University of North Carolina at Chapel Hill
Clinical Nutrition Research Unit
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Organization and Goals

The University of North Carolina (UNC) at Chapel Hill Clinical Nutrition Research Unit (CNRU) bridges nutrition science at the interface between medicine and public health. The goal of this CNRU is to provide expertise and core services that increase and enhance: conduct of nutrition-related basic science, epidemiologic and intervention (including classical clinical nutrition) research; translation from basic to epidemiologic to intervention nutrition research and vice versa; and recruitment of investigators from non-nutrition disciplines so that they include nutrition-relevant measures and questions in their research.

The UNC CNRU deploys modern molecular biological and biochemical, epidemiological, behavioral and innovative multi-media methods to assist investigators with nutrition research in humans and in animal models for human diseases. While we have the capacity to assist with individual-based studies in classical clinical nutrition research, we also assist with the population-based studies that are so important for prevention research. Given where nutrition science is in 2005, population-based studies are the natural extension of the clinical trial.

The specific aims of the UNC CNRU are to:

1. Support and enhance the conduct of human nutrition research.
2. Create synergies by enhancing cross-disciplinary collaboration in nutrition research.
3. Increase the research base in nutrition sciences at UNC (funding and number of investigators).
4. Develop and assist young investigators entering nutrition research.
5. Attract investigators from disciplines outside of nutrition for collaborations which include a nutrition focus.
6. Establish nutrition foci within other large NIH-funded research centers at UNC.
7. Enhance nutrition education for health professionals and nutrition scientists.
8. Translate findings from nutrition research so the general public can use this information to improve their health.

Core Laboratories

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Pilot and Feasibility Studies

Hormonal Determinants of Bone Turnover During Lactation in Healthy Postpartum Women. Sue Brown, M.D., Assistant Professor of Medicine. Research in osteoporosis has made great strides in understanding how endogenous and exogenous factors such as calcium and estrogen act on the bone remodeling cycle to slow bone resorption and increase bone mass. However, much less progress has been made in identifying anabolic factors responsible for enhancing bone formation especially during acquisition of peak bone mass. A physiologic model of bone accrual not fully explored previously is the period following extended lactation in postpartum women. Women who breastfeed for more than 3-5 months have significant bone density loss—3-8 percent at the spine and 2-5 percent at the hip. Yet, it is intriguing that bone mass is completely regained after weaning. Although the rate of bone mass recovery has been partially linked to increasing estrogen levels, these changes alone cannot account for the rapid increases in bone density. The rate of bone loss exceeds that normally found in postmenopausal women and the rate of bone gain surpasses that seen with estrogen administration alone. Understanding the interaction of anti-resorptive and anabolic (bone-forming) hormones during weaning and their relationship to bone mass accrual could provide important insights into optimizing conditions for bone mass accrual in osteoporosis.

This project hopes to elucidate the hormonal determinants of this bone mass gain by prospectively examining postpartum women during and after extended lactation. This project will focus on serum insulin-like growth factor=I (IGF-I), a peptide that has both endocrine and autocrine/paracrine anabolic effects on skeletal tissue, its relationship to serum estradiol and its impact on skeletal re-acquisition. The primary hypothesis is that a larger percent increase in

IGF-I levels will result in greater recovery of bone mineral density in lumbar spine after weaning in women with extended lactation and will be related to serum estradiol, PTH and 1,25 dihydroxyvitamin D. Another important objective is to identify modifiable factors such as protein intake and weight retention to characterize their relationship to bone re-accrual. Our specific aims are to: 1) examine the relationship between serum IGF-I levels and bone re-accrual during and after lactation; 2) determine whether serum IGF-I levels during the bone recovery phase are influenced by important bone and calcium regulating hormones such as estradiol, parathyroid hormone (PTH), parathyroid hormone-related peptide (PTHrP) or 1,25 dihydroxyvitamin D; and 3) characterize the relationship between protein intake, IGF-I levels, weight loss/retention, and bone re-accrual postpartum.

The PIN Pediatric Study. Julie Daniels, Ph.D., Assistant Professor, Department of Epidemiology. Long chain fatty acids contribute to the structure and function of brain and retina during normal development, which begins in gestation and continues through early childhood. Clinical trials have indicated that supplementing infant formula with specific fatty acids may improve visual acuity and cognitive function, especially among preterm infants. Little is known, however, about whether variation in the natural maternal fatty acid profile during pregnancy might be associated with the infant's visual and cognitive development. This study takes advantage of the Pregnancy, Infection and Nutrition (PIN) Study and the PIN Postpartum Study. PIN collects considerable information on the women during pregnancy, including diet, stress, infection, and blood samples. PIN Postpartum will conduct a home visit with the women 3 and 12 months after delivery to assess postpartum diet, physical activity, and psychosocial factors. Children born to participants of the PIN Postpartum Study will be eligible to participate in the PIN Pediatric Study. This study will add an evaluation of the child's development and collection of biological specimens to the mother's scheduled postpartum home visit. The developmental evaluation will include a test of visual acuity using Teller Acuity Cards, assessment of mental and motor skills using the Bayley Scales of Infant Development, and assessment of early language and communication skills by the MacArthur Communicative Development Indices. This study will analyze the maternal prenatal fatty acid profile from erythrocyte samples that were collected during pregnancy and stored by the PIN Study, the mother's postnatal fatty acid profile through breast milk samples, and the infant fatty acid profile from cheek cells. We will evaluate the overall variability in maternal and infant fatty acid levels and how they correlate with reported diet and the correlation between the maternal and infant levels. We will also conduct a preliminary investigation of the relation between maternal fatty acid levels and child's neurodevelopment. This pilot data will be used to apply for NIH funding of a larger study that will distinguish more subtle associations between fatty acids and neurodevelopment and allow follow-up of the children as they age.

We propose to examine the association between maternal and infant omega fatty acid levels and child neurodevelopment, specifically evaluating the effect of normal variation in the maternal omega fatty acid profile during pregnancy and the infant fatty acid profile at 3 and 12 months. This investigation will take advantage of a unique opportunity to add a child prospective cohort study onto an existing, data-rich pregnancy cohort, the PIN Study. The specific aims of this study are to: 1) recruit $\geq$ 80 percent of the infants born to mothers participating in the PIN Postpartum Study during the current study year (n=290); 2) conduct visual and cognitive developmental assessments of these children at 3 and 12 months of age; 3) collect breast milk samples from lactating mothers to analyze postnatal fatty acid levels; 4) collect cheek cells from infants at 3 and 12 months to analyze infant fatty acid levels; 5) analyze the maternal prenatal fatty acid levels in erythrocytes samples, collected and stored by the PIN Study; 6) conduct a

preliminary evaluation of the relation between the fatty acid levels (maternal and infant) and the child's neurodevelopment; and 7) evaluate the correlation between dietary data and fatty acid measures from the different maternal and child samples.

Selenium and Gastric Cancer in a High Incidence Region in Central America. Doug Morgan, M.D., Assistant Professor of Medicine. Gastric cancer is the second leading cause of cancer morbidity and mortality in the world with significant geographic variability. Asia, Latin America, and Eastern Europe have regions of high incidence. Carcinogenesis is multifactorial and with regional differences, with host genetic, nutritional, and environmental factors operative. *Helicobacter pylori* has a confirmed role in ulcer disease and gastric adenocarcinoma. The understanding of gastric cancer has recently entered a new era with the discovery of the first host genetic factor. Specific interleukin-1β genotypes have been associated with gastric adenocarcinoma in *H. pylori* infected patients in Europe and Asia. In the setting of *H. pylori* infection, the altered regulation of these inflammatory cytokines predisposes to gastric inflammation and *H. pylori* pangastritis with subsequent intestinal metaplasia. In the setting of imbalance of specific dietary insults and protective factors, the carcinogenesis pathway is promoted. Over two decades of investigations have suggested a role for nutritional factors in gastric cancer. Studies are consistent with respect to certain protective factors (fresh vegetables, fresh fruit, vitamin C, and carotenoids) and certain insults (high salt diet). Evidence for selenium and vitamin E are less clear, though well-designed studies are limited. The putative role of nitrates will remain difficult to prove. A systematic evaluation of gastric cancer risk factors (host genetic, bacterial, nutritional, and environmental) within a population-based study design is lacking. None of the host cytokine polymorphism studies to date include concomitant analysis of cofactors. In addition, the examination of cytokine polymorphisms has been limited to European and Asian populations. The western region of Honduras has been newly identified as having a high incidence of gastric cancer (annual incidence/100K: 39, 21 male, female). Western Honduras is likely the highest gastric cancer incidence region in closest proximity to the United States. Pilot study data, utilizing a population-based case-control design, suggests a striking genetic susceptibility of the population (IL-1β–511T prevalence: 97 percent)—unique in the world. Endemic *H. pylori* infection is confirmed (88 percent). This effort also demonstrates the utility of the novel, image-based dietary instrument (DietHistory®) for nutritional epidemiology in this setting.

The current proposal seeks to systematically assess the role of nutritional factors, specifically selenium and other antioxidants, in gastric cancer patients in this region, within a prospective, population-based case-control study. The proposal is unique in the following respects: genetically susceptible population, endemic *H. pylori* infection, Latino racial group, and novel nutritional epidemiology image software. The effort may provide significant scientific and public health contributions.

The current proposal seeks to assess the role of selenium and other potential dietary factors in gastric carcinogenesis in Western Honduras, a population with endemic genetic susceptibility and endemic *H. pylori* infection. This is done in the framework of a systematic gastric cancer epidemiology effort within a prospective case-control study design.

One specific aim of this study is to examine the role of selenium in gastric carcinogenesis in patients in Western Honduras with the use of the DietHistory® instrument, validation selenium assays, and soil selenium. Our three hypotheses include: 1) selenium intake is decreased among cancer patients, versus the control population; 2) the general population of Western Honduras is

not selenium deficient, but demonstrates intake in the low range; and 3) soil selenium levels in this region of the Central American isthmus will also be in the low range.

Another aim of this study is to assess the relationship between gastric cancer and other dietary factors with the DietHistory®. Our hypothesis is that negative associations include alphacarotene and lutein. Positive associations include salt intake and caffeine.

A third aim of this study is to validate the DietHistory® instrument in the Central American population with incorporation of nutritional database information and research from INCAP (see below), based upon the local agriculture and diet habits. Our two hypotheses include: 1) serum selenium levels will correlate with those estimated by the DietHistory® instrument and 2) certain nutritional components, specifically antioxidants, are overestimated by the North American version of the DietHistory®.

Isothiocyanate Excretion and GST Polymorphisms. Susan Steck Scott, Ph.D., Research Assistant Professor, Department of Nutrition. Cruciferous vegetables, such as broccoli and brussel sprouts, contain phytochemicals called glucosinaolates. Isothiocyanates (ITCs) are metabolic breakdown products of glucosinolates that have been shown to be anticarcinogenic in experimental models. ITCs are substrates for the glutathione S-transferase (GST) enzymes which are polymorphic in human populations. In several observational studies, individuals who consumed cruciferous vegetables and had the null or less active forms of GSTs had reduced risk for lung and colon cancer compared to individuals who did not consume cruciferous vegetables and had the active forms of the GSTs. The biologic explanation for this finding is that having the null or less active form of the genes encoding GSTs may be related to decreased metabolism and urinary excretion of ITCs, thus offering more exposure to these protective phytochemicals. This hypothesis has been supported in one observational study, and we propose to examine it in a controlled feeding study. One hundred subjects will be recruited and enrolled into the study protocol. Subject will avoid dietary sources of glucosinolates for 2 days prior to study initiation and for the 24 hours of study participation. All participants will consume a test diet of 200 grams of broccoli and then collect urine specimens for the following 24 hours. ITCs will be measured in urine samples using HPLC, and levels will be categorized into low or high ITC excretion. Polymorphisms in GSTM1, GSTT1, and GSTP1 will be determined from blood samples from each individual. Using the chi-square test, differences in ITC excretion between the different GST genotypes will be examined. It is hypothesized that individuals with the null or less active forms of the GSTs will have reduced ITC excretion compared to individuals with the active forms of the GSTs. This study will provide preliminary data for a grant proposal to examine the associations between specific fruits and vegetables and polymorphic genes that are modulated by components in fruits and vegetables and risk of cancer in humans.

The primary aim of the proposed study is to test the hypothesis that individuals with the null or less active genotype for GSTM1, GSTT1, and GSTP1 have decreased urinary excretion of isothiocyanates compared to subjects with active genotypes following intake of a controlled dose of cruciferous vegetables.

Midkine Expression and Colorectal Adenomas. Temitope Keku, Ph.D., Research Associate Professor, Department of Medicine. Factors that promote cell growth play an important role in carcinogenesis. Experimental studies suggest that growth factors such as cytokines, adipokines, insulin, and insulin-like growth factors influence colorectal cancer risk. However, the role of growth factors in the early events leading to the transformation of normal colon to cancer is not

fully defined. In addition, the mechanisms underlying the growth-promoting effects of these factors are also not clear but could be mediated through deregulation of apoptosis. In a preliminary analysis, we observed an association between elevated insulin and low apoptosis in the normal mucosa of subjects with colorectal adenoma. These data provide preliminary evidence that other growth factors may be involved early in the transformation to malignancy in the colon. Midkine, a heparin binding cytokine (growth factor) regulated by retinoic acid, is anti-apoptotic and promotes cell growth, cell survival, migration, and angiogenesis. Midkine expression is elevated in several cancers and correlates with a poor prognosis in patients with bladder cancer.

This study was designed to test the hypothesis that elevated plasma midkine levels and increased local midkine expression in colonic mucosa are associated with increased adenoma risk and decreased apoptosis. We used specimens and data from 250 subjects enrolled in the Diet and Health Study, a case control study of colorectal adenomas. The specific aims of the project are to: 1) determine the association between plasma midkine levels, mRNA, and protein expression in subjects with and without colorectal adenomas; 2) evaluate the relationship between midkine protein expression and apoptosis in subjects with and without adenomas; 3) assess the relationship between plasma levels and tissue expression levels of midkine, plasma retinoic acid, β-carotene, and dietary factors in subjects with and without colorectal adenomas.

The primary aim of this study is to determine the association between plasma midkine levels, midkine mRNA, and protein expression in subjects with and without colorectal adenomas. We evaluated whether plasma midkine was associated with colorectal adenomas using enzyme-linked immunosorbent assays (ELISA) and assayed plasma midkine in 250 subjects. Surprisingly, we found that with low plasma midkine as a referent, the upper three quartiles (Q) of midkine were inversely associated with adenoma risk (Q2 OR 0.5, 95 percent CI 0.2-1.1; Q3 OR 0.7, 95 percent CI 0.3-1.5; Q4 OR 0.4, 95 percent CI 0.1-0.8 p for trend =0.03). There was a modest positive correlation between dietary vitamin A intake and plasma midkine (Pearson correlation coefficient =0.13, p=0.05). The plasma midkine data was accepted for presentation at the Digestive Disease week in Chicago in May 2005. The midkine gene expression assays using reverse transcriptase polymerase chain reaction (RT-PCR) will begin in May. The technical assistant who is available for 20 percent effort is currently completing protein expression immunohistochemical staining assays before proceeding to RT-PCR.

A secondary aim of this study is to evaluate the relationship between midkine protein expression and apoptosis in subjects with and without adenomas. Due to initial problems with immunohistochemical (IHC) staining protocols, progress in this aim was delayed. We now have a working protocol and have stained and scored specimens from 50 subjects for midkine IHC protein expression. The protein expression data will be correlated with existing apoptosis data when all the midkine IHC have been completed.

This study also seeks to assess the relationship between circulating levels and tissue expression levels of midkine, plasma retinoic acid, β carotene, and dietary factors in subjects with and without colorectal adenoma. For this aim, we prepared specimens and sent them to the Biochemistry core for analysis of plasma retinoic acid and β-carotene. We will merge the plasma retinoic acid and β-carotene data with existing dietary data when the assays are completed.

Surprisingly, the initial results on plasma midkine and adenomas suggest an inverse association between plasma midkine and colorectal adenoma risk. Thus, midkine may not be a reliable serological marker of colorectal adenomas. In a recent study of insulin-like growth factor binding protein-3 (IGFBP-3) and colorectal adenomas, we found no association between plasma IGFBP-3 and adenomas; however high tissue expression of IGFBP-3 was associated with increased apoptosis and reduced risk of colorectal adenomas. If this pattern is consistent, midkine protein and gene expression in the tissue may be better markers and correlate with adenoma risk.

Life Span, Adipose Mass Reduction, and Basal Glucose Metabolism. Terry P. Combs, Ph.D. (Young Investigator), Assistant Professor of Nutrition. The treatment of diseases related to obesity is often linked to the reduction of basal circulating insulin, reflecting an increase in whole body insulin sensitivity. Many interventions that decrease adipose mass and increase lifespan in mice also increase whole body insulin sensitivity. However, the effect on glucose metabolism, the major target of insulin, is not clear. Dr. Combs' preliminary studies show the rate of hepatic glucose production (HGP) is suppressed in four mouse models that exhibit reduced adipose mass and an increase in lifespan. Dietary restriction, a well known method for reducing adipose mass and increasing lifespan in rodents, decreased HGP from 3.7 to 3.0 mg/dl/min ($P>0.05$). A similar relationship between HGP, adipose mass, and life span was seen in mice with the dwarf (dw/dw) or little (lit/lit) mutations, whereas the obese (ob/ob) mutation had the opposite effect on HGP. HGP values were, respectively, 1.4 and 3.7 mg/dl/min in dw/dw and wild-type controls, 2.2 and 4.6 mg/dl/min in lit/lit and wild-type controls and 4.2 and 3.7 mg/dl/min in ob/ob and wild-type controls (paired t-test; $P<0.05$; NP). Thus, the life-extending effects of adipose mass reduction may be linked specifically to hypometabolism of glucose. A long-term objective will be to determine whether suppressing HGP can extend lifespan. Adiponectin is a good candidate for a circulating signal that triggers the suppression of HGP because its levels increase with all four interventions that lead to HGP suppression, adipose mass reduction, and life extension. Furthermore, adiponectin increases insulin's inhibitory effect on glucose production. We will test the hypothesis that HGP is suppressed by elevated circulating adiponectin. Identifying a circulating signal that triggers metabolic changes consistent with adipose mass reduction and life extension will have important public health implications.

One aim of this study is to determine if HGP increases in response to the suppression of circulating adiponectin previously described in mice and people during late gestation and lactation. A secondary aim is to determine if circulating adiponectin levels fluctuate over the course of the estrus cycle. Vaginal smears and body-weight measurements from cycling, pregnant, and lactating mice have been obtained and analyzed to identify proestrus and days 14-18 of pregnancy. We will measure insulin, PRL and HGP.

This study also seeks to determine if HGP is suppressed when circulating adiponectin is elevated by a transgenic modification (the ΔGLY mouse) that causes a threefold increase in plasma adiponectin. A secondary aim is to measure HGP in ΔGLY mice that also carry a caveolin-1 (CAV1) heterozygous null (+/-) mutation. We have raised and genotyped a colony of ΔGLY mice, and we are breeding ΔGLY x CAV1 (+/-) mice. Measurements of insulin, adiponectin, and HGP will be made in 3-6 month old male mice.

The study wishes to determine if the suppression of HGP in the dw/dw mouse depends on the elevation of adiponectin. We will test dw/dw mice that carry the adiponectin (-/-) mutation. The

adiponectin (-/-) mutation will be replaced with adiponectin transgenic (ΔGLY) mutation. Two successive crosses will be needed to obtain the desired genotype.

We have developed a novel method to measure HGP for Aims 1-4. We asked whether the radioactivity measured in plasma after injecting [^{3}H]glucose is [^{3}H]glucose alone or [^{3}H]glucose plus a metabolite that has undergone [^{3}H] exchange. HPLC analysis showed the retention time of pure [^{3}H]glucose and the radioactive compound in plasma after injecting [^{3}H]glucose injection are identical. The time course of radioactivity disappearance from plasma correlates with the disappearance of [^{3}H]glucose. Thus, no other labeled metabolite is present, and we can use this new technique to measure HGP.

Funding Derived From Pilot and Feasibility Studies

Isothiocyanate Excretion and GST Polymorphisms. Susan Scott, Ph.D. Funding: UNC-CH Junior Faculty Award, UNC Chapel Hill; $5000.

Bone Accrual and Hormones in Response to Lactation. Sue Brown, M.D. Funding: NIH, NIAMS K23 AR051483; 9/1/04-8/31/09; $126,170.

Assessment of Perinatal PBDE Exposure and Related Child Behavior and Cognitive Developmental Effects. Julie Daniels, Ph.D. Funding: EPA, 10/1/05-3/31/08; $749,986.

The Effects of Adiponectin on Liver Insulin Resistance. Terry Combs, Ph.D. Funding: NIH, K01 DK075573-01, 07/01/06 to 06/30/09; $319,707, pending.

Cytokine Gene Polymorphisms, Inflammation and Colorectal Cancer. Temitope Keku, Ph.D. Funding: NIH, R01 CA 116760, 4/01/06 to 3/31/11; $ 1,414,292, pending.

Diet, DNA Methylation and Colorectal Adenomas. Temitope Keku, Ph.D. Funding: NIH, NCI R03, 4/01/06-3/31/08; $100,000, pending.

Scientific Advances/Accomplishments

The UNC CNRU is integral to the multidisciplinary research in nutrition across the campus. The provision of services to funded investigators in a cost-effective manner, the training in research methods, and the mentoring of young investigators all serve to make the CNRU unique and successful. Below are some examples of the advances in nutrition that were made possible by the Center.

Choline Requirement in Humans. Several studies by CNRU investigators, supported with sample analysis by the Metabolism Core, advanced our knowledge of the effects of choline on brain development. One study examined elevated concentrations of homocysteine in blood and whether this may be an independent risk factor for the development of atherosclerosis. Elevated homocysteine concentrations can be caused by decreased methylation of homocysteine to form methionine, as occurs in folate deficiency. A parallel pathway exists for methylation of homocysteine, in which choline, by way of betaine, is the methyl donor. The authors' goal was to determine whether choline deficiency results in a decreased capacity to methylate homocysteine. C57BL/6J mice were fed diets containing 0, 10, or 35 mmol choline/kg diet for 3 weeks. Then they received an oral methionine load and the authors measured plasma homocysteine

concentrations. Also, they studied men who were fed a diet providing 550 mg choline/d per 70 kg body weight for 10 days, followed by a diet providing almost no choline, until the subjects were clinically judged to be choline deficient or for <or=42 days. A methionine load was administered at the end of each dietary phase. Two hours after the methionine load, choline-deficient mice had plasma homocysteine concentrations twice those of choline-fed mice. Four hours after the methionine load, clinically choline-depleted men had plasma homocysteine concentrations that were 35 percent greater than those in men not choline depleted. These results suggest that choline, like folate, plays an important role in the metabolism of homocysteine in humans and that response to a methionine load may be useful when assessing choline nutriture.

Another study supported by the CNRU Nutritional Biochemistry Core examined whether single nucleotide polymorphisms (SNPs) in genes of folate metabolism increase the susceptibility of humans to developing signs of organ dysfunction when fed a low-choline diet. Choline is a required nutrient, and some humans deplete it quickly when fed a low-choline diet, whereas others do not. Endogenous choline synthesis can spare some of the dietary requirements and requires one-carbon groups derived from folate metabolism. Dr. Steven Zeisel, CNRU director, and other CNRU investigators examined whether major genetic variants of folate metabolism modify susceptibility of humans to choline deficiency. Fifty-four adult men and women were fed diets containing adequate choline and folate, followed by a diet containing almost no choline, with or without added folate, until they were clinically judged to be choline-deficient, or for up to 42 days. Criteria for clinical choline deficiency were a more than five times increase in serum creatine kinase activity or a >28 percent increase of liver fat after consuming the low-choline diet that resolved when choline was returned to the diet. Choline deficiency was observed in more than half of the participants, usually within less than a month. Individuals who were carriers of the very common 5,10-methylenetetrahydrofolate dehydrogenase-1958A gene allele were more likely than noncarriers to develop signs of choline deficiency (odds ratio, 7.0; 95 percent confidence interval, 2.0-25; $P < 0.01$) on the low-choline diet unless they were also treated with a folic acid supplement. The effects of the C677T and A1298C polymorphisms of the 5,10-methylene tetrahydrofolate reductase gene and the A80C polymorphism of the reduced folate carrier 1 gene were not statistically significant. The most remarkable finding was the strong association in premenopausal women of the 5,10-methylenetetrahydrofolate dehydrogenase-1958A gene allele polymorphism with 15 times increased susceptibility to developing organ dysfunction on a low-choline diet.

Food Nutrient Content. The Nutrition Epidemiology Core has linked the glycemic index values from the American Journal of Clinical Nutrition publication and the UDSA Choline values to the Block 98 and Willett (Choline only) Food Frequency Questionnaire. This information is being used by Block's company and is being provided to everyone using this questionnaire. The Core also facilitated the National Birth Defects Center's effort to update the folate values in its nutrient composition database using the USDA Ref 16. The Core is assisting Dr. Lynn Bailey with her research at the University of Florida in Gainesville. These activities include adapting a food frequency questionnaire to assess vitamin B12 intake and processing of the Food Frequency Questionnaire for nutrient analysis and guidance in the data analysis regarding the dietary data.

Cystic Fibrosis. Former PF investigator Dr. Robert Aris continues to advance the field of cystic fibrosis (CF) research, building upon his pilot study funded by and utilizing the services of the CNRU. CF is the most common genetic disease within the Caucasian population and leads to premature respiratory failure. Approximately 60,000 individuals are currently living with CF in

North America and Europe, 40 percent of whom are adults. The life span of these patients has increased from approximately 2 to 32 years of age over the last three decades. Bone disease has emerged as a common complication in long-term survivors of CF. Some studies have observed that 50-75 percent of adults have low bone density and increased rates of fractures. Prevention and treatment of CF-related bone disease must address the myriad risk factors (decreased absorption of fat-soluble vitamins due to pancreatic insufficiency, altered sex hormone production, chronic lung infection with increased levels of bone-active cytokines, physical inactivity, and glucocorticoid therapy) for poor bone health. This review is a condensed and updated summary of the Guide to Bone Health and Disease in Cystic Fibrosis: A Consensus Conference, a statement that evolved from a meeting convened by the Cystic Fibrosis Foundation in May 2002 to address the pathogenesis, diagnosis, and treatment of bone disease in CF. The goal of this conference was to develop practice guidelines for optimizing bone health in patients with CF.

Cancer Research

Colorectal Screening. The CHAI Core has provided over 1000 hours of service for usability testing for a new project entitled Increasing Colorectal Screening in Healthplan Members, funded by the Centers for Disease Control and Prevention (CDC). Colorectal cancer is the second most common cause of cancer death in the United States. Early detection and intervention can significantly reduce morbidity and mortality from colorectal cancer (CRC), and current guidelines recommend that asymptomatic adults over age 50 periodically obtain screening by one of several modalities: fecal occult blood test (FOBT), sigmoidoscopy, colonoscopy, or double contrast barium enema. However, CRC screening remains substantially underutilized in the United States, and more than half of all adults do not adhere to these recommendations. Because key predictors of CRC screening utilization include a physician recommendation and having health insurance, and given the availability of evidence-based strategies for increasing screening uptake, it is important to conduct effectiveness studies in health plan member populations. Investigators are conducting participatory research with a major health insurer in order to test the transferability of community-based behavioral interventions that can increase provision of colorectal cancer screening. Researchers are conducting a cluster-randomized trial in health practices in Georgia and North Carolina to test the effectiveness of a videotape-based decision aid and academic detailing for increasing adherence to CRC screening guidelines. Twenty-six large group practices will be recruited and randomized to receive usual care or the combined videotape-based decision aid and academic detailing intervention. In each practice, 30 patients between the ages of 52 and 75, without current CRC screening history, will be enrolled into the study. The intervention will continue for up to 2 years for still-unscreened participants. The main outcome will be provision (or receipt) of an evidence-based modality of CRC screening according to the U.S. Preventive Services Task Force Guidelines (FOBT, flexible sigmoidoscopy, colonoscopy, or double contrast barium enema). The research team has already begun a participatory research process with key leaders in Quality Improvement and the Medical Economics Units at Aetna, one of the nation's largest health insurers. Unique features of the proposed study include its potential to establish systems to increase screening uptake that will help fulfill Health Plan Employer Data and Information Set (HEDIS) requirements; improving our understanding of how screening promotion interventions work in both White and Black populations; and forging collaborative relationships between public health and healthcare researchers, and the affected communities of health plans and healthcare providers.

Folate, B Vitamins, and Cancer. CNRU investigators collaborated on a study to investigate the accumulating evidence from epidemiologic studies which suggests that risk of breast cancer is reduced in relation to increased consumption of folate and related B vitamins. Gammon and colleagues investigated independent and joint effects of B vitamin intake as well as two polymorphisms of a key one-carbon metabolizing gene [i.e., methylenetetrahydrofolate reductase (MTHFR) 677C>T and 1298A>C] on breast cancer risk in 1,481 cases and 1,518 controls. Significant inverse associations between B vitamin intake and breast cancer risk were observed among non-supplement users. The greatest reduction in breast cancer risk was observed among non-supplement users in the highest quintile of dietary folate intake [odds ratio (OR), 0.61; 95 percent confidence interval (95 percent CI), 0.41-0.93] as compared with non-supplement users in the lowest quintile of dietary folate intake (high-risk individuals). The MTHFR 677T variant allele was associated with increased risk of breast cancer (P, trend = 0.03), with a multivariate-adjusted OR of 1.37 (95 percent CI, 1.06-1.78) for the 677TT genotype. The 1298C variant allele was inversely associated with breast cancer risk (P, trend = 0.03), and was likely due to the linkage of this allele to the low-risk allele of 677C. The MTHFR-breast cancer associations were more prominent among women who did not use multivitamin supplements. Compared with 677CC individuals with high folate intake, elevation of breast cancer risk was most pronounced among 677TT women who consumed the lowest levels of dietary folate (OR, 1.83; 95 percent CI, 1.13-2.96) or total folate intake (OR, 1.71; 95 percent CI, 1.08-2.71). From a public heath perspective, it is important to identify risk factors, such as low B vitamin consumption, that may guide an effective prevention strategy against the disease.

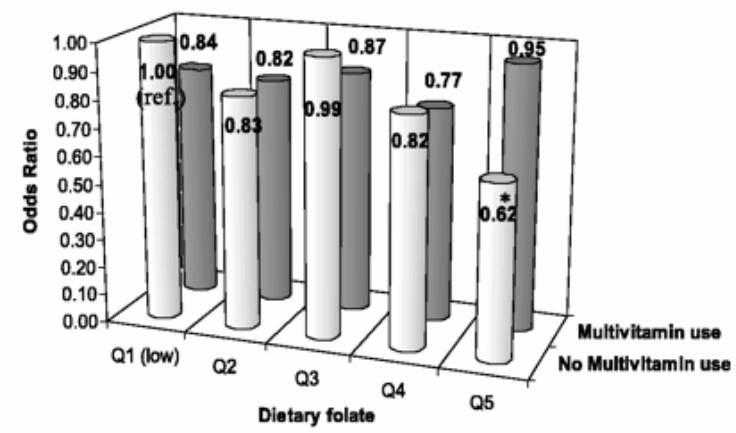

FIGURE 1. The diagram demonstrates the relationship between dietary folate intake and risk of breast cancer with respect to multivitamin use in the Long Island Breast Cancer Study Project, 1996-1997. The ORs were adjusted for age, family history of breast cancer in first-degree relatives, history of benign breast disease, education, body mass index at age 20, and daily caloric intake. *P* interaction = 0.04. * $P < 0.05$.

Specific Accomplishments

Women's Health. The CNRU CHAI Core continues to stand out in its ability to provide integrated and expert health communications services to investigators at an extremely low cost to the investigator. One example of this service is work on the Trial for Activity in Adolescent Girls (TAAG), a massive, multi-million dollar, multi-center intervention trial. Currently, the Core's graphic designer, intervention specialist, and health communication specialist are creating

print materials for TAAG, an NIH-funded intervention focusing on physical activity and nutrition for adolescent girls. Materials include school-based curricula, posters, passports (activity tracking and goal setting guide), and other support items. Without the availability of such a specialized Core which is able to handle all aspects of the material development, design, and production, the investigator would have had to contract these services at a much higher cost from multiple sources, thereby greatly increasing the cost of the project. They would also not have been able to benefit from the central team that the Core provides.

Nutrition Intervention. The CNRU continues to provide services to develop theory-based intervention materials to Dr. Laura Linnan's Bringing Education and Understanding to You Project (BEAUTY) Project. Dr. Linnan recently published results from the North Carolina BEAUTY and Health Pilot Project. This pilot study used a community-based participatory research approach to recruit and train five licensed cosmetologists from two beauty salons to deliver health promotion messages to their customers. Stylists attended a 4-hr workshop to develop skills for delivering targeted health messages, and educational displays in the salons reinforced these messages. Satisfaction, readiness to change, and self-reported health behavior changes in customers were assessed immediately following the intervention and 12 months later. Trained stylists reported they would continue delivering health messages after the 7-week pilot was completed; the majority of customers read the educational displays and talked with their cosmetologist about the BEAUTY Project. At 12 months, most customers still reported making changes in their health because of the conversations they had with their cosmetologist. Customers who spoke more often with their cosmetologists about health also reported a higher percentage of self-reported behavior changes. It appears that trained licensed cosmetologists are effective in promoting health messages to their customers.

Pregnancy. The Nutritional Epidemiology Core is actively involved in providing dietary assessment services to numerous human studies. The purpose of this particular study was to show that maternal folate status during pregnancy may be related to preterm birth. Women were recruited at 24 to 29 weeks' gestation from 1995 to 2000 into the Pregnancy, Infection, and Nutrition Study. Those who completed an interview and a food frequency questionnaire or provided a blood sample for radioassay of serum (n = 2026) and red blood cell (n = 1034) folate were included. Results from Food Frequency Questionnaires (FFQs) administered by CNRU investigators showed that mean daily dietary folate intake was 463 microg (SD +/- 248). Intake </=500 microg was associated with increased preterm delivery (RR = 1.8, 95 percent CI 1.4-2.6), controlling for total energy intake. Serum folate levels <16.3 ng/mL and red blood cell folate levels </=626.6 ng/mL yielded adjusted risk ratios of 1.8 (95 percent CI 1.3-2.5) and 1.7 (95 percent CI 1.1-2.6), respectively. Patterns were similar for spontaneous and overall preterm birth. These results support the hypothesis that low folate levels during the second trimester of pregnancy are associated with an increased risk of preterm birth.

Minority Health.

Racial Differences in Prostate Cancer. Research continues on Prostate cancer (CaP) with former Pilot and Feasibility investigator Dr. Susan Steck as the primary investigator in a study entitled Racial Differences in Lifestyle Modification in Men with Newly-Diagnosed Prostate Cancer, funded by the U.S. Army Department of Defense. The Nutrition Epidemiology Core is conducting 24-hour recalls. The goal of the study is to create data on patterns of health behaviors among men diagnosed with CaP by race. This project will provide important information on changes in modifiable lifestyle factors (diet, use of dietary supplements, and physical activity) among men diagnosed with CaP, and the extent to which the changes differ by race.

Identification of dietary effects on CaP prognosis would suggest the importance of lifestyle behavioral factors in CaP outcome. Further, the determination of racial differences in health behaviors post-diagnosis may provide insights into disparities in CaP prognosis between African Americans and Caucasian Americans. Together, these data would provide information that could be used to develop appropriate interventions to lower the risk of fatal CaP and reduce racial disparities in CaP prognosis. The hypothesis of this project is that men diagnosed with CaP modify lifestyle factors (dietary intake, dietary supplement use, and physical activity) differently by race, which alters prognosis. Specifically, African Americans diagnosed with CaP make fewer healthy changes than Caucasian Americans, which might contribute to worse prognosis among African Americans. Therefore, this project attempts to determine whether men diagnosed with CaP make changes in dietary intake, use of dietary supplements, and physical activity, and the extent to which the changes differ by race. Also, the question of whether alterations in dietary intake, dietary supplement use, and physical activity upon diagnosis of CaP are associated with oxidative DNA damage in lymphocytes and CaP prognosis will be examined.

Dietary Intake Among African Americans. The Nutritional Epidemiology Core provides support for a study investigating reading nutrition labels on food packages and subsequent improvement in food choices to enable healthful dietary practices. This report describes the prevalence of nutrition label use and its association with demographic, behavioral, and psychological factors and diet among African American adults. Self-reported data was collected from a population-based cross-sectional survey of 658 African Americans, aged 20 to 70 years, in North Carolina. This questionnaire assessed nutrition label use, fruit and vegetable consumption, total and saturated fat intakes, fat-related dietary behaviors, diet-related psychosocial factors, and demographic and behavioral characteristics. The mean age of participants was 43.9±11.6 years, 41 percent were men, 37 percent were college graduates, and 75 percent were overweight or obese. Seventy-eight percent of respondents read nutrition labels when they purchased packaged foods. Nutrition label use was significantly higher among participants who were women, older, educated beyond high school, and obese ($P<.05$). After adjusting for demographic characteristics, the strongest psychosocial predictors of nutrition label use were healthful eating self-efficacy, strong belief in a diet-cancer relationship, and an attempt to lose weight. Those who used labels regularly had higher fruit and vegetable consumption and lower fat intakes. Nutrition information on packaged foods appears to be a useful way to conduct point-of-purchase nutrition education among African Americans in North Carolina. Most respondents used food labels at least sometimes, but only about half usually or often did so. Efforts should be made to determine how all consumers could use nutrition labels effectively.

AIDS.

Nutrient Status of AIDS Patients During Treatment. CNRU Body Composition Core evaluates the nutrient status of AIDS patients through dual energy x-ray absorptiometry (DEXA) analysis. Dr. Joseph Eron, CNRU investigator, continues work on this multidisciplinary multi-year research program entitled Adult Therapeutic Clinical Trials Program for AIDS, which integrates institutional expertise in infectious diseases, neurology, ophthalmology, gynecology, pharmacology, immunology, retrovirology, herpes viruses, and numerous clinical resources in North Carolina. The main focus is the evaluation of novel therapies for HIV-infected persons. Clinical investigators at the UNC and two satellite units, Greensboro and Charlotte, investigate new compounds active against HIV and associated infections, malignancies, and neurologic disorders in new patients and follow previously enrolled patients. Investigators continue a high rate of accrual among minorities, women, and intravenous (I.V.) drug users. The trials are of all Phases (I, II, and III) and types. Patients are followed for *in vivo* evidence of study drug effects

on HIV, Mycobacterium avium intracellular complex (MAC), cytomegalovirus (CMV), herpes simplex virus (HSV), and other opportunistic infections using the ACTG-certified retrovirology and immunology virus laboratory, as well as UNC hospital laboratories. Pharmacokinetics (PK) are monitored in the General Clinical Research Center (GCRC) and Microbiology and Pharmacology Laboratories.

Breastfeeding and HIV. The CNRU provided consultation to investigators on a study related to HIV-positive women and perception of their own bodies, health, and well-being, particularly in light of their infection, and whether these perceptions influenced their infant feeding practices and their perceived ability to breastfeed exclusively through 6 months. Twenty-two HIV-positive women living in semi-rural areas on the periphery of Lilongwe, Malawi participated in in-depth interviews. In an adaptation of the body silhouette methodology, nine culturally appropriate body silhouettes, representing a continuum of very thin to very large shapes, were used to elicit women's views on their present, previous-year, and preferred body shapes, and on the shape they perceived as healthy. The narrative scenario method was also used to explore women's views on two fictional women infected with HIV and their ability to exclusively breastfeed. Women perceived larger body shapes as healthy because fatness is considered a sign of good health and absence of disease, and many recognized the role of nutrition in achieving a preferred or healthy body shape. Women were concerned that breastfeeding may increase the progression of HIV, suggesting that international guidelines to promote appropriate infant feeding practices for infants whose mothers are infected with HIV should focus on the mother's health and well-being as well as the infant's.

Obesity.
CNRU investigators have attracted major research funding in obesity, including the NIH-funded TAAG study on activity in adolescents; an NIH P20 RoadMap grant to create an interdisciplinary research group focusing on environmental and biological factors contributing to obesity; multiple R01 and R21 grants on adipocyte biology, specifically molecular mechanisms involved in obesity; epidemiologic research on obesity and nutrition intervention obesity research; and a $4 million grant from Gatorade to fund research on community-based approaches to childhood overweight.

With generous funding from the NIH totaling close to $1.7 million, UNC has developed a critical mass of expertise in the obesity area and now has more than 75 faculty members, most of whom are CNRU investigators, with active research programs who comprise the core of UNC's Interdisciplinary Obesity Center (IDOC). The Nutrition Intervention Core has assisted the IDOC initiative by providing graphic design services for promotional materials. The aim of this new center is to bring together researchers from diverse disciplines to create a new transdisciplinary science of obesity and investigate innovative prevention and treatment methods. This unique group of scientists includes national and international leaders with active research in areas as varied as dietary and physical activity patterns, trends and behaviors in both the United States and globally, metabolic syndrome, use of advanced forms of the media (internet, video games), eating disorders, appetite control, addictive behaviors, nutrition and weight dynamics during pregnancy and infancy, animal and human genetics, inflammatory diseases, lipid metabolism, and many others. IDOC is organized in seven overlapping program areas addressing obesity from a "cell-to-society" perspective. These areas include: Genetics, Metabolic Syndrome, Chronic Disease/Epidemiology, Clinical/Behavioral, Obesity Prevention, Health Communications, and Macro and Built Environment.

Obesity Interventions. The CNRU, through its Nutritional Epidemiology and CHAI Cores, continues to support several obesity research projects, both at the national and global level. A sample of these includes the Add Health Project; TAAG; Pregnancy Related Weight Gain: A Link to Obesity; Infant Care, Feeding and Risk of Obesity; and the Gatorade-funded Get Kids in Action project. A follow-up project to TAAG was recently submitted for funding.

UNC was awarded a $3 million, 5-year NIH grant (started in September 2005) to conduct a three-phase project in an existing primarily rural practice network serving Medicaid families. The project, entitled Primary Care and Communities Tackling Obesity in Kids, consists of: Phase I -- Refine culturally appropriate, evidence-based, arid theory-driven intervention materials and strategies to guide clinic-based interventions; Phase II -- Conduct a randomized controlled trial to determine the effectiveness and cost effectiveness of the already developed and pretested, Provider Toolkit and Local Care Manager (LC Manager) interventions on 4-11 year old Medicaid children (20 children in each of 24 practices), and assess intervention impact on providers; and Phase III -- Determine whether primary care providers, after implementing a practice-based, pediatric obesity intervention in the clinical setting (Phase II) can subsequently initiate environmental/policy change in their local communities. Dr. Alice Ammerman, CNRU investigator, Associate Professor, Department of Nutrition, Schools of Public Health/Medicine, UNC and the Director of the CDC Prevention Research Center is the principal investigator on this study.

The CNRU continues to provide services for the $2.5 million, five-year grant to examine potential risk factors for development of obesity in the first 2 years of life. Funding for the study, entitled Infant Care, Feeding, and Risk of Obesity, is provided by the National Institute of Child Health and Human Development. Dr. Peggy Bentley, CNRU investigator and professor in the department of nutrition and a fellow at the Carolina Population Center, is the project's principal investigator. The Nutritional Epidemiology Core provided considerable input during the grant development and is now providing dietary assessment services to the project. The study is being conducted among African American mothers and infants in North Carolina, a group at high risk for the development of obesity.

The CNRU continues to be in the forefront of research on childhood overweight. The CNRU CHAI and Epidemiology Cores continue to provide dietary assessment services for the Gatorade -funded research on a childhood overweight prevention program using a multidisciplinary, community-based approach targeting the full range of individuals who impact this complex problem including doctors, community leaders, and families. Through research, education, and outreach, Get Kids in Action is identifying real and proven solutions to increase physical activity that can be replicated in communities across the United States. Not only is the CNRU providing services to develop the intervention component of the grant, but it is also working with several investigators who have received pilot money from the grant to carry out small research projects. The increased visibility brought to the issue of obesity has also led to the submission of several new grants that address prevention and treatment of obesity by CNRU investigators. Get Kids in Action has a website developed by the CNRU at *www.getkidsinaction.org*.

Dr. Deborah Tate, principal investigator and CNRU member, has recently developed and tested an Internet behavioral weight-loss program and compared it to an Internet educational program in a randomized trial. She found that the behavioral program produced significantly better weight losses (4.1 kg) at 6 months. The CNRU CHAI Core is providing graphic design and computer programming services for this research entitled Enhanced Internet Behavior Therapy for Treating

Obesity, which clearly establishes the potential for using the Internet to deliver alternative treatment programs; however, treatment efficacy research is needed to further develop an Internet approach that will promote longer term weight loss. The objectives of this study are to: enhance our Internet program to develop a state-of-the-art Internet Cognitive-Behavior Therapy (I-CBT) program for obesity treatment and conduct a randomized trial comparing the enhanced program with a Minimal CBT program also delivered via the Internet. Recruitment of 100 overweight adults is expected with random assignment to the Enhanced Internet CBT or Minimal Internet CBT programs. The Minimal I-CBT participants are given links to weight-loss websites, weekly structured cognitive-behavioral lessons for weight loss, weekly prompting, and an online bulletin board. The Enhanced I-CBT program has these same features plus weekly on-line group therapy sessions, computer-aided self-monitoring diaries, and weekly individual e-mail feedback from a therapist. The primary outcome is weight loss from 0-12 months. Secondary outcomes examine patterns of weight change and changes in waist, diet, physical activity, and social support. This research has significant implications for expanding the audience served by obesity treatment programs by using the Internet. This study utilizes an innovative approach and extends our programmatic research on the development of a cognitive-behavioral Internet treatment for obesity.

The CNRU CHAI Core has provided over 1200 computer programming service hours to a research study entitled Interventions to Control Obesity in Community Colleges. Despite the fact that obesity is at epidemic proportions and costs U.S. employers an estimated $78.5 billion annually, national data indicate that less than 25 percent of employers are offering disease management programs to address obesity. Effective weight-loss programs that are adaptable to busy work environments and maintain employee interest are needed, but few rigorous tests of these programs have been attempted. In collaboration with the North Carolina Community College System, NC Blue Cross Blue Shield, and the State Teachers and Employee Medical Plan, Laura Linnan, principal investigator and CNRU member, is conducting a 3-year group-randomized weight-loss intervention study where 1300 overweight/obese employees nested within 13 community colleges will be randomly assigned to receive one of three promising, state-of-the-art, theory-linked interventions: Environment/Usual Care (E); Web-based Weight Loss Program + Environment (WEB+E); or Web + Environment +Incentives (WEB+E+I). College is the unit of randomization and intervention; employee is the unit of analysis. After formative research in Year 1 to adapt interventions for community college employees, we will rigorously test the effects of these interventions on 12-month weight loss (primary outcome). Weight will be measured at baseline, 3, 6, 9, and 12 months, and most secondary outcomes (weight-loss behaviors, moderate-vigorous physical activity, total calories, percent body fat, fruit/vegetable intake, absenteeism, productivity, medical expenditures, and quality of life) will be assessed at baseline, 6 and 12 months along with potential mediators/moderators of weight loss outcomes. Process tracking data will measure fidelity, dose delivered/received, and acceptability/satisfaction with the interventions. Extensive cost- and cost-effectiveness analysis, including return on investment, will be undertaken. If proven effective, this strong partnership between community colleges, the State Health Plan, and the research team, will help guide program adoption and institutionalization/dissemination throughout the community college campus system.

Obesity and Increased Risk to Disease. CNRU investigator and Core Director, Melinda Beck, has started a new research focus examining the effect of obesity on susceptibility to infectious disease. Using a diet-induced animal model, this research laboratory found that obese mice had a much higher mortality rate (40 percent) than lean mice (4 percent) when infected with influenza

virus. In addition, the immune system of the obese mice was compromised in comparison to the lean animals. Adipose tissue was also found to respond to the lung infection by upregulating cytokine and chemokine mRNA levels in both lean and obese animals, although the obese response was exaggerated compared with the lean response. This work was presented at Experimental Biology in April 2005 and currently several manuscripts are being prepared.

Breastfeeding and Obesity. The Nutrition Epidemiology Core assisted this research which uses nationally representative U.S. data from the National Longitudinal Study of Adolescent Health (1994-1996) to perform traditional cohort analyses (n=11,998) using logistic regression to estimate the relation between breastfeeding and adolescent overweight (body mass index > or = 85 percentile, based on year 2000 CDC growth charts), controlling for known potential confounders. Breastfeeding also was assessed in a subsample of 850 sibling pairs to account for unmeasured genetic and environmental factors. Among girls in the full cohort, the odds of being overweight declined among those who had been breastfed at least 9 months; odds ratios ranged from 0.90 (95 percent confidence interval = 0.74-1.09) for <3 months of breastfeeding to 0.78 (0.64-0.96) for > or = 9 months. A similar effect was seen in boys, although these trends were less consistent. In contrast, an analysis of sibling pairs provided no evidence of breastfeeding effects on weight within discordant trends. Cohort data indicate that odds of being overweight decrease as breastfeeding duration increases, at least among girls. However, sibling analyses suggest that this relationship may not be causal but rather attributable to unmeasured confounding related to mothers' choice to breastfeed or to other childhood risk factors for overweight. The results illustrate the utility of sibling analyses in understanding the true effect of early life exposures (such as breastfeeding) on health outcomes over time, independent of confounding factors that may not be satisfactorily controlled using traditional prospective cohort methods.

Antipsychotic Medications and Obesity. Weight gain is a commonly observed adverse effect of atypical antipsychotic medications, but associated changes in energy balance and body composition are not well defined. Karen Graham, CNRU investigator, and colleagues report the effect of olanzapine on body weight, body composition, resting energy expenditure, and substrate oxidation as well as leptin, insulin, glucose, and lipid levels in a group of outpatient volunteers with first-episode psychosis. After approximately 12 weeks of olanzapine therapy, the median increase in body weight was 4.7 kg, a significant increase of 7.3 percent from first observation. Body fat, measured by dual-energy x-ray absorptiometry, increased significantly, with a propensity for central fat deposition. Lean body mass and bone mineral content did not change. Resting energy expenditure, measured by indirect calorimetry, did not change. Respiratory quotient significantly increased 0.12 with olanzapine and was greatest in those who gained >5 percent of their initial weight. Fasting insulin, C-peptide, and triglyceride levels significantly increased, but there were no changes in glucose levels; total, high density lipoprotein, or low density lipoprotein cholesterol levels; or leptin levels. Olanzapine appears to have induced an increase in central body fat deposition, insulin, and triglyceride levels, suggesting the possible development of insulin resistance. The decrease in fat oxidation may be secondary or predispose patients to olanzapine-induced weight gain.

Health Promotion and/or Disease Prevention. The UNC Center for Health Promotion and Disease Prevention (HPDP Center) is expanding State and local partnerships, extending its successful research agenda, and strengthening the scientific basis and infrastructure for the delivery of improved public health and preventive services to the people of North Carolina, the Southeast, and beyond. CNRU investigators Alice Ammerman and Thomas Keyserling are two

principal investigators in this center who have established a close partnership with State and local leaders and the Community Advisory Committee in Sampson and Duplin Counties, where the Core Research Project, HOPE Works, will be implemented. Six specific aims for the 5-year cycle are to: 1) Develop a 5-year HPDP Center evaluation strategy with 15 specific performance indicators, addressing each of the six aims, that will monitor Center progress, link with the PRC Program Information System and provide continuous quality improvement; 2) Use participatory planning approaches to strengthen partnerships: a) at State and local levels with health departments and Healthy Carolinians, b) with campus and State community development experts, and c) in Sampson and Duplin counties, deepening existing partnerships and expanding by adding 30 new partners from among a wide range of local agencies and organizations; 3) Implement the 5 Year HPDP Center research agenda in collaboration with our partners (with a focus on Hope Works in Sampson and Duplin counties), increase the number of HPDP Center research projects, and ensure that the research efforts are linked to State/National Health Objectives while producing enhancements to prevention research; 4) Strengthen HPDP Center Communication and Dissemination Activities by formalizing a 5-year plan, expanding expert resources, using and evaluating several methods to disseminate results, broadening partnerships with public health professionals and community groups, and producing evidence of an impact on communities, NCDHHS and university partners; 5) Strengthen the HPDP Center infrastructure with the addition of a formal evaluation unit, expanded dissemination, training and community development expertise, reorganized biostatistical supports, expansion of the Scientific and Community Advisory Committees, and an information system that reports progress, tracks evaluation results, and feeds the continuous quality improvement process; and 6) Expand HPDP Center training activities to meet community and campus training needs identified through a systematic assessment process, with continuous quality improvement. The following proposals for five Special Interest Projects (SIPs) have been submitted for funding though this center: SIP# 04-05: Barbers Trimming Cancer Risk among Black Men SIP# 05-05: Increasing CRC Screening in Urban African American Communities via Churches SIP# 08-05: Cardiovascular Health Promotion Network-Coordinating Center SIP# 09-05: Cardiovascular Health Promotion Network-Collaborating Center SIP# 16-05: Promoting Healthy Weight through Child Care: The NAP SACC Program.

Professional/Public Nutrition Education Efforts.

Evaluation of Nutrition Education Websites. The CHAI Core continues to lead the field of tailored nutrition messages, providing state-of-the-art services to investigators involved in intervention research. Using the expertise of the CHAI Core, investigators evaluated the content quality, general readability, and usability characteristics of consumer nutrition information on the World Wide Web. Almost 500 websites were identified for evaluation through two different approaches. Of these, 150 were included for further evaluation. Each site was rated on a 27-item tool covering content quality, readability, and usability. Summary statistics, means, ranges, and standard deviation were calculated for each study variable. The statistical significance of differences between item means by search strategy was determined using Student's t tests. Websites identified using popular search engines scored significantly lower for content quality ($P < .0001$), were easier to navigate ($P < .001$), had better overall adherence to usability standards ($P < .0001$), and had lower reading levels compared with those sites identified using a government web portal. Nutrition websites obtained using popular search engines may be aesthetically appealing and easy to use, but they often provide inaccurate nutrition information. As consumers increasingly turn to the World Wide Web for nutrition advice and education, it is imperative that the needs of diverse user populations be identified and addressed. Future

nutrition education research should build on these findings by creating strategies that help users find reliable user-friendly gateways to accurate nutrition information on the Internet.

Nutrition in Medicine (NIM) Curriculum. The CNRU continues to provide nutrition education at medical schools around the globe. The CD-ROM system provides a means to deliver consistent nutrition education across institutions and instructors. Our database records indicate that this curriculum has been distributed to all 125 U.S. medical schools, to most U.S. osteopathic schools and to 110 international medical schools. Ongoing surveys show at least 129 medical schools use the modules in some way (92 U.S. schools, 37 international schools), and an additional 56 medical schools are planning on using or are evaluating the modules for incorporation. Fifty U.S. medical schools are actively using one or more titles as an integral part of a course. The purpose of this report is to describe the evolution of NIM in response to the barriers identified by us and others. Ultimately, we expect these advances will help to reach our goal of incorporating more nutrition into the curriculum and better meet instructors' needs. This curriculum has expanded access to users to include online modules in the fall of 2005. In addition, a new course on Pediatric Overweight is now being offered. A distinctive feature of this new curriculum is its modular approach to instruction. The web-based curriculum consists of multiple discrete instructional units. Each unit contains content designed to meet one specific learning objective; thus these units are the building blocks of each learning module. This organization into smaller instructional units allows the NIM team to construct modules that are tailored to specific needs. Another distinctive feature is the new format for the case practices; these video segments are shorter and more targeted to focus on specific clinical skills. This modification makes the most effective use of limited time in the curriculum and portrays the reality of clinical practice today. Other impressive features of this new curriculum are the ease of updating material and the immediate accessibility to that information once it is posted. This is important, as nutrition science and guidelines are constantly evolving.

Educational Activities/Accomplishments

Clinical Nutrition Seminar Series. Seminars were held every 2 to 4 weeks. The seminars are open to the entire University of North Carolina faculty, staff, and students, as well as to the public. The average seminar usually draws from 40-50 attendees. Speakers include University of North Carolina faculty, visiting professors, and scientists, as well as graduate students who are defending their research theses.

Visiting professors who present research seminars often meet with CNRU investigators to discuss their research and provide an external view of the investigator's work. This can be beneficial both to the speaker and to the investigator. The visiting professors also meet with graduate students and postdoctoral fellows to provide insight and offer perspective on nutrition education, research training, and possible career opportunities.

Dietary Assessment Seminars. The Nutrition Epidemiology Core hosts regular seminars on Dietary Assessment methodology. Participation in this discussion group averages 20 scientists and is composed of faculty and students from the UNC School of Public Health, School of Nursing, School of Pharmacy, and School of Medicine. In this setting, we encourage questions and spur discussion in hopes of providing an active sharing and learning atmosphere. In addition to providing a medium to practice talks for national meetings, the topics and speakers over the past year included: *Seeing is Believing: Using Observations of School Meals to Validate Using Portions of Dietary Recalls by Elementary School Children*, presented by Suzanne Domel

Baxter, Ph.D., R.D., F.A.D.A., University of South Carolina Center for Research in Nutrition and Health Disparities. The seminars were fewer than normal during 2005 due to staff turnover. The Nutrition Epidemiology Core will resume their normal seminar schedule in 2006.

Nutritional Biochemistry and Metabolism Seminars. The Nutritional Biochemistry and Metabolism Core hosts monthly seminars which are attended by faculty and students from the UNC Schools of Public Health and Medicine. Some of these seminars in 2005 included: Selenium and the Immune Response to Infectious Disease, presented by Patricia Sheridan, Ph.D., UNC Chapel Hill Department of Nutrition; What We are Learning About Fatty Acids Partitioning in Cells – the Role of Long Chain Acyl-CoA Synthetases, presented by Douglas Mashek, Ph.D., UNC Chapel Hill Department of Nutrition; Diet, APOE, and Neurodegenerative Disease, presented by Patrick Sullivan, Ph.D., Duke University; Genetic Architecture of Obesity Predisposition, presented by Daniel Pomp, Ph.D., UNC Chapel Hill Department of Nutrition; and Epigenetics and Adult Disease Susceptibility, presented by Randy Jirtle, Ph.D., Duke University.

Intervention Research Methodology. The CHAI Core holds a 1-day intensive workshop once a year on Using Focus Groups in Health Behavior Research. Four main topics are covered: using focus groups as a data collection method, focus group design and recruitment, focus group facilitation, and analyzing focus group data. The workshop has been very popular and has attracted students and faculty from several schools and programs at UNC and other academic institutions.

Annual Public Health Nutrition Update. Each year, the CNRU helps sponsor the Annual Public Health Nutrition Update. This year's topic was To Supplement or Not. Sessions included the keynote speech by Dr. Reinhold Vieth from Mount Sinai Hospital and University of Toronto on Evaluation of Nutritional Risk for Vitamin D: An Evolving Issue. Other topics included: Who is Using Nutrient Supplements in the US?; What Have Randomized Controlled Trials Taught Us About Supplements?; Practical Applications for Health Professionals; Case Studies of Supplement Use in Adolescents; Supplements in Disease Treatment of Individuals With Diseases; Customizing Dietary Supplements in Health and Disease; and the Panel Discussion: Who Should Be Using Supplements?

Medical School Nutrition Education. UNC sustains a required nutrition component of the second year curriculum for medical students, directed by Dr. Martin Kohlmeier, CNRU investigator. In 2005, 165 students completed the course. In addition, the UNC CNRU continues to provide assistance with the development of important computer-based components of the nutrition curriculum at UNC Medical School. The CD ROMs for each series are listed: The Disease Series (Nutritional Anemias, Nutrition and Stress, Nutrition and Cancer, Diet, Obesity and Cardiovascular Disease, and Diabetes and Weight Management: Aberrations in Glucose Metabolism); The Lifecycle Series (Maternal and Infant Nutrition, Nutrition and Growth, and Nutrition for the Second Half of Life), and the Special Topics in Nutrition Series (Nutrition Supplements and Fortified Foods, and Sports Nutrition). In addition, a new course on Pediatric Overweight is now being offered and the web-based delivery of the modules is being enhanced for greater ease of access for students.

In 2005, this curriculum had been distributed to all 125 U.S. medical schools, to most U.S. osteopathic schools, and to 110 international medical schools. Ongoing surveys show at least 129 medical schools use the modules in some way (92 U.S. schools, 37 international schools),

and an additional 56 medical schools are planning on using or are evaluating the modules for incorporation.

Brochure and Website. The UNC CNRU brochure and website (*www.cnrc.unc.edu*) serve as two ways in which scientists can get information about the CNRU. The brochures are sent to investigators in various health sciences departments at UNC and to any visiting scientists to the department of nutrition at UNC. The website is frequently updated with information that will help other researchers find the resources that they need at the CNRU. In addition to the general CNRU brochure, a Unique Services brochure was created to increase our level of support to other research centers in the nation. The Unique Services brochure lists all services that are unique to the UNC CNRU. To help encourage investigators acknowledge the NIH-CNRU in their publications, we send quarterly reminders to cite the CNRU grant when preparing publications.

Community Education. The CNRU enrichment activities are designed to increase the visibility of clinical nutrition research on the UNC campus and in the communities with which we interact. CNRU members make presentations at community organizations on nutrition-related topics, such as "Fad Diets" and "Heart Healthy Diet." Dr. Steven Zeisel, UNC CNRU director, participated in interviews for the local and national newspaper and broadcasting on topics such as pediatric obesity, choline and the brain, and dietary supplements. In addition, research by numerous CNRU investigators was covered in the popular press, reaching the public across the world.

The former CNRU Administrator, Karen Erickson, served as a member of the Carolina Speakers Bureau, a UNC-Chapel Hill sponsored group that speaks on various topics in the community across North Carolina. Ms. Erickson's presentations in the past project year included Nutrition After 50 and Obesity Management. She also contributed quarterly articles for the Good Medicine Column, which is a web and print column produced by UNC Health Care. The column appears on the UNC Health Care website, the websites for several North Carolina newspapers, and in the print editions of the newspapers. Good Medicine column writers are predominantly UNC physicians and the column is geared towards educating the public about health topics. Ms. Erickson contributed three columns this year on soy foods, functional foods, and healthy eating for the holidays. The current CNRU administrator, Kelly Nordby, submitted two articles on Metabolic Syndrome to the Durham Herald-Sun, a local newspaper, and the UNC Health Care website and plans to continue speaking in the community and writing articles on current nutrition topics.

Benefits and Interactions Resulting from the Existence of the CNRU

The UNC CNRU demonstrates success at coordinating nutrition research efforts and bringing new investigators into the field of nutrition research. Services offered by the cores are unique, cost effective, and integral to the demonstrated success of CNRU investigators. The Cores continue to bring new investigators into the Center, develop new methodologies and tools, and offer unmatched services in a coordinated and efficient manner.

Collaborations With Other Centers. The CNRU has materially changed the structure and function of several major research centers on campus. In its competing renewal, the Lineberger Comprehensive Cancer Center was funded for increasing their support of our CHAI Core. The General Clinical Research Center was provided renewal funds for the shared Body Composition

Core with the CNRU. An extra research dietitian was also funded because of increased use of the GCRC by nutrition investigator members of the CNRU. The Center for Environmental Health and Susceptibility was funded to provide shared support for CNRU core facilities to increase use by investigators studying nutrition and environment interactions. The focus on nutrition brought to the Center by the CNRU has led to the inclusion of an Obesity Research Core in the Center's competing renewal submitted to NIEHS in 2004.

Leading Research Initiatives. The CNRU director is currently leading an initiative in collaboration with North Carolina State University to propose the creation of a new United States Department of Agriculture Human Nutrition Center, scheduled to open in 2007, which will be focused on using cutting edge genomic, proteomic, and metabolomic biotechnology to develop innovative approaches to designing healthier agricultural products and to understanding the role of diet and activity in normal brain development, preventing cancer and preventing obesity. This Center will be located in Kannapolis, NC, and will result in a breakthrough in how we use nutrition to enhance human health, using individual variations in metabolism to develop custom-tailored solutions that target individual susceptibilities and differences. Until now, nutritionists have had to rely on general advice, but new technology makes it possible to understand metabolism at the level of the individual. Resources already committed by industry and universities will be focused by the creation of this center, thereby accelerating progress in this critical area.

The CNRU continues to be in the forefront of research on childhood overweight and adult obesity. The Department of Nutrition was recently awarded $4 million by Gatorade to fund research on childhood overweight. Not only is the CNRU providing services to develop the intervention component of the grant, but it is also working with several investigators who will receive pilot money from the grant to carry out small research projects. The increased visibility brought to the issue of obesity has also led to the submission of several new grants that address prevention and treatment of obesity by CNRU investigators.

Cost-effective Services for Investigators. The presence of the CNRU allows for unique and cost-effective services for investigators involved in research with nutrition components. The Administrative Core offers coordinated biostatistics services that would be considerably more expensive and labor intensive if an investigator was to procure the services individually. The Epidemiology Core offers extensive shared nutrition databases, expert assistance with methods development, and facilities for creating food images, all of which are not typically readily available to investigators. The coordination and central availability of these services in the Core also contributes to its cost effectiveness. Services of the CHAI Core, in addition to being offered in a unique mix to which there is no comparison, are offered at a discounted rate with grant development and consultation provided free of charge.

The Nutrition Epidemiology Core offers a unique service by providing the necessary resources (trained staff and top-of-the-line software, i.e. NDS-R) for the purpose of collecting 24-hour recalls. NDS-R costs make it prohibitive for each research project to purchase and maintain (aside from the initial purchasing price, there is a yearly license charge). Additionally, staff must be trained and certified to use the software, at an additional cost to the project. The Nutrition Epidemiology Core offers investigators the ability to afford high-quality dietary measurements at cost without having to purchase the software or hire trained personnel. An example of this cost savings can be expressed in a recent service agreement completed by the Core for Joanne Harrell in the UNC School of Nursing. As part of a nationwide diabetes prevention pilot study (U01

DK061223), the Core was contracted to perform three 24-hour recalls on 70 English/Spanish speaking adolescents in a month time period by phone. The Core hired three staff members, in addition to the coordinator, had them certified by NDS and had available three copies of the program, three laptop computers, and phone service to complete the task for a total price of $6,200. This included extensive quality control that coordinated across all nine sites of the pilot study. Ordering the NDS-R software, training the four staff, and paying for the labor would have cost the project, if they had done it on their own, at least $38,000. The investigator saved money by using the Core to conduct the recalls. In addition, the Nutrition Epidemiology Core provided service in the development of the infant portion size instrument used for Peggy Bentley's Infant Feeding Study (R01 HD042219) by providing our photographer to take standardized pictures of different foods appropriate for this age group. Additional services for this project included development of a 5-day food record to be maintained by the childcare provider, NDS-R training for the Infant Feeding study staff, and quality assurance of dietary recalls. The PI has recently contacted us to begin the collection of dietary data since it has been too difficult to maintain a trained staff for this purpose.

The Nutritional Biochemistry and Metabolism Core offers important advantages for investigators using the Core facilities. These include the fact that they can be trained in these techniques or use them without cost. This is important for investigators who want to develop new techniques for future grant submissions because it is difficult to obtain grant support to develop methods to gain preliminary data. In addition, purchasing reagents in bulk and the routine use of these assays is cost effective. For example, an analysis of homocysteine by the UNC Hospital laboratories costs $150 per sample, but the same assay performed by the Core costs less than $30 (reflecting our incremental costs for the assay). In addition, by providing support services for investigators who use other campus core facilities, rather than duplicating these services, the CNRU can provide a cost-effective and efficient service. For example, we will prepare samples for microarray analysis rather than providing the microarray service itself, which is already available on campus, thereby providing cost-effective and state-of-the-art molecular biological techniques. In addition, offering a new core service, real-time PCR, provides a cost-effective mechanism for this important technique that is not otherwise available as a core service on this campus. The high cost of purchasing the machine required for real-time PCR analysis would be prohibitive for most investigators. For the Human Body Composition Subcore, the use of the dual energy x-ray absorptiometry (DEXA) is provided at no charge. This compares to fees of $300-600 for use of the DEXA in UNC Hospitals. Another advantage to investigators is the high-quality of scans that are acquired at research standards as well as ease of scheduling access to an instrument that is used for research purposes only. Similarly, access to the MRI for small animals and the small animal DEXA would be prohibitively expensive if individual investigators did not have access to the CNRU's instrumentation.

The CHAI Core provides researchers with an integrated set of services not readily available elsewhere. The CHAI Core has assembled a strong team of faculty and staff experts and state-of-the-art equipment to assist with nutrition behavior intervention research from concept to implementation and evaluation. In addition to contributing to research by incorporating behavioral science into interventions and evaluations, the Core added value through linkages, methods development, and savings/efficiency. The Core has helped link investigators across the campus sharing interests from the Schools of Information and Library Science, Journalism and Mass Communication, and Social Work to create more innovative interdisciplinary research teams. The CHAI Core now has two full-time programmers who are able to tailor web-based surveys and interventions for the specific needs of each research project. CHAI Core has

invested staff time and resources to develop innovative methods and studies that will further behavioral science and health communication research. For example, Dr. Lisa Sutherland and Beth Fowler have developed methodology and protocol to conduct rigorous usability research and testing with interactive health communication applications in "real world" and field-based rather than laboratory settings. A CNRU investigator recently stated "CHAI Core does EVERYTHING!" and this statement accurately reflects the Core's goal to provide the expertise and services needed by researchers from the formative research through graphic design and web development to the analysis phase thus saving CNRU members time and money on staff hiring, consulting services, training, retention, and administration.

Attracting Investigators to Nutrition Research. When we first applied for funding, the UNC CNRU's research base was dominated by faculty members holding a primary appointment in the Nutrition department. Now we reach more than 75 faculty members from other departments. Many of these are including a significant component of nutrition research in their funded studies for the first time and did so because of the availability of assistance from the CNRU. For a good number of investigators, our cores helped them to demonstrate expertise in nutrition and provided the preliminary data needed to support successful grant applications.