior findings that childhood components were highly specific, but were not sensitive when used to screen for children at risk for adult disease, suggesting that metabolic markers in childhood might be better characterized as screening tools for individuals at low risk rather than for individuals at high risk (Schubert et al, In Press). Consistent with prior research, this paper also showed that the combination of metabolic risk factors increased the probability that those with a positive test were truly diseased in adulthood, even though only a fraction of the diseased adult population could be identified by these childhood biomarkers.

Because of the ongoing debate on the role of body mass index (BMI) versus waist circumference in screening for risk among children, an additional paper examined the predictive probability of adding waist circumference as well as family history of T2DM or cardiovascular disease to BMI in relation to the adult metabolic syndrome. This analysis found that the combination of a positive family history and overweight status (defined as BMI between the 85th and 94th percentile) in childhood yielded a greater than 50 percent probability of having the metabolic syndrome in adulthood (Schubert et al, In Press). This figure represents an 80 percent increase in risk above that predicted by child overweight status alone. The use of all three variables did not seem to improve the prediction overall. Given the recent recommendation from the American Medical Association Expert Committee that physicians perform detailed blood screening of all

youth whose BMI is between the 85th and 94th percentile, these findings have important clinical implications.

Another paper fitted growth curves to waist circumference and lipids by fixing the risk thresholds at age 18 years on the Adult Treatment Panel III criteria (Cook et al, In Press). This article is the first paper to conduct these analyses, using both National Health and Nutrition Examination Survey data as well as data from existing longitudinal cohorts, in children ages six years and older, providing a population-based reference for U.S. youth. Using extensive serial data from the Fels Longitudinal Study, researchers also showed that an accelerated versus a retarded tempo of growth during childhood and adolescence, as assessed by the timing of peak height velocity, predicted adult metabolic outcomes (Sun et al, In Press). This paper provided a preview of additional biomarkers, which could be used to discover childhood origins of adult disease. (Please see *Appendix D* for a list of references.)

APPENDIX F: MULTILEVEL OBESITY INITIATIVES

The Obesity Research Strategic Core (ORSC), a virtual research entity within the NICHD Office of the Director and led by staff from the ENGB, aims to leverage resources and to coordinate a synergistic, multilevel, or systems approach to childhood obesity research using the following tactics.

FRAMING OBESITY AS A COMPLEX SYSTEMS PROBLEM

Public discourse on obesity is influenced through publications, NIH and public presentations, as well as the language used in ENGB-sponsored or co-sponsored initiatives. Through these means, the ORSC has made significant progress to mainstream the concept of multilevel research at the NICHD and across the NIH. There is increased acknowledgement of the need to move the field beyond discipline-specific research and individual behavior-based interventions.

ENCOURAGING CROSS-LEVEL AND CROSS-DISCIPLINARY HYPOTHESES

Through the initiatives it is leading, co-sponsoring, or planning, the ENGB is encouraging investigators to submit applications for projects to connect the complex range of biological, socio-environmental, and policy factors that influence energy balance downstream. In addition, the Branch is also encouraging interventions that encompass multiple settings and multiple components.

INVESTING IN STRUCTURAL INTERVENTIONS

The ENGB, in collaboration with other NIH Institutes and Centers, has led or co-organized a number of workshops during the last two years that pertain to different aspects of policy research relevant to childhood obesity, including: *Policy Research and Obesity* (June 2007), *Measurements of the Food and Physical Activity Environments Relevant to Policy Research* (November 2007), and *Environmental Systems in Public Health* (September 2008). These meetings resulted in publications that addressed:

- An obesity policy research framework (Mckinnon et al, 2009);
- The potential linkage between obesity prevention and climate change (Huang, 2009); and
- Food and physical activity environments (Story et al, 2009).

The ENGB recently issued a Program Announcement focused on fostering teams of obesity researchers and policy makers at the local, state, or regional level. The ENGB is also working with the National Cancer Institute (NCI) to develop an initiative focused on the influence of nutrition and physical activity policies on school environment and obesity outcomes.

BUILDING CAPACITY

The ENGB recognizes that creating a new generation of multilevel actors is essential for sustaining the multilevel research agenda. As a result, the Branch supports institutional training awards that incorporate systems science into Ph.D. and M.D. training programs. ENGB staff have also worked with staff of the Fogarty International Center to develop the Millennium Training Award on Chronic Diseases, which calls for international applications on systems science curricula. The ENGB is funding institutional training grants to train predoctoral students on the application of a systems approach to obesity research.

In addition to training new multilevel scientists, capacity building, in the form of coalescing interested organizations, has also been an important strategy to further the goals of the multilevel agenda. For example, as a result of the Branch's efforts, the NICHD now has a formal agreement with the Centers for Disease Control and Prevention (CDC) to collaborate on advancing the goals of the multilevel framework. Last year, the Directors of the NICHD, the National Heart, Lung, and Blood Institute, the NCI, the National Institute of Diabetes and Digestive and Kidney Disorders, and the NIH Office of Behavioral and Social Science Research (OBSSR) joined with the Directors of the CDC and the Robert Wood Johnson Foundation to establish the National Collaborative on Childhood Obesity Research (NCCOR)—an organization dedicated to promoting research on ways to reduce the prevalence of childhood obesity. ENGB staff also serve on the planning committee of the McGill Health Challenge Think Tank, which examines the proximal and distal factors affecting energy balance to develop strategies that influence national and international policies towards more healthful social and economic models.

INVESTING IN SYSTEMS METHODOLOGY

As a result of the recently issued Request for Applications entitled *Innovative Statistical and Computational Methodologies for the Design and Analysis of Multilevel Studies on Childhood Obesity*, the Branch is awarding eight applications, which represent a wide range of statistical and computational techniques, including Bayesian statistics, agent-based modeling, systems dynamics modeling, and Markov simulations. Systems methodology is essential to quantify and qualify the layers and volumes of data with multiple feedback loops. This research will generate plausible hypotheses regarding the complex causal chain of obesity to model and test intervention strategies prior to field experiments, and to predict future projections of the obesity epidemic. The ENGB is also co-sponsoring efforts led by the OBSSR to solicit research that applies systems methodology to public health problems, including childhood obesity.

ENHANCING A GLOBAL PERSPECTIVE

Childhood obesity is increasing at an alarming rate outside of the developed world, with dire consequences for the United States and the global economy. Many countries will be unable to cope financially with the rising prevalence of obesity-related chronic diseases. Several macro-level determinants of energy balance are global in nature, necessitating studies across populations and contexts to gain sufficient variance for meaningful analyses. These comparative

studies will also help the field better understand health disparities among minority or immigrant populations within the United States. Additionally, many systems-oriented multilevel interventions have progressed more rapidly in Europe and Canada and are often more feasible in non-U.S. contexts, given the major differences in socio-political structures between the United States and other countries. Understanding the processes and outcomes of these interventions can provide important insight into the design of effective and sustainable interventions in the United States.

APPENDIX G: MODULE PAPERS ON THE PREVENTION OF CHRONIC DISEASES

(Staff names appear in **bold**.)

Braveman P. (2009). A health disparities perspective on obesity research. *Preventing Chronic Disease, 6*(3), A90.

Esposito L, Fisher J, Mennella J, Hoelscher D, & **Huang TT**. (2009). Developmental perspectives on nutrition and obesity from gestation to adolescence. *Preventing Chronic Disease, 6*(3), A93.

Haemer M, **Huang TT**, & Daniels SA. (2009). Effect of neurohormonal factors, epigenetic factors, and gut micro biota on risk of obesity. *Preventing Chronic Disease, 6*(3), A95.

Hammond RA. (2009). Complex systems modeling for obesity research. *Preventing Chronic Disease, 6*(3), A96.

Huang TT, & Yaroch AL. (2009). A public-private partnership model for obesity prevention. *Preventing Chronic Disease, 6*(3), A110.

Huang TT, Drewnowski A, Kumanyika S, & Glass TA. (2009). A systems-oriented multilevel framework for addressing obesity in the 21st century. *Preventing Chronic Disease, 6*(3), A97.

APPENDIX H: DATA FROM THE HYPERGLYCEMIA ADVERSE PREGNANCY OUTCOME (HAPO) STUDY

OUTCOME DATA FOR MOTHERS AND OFFSPRING

Outcome	Fasting Plasma Glucose (mg/dL)	
	< 75+	**≥ 100***
90th Centile C-Peptide	4%	32%
Cesarean Section	13%	26%
Macrosomia	5%	26%
Neonatal Hypoglycemia	2%	5%
Preeclampsia	3%	15%
	Two-hour Oral Glucose Tolerance Test (mg/dL)	
	≤ 90+	**≥ 178#**
Preterm Birth	6%	14%

+ Levels categorized as normal.
* Levels categorized as Impaired Glucose Tolerance or Pre-diabetes.
# Level categorized as Diabetic.

APPENDIX I: DIABETES RESEARCH IN CHILDREN NETWORK (DIRECNET) MANUSCRIPTS, 2004-2009

Buckingham BA, Block JM, Burdick J, Kalajian A, Kollman C, Choy M, Wilson DM, & Chase HP for the DirecNet Study Group. (2005). Response to nocturnal alarms using a real-time glucose sensor. *Diabetes Technol Ther, 7*(3), 440-447.

DirecNet Study Group. (2004). Lack of accuracy of continuous glucose sensors in healthy, nondiabetic children: Results of the DirecNet accuracy study. *J Pediatr, 144*, 770-775.

DirecNet Study Group. (2005). A randomized multicenter trial comparing the GlucoWatch biographer with standard glucose monitoring in children with type 1 diabetes. *Diabetes Care, 28*, 1101-1106.

DirecNet Study Group. (2005). Accuracy of newer generation home blood glucose meters in a DirecNet inpatient exercise study. *Diabetes Technol Ther, 7*(5), 675-680.

DirecNet Study Group. (2005). Accuracy of the modified Continuous Glucose Monitoring System (CGMS) sensor in an outpatient setting: Results from a DirecNet Study. *Diabetes Technol Ther, 7*, 109-114.

DirecNet Study Group. (2005). Comparison of fingerstick hemoglobin a1c levels assayed by DCA 2000 with the DCCT/EDIC central laboratory assay: Results of a DirecNet Study. *Pediatr Diabetes, 6*, 13-16.

DirecNet Study Group. (2005). Diabetes self management profile for flexible insulin regimens: Cross-sectional and longitudinal analysis of psychometric properties in a pediatric sample. *Diabetes Care, 28*, 2034-2035.

DirecNet Study Group. (2005). Eight-point glucose testing versus the Continuous Glucose Monitoring System (CGMS) in evaluation of glycemic control in type 1 diabetes. *J Clin Endocrinol Metab, 90*, 3387-3391.

DirecNet Study Group. (2005). Impact of exercise on overnight glycemic control in children with type 1 diabetes. *J Pediatr, 174*, 528-534.

DirecNet Study Group. (2005). Youth and parent satisfaction with clinical use of the GlucoWatch G2 biographer in the management of pediatric type 1 diabetes. *Diabetes Care, 28*, 1929-1935.

DirecNet Study Group. (2006). Evaluation of factors affecting CGMS calibration. *Diabetes Technol Ther, 8*(3), 318-325.

DirecNet Study Group. (2006). Prevention of hypoglycemia during exercise in children with type 1 diabetes by suspending basal insulin. *Diabetes Care, 29*, 2200-2204.

DirecNet Study Group. (2006). Psychological aspects of continuous glucose monitoring in pediatric type 1 diabetes. *Pediatr Diabetes, 7*, 32-38.

DirecNet Study Group. (2006). The effects of aerobic exercise on glucose and counter-regulatory hormone concentrations in children with type 1 diabetes. *Diabetes Care, 29*, 20-25.

DirecNet Study Group. (2007). Continuous glucose monitoring in children with type 1 diabetes. *J Ped, 151*, 388-393.

DirecNet Study Group. (2007). Impaired overnight counterregulatory hormone responses to spontaneous hypoglycemia in children with type 1 diabetes. *Pediatric Diabetes, 8*, 199-205.

DirecNet Study Group. (2007). Relative accuracy of the BD Logic® and FreeStyle® blood glucose meters. *Diabetes Technol Ther, 9*(2), 165-168.

DirecNet Study Group. (2007). Relative inaccuracy of the A1cNow® in children with type 1 diabetes. *Diabetes Care, 30*, 135-137.

DirecNet Study Group. (2007). The accuracy of the FreeStyle Navigator™ continuous glucose monitoring system in children with type 1 diabetes. *Diabetes Care, 30*, 59-64.

DirecNet Study Group. (2007). The effect of glucose variability on the risk of microvascular complications in type 1 diabetes: Response to Kilpatrick et al, and Bolli. *Diabetes Care, 30*, 185.

DirecNet Study Group. (2007). Use of the DirecNet Applied Treatment Algorithm (DATA) for diabetes management with a real-time continuous glucose monitor (FreeStyle Navigator™). *Pediatric Diabetes, 8*, 1-6.

DirecNet Study Group. (2008). Adiponectin and catecholamine concentrations during acute exercise in children with type 1 diabetes. *Pediatric Diabetes, 9*, 221-227.

DirecNet Study Group. (2008). FreeStyle Navigator™ continuous glucose monitoring system use in children with type 1 diabetes using glargine-based multiple daily dose regimens: Results of a pilot trial. *Diabetes Care, 31*, 525-527.

DirecNet Study Group. (2008). Low fat versus high fat bedtime snacks in children and adolescents with type 1 diabetes. *Pediatric Diabetes, 9*(Pt. 1), 320–325.

DirecNet Study Group. (2008). The accuracy of the Guardian® RT continuous glucose monitor in children with type 1 diabetes. *Diabetes Technol Ther, 10*(4), 266-272.

DirecNet Study Group. (2008). The relationship of A1c to glucose concentrations in children with type 1 diabetes: Assessments by high-frequency glucose determinations by sensors. *Diabetes Care, 31*, 381-385.

DirecNet Study Group. (2009). Prolonged use of continuous glucose monitors in children with type 1 diabetes on continuous subcutaneous insulin infusion or intensive multiple-daily injection therapy. *Pediatric Diabetes, 10*, 91-96.

Kollman C, Wilson DM, Wysocki T, Tamborlane WV, & Beck RW for the DirecNet Study Group. (2005). Limitations of statistical measures of error in assessing the accuracy of continuous glucose sensors. *Diabetes Technol Ther, 7*(5), 665-672.

Messer L, Ruedy K, Xing D, Coffey J, Englert K, Caswell K, & Ives B for the DirecNet Study Group. (2009). Educating families on real-time continuous glucose monitoring: The DirecNet Navigator pilot study experience. *Diabetes Educator, 35*, 124-135.

Ruedy KJ, Beck RW, Xing D, & Kollman C for the DirecNet Study Group. (2007). Diabetes Research in Children Network (DirecNet): Availability of protocol datasets. *J Diabetes Sci Technol, 1*, 164-171.

Tamborlane WV for the DirecNet Study Group. (2007). Triple jeopardy: Nocturnal hypoglycemia after exercise in the young with diabetes (editorial). *JCEM, 92*(3), 815-816.

Tsalkian E, Beck RW, Kalajian A, Janz JF, & Tansey MJ for the DirecNet Study Group. (2005). Function of the GlucoWatch G2 biographer during exercise (letter to the editor). *Diabetes Technol Ther, 7*(1), 230.

APPENDIX J: MODULE PAPERS FOR THE MATERNAL NUTRITION AND OPTIMAL INFANT FEEDING PRACTICES CONFERENCE

(Branch staff names appear in bold.)

Abrams SA. (2007). *In utero* physiology: Role in nutrient delivery and fetal development for calcium, phosphorus, and vitamin D. *Am J Clin Nutr, 85*(Supp.), 604S-607S.

Antony AC. (2007). *In utero* physiology: Role of folic acid in nutrient delivery and fetal development. *Am J Clin Nutr, 85*(Supp.), 598S-603S.

Battaglia FC. (2007). Placental transport: A function of permeability and perfusion. *Am J Clin Nutr, 85*(Supp.), 591S-597S.

Denne SC. (2007). Regulation of proteolysis and optimal protein accretion in extremely premature newborns. *Am J Clin Nutr, 85*(Supp.), 621S-624S.

Fewtrell MS, Morgan JB, Duggan C, Gunnlaugsson G, Hibberd PL, Lucas A, & Kleinman RE. (2007). Optimal duration of exclusive breastfeeding: What is the evidence to support current recommendations? *Am J Clin Nutr, 85*(Supp.), 635S-638S.

Georgieff MK. (2007). Nutrition and the developing brain: Nutrient priorities and measurement. *Am J Clin Nutr, 85*(Supp.), 614S-620S.

Goldenberg RL, & Culhane JF. (2007). Low birth weight in the United States. *Am J Clin Nutr, 85*(Supp.), 584S-590S.

Krebs NF, & Hambidge KM. (2007). Complementary feeding: Clinically relevant factors affecting timing and composition. *Am J Clin Nutr, 85*(Supp.), 639S-645S.

Neu J. (2007) Gastrointestinal development and meeting the nutritional needs of premature infants. *Am J Clin Nutr, 85*(Supp.), 629S-634S.

Raiten DJ, Kalhan SC, & Hay HW. (2007). Maternal nutrition and optimal infant feeding practices: Executive summary. *Am J Clin Nutr, 85*(Supp.), 577S-583S.

Sauer PJJ. (2007). Can extrauterine growth approximate intrauterine growth? Should it? *Am J Clin Nutr, 85*(Supp.), 608S-613S.

Shanler RJ. (2007). Evaluation of the evidence to support current recommendations to meet the needs of premature infants: The role of human milk. *Am J Clin Nutr, 85*(Supp.), 625S-628S.

APPENDIX K: MODULE PAPERS FOR THE VITAMIN D AND HEALTH IN THE 21ST CENTURY CONFERENCE

(Branch staff names appear in bold.)

Calvo MS, Whiting SJ, & Barton CN. (2004). Vitamin D fortification in the United States and Canada: Current status and data needs. *Am J Clin Nutr, 80*(Supp.), 1710S-1716S.

Cantorna MT, Zhu Y, Froicu M, & Wittke A. (2004). Vitamin D status, 1,25-dihydroxyvitamin D_3, and the immune system. *Am J Clin Nutr, 80*(Supp.), 1717S-1720S.

Dawson-Hughes B. (2004). Racial/ethnic considerations in making recommendations for vitamin D for adult and elderly men and women. *Am J Clin Nutr, 80*(Supp.), 1763S-1766S.

DeLuca HF. (2004). Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr, 80*(Supp.), 1689S-1696S.

Fleet JC. (2004). Genomic and proteomic approaches for probing the role of vitamin D in health. *Am J Clin Nutr, 80*(Supp.), 1730S-1734S.

Greer FR. (2004). Issues in establishing vitamin D recommendations for infants and children. *Am J Clin Nutr, 80*(Supp.), 1759S-1762S.

Heaney RP. (2004). Functional indices of vitamin D status and ramifications of vitamin D deficiency. *Am J Clin Nutr, 80*(Supp.), 1706S-1709S.

Holick MF. (2004). Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr, 80*(Supp.), 1678S-1688S.

Hollis BW, & Wagner CL. (2004). Vitamin D requirements during lactation: High-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. *Am J Clin Nutr, 80*(Supp.), 1752S-1758S.

Pawley N, & Bishop NJ. (2004). Prenatal and infant predictors of bone health: The influence of vitamin D. *Am J Clin Nutr, 80*(Supp.), 1748S-1751S.

Pettifor JM. (2004). Nutritional rickets: Deficiency of vitamin D, calcium, or both? *Am J Clin Nutr, 80*(Supp.), 1725S-1729S.

Raiten DJ, & Picciano MF. (2004). Vitamin D and Health in the 21st Century: Bone and Beyond—Executive Summary. *Am J Clin Nutr, 80*(Supp.), 1673S-1677S.

Specker B. (2004). Vitamin D requirements during pregnancy. *Am J Clin Nutr, 80*(Supp.), 1740S-1747S.

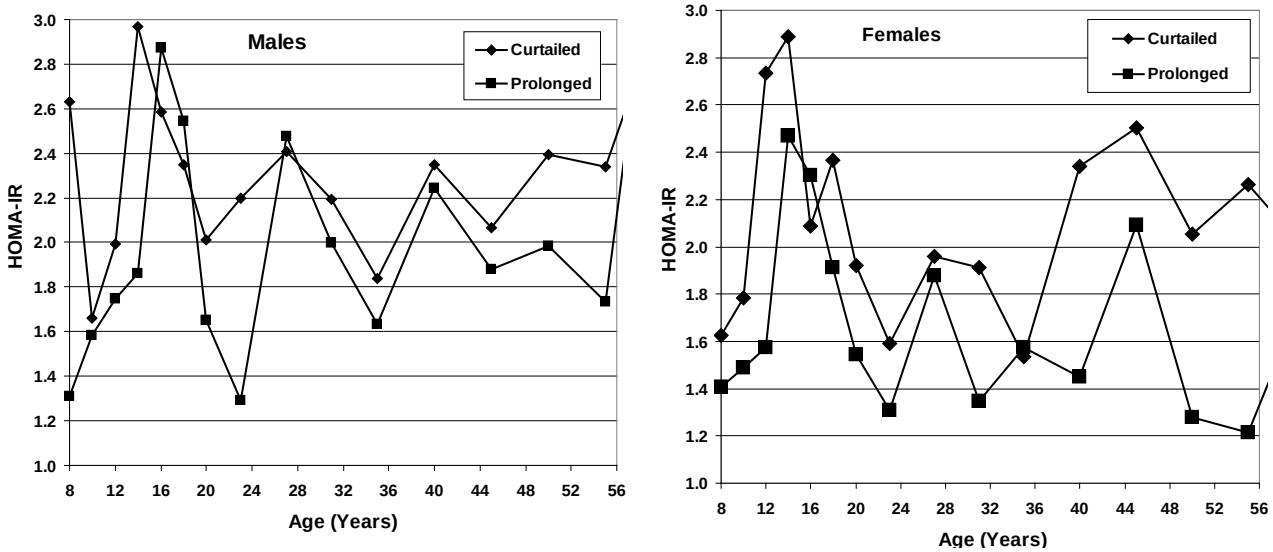
Weaver CM, & Fleet JC. (2004). Vitamin D requirements: Current and future. *Am J Clin Nutr, 80*(Supp.), 1735S-1739S.

Weisberg P, Scanlon KS, Li R, & Cogswell ME. (2004). Nutritional rickets among children in the United States: Review of cases reported between 1986 and 2003. *Am J Clin Nutr, 80*(Supp.), 1697S-1705S.

Welsh J. (2004). Vitamin D and breast cancer: Insights from animal models. *Am J Clin Nutr, 80*(Supp.), 1721S-1724S.

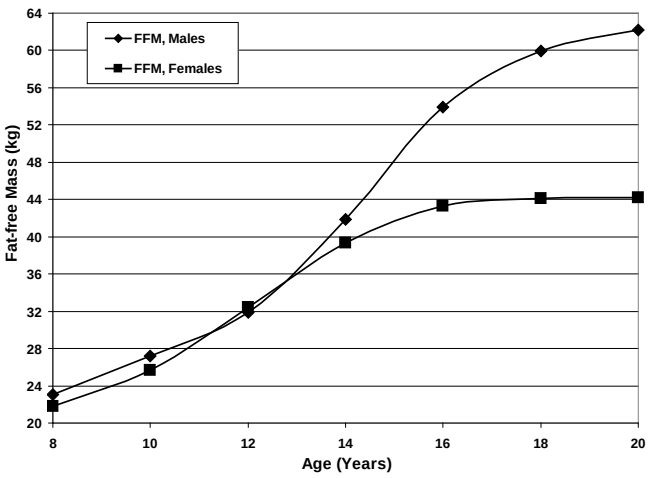
APPENDIX L: DATA FROM THE FELS LONGITUDINAL STUDY (FLS) OF PHYSICAL GROWTH AND DEVELOPMENT

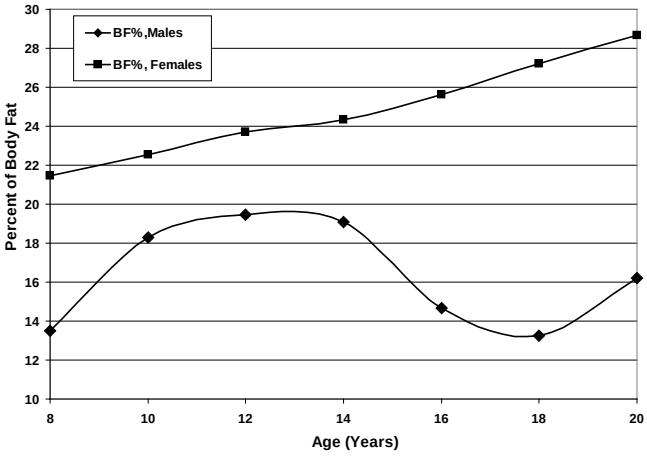
SERIAL MEAN LEVELS OF HOMEOSTATIC MODEL ASSESSMENT-INSULIN RESISTANCE (HOMA-IR) WITH PROLONGED AND CURTAILED JUVENILE STATES FOR MALES AND FEMALES IN THE FLS



In these graphs, the HOMA-IR levels plotted against age show that both boys and girls develop marked insulin resistance during puberty. The figure also shows that both boys and girls with curtailed juvenile states reach a given level of insulin resistance two years to six years before boys and girls with prolonged juvenile states, and that both boys and girls with prolonged juvenile states are less insulin resistant than boys and girls with curtailed juvenile states. This discrepancy can be appreciated by noting that neither male nor female subjects with a curtailed juvenile state ever reach levels of HOMA-IR below a mean of 1.5, but that males with prolonged juvenile states in the first and third decades of life and females with prolonged juvenile states in the first, third, fourth, fifth, and sixth decades do reach mean values below this level. These preliminary results indicate gender-specific effects of a prolonged juvenile state on blood pressure and IR later in life.

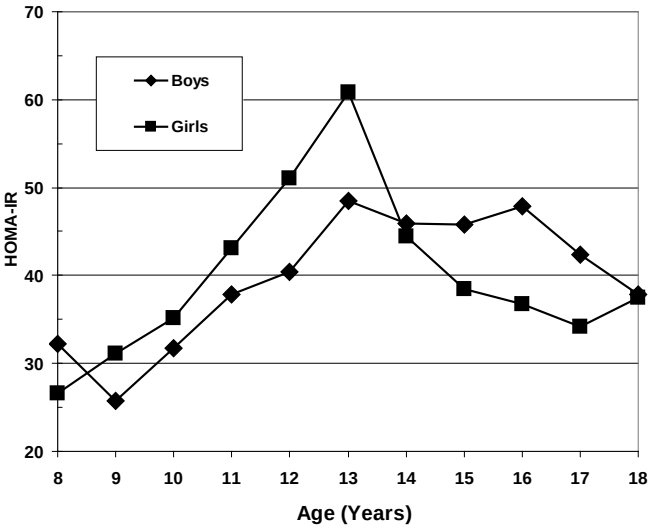
SERIAL MEAN LEVELS OF FAT MASS AND FAT-FREE MASS IN THE FLS

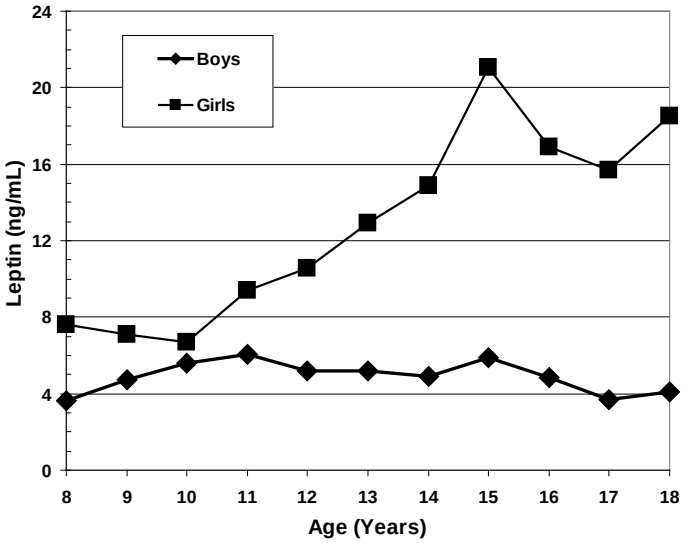




FLS data indicate that the percent of body fat in girls increases steadily from age 8 years on, reaching 28 percent at age 20 years; whereas, the percent body fat in boys reaches a peak of 20 percent at age 12 years and declines steadily thereafter to 13 percent at age 18 years. Between ages 14 years and 20 years, the rates of increase in fat-free mass show pronounced sexual dimorphism. Fat-free mass climbs steadily in boys, reaching a mean of 62 kg at age 20 years; but in girls, fat-free mass increases more gradually to reach a mean of 44 kg at age 20 years. FLS researchers expected that an increased fat mass early in life would to early insulin resistance and to increased leptin levels, which research has shown to be associated with pubertal onset (Maqsood et al, 2007). Early puberty is associated with an accelerated skeletal development, leading to a bone age in advance of chronological age. All of these accelerators are consistent with the overfeeding models of obesity in animal models (Keenan et al, 1997; Armitage et al, 2005) and lead to the appearance of metabolic syndrome risk factors as early as the second decade of life. These risk factors, in turn, pave the way for early Type 2 Diabetes Mellitus (T2DM) and cardiovascular disease. Other research has shown that accelerated weight gain in the first or second years of life can cause an early adiposity rebound, followed by an acceleration of other physiologic milestones and the early appearance of the unhealthy side effects of an increased fat mass early in life (Bhargava et al, 2004; Garemo et al, 2006). An excessive increase in Body Mass Index and fat mass early in the first decade of life curtails the juvenile state and hastens the onset of the metabolic syndrome, T2DM, and cardiovascular disease.

SERIAL MEAN VALUES OF LEPTIN AND HOMEOSTATIC MODEL ASSESSMENT-INSULIN RESISTANCE (HOMA-IR) FOR BOYS AND GIRLS IN THE FLS



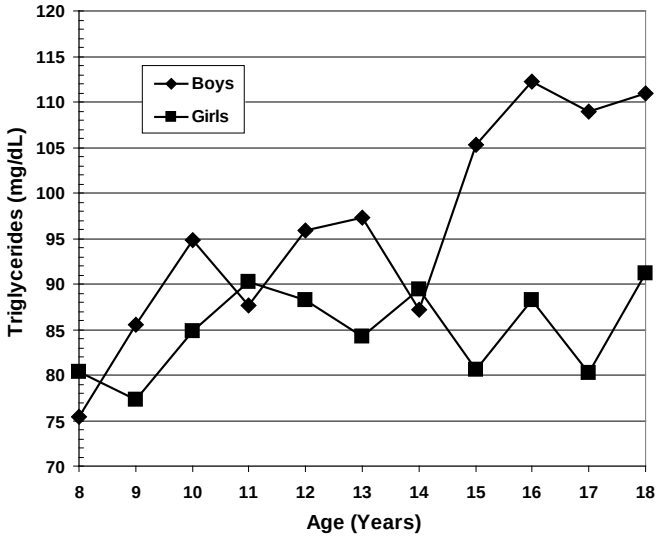


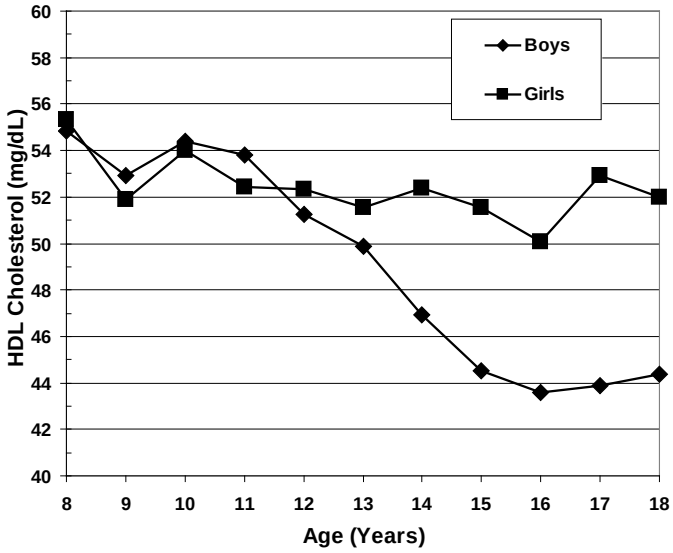
The line graph on the left illustrates longitudinal data on leptin levels for 57 boys and 51 girls in the FLS. These data show stable leptin levels in boys and a tripling of leptin levels in girls during puberty, and data agree with cross-sectional data for subjects in the FLS reported by Demerath et al, 1999.

The line graph on the right illustrates longitudinal data on HOMA-IR for 57 boys and 51 girls in the FLS. HOMA-IR increased with age and reached a peak at age 13 in girls and in boys. HOMA-IR declined thereafter to nearly pre-pubertal levels in both sexes. Girls in the study were more IR than boys before age 14 years, but after age 14 years, boys were more insulin resistant than girls. The age-dependent difference in insulin resistance probably reflects the earlier onset of puberty in girls.

SERIAL MEAN LEVELS OF PLASMA TRIGLYCERIDES AND HIGH-DENSITY LIPOPROTEIN (HDL) CHOLESTEROL FOR BOYS AND GIRLS IN THE FLS

These graphs show, using data from the same 57 boys and 51 girls in the FLS, that boys develop higher levels of fasting plasma triglycerides and lower levels of fasting plasma HDL cholesterol during puberty than do girls. These data indicate the development an atherogenic profile in adolescent boys during and after sexual maturation.





APPENDIX M: PEDIATRIC SCIENTIST DEVELOPMENT PROGRAM (PSDP) INSTITUTIONS

(Note: Each institution has one fellow unless otherwise indicated.)

- Baylor College of Medicine
- Children's Hospital Boston (Four Fellows)
- Duke University
- Michigan State University
- Stanford University
- University of California, Los Angeles
- University of California, San Francisco (Two Fellows)
- University of Cincinnati
- University of Michigan
- University of Pennsylvania (Two Fellows)
- University of Texas Southwestern
- Vanderbilt University
- Washington University (Two Fellows)
- Yale University

Please see Figure 8 for PSDP locations.

APPENDIX N: CHILD HEALTH RESEARCH CAREER DEVELOPMENT AWARD (CHRCDA) PROGRAM, FISCAL YEAR 1990 THROUGH FISCAL YEAR 2007

Institution	Dates of Funding Support
• John Hopkins University • Rocky Mountain (Included University of Utah, University of New Mexico, and University of Colorado) • Texas Children's Hospital/Baylor College of Medicine • University of Iowa • University of Texas, Galveston • Yale University	September 1990 to September 1995
• Children's Hospital, Boston • Children's Hospital, Cincinnati • Mt. Sinai Medical Center • University of Alabama • University of Michigan • Vanderbilt Unviersity	September 1991 to September 1996
• Children's Hospital, Philadelphia • Duke University • Medical College of Virginia • University of California, San Francisco • University of Pittsburgh • University of Virginia • University of Washington (Seattle)	September 1992 to September 1997
• Baylor University • Stanford University • University of Minnesota • University of Oregon • Washington University (St. Louis) • Yale University	December 1995 to December 2000
• Children's Hospital, Boston • Children's Hospital, Cincinnati • Johns Hopkins University • University of California, Los Angeles • University of Iowa • University of Michigan	December 1996 to December 2001
• Children's Hospital, Columbus • Children's Hospital, Philadelphia • Columbia University • Mt. Sinai Medical Center • University of Alabama • University of California, San Francisco • University of Texas, Galveston • University of Washington (Seattle)	December 1997 to December 2002

Institution	Dates of Funding Support
• University of Oregon • University of Minnesota • Washington University (St. Louis) • Yale University • University of Virginia • Children's National Medical center	December 2000 to December 2005
• Children's Hospital, Cincinnati • John Hopkins University • Texas Children's Hospital/Baylor College of Medicine • University of California, Los Angeles • University of Iowa • University of Michigan	December 2001 to December 2006
• Children's Hospital of Philadelphia • Children's Hospital, Columbus/Ohio State University • Columbia University • Duke University • University of Alabama • University of Chicago • University of Utah • University of Washington (Seattle)	December 2002 to December 2007

For locations of current CHRCDA sites, please see Figure 9.

APPENDIX O: BRANCH-FUNDED NATIONAL RESEARCH SERVICE AWARD (NRSA) INSTITUTIONAL TRAINING GRANTS

- NICHD Institutional Training for Pediatricians Research Institute Nationwide, Children's Hospital, Columbus, Ohio
- Translational Research Training in General Pediatrics, University of California, San Francisco, California
- Pediatric Outcomes Research Training, Seattle Children's Hospital, Washington
- Institutional Training in Pediatrics, Children's Hospital of Philadelphia, Pennsylvania
- Conducting Child Health Care Research in Vulnerable Populations, Vanderbilt University, Tennessee
- Reproductive, Perinatal, and Pediatric Epidemiology Training: The REPPET Program, Columbia University Health Sciences, New York
- Pediatrician-Scientist Training Program, Children's Hospital Boston, Massachusetts
- Baylor Research Training Program for Pediatricians, Baylor College of Medicine, Texas
- Research Training in Maternal, Infant, and Child Nutrition, Baylor College of Medicine, Texas
- The Clinical Interface of Molecular and Cellular Biology, University of Pittsburgh, Pennsylvania
- Training in Maternal and Child Nutrition, Cornell University, New York
- Pediatric Research: Bench to Bedside to Curbside, University of Rochester, New York
- Fellowship Training in Pediatric Endocrinology and Diabetes at Washington University School of Medicine, Washington University, Missouri

Please see Figure 8 for NRSA site locations.

APPENDIX P: DR. STANLEY COHEN'S RESEARCH CONTRIBUTIONS ON EPIDERMAL GROWTH FACTOR (EGF): R01HD00070-35

Dr. Stanley Cohen of Vanderbilt University isolated, purified, and sequenced the 53 amino-acid polypeptide Epidermal Growth Factor (EGF). He attained a major conceptual milestone when he found that a tyrosine kinase co-purifies with the EGF receptor protein—a key observation, which then led to the discovery that the intracellular domain of the EGF receptor is a tyrosine kinase. After this finding was published, the growth factor field took on much broader significance because the protein product of the Rous avian sarcoma virus was also known to be a protein kinase. This discovery led to a union of the oncogene and growth factors fields and helped to explain how both sets of effectors work.

These fields were shown to be even more closely related than expected when researchers noted a striking sequence homology between the tyrosine kinase domain of the EGF receptor protein and the transforming gene product of the avian erythroblastosis virus. In fact, the oncogene product resembles a truncated EGF-receptor protein, but it lacks the extracellular EGF binding domain, the element governing the activity of the intracellular tyrosine kinase. Without its governing extracellular receptor domain, the intracellular protein kinase operates constitutively and causes cellular neoplastic transformation. The EGF receptor is activated by several ligands involved in normal breast development and lactation and is aberrantly expressed in breast cancers, especially those with poor prognosis. This observation led to using the EGF family of receptors in planning treatment regimens for women with breast cancer.

Over a 35-year period, 1964 through 1999, of NICHD funding, Dr. Cohen's research endeavor produced and led to many biomedical advances, including the discovery of 20 other structurally related growth factors, such as heregulin and amphiregulin, which are involved in mammary gland neoplasia. His research also led to the use of EGF to treat corneal ulcers by accelerating epithelial regeneration and to treat severe burns by augmenting epithelial growth. EGF also prevents the onset of necrotizing enterocolitis (NEC) in a newborn rat model; these findings are promising enough to consider implementing a trial of EGF in preterm infants at risk for NEC. As a result of studies of EGF and its tyrosine kinase receptor, researchers now understand the mechanism of action of receptors for insulin and for platelet-derived growth factor.

This productive research was recognized internationally in 1986, when Dr. Cohen received the Nobel Prize in Medicine or Physiology.

APPENDIX Q: DR. MARIA NEW'S RESEARCH CONTRIBUTIONS ON DISORDERS OF STEROID METABOLISM: R01HD00072-44

Congenital adrenal hyperplasia (CAH) is a family of genetic disorders caused by mutations of the genes that encode adrenal enzymes essential for cortisol biosynthesis. Recent molecular advances have revealed the genetic basis for the phenotypic variability in CAH and have provided a means for genotyping relatives of index patients. These advances now permit prenatal genotype identification of fetuses at risk for the disorder and defined hormonal criteria for the spectrum of CAH disorders. Biochemical advances have simultaneously aided the diagnosis and therapeutic monitoring of CAH patients.

In 2001, Dr. New and her colleagues reported on their 15-year experience with prenatal diagnosis of CAH in 532 pregnancies, of which 281 were treated prenatally with dexamethasone. This novel fetal therapy prevented the adrenal gland from overproducing masculinizing steroid precursors, resulting in girl babies who have normal genitalia, despite their defective alleles for genes encoding 21-hydroxylase or 11 beta-hydroxylase. This prenatal therapy prevents or minimizes virilizing sequelae in the majority of affected girls, but may be associated with some maternal side effects. Thus, prenatal diagnosis and proper prenatal treatment of CAH effectively reduce or eliminate virilization and decrease the likelihood of genital ambiguity, genital surgery, and gender misassignment.

Newborn screening for CAH also contributes to the prevention of morbidity, resulting from delayed diagnosis of CAH, in more than two-thirds of affected neonates. Current treatment methods, however, may not be optimal for achieving normal genetic height and appropriate weight in CAH patients; therefore more effective approaches to treating CAH are being explored. Severe short stature in the adult patients with CAH remains a significant problem. Researchers showed that treatment with human growth hormone (hGH) alone or with a combination of growth hormone and analogues of gonadotropin-releasing hormone improves growth rate and height prediction in CAH patients (Bernardo et al, 2001).

Dr. New and her colleagues also discovered eight functionally important point mutations on the gene encoding 21-hydroxylase, as well as a several gene deletions and gene conversions at the CYP21 and the CYP21 pseudogene loci on the short arm of chromosome 6. These mutated alleles engender various levels of 21-hydroxylase activity in affected individuals and may be present as compound heterozygotes in affected children. Combinations of faulty alleles and the variety of enzyme activities associated with these mutations explain the spectrum of clinical phenotypes in CAH.

Affected individuals may suffer life-threatening degrees of salt loss, virilization with severe hypertension, obesity, hirsutism, and infertility. The successful explanation of how a single-gene defect could engender such a wide spectrum of clinical presentations stands as a model of how molecular biology can inform clinical observations. In the course of these genotype-phenotype explorations, Dr. New showed that non-classical CAH is one of the most common autosomal recessive genetic disorders known, occurring in about one out of every 30 Ashkenazi Jews, and in one in 100 individuals in a mixed Caucasian population. Thus, the non-classical allele of the 21-hydroxylase gene may be the most common autosomal recessive gene in human populations.

Researchers are also examining rare forms of CAH, such as inherited 3 beta-hydroxysteroid dehydrogenase (3ß-HSD) deficiency to determine the phenotypic correlates of severe and mild forms of the disease, and to explore the potential relationship of 3ß -HSD deficiency to polycystic ovary syndrome (PCOS), which includes hirsutism, menstrual disorders, and infertility (Carbunaru et al, 2004). Investigators recently pursued newly proposed hormonal criteria to accurately predict inherited 3ß-HSD.

Dr. New and her college Dr. Cerame also concentrated on exploring genotype-phenotype correlations in two inherited endocrine disorders, which are responsible for hormonal hypertension in children: 11-beta-hydroxylase (CYP11B1) deficiency, and apparent mineralocorticoid excess (AME), also discovered by Dr. New and her colleagues (Cerame & New, 2000). The CYP11B1 deficiency disorder results from an autosomal recessive defect on the enzyme protein-encoding gene *CYP11B1*. AME is a potentially fatal genetic disorder, caused by a deficiency of 11-beta-hydroxysteroid dehydrogenase type 2, an adrenal enzyme necessary for converting the potent steroid cortisol into its less-active form cortisone, which leads to juvenile hypertension as well as prenatal and postnatal growth failure. The disorder is characterized by low to undetectable levels of serum potassium, renin, and aldosterone. The researchers not only discovered AME, but also elucidated its pathophysiology and were first to use a mineralocorticoid receptor antagonist to treat the condition.

Dr. New and her colleagues also discovered a previously unreported condition, which they named multiple steroid resistance syndrome (New et al, 2001), while evaluating a 14-year old girl of the Iroquois Nation for possible AME. Despite high cortisol levels and elevated levels of adrenal androgens, the girl exhibited no features typical of excessively high levels of steroids, such as truncal obesity, hyperglycemia, and masculinization. The patient's sister had similar features. Both girls demonstrated resistance to exogenously administered glucocorticoids and mineralocorticoids. The pathogenesis of this unusual condition, then, may involve defective coactivators necessary for proper steroid receptor-gene expression.

APPENDIX R: BRANCH PUBLICATIONS

(Branch staff names appear in **bold**.)

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APPENDIX S: BRANCH STAFF

Gilman Grave, M.D., a graduate of Harvard College and Harvard Medical School, is board certified in internal medicine, having completed an internship and residency in this field at the Massachusetts General Hospital, during which time he also completed a six-month immersion in pediatrics on the Burnham ward. Dr. Grave began his NIH career as a research associate and staff fellow in the Laboratory of Cerebral Metabolism at the National Institute of Mental Health, where he worked to develop radiolabeled 2-deoxyglucose as an agent for functional imaging of the brain. Since 1985, Dr. Grave has served as chief of the ENGB at the NICHD. Since February 2008, Dr. Grave has also served as acting director of the NICHD Center for Research for Mothers and Children. Dr. Grave chairs the NICHD Institutional Review Board, for which he received the NIH Director's Award and the Outstanding Service Medal of the U.S. Public Health Service (USPHS). He has developed a large research program on the childhood antecedents of adult disease, for which he received the USPHS Meritorious Service Medal. Dr. Grave is especially interested in disease prevention and in ascertaining the earliest antecedents of obesity, type 1 and type 2 diabetes, atherosclerosis, and osteoporosis. He has encouraged multidisciplinary research in these areas and organized an international conference on the fetal origins of adult disease. He is the project officer for two large international diabetes projects and serves on the external advisory board for the Early Nutrition Effectiveness and Safety Trials Project, funded by the European Commission, with sites in 18 European countries. In 2008, Dr. Grave and Dr. Winer received an NIH Director's Group Award for their activities in planning future projects in the area of diabetes research. Dr. Grave supervised the growth and development of the Pediatric Pharmacology Research Unit Network from 1994 through 2004 and organized the nucleus of staff and resources of what is now the Obstetric Pharmacology Research Unit Network and the Obstetric and Pediatric Pharmacology Branch.

Karen Winer, M.D., a board-certified pediatric endocrinologist, is a program officer for the ENGB pediatric endocrinology and osteoporosis prevention programs. She completed her pediatric residency training at the Mount Sinai Medical Center, New York, and went on to receive subspecialty training in pediatric endocrinology from the Developmental Endocrinology Branch of the NICHD. As an endocrine fellow, she was the first to demonstrate the safety and efficacy of synthetic human parathyroid hormone (PTH) for the treatment of hypoparathyroidism. She remains at the forefront in investigating the long-term effects of PTH on bone. As a program officer, she is responsible for training grants, including the Child Health Career Development Award Program and for the endocrine and bone programs. She is also the project officer for the Bone Mineral Density in Childhood Study and for the Diabetes Research in Children Network.

Daniel J. Raiten, Ph.D., is the program official for the nutrition portfolio within the ENGB. He received his doctorate in human nutrition from the Pennsylvania State University, followed by a postdoctoral fellowship at the Child Study Center of Yale University Medical School. In addition to his role as program officer, he is the project leader for the NICHD Iron and Malaria Project, which is co-sponsored by the Bill and Melinda Gates Foundation. Dr. Raiten's other responsibilities include serving as the secretariat for two bilateral programs between the United States and India: one on Contraception and Reproductive Health Research, and the other on

Maternal and Child Health and Human Development Research. Dr. Raiten also serves on numerous domestic and international committees, including service as a member of the World Health Organization Technical Advisory Group on Nutrition and HIV/AIDS.

Terry Huang, Ph.D., M.P.H., is director of the Obesity Research Strategic Core (ORSC) at the NICHD. Dr. Huang plays a major role in developing new research directions and funding priorities in the area of pediatric obesity at the NICHD and across the NIH. He is currently leading an agenda on global multilevel research in pediatric obesity and has special interest in societal-biological interactions in obesity and chronic disease, multilevel prevention strategies, international health, pediatric metabolic syndrome, fetal and childhood antecedents of obesity and metabolic abnormalities, and the translation of science to policy in obesity and chronic disease prevention. Dr. Huang is Fellow of The Obesity Society and is Councilor on the Pediatric Obesity Section of that organization. In addition, he serves on the five-member Senior Leadership Group of the NIH Obesity Research Task Force and represents the NICHD nationally and internationally on panels related to pediatric obesity. Dr. Huang also serves as a senior scientific advisor to childhood obesity programs for the Robert Wood Johnson Foundation. Dr. Huang received his doctorate in preventive medicine and his M.P.H. in epidemiology and biostatistics from the University of Southern California. He earned his bachelor's degree in psychology from McGill University. Prior to joining the NIH, he served on the faculty of the University of Kansas Medical Center and Tufts University's Friedman School of Nutrition Science and Policy.

Layla Esposito, Ph.D., M.A., is in her second year as a Society for Research in Child Development Executive Branch Fellow working in the NICHD. In this position, she is the coordinator of the NICHD ORSC. Additionally, she works on a variety of cross-cutting issues in child development and their policy implications. Dr. Esposito completed her Ph.D. in social psychology at Virginia Commonwealth University (VCU). During this time, she coordinated research to evaluate violence prevention programs and a culturally enhanced drug and sex education program in middle schools. She received her master's in clinical psychology and her undergraduate degree in developmental psychology. Dr. Esposito's other research interests include peer victimization, aggression, psychosocial function and adjustment in children, and child psychopathology. In addition, she has been involved in various research projects with the Infant Studies Unit at the University of Sussex, the Child Conduct Clinic at Yale University, and Bradley Children's Hospital at Brown University. While completing her graduate studies, Dr. Esposito also taught numerous undergraduate psychology courses at VCU.

Sorrel Namaste, M.H.S., is a program manager within the ENGB. She is the project manager for the NICHD Iron and Malaria Project, co-sponsored by the Bill and Melinda Gates Foundation**.** Prior to her role with ENGB, she served as the coordinator for the Middle East and North Africa Newborn Screening Initiative for the NICHD Office Prevention Research and International Projects, within the NICHD Office of the Director. Her educational background includes studies in psychology and biology. In 2008, she received her master's degree from the John Hopkins Bloomberg School of Public Health in global disease epidemiology and control and is currently pursuing a Ph.D. in global health. Her research interests include maternal and child health, with a particular focus on nutrition, and infectious diseases in resource-limited settings.

APPENDIX T: EXPERT PANEL MEMBERS

Dennis M. Bier, M.D.
Professor of Pediatrics
Baylor College of Medicine
Director
Children's Nutrition Research Center,
Agricultural Research Service
U.S. Department of Agriculture
Houston, Texas

Sherin Devaskar, M.D.*
Executive Vice Chair
Department of Pediatrics
Neonatal-Perinatal Medicine, Mattel
Children's Hospital
David Geffen School of Medicine
University of California, Los Angeles
Los Angeles, California

Michael Georgieff, M.D.
Professor of Pediatrics and Child
Psychology
Director, Division of Neonatology
Department of Pediatrics
University of Minnesota
Minneapolis, Minnesota

Matthew W. Gillman, M.D.
Professor
Department of Ambulatory Care and
Prevention
Harvard Pilgrim Health Care
Harvard Medical School
Boston, Massachusetts

Jonathan D. Gitlin, M.D.*
Physician in Chief
Monroe Carell, Jr. Children's Hospital
James C. Overall Professor & Chairman
Division of Neonatology, Department of
Pediatrics
Vanderbilt University
Nashville, Tennessee

Nancy F. Krebs, M.D.
Professor
Department of Pediatrics
University of Colorado, Denver, School of
Medicine
Aurora, Colorado

Nelly Mauras, M.D.
Director
Division of Endocrinology
Nemours Children's Clinic
Jacksonville, Florida

Mark R. Palmert, M.D., Ph.D.
Associate Professor
Department of Pediatrics
University of Toronto
Head of Division of Endocrinology,
Hospital for Sick Children
Toronto, Ontario
Canada

Cliff Rosen, M.D.
Director & Senior Scientist
Medical Center Research Institute
Maine Center for Osteoporosis Research
St. Joseph's Hospital
Bangor, Maine

Mary Story, Ph.D., R.D.
Professor
Division of Epidemiology & Community
Health
University of Minnesota
Minneapolis, Minnesota

Shumei S. Sun, Ph.D.
Professor & Chair of Epidemiology
Department of Biostatistics
Virginia Commonwealth University
Richmond, Virginia

W. Allan Walker, M.D.
Conrad Taff Professor of Nutrition and
Pediatrics
Harvard Medical School
Director, Mucosal Immunology Laboratory
Massachusetts General Hospital for Children
Charlestown, Massachusetts

* Denotes NACHHD Council Member