University of Alabama at Birmingham
Clinical Nutrition Research Unit
Start Date: 2000
Status: Ongoing
Source of NIH Support: NIDDK
Website: www.uab.edu/cnrc

Organization and Goals

The goal of the University of Alabama at Birmingham (UAB) Clinical Nutrition Research Unit (CNRU) is to foster a multidisciplinary approach to basic, clinical, and translational research with an emphasis on understanding the metabolic factors, environmental influences, and associated genetic traits underlying nutrition and obesity-related disorders, particularly in the Southeast. This is appropriate, if not necessary, because: nine of the 10 States with the highest death rates are in the South, with Alabama ranking fifth in the nation in the rate of overall mortality and about two-thirds of adult deaths in Alabama are due to heart disease and cancer, which are nutrition and obesity-related illnesses. Further, because Alabama has the third least migratory population in the nation, this is an ideal environment for studying genetic and socio-economic patterns which predispose this population to such high rates of nutrition and obesity-related disorders. According to Behavioral Risk Factor Surveillance System data in the last several years, Alabama has consistently had among the highest rates of obesity and diabetes in the U.S. (See: *www.cdc.gov/brfss/*).

The specific aims of the CNRU are:

- *Research:* To strengthen current multidisciplinary research efforts and to focus on the multiple biological bases for nutrition/obesity-related disorders which are prevalent among populations throughout the world and especially in minority groups, the poor, and in Alabama and the Southeast. This occurs by fostering highly integrated and multidisciplinary research efforts in nutrition/obesity, among UAB scientists skilled in areas such as translational medicine, molecular biology/genetics, biostatistics, comparative anatomy/physiology, epidemiology, psychology, endocrinology and diabetes, pathology, NMR spectroscopy, exercise physiology/muscle metabolism, and pediatric/adult medicine.
- *Training:* To strengthen the nutrition training environment at UAB in order to improve the education of medical students, house staff, practicing physicians, graduate and postgraduate trainees, allied health professionals, and research scientists. This occurs through our Core Laboratories, our Nutrition/Obesity Seminar Series, and an Academic Enrichment Program which fosters intramural and extramural collaborative research, as well as enhancement of our well established health professions nutrition training programs.
- *Information Services:* To enhance patient care and public health through translation of relevant research findings into applicable information for the public, especially in the State of Alabama and the Southeast. This occurs through activities of our EatRight Information Service and related community projects to increase awareness and knowledge about nutrition among the public and health professionals.

Core Laboratories

Administrative Core: David B. Allison, Ph.D., Director, W. Timothy Garvey, M.D., Associate Director, Nancy Bell, Financial Associate

External Advisory Group members:

Sheila Collins, Ph.D., Senior Investigator, Director, Endocrine Biology Program, CIIT Centers for Health Research

Michael Jensen, M.D., Professor and Associate Program Director, GCRC, Mayo Clinic, Rochester

David Kelley, M.D., Professor, Department of Medicine, University of Pittsburgh

Eric Ravussin, Ph.D., Professor, Chief, Division of Health and Performance Enhancement, Pennington Biomedical Research Center, Department of Human Physiology, Louisiana State University (ad hoc member)

Steven Zeisel, M.D., Ph.D., Professor and Chair, Department of Nutrition, CNRU Director, University of North Carolina, Chapel Hill

Tom Wadden, Ph.D., Professor of Psychology, University of Pennsylvania

Energy Metabolism/Body Composition Core: Barbara Gower, Ph.D., Director

Genetics Core: W. Timothy Garvey, M.D., Interim Director

Small Animal Phenotyping Core: Tim R. Nagy, Ph.D., Director, Philip Wood, D.V.M., Ph.D., Associate Director

Biostatistics Core: Seng-jaw Soong, Ph.D., Director; Renee Desmond, Ph.D., Acting Director

Pilot and Feasibility Studies

Our pilot and feasibility (P/F) grant program has been successful in helping young investigators make the transition from beginning scientist to independently funded investigator. Here we list only our active P/F grants.

P/F grants receiving a second year of funding after competitive review:

Long-term Follow Up of EatRight Weight Management Program Participants. Jamy Ard, M.D. This P/F project will conduct follow-up anthropometric, body composition, and dietary measurements on former participants of the EatRight Weight Management Program who are in the database from the year 2001 through 2004. The first year of study was completed successfully and the second year aims include: recruiting 100 control participants and 75 new follow-up participants, and completing the second follow-up visit for study participants who were evaluated during year 1.

Mitochondrial Dysfunction and NASH. Shannon Bailey, Ph.D. This P/F project is designed to investigate the role of the mitochondrion in the development of nonalcoholic steatohepatitis (NASH), a precursor to serious liver diseases including cirrhosis and hepatocellular carcinoma. During year one a dietary mouse model was successfully established with results indicating the presence of NASH in livers, mitochondrial dysfunction, and alterations in the mitochondrial proteome. The aims of year two of this study are to characterize protein alterations in

mitochondria and to investigate protein post-translational modifications, specifically to protein thiol groups.

A Family-Based Intervention for African American Children at Risk for Overweight and Obesity. Monica Baskin, Ph.D. The overall objective of this study is to develop and pilot test a family-based nutrition and physical activity intervention for African American children at risk for becoming overweight and obese. The specific aims are to: describe barriers and facilitators of healthy lifestyles among African American families; design the format and content of a family-based nutrition and physical activity intervention for African American children based on barriers and facilitators identified above; test the intervention with 12-16 families with at least one child at risk for overweight (85^{th} percentile < BMI > 95th percentile for age and sex) age 6 to 10; and evaluate the potential positive impact of the pilot intervention on child and parent body mass index, diet, sedentary behavior, and physical activity.

The Molecular Determinants of Human Melanocortin-3 Receptor (MC3R) Responsible For Ligand Binding. Yingkui Yang, Ph.D. There are two hypotheses in this study: that there are two main binding pockets in the transmembrane domain of MC3R and that different domains are responsible for ligand specificity. Two specific aims will be tested in year two of this project: to examine the molecular determinants of MC3R that are responsible for agonist α- Melanocortin Stimulating Hormone binding and to determine the molecular basis of MC3R for Agouti-related Protein antagonist activity.

New awards for 2005:

Characterizing the Diet/Nutrition Effect on Gene Alternative Transcripts Using Affymetrix Microarray Data. Xiangqin Cui, Ph.D. This P/F project seeks to determine if oligoarray chips can be used to assess differential expression of splice variants of genes that are regulated by diet/nutrition. The hypothesis is that alternative probes detect different coding sequences in genes, and therefore will differ in response if the coding sequence in question is only expressed in the longer splice variant of the gene. A published microarray data set from a calorie restriction study will be characterized and mixed effect ANOVA models and test statistics for identifying genes whose alternative transcripts are affected by diet and/or nutrition. Significant changes in expression of alternative transcripts will be validated using real-time PCR.

Buffering DNA Replication by Regulation of Threonine Metabolic Flux. John Hartman, Ph.D. This proposal investigates the concept of "genetic buffering", i.e., genetic selection that ensures phenotypic stability by the activities of genes that functionally compensate for the effects of a metabolic perturbation. The concept of genetic buffering is a first step toward understanding how whole cellular systems work. There are three aims in this proposal designed to test the hypothesis that DNA replication is buffered by interactions in a network of genes that regulate threonine metabolic flux. The first aim will explore how gene buffering can compensate for perturbations in ribonucleotide reductase (RNR) activity or transcription. The second aim will measure dNTP levels when genes that buffer RNR activity are absent. The third aim will measure threonine uptake in response to RNR perturbation.

Insulin-Like Growth Factor-1 (IGF-1) And Growth Hormone (GH) Signaling In Pancreatic Islet B-Cells: Potential Roles In Obesity-Linked Type 2 Diabetes. Yao Huang, Ph.D. This P/F project examines the hypothesis that Growth Hormone (GH) and Insulin-Like Growth Factor -1 (IGF-1) serve a costimulatory function in the replication and survival of pancreatic cells.

There are two specific aims: to characterize the biochemical relationship between GH and IGF-1 signaling in ß–cells and to assess the impact of the GH/IGF-1 collaboration on ß–cell growth and survival. Successful completion of this study will provide insight into the ability to respond to hyperglycemia with an increase in beta cell mass, allowing increased insulin secretion, and a glimpse into the roles of specific growth factors and hormones in this beta cell compensation.

Cilia Function and Regulation of Energy Homeostasis. Brad Yoder, Ph.D. This new P/F study will investigate the role of cilia in the development of obesity. Preliminary data from floxed polaris alleles in the mouse (an axonemal/IFT protein) indicate a postnatal obesity phenotype potentially characterized by loss of satiety. The proposed series of experiments will investigate the potential localization of known receptors of the leptin pathway to the ciliary axoneme; undertake detailed phenotypic studies in the mice examining body composition, energy metabolism, and glucose homeostasis; and investigate the possible link between specific neuronal subtypes and the development of obesity.

Scientific Advances/Accomplishments

The UAB CNRU has facilitated and/or provided direct support for the following lines of research, which are directly relevant to areas of public health importance.

Antipsychotic Drug-induced Weight Gain: Development of an Animal Model. As recognized by several academic societies (American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; and North American Association for the Study of Obesity) and the NIH (Program Announcement (PA) Number: PA-05-104), most atypical antipsychotic drugs (AAPDS) cause some weight gain and in many cases, the magnitude is quite large (e.g., ~15-16 kg after 1 year of treatment on olanzapine). Moreover, AAPDS are among the most commonly prescribed drugs and often are taken for life. Yet, the mechanisms are not fully understood and no well-established mouse models exist for investigating the mechanisms. Thus, CNRU investigators developed a mouse model to evaluate the effects of AAPDs on eating, body weight (BW), and body composition. Female C57BL/6J mice were used to test olanzapine, quetiapine, ziprasidone, and risperidone. Mice were acclimated to individual housing, given ad libitum access to chow and water, dosed with placebo peanut butter pills for 1 week, and then dosed daily with AAPD-laced peanut butter pills for 4 weeks. Weekly food intakes and BWs were measured and body compositions were determined at the end of each experiment. After 4 weeks of treatment, olanzapine, quetiapine, ziprasidone, and risperidone caused significant weight increases, but only olanzapine and quetiapine were associated with significantly increased food intake. Body composition data revealed that olanzapine-treated mice had more relative fat mass and risperidone-treated mice had more relative lean mass than did control mice. Quetiapine and ziprasidone did not significantly affect relative body composition even though BW was increased. Our mouse model of AAPD-induced weight gain resembles the human response to these medications and offers an important resource to the scientific community to investigate the mechanisms for AAPD-induced weight gain and fat accumulation. This research depended heavily on the CNRU's small animal phenotyping core.

Metabolic Factors in the Etiology of Obesity. Investigators from several academic units across campus collaborate in two projects entitled, Role of Metabolism and Exercise in the Etiology of Obesity and The Effects of Exercise Training on Weight Maintenance in Black and White Women. These projects rely heavily on the resources of the CNRU Energy Metabolism/Body

Composition Core for sophisticated analyses of energy metabolism, body composition, and exercise physiology. The results to date have demonstrated the following major outcomes: 1) Neither REE nor fuel utilization patterns distinguished post-obese white and black women from race-matched never-obese controls or predicted weight regain in post-obese women. By contrast, weight regain was associated with lower levels of free-living physical activity and physical fitness, both modifiable factors. 2) Despite comparable fat and fat-free mass, black women had lower sleeping and resting EE and lower energy cost of exercise than white women. In addition, post overweight black women but not never obese black women overestimate participation in free-living energy expenditure and experience more difficulty in being physically active than white women. Several factors have been found to be suggestive as contributors for racial differences in weight gain patterns. Despite being more economical in walking, black women have lower aerobic capacity (VO2max), less exercise endurance, and higher heart rates during submaximal work tasks such as walking, bicycling, and climbing stairs. These "exercise fitness" variables explain racial differences in long term weight gain. Several of the most recent findings that have resulted from these studies are focused on mechanisms for explaining findings from our previous studies. For example, we have shown that gastrocnemius tendon is longer in black women, that tendon length is related to walking economy (probably because greater use of elastic recoil during the walking cycle), and that tendon length explains differences in walking economy between black and white women. Aerobic capacity differences between black and white women seem to be explained by racial differences in blood hemoglobin concentration and maximum cardiac output. We have shown that fast twitch muscle fiber is negatively related to muscle metabolic economy, and muscle metabolic economy is negatively related to aerobic capacity of muscle as well as maximum oxygen uptake. In addition, muscular strength and aerobic capacity are positively related to endurance capacity. Despite this, endurance capacity and muscular strength are positively related and muscle metabolic economy is negatively related to subsequent 1 year weight gain. Taken together, these results suggest that individuals who have a higher percentage of inefficient fast twitch muscle fibers will tend to do work less efficiently, thus choosing to be less physically active because it is energetically costly. The reduction in physical activity then contributes to more weight gain, completing a positive feedback loop that contributes to further reductions in physical activity and more weight gain. Preliminary results from our exercise training studies suggest that both aerobic and strength training are associated with improved endurance and better long term weight maintenance.

Other studies have explored the role of obesity in the Insulin Resistance Syndrome (or the Metabolic Syndrome). These studies have demonstrated that, while obesity exacerbates insulin resistance, the severity of insulin resistance is largely explained by obesity-independent factors in populations. Furthermore, insulin resistance in lean or obese individuals is accompanied by alterations in VLDL, LDL, and HDL subclass particle sizes and concentrations assessed by NMR. Furthermore, the ATPIII criteria for diagnosis of the Metabolic Syndrome has very low sensitivity for detecting insulin resistance accompanied by dyslipidemia, indicating that more stringent clinical criteria are necessary for cardiovascular disease risk surveillance.

Racial/Ethnic Differences in Obesity or Nutrition Related Traits and Treatments for Obesity in Ethnic Minorities. In collaborative studies of faculty of the Departments of Nutrition Sciences, Pediatrics, Health Behavior; and Biostatistics, studies are underway to understand racial and ethnic differences (i.e., health disparities) in obesity related traits. A longitudinal study is underway to determine if and why glucose tolerance deteriorates more rapidly in African American female adolescents than in African American male adolescents or Caucasian adolescents. In a parallel study among collaborators in Nutrition Sciences and the Division of

Endocrinology and Metabolism, ethnic differences in insulin sensitivity are being examined. Specifically, the investigators are characterizing insulin sensitivity, secretion, and clearance in African Americans and Caucasian Americans of three age groups to determine whether greater insulin resistance or hyperinsulinemia is likely to be the primary event that ultimately results in the development of type 2 diabetes among African Americans. Further research has been established at the Department of Nutrition Sciences to understand the etiology of these differences in insulin response and action. Under the model that ethnic differences respond to both genetic and environmental factors, the genetic admixture approach has been used to determine the ancestral genetic contributions to obesity and diabetes related traits in African- and Caucasian American individuals. Environmental factors such as socioeconomic status, dietary consumption and physical activity have been used to explore the nongenetic contribution to these differences in advanced statistical models developed in collaboration with the Section on Statistical Genetics of the Department of Biostatistics. Each of these studies is dependent on resources of the Biostatistics Core and the Energy Metabolism/Body Composition Core which provides state-of-the-art assessments, including body composition analysis by the four-compartment model (DEXA, Bod Pod, deuterium dilution); CT scans for analysis of body fat distribution; analyses of hormones, substrates, and insulin sensitivity; and analysis of stable isotopes by isotope ratio mass spectrometry (IRMS). These are just a few examples of our work in this area.

Genetic Factors in the Etiology of Obesity and Nutrition Related Traits. Many genetically related studies have been completed and/or are ongoing. These studies involve mice, humans, and other species, many phenotypes related to nutrition, obesity, and diabetes, and use many methodologies ranging from gene expression profiling, family studies, twin studies, cohort studies, and experimental crosses in animal models. This work has been greatly facilitated by the CNRU Genetics Core Facility and the Biostatistics Core.

Dr. Fernandez' NIDDK-funded Amerigo Project is one example of an ongoing genetics project. Dr. Fernandez' abstract states: "Racial and ethnic differences in the incidence of diabetes have been identified in epidemiological studies. Although recent investigations have associated genetic markers and environmental factors contributing to the diabetes-related phenotypes within populations, the extent to which these factors in fact account for racial/ethnic differences is still unclear. The main objective of this study is to investigate the effect of genetic and environmental parameters on racial/ethnic differences in diabetes-related traits by modeling individual estimates of genetic admixture and environmental measures of energy intake, energy expenditure and socioeconomic status (SES) on measures of fasting insulin, sensitivity to insulin and initial phase of insulin secretion after exposure to glucose. A sample of 120 African-American (AA), 120 European-American (EA) and 120 Hispanic-American (HA) boys and girls of 7-13 years of age will be tested to obtain outcomes of insulin action and response, body composition, energy intake and energy expenditure to questionnaire and SES. The specific aims of this investigation are: (a) To test the role of European genetic admixture on diabetes-related measures of fasting insulin (FI), insulin sensitivity (Si) and insulin response to glucose (AIRg) after adjusted for body composition parameters (2) To investigate how the relationship between the environmental parameters energy intake, energy expenditure and socioeconomic status differ as a function of admixture and diabetes-related measures of fasting insulin (FI), insulin sensitivity (Si) and insulin response to glucose (AIRg), and (3) To test phenotype-genotype associations between ancestry-informative markers (AIMs) and measures of FG, Si and AIRg after adjusted for body composition and environmental parameters in a sample of AA, HA and EA prepubertal children. The proposed investigation will provide meaningful and important insight into the understanding

of biological, non-biological and the interaction of both components in racial/ethnic differences in diabetes-related traits. Furthermore, the results of this investigation will serve as a tool for the development of effective preventive strategies to reduce the prevalence of diabetes and its related traits in racial/ethnic populations."

Another example is Dr. Arnett's NHLBI-funded project involving gene-environment interaction. Dr. Arnett's abstract states: "Hypertriglyceridemia is emerging as important predictor of atherosclerosis, and recent evidence suggests related phenotypes of triglycerides (TGs), such as TG remnant particles and small LDL particles, are particularly atherogenic. There is considerable variation in the response of TGs and related phenotypes to the environment. The aim of the proposed study is to characterize the genetic basis of the variable response of TGs to two environmental contexts, one that raises TGs (dietary fat), and one that lowers TGs (fenofibrate treatment). We will recruit 2,400 family members from 3-generational pedigrees of the ongoing NHLBI Family Heart Study (FHS) in two genetically homogeneous centers (Minneapolis and Salt Lake City). We will collect measurements before and after a dietary fat challenge to assess postprandial TGs and related atherogenic phenotypes (VLDL TGs, chylomicron TGs, TG remnant particles, HDL and LDL particle sizes, total cholesterol, LDL-C, and HDL-C). In families with 2 or more members in a sibship with TGs >= 130 mg/dl, we will conduct a short-term, placebo-controlled, randomized trial of fenofibrate in all willing and eligible family members (anticipated sample size = 1,200). A two-period crossover design will be executed with a 2-week washout between two 3-week treatment periods (placebo or micronized fenofibrate, 160 mg). About 1,000 family members have a Marshfield genome marker set available as part of NHLBI FHS; the remaining 1,400 will be typed using the same marker set. We will conduct genome-wide linkage analyses using state-of-the-art methods to localize novel genetic loci contributing to TG response in the context of fat loading and fenofibrate treatment. We will type 15 single nucleotide polymorphisms (SNPs) in ten candidate genes known to contribute to the response of TGs to dietary fat and fenofibrate, and create haplotypes for association studies. We will use combinatorial partitioning methods and neural networks to test association of the individual SNPs and haplotypes with response to the two environmental interventions. The identification of genetic loci that predict TG response in the presence of two disparate contexts, fat loading and fibrate therapy, may provide insights into genetic pathways (a) predisposing to hypertriglyceridemia, ultimately leading to avenues for primary prevention, and (b) predicting response to TG lowering, leading to new drug targets for hypertriglyceridemia."

Other examples include genetic studies in community-based populations and national cohort studies. CNRU investigators have ascertained over 1,300 Gullah-speaking African Americans with and without diabetes, living in the South Carolina barrier islands and coastal communities. Population genetic studies have defined this population as a relatively homogeneous community with far lower Caucasian genetic admixture than any other African American population yet identified. An application has been submitted to the Center for Inherited Disease Research to complete a whole genome scan for diabetes genes in collaboration with investigators at Wake Forest University. Candidate gene studies have also been performed in the national cohort of patients in the Diabetes Control and Complications Trial. Over the past year, this has led to increased insight regarding the contribution of multiple genes, including fibrinogen, apoCIII, hepatic lipase, and apoE, to microvascular and macrovascular disease complications.

Mouse Models of Disorders of Fat Metabolism. Members of the CNRU Genetically Defined Mouse Models Subcore of the Small Animal Phenotyping Core have consulted with several investigators to develop specific mouse models by genetic combinations or genetic manipulation

to investigate disease processes that involve lipid metabolism. Drs. Wood and Robert Hardy have begun development of a transgenic mouse model that will endogenously desaturate long-chain fatty acids and produce long-chain ω-3 fatty acids by expressing an adipose tissue specific transgene that includes the long-chain fatty acid desaturase gene (*fat-1*) from C. elegans. The goal of this project is to focus on the potential beneficial properties of long-chain ω-3 fatty acids on maintenance of fully functioning adipocytes to maintain health. Other mouse models underway include three involved with lipoprotein metabolism, insulin resistance, diabetes, and obesity.

Translational Research/Public Health. A primary clinical activity of the CNRU is based in the UAB EatRight Program. The EatRight Weight Management Program is a 12-week lifestyle-oriented weight control program (*www.uab.edu/eatright*). Developed at UAB, EatRight is based on the concept of "time-calorie displacement," which emphasizes the ingestion of large quantities of high-bulk, low-energy-density foods (primarily vegetables, fruits, high-fiber grains, and cereals) and moderation in high-energy-density foods (meats, cheeses, sugars, and fats). Clinical initiatives in EatRight benefit from ongoing research activities within the CNRU. Specifically, findings from the study entitled Role of Metabolism and Exercise in the Etiology of Obesity referenced above will allow us to develop more effective weight loss interventions for African American populations. One specific example of ongoing translational activity that will incorporate research findings from CNRU studies includes the development of a culturally appropriate weight management intervention based on the EatRight program. This developing intervention is being designed to target African Americans at increased risk of cardiovascular disease. The development process involves the use of cognitive mapping to define cultural variables that impact weight related behaviors. Understanding the relevant cultural variables that serve as barriers or facilitators to behavior change in African American populations will allow for a higher level of success in intervention implementation. Combining this knowledge with findings related to ethnic specific metabolic responses to energy restriction and physical activity provides the basis for a comprehensive intervention that is well informed from the behavioral, sociocultural, and physiologic perspectives. For effective dissemination within the community, this program will include collaborative efforts between the CNRU and Birmingham-based civic organizations. Utilizing the community infrastructure and existing relationships between UAB and Birmingham civic organizations, the EatRight program can provide the professional nutrition support to address the problem of obesity in Alabama.

In an Agency for Healthcare Research and Quality funded study led by Dr. Michael Harrington, The Alabama Practice Based Research Network (APBRN) was formed in cooperation with the Department of Family and Community Medicine at UAB. This network conducts research and translates research findings into practice using personal digital assistants (PDAs). They recruited new physician members into APBRN, particularly minorities; assessed members' technical capacity and needs and practiced population demographics; provided assistance and training in PDA use in clinical practice to members; and assisted members and their clinical staff in achieving IRB training. They then conducted a pilot feasibility study on obesity, using PDAs to gather data that is hoped to serve as the basis for a larger study aimed at improving patient care and reducing morbidity and mortality related to obesity.

Specific Accomplishments

The UAB CNRU has facilitated several lines of research which have direct relevance to the following specific areas of research. Several examples are listed under each area.

Women's Health. In the area of women's health, UAB investigators have:

- Identified obesity as a risk factor for dropout of cardiac rehabilitation among women.
- Evaluated the appropriateness of existing norms for serum ALT in obese women.
- Evaluated a series of obstetrical and surgical issues among obese women.
- Showed that weight loss and race modulate nitric oxide metabolism in overweight women.
- Collected data suggesting that the prevalence of cardiovascular disease risk in African American women may be underestimated based on the sole use of standard criteria and that insulin resistance develops before other metabolic syndrome indicators and therefore is a useful early indicator of metabolic syndrome in this population.
- Participated in the identification of risk factors for and evaluation of treatment of incontinence in obese women.

Minority Health. See section above entitled, "Racial/Ethnic differences in obesity or nutrition related traits and treatments for obesity in ethnic minorities."

Obesity. CNRU investigators have contributed to our understanding of obesity in many ways, including, but not limited to:

- Leading or participating in studies evaluating treatments for obesity or obesity-related sequelae.
- Developing novel statistical methods for the analysis of obesity related questions in epidemiologic research.
- Via studies of the neurobiology and physiology of food intake and body weight regulation using rodent models.
- The neuropeptide PYY3-36, an endogenous Y2-receptor agonist, has been touted as a potentially important anti-obesity compound. UAB Investigators participated in a report of 41 different rodent studies conducted in 16 independent labs worldwide that, in general, failed to reproduce initial reported effects of PYY3-36 on food intake or body weight. This report in the prestigious journal Nature and subsequently followed up with a longer report in Obesity Reviews provoked important scientific dialogue and has spurred increased and more rigorous research into this topic.
- In a series of investigations, UAB CNRU investigators have been helping to uncover the genomic regions and elucidate specific genetic influences on adiposity-related variables in novel model organisms and humans alike.

Health Promotion and Disease Prevention. CNRU investigators have studied the connections among social isolation, support, and capital and nutritional risk in older adults.

- High 5 + (PI: Frank Franklin, M.D., Ph.D.), a continuation of the original High 5 Alabama program, tested the efficacy to increase fruit and vegetable intake of a school-based intervention (cafeteria, curriculum, homework) with that school program combined with an enhanced family intervention (Family Fun Nites of meals together and games) compared to a delayed intervention control in third to fifth graders and their families. At 1 year follow-up, the school + family condition increased fruit and vegetable intake in both children and their parents by 0.6 servings/day and was efficacious without regard to race, SES, literacy, or family group. At 1 year follow up, the school alone program increased fruit and vegetable intake only in the children. Neither intervention was effective at 2 year follow up. A mediation analysis suggested that the school + family condition increase fruit and vegetable intake by increasing the intention of the mother to

adopt facilitators of fruit and vegetable intake but did not modify their barriers to fruit and vegetable intake.

- Head Start (PI: Frank Franklin, M.D., Ph.D.): The goal of this NCI funded study is to examine race/ethnic differences, comparing the fruit and vegetable relevant perceptions among African American, non-Hispanic white, and Hispanic families. The study is a collaborative program between UAB and Tom Baranowski, Ph.D. and Theresa Nicklas, Dr.PH. at the Baylor Children's Nutrition Research Center. Parents and experts provided an inclusive set of ways parents use to help their preschool child eat more healthy foods. We are currently recruiting 800 families to examine the relationship between the parents' use of these practices and the intake of fruits and vegetables and the overall dietary pattern in Head Start children and their parents. These relationships will be compared among the three race/ethnic groups and ultimately provide the objectives for an intervention program.
- PRIDE (PI: Frank Franklin, M.D., Ph.D.): The Program to Reduce Incontinence in Incontinent Women (PRIDE) is a NIDDK funded study to examine the efficacy of weight loss using a cognitive behavioral intervention for 6 months on incontinence in overweight women. The maintenance of weight loss between 6 to 12 months under two conditions—a continued cognitive behavioral condition and a motivational condition—will be compared. We are currently recruiting the first cohort of study participants. The UAB site is collaborating with a clinical center at Brown University, directed by Rena Wing, Ph.D. and the coordinating center at University of California San Francisco, directed by Deborah Grady, M.D.

Professional/Public Nutrition Education Efforts.

- Dr. Allison has led a highly successful NIDDK-funded short course on statistical genetics for nutrition and obesity researchers. The sixth annual course will be offered in early 2006. Courses have been videotaped, synched with PowerPoint slides, and placed on the web for free public viewing.
- UAB will be hosting a 2 day NIDDK-funded conference aimed at Alabama practitioners entitled, "Health Disparity in Obesity and Diabetes."
- Our CNRU posts all of its seminars in video format on the web for free public viewing.
- UAB provides intensive and comprehensive nutrition education for health professionals. Programs include required and elective educational opportunities for medical students throughout their 4 years of training, for nursing and dental students, for medical residents, and for medical doctors training to be physician-nutrition specialists.
- The EatRight Information Service provides nutrition information to both the public and health professionals through community programs and through a nationwide 1-800 toll-free line.
- The Intersociety Professional Nutrition Education Consortium (IPNEC) is a consortium of all of the major nutrition societies and certifying bodies for nutrition specialists. Directed through UAB, IPNEC has established a credentialing examination for physician-nutrition specialists in the U.S.
- CNRU faculty are part of the Alabama State Obesity Task Force.

Educational Activities/Accomplishments

The CNRU provides an inter-departmental Enrichment Program which includes a weekly Nutrition and Obesity Seminar Series for CNRU investigators. The weekly seminars currently attract an average of 45 participants, including CNRU investigator members as well as potential

new investigators attracted to the area of nutrition/obesity research. The number of extramural guest speakers generally includes three invited speakers each month, made possible by additional funding support of the Enrichment Program from private sources, complementing funds available from the CNRU. Each guest professor has a casual lunch time set aside to meet with interested graduate students and postdoctoral trainees. A few examples of extramural speakers the 2004-2005 academic year included the following persons:

- Sep. 14 – *Genetics of Bitter Taste Perception.* Dennis Drayna, Ph.D., NIH
- Sep. 21 – *Inflammation in Cardiovascular Disease.* Ronenn Roubenoff, M.D., Professor of Nutrition and Medicine, Tufts University
- Sep. 28 – *Analysis of Metabolic Syndrome in Multigenic Obesity Deprived Mouse Strains*. Daria Estrada-Smith, Gonda Goldschmeid Research Center, UCLA
- Oct. 19 – *Not Your Father's Aging Rodent: New Mouse Models for Aging Research.* Richard Miller, M.D., Ph.D., Professor of Pathology, University of Michigan
- Nov. 9 – *Pharmacogenetics of Antipsychotic Drug Response.* Anil Malhotra, M.D., Stony Brook University, New York
- Nov. 23 – *Understanding the Endocrine Role of Adipose Cells in Metabolic Diseases.* Xiaoli Chen, X. M.D., Ph.D., NIH/NIDDK
- Dec. 7 – *Glycogen Snythase Kinase 3: A Potential Target in Diabetes and Obesity*. Theodore P. Ciaraldi, Ph.D., Project Endocrinologist, Department of Medicine, University of California, San Diego
- Feb. 1 – *Use of RNAi Technology to Develop Molecular Medicines to Treat Obesity and Type 2 Diabetes.* Mark A. Tepper, Ph.D., CytRx Laboratories, Inc., Worcester, Ma.
- Feb. 18 – *Metabolic Action of IKK/NF-kB in Tissue-Specific Manner: From Insulin Resistance, Obesity to Muscle Wasting*. Dongsheng Cai, M.D., Ph.D., Joslin Diabetes Center, Harvard Medical School
- Mar. 1 – *AMPK and Cortisol as Metabolic Targets in a Clinical Drug Development Perspective.* Fredrik Lonnqvist, M.D., Ph.D., Associate Professor, Vice President, Clinical Science, Biovitrum, Stockholm, Sweden
- Mar. 22 – *Obesity and the Vasculature: Is the Damage Permanent or Can Our Arteries Bounce Back.* Rachel Wildman, Ph.D., Assistant Professor, Department of Epidemiology, Tulane University
- Apr. 15 – *Mining the Mouse Genome for Diabetes Susceptibility Genes.* Alan Attie, Ph.D., Professor, Department of Biochemistry, University of Wisconsin – Madison (co-sponsored by the Department of Genetics and Heflin Genetics Center)
- May 17 – *Hormonal Influences on Male- and Female- Advantage Components of Spatial Cognition.* Elizabeth Blum, Ph.D., Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Website. As part of the Academic Enrichment Program, a CNRU web page (*www.uab.edu/cnrc*) provides information about the CNRU's research and educational programs and social activities.

Training Program. In July 2004, Drs. David Allison and Tim Garvey were awarded a T32 grant for postdoctoral training in the area of obesity. This program is expected to further expand the research educational opportunities at UAB and to add an important dimension to the training activities of the CNRU.

Benefits and Interactions Resulting from the Existence of the CNRU

Leveraging of Funding Support Due to CNRU. Below are examples of how the UAB CNRU has leveraged its NIDDK support to attract other funding and resources to expand the nutrition/obesity-related research effort at UAB:

Space.

- The 800 square foot Stewart M. Dansby Research Laboratory was created within the CNRU Energy Metabolism/Body Composition Core with $200,000 from institutional and private donations. The laboratory, which became fully operational in 2001, is dedicated to the development of new techniques for assessment of body composition in small animal models.
- The Webb Clinical Research Facility has been opened in the past year. This center is designed to facilitate clinical research protocols conducted by CNRU investigators and to enable collaborations between clinical and molecular investigators. The facility consists of a patient waiting and reception area, nurse's station, large procedure room for infusion studies and procurement of timed specimens, four patient examination rooms, laboratory for specimen processing, lock-down area for pharmaceutical storage and dispensing, a metabolic cart indirect calorimeter, two DEXA scanners for assessment of bone density and body composition, sample storage room with ultralow freezers, computer room, patient classroom, and demonstration kitchen. The facility interacts with other core facilities also in the Webb Nutrition Sciences Building, which allows the center to apply a wide array of methodologies in human metabolism and nutrition.

Intramural Grants.

- As a result of CNRU funding, in 2000, the UAB University-wide Multidisciplinary Research Centers Program awarded the CNRU a 2 year grant of $249,823. This Centers Program is a competitive intramural funding opportunity for research centers. The CNRU received a priority score of 1.4 and full requested funding to enable the Energy Metabolism /Body Composition Core to expand its stable isotope capabilities.
- In 2001, members of the CNRU Genetics Core contributed to successfully obtaining intramural funding of $412,555 for establishment of a university-wide Molecular and Genetic Bioinformatics and Array Facility. The array facility provides investigators standard expression Affymetrix probe arrays and services.
- In 2001, members of the CNRU Energy Metabolism/Body Composition Core received an intramural grant of $125,000 to purchase a Lunar Prodigy DEXA and a Stratec/Norland pQCT.
- In 2002, members of the CNRU Energy Metabolism/Body Composition Core received an intramural grant of $62,950 to purchase a Luminex system for simultaneous analysis of multiple hormones and peptides.
- In 2003, members of the Small Animal Phenotyping Core received an intramural grant of $187,000 to purchase a small animal micro-computed tomography instrument.
- In 2005, our CNRU was awarded an intramural grant of approximately $160,000 per year for the next 3 years to supplement our NIDDK CNRU grant.

Shared Core Resources.

- The CNRU and the UAB General Clinical Research Center (GCRC) operate a shared Core Laboratory to provide measurements of various hormones and stable isotopes for basic and clinical researchers. With NIH approval, the GCRC currently contributes

approximately $120,000 per year to the operational costs of the Energy Metabolism/Body Composition Core Laboratory, enhancing its capabilities to provide measurements of hormones, substrates, insulin sensitivity, and stable isotopes of oxygen and hydrogen to CNRU and GCRC investigators.

- In 2001, the Animal Phenotyping Subcore of the Energy Metabolism/Body Composition Core (now the Small Animal Phenotyping Core) was invited to become a shared core resource with the UAB NIH-funded Center for Metabolic Bone Disease. The Metabolic Bone Center currently provides to the Energy Metabolism/Body Composition Core additional support of $28,000/year to support noninvasive bone density measurements in small animals using DEXA and pQCT.

Faculty/Trainee Development Through CNRU Pilot/Feasibility (P/F) Studies Program. Since its inception in 2000, the UAB CNRU Pilot/Feasibility program has funded 20 different investigators from 87 applications received; these applications were from six different UAB schools. The funded investigators represent ten departments in four schools at UAB. Thus, this program is fostering an interest in nutrition/obesity research across the entire UAB campus. Of the ten investigators funded from 2000 – 2003, seven have received NIH or NSF funding. Grants received include seven R01's, three R03's and a grant from NSF. Notable recent successes include first R01 funding for Jose Fernandez, Paul Brookes, Shannon Bailey, and Chandrika Piyathilake and R03 funding to Yinkui Yang and Mary Boggiano.

New Research Interactions Due to CNRU. At its inception in June 2000, the CNRU included 53 investigator members. Membership has since increased to 89 investigators from 9 different schools. Investigative faculty use CNRU Cores, have leadership positions in the Center, and/or actively participate in its Enrichment Program activities. Investigators' research interests span the age spectrum and encompass basic and applied, animal, and human studies with perspectives that range from medicine, biochemistry, psychology, molecular biology, nutrition, genetics, statistics, and neuroscience. Although most of the original investigators were already involved in some area of nutrition/obesity-related research, it is estimated that approximately 50 percent either did not consider themselves nutrition/obesity investigators and/or did not collaborate with established nutrition investigators on campus at the time the CNRU was formed. Since the CNRU was established, these investigators have made substantial commitments of their time and laboratory resources to nurture cross-campus collaboration and publish their research. Currently, we are aware of at least 26 examples of interdisciplinary collaborative research projects fostered or supported by the Center. This estimate is based primarily on the Center's core faculty and is illustrative, not exhaustive.

Role of CNRU to Recruit New Investigators. Dr. Marie-Pierre St. Onge, Assistant Professor in the Department of Nutrition Sciences; Dr. Robert Kesterson, Assistant Professor in the Department of Genetics; and Dr. Edmund Kabagambe, Assistant Professor of Epidemiology, have been recruited to UAB within the last 24 months. Notably, each focuses on obesity and diabetes. Dr Donna Arnett has joined the UAB faculty and CNRU as the Chair of the Department of Epidemiology. The Clinical Nutrition Research Center played a critical role in the recruitment of these individuals. In addition, several prospective recruits are currently being considered (names withheld due to confidentiality) and, again, the CNRC is a major player in the recruitment of these individuals.

Contribution to Minority Development. The UAB CNRU leadership takes seriously its commitment to fostering the growth of minority students, trainees, and scientists. Last year, we

played a key role in recruiting two young African American scientists (Drs. Ard and Baskin) to work on obesity treatment and prevention in minority populations. In addition, a Hispanic P/F recipient (Dr. Hagan) has recently had an NIH R03 grant funded with help from CNRU core labs and personnel. Another P/F recipient and minority scientist, Dr. Jose Fernandez, recently received obesity-related R01 funding from the NIDDK. Dr. Allison recently recruited two new African American fellows (Drs. Jasmin Divers and Solomon Musani) to work on the genetics of stroke and obesity from a statistical point of view. Dr. Musani has now been promoted to faculty and has received a 2-year minority supplement from the NIDDK. We now send at least 1 faculty member to at least 1 conference per year oriented toward minority investigators and students.

Diversity Promotion Panel. Two years ago, we developed a Diversity Promotion Panel (DPP) (see: *www.soph.uab.edu/statgenetics/People/diversity.htm*). The DPP's purpose is to: convey to current and prospective students, fellows, and faculty that we value diversity and are earnest in our desire to create an environment in which a diversity of individuals can be happy and productive and provide proactive advice regarding recruitment and retention of diverse individuals and on creating an environment in which diverse individuals can work happily and productively. The DPP is jointly sponsored by several UAB entities including UAB's CNRU. It consists of 8 individuals. Members are established successful scientists, engineers, and academics. The DPP has representation from both genders, people descended from African, Asian, Hispanic, European, and Native American populations, and people with diverse sexual orientations. DPP members visit UAB periodically to advise us and meet with trainees and are available for telephone and e-mail consultation as needed.