

Minnesota Nutrition Obesity Research Center

Start Date: 1995

Status: Ongoing

Source of NIH Support: NIDDK

Website: <http://www1.umn.edu/mnoc/>

Organization and Goals

The Minnesota Nutrition Obesity Research Center (NORC) was established in 1995 and is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The mission of the Minnesota NORC is to find ways to prevent weight gain, obesity, and the complications of obesity. Obesity is a major source of illness and death, and is now the most important public health problem in the United States. Despite its prevalence, little is known about effective measures to prevent obesity and its attendant complications. Further, it is well known that obese individuals more easily lose weight than maintain the loss. The major emphasis of the Minnesota NORC is prevention of initial weight gain, prevention of regain after weight loss, and prevention of obesity complications.

With the mission of prevention defined, the Minnesota NORC has established four goals:

- Find the underlying problems that lead to obesity.
- Identify behaviors that lead to obesity and find ways to help change those behaviors.
- Seek means to prevent obesity-related co-morbidities.
- Determine public health and public policy measures that will reduce the frequency and severity of obesity.

The Minnesota NORC is primarily a research center. It encourages and supports studies directed at these goals through the following specific aims:

- Build the research base and research activity addressing obesity through leveraging of resources, provision of key services, advocacy, and interactions.
- Increase support for obesity investigators by providing Center resources, by encouraging application of Minnesota resources, and by enabling competitive external funding.
- Support development of new obesity scientists and movement of established scientists into obesity science.
- Provide translational information for clinical obesity prevention and treatment, public policy efforts, and community groups to help combat obesity and reduce healthcare costs.

The Minnesota NORC incorporates 73 investigators from five institutions: the University of Minnesota (UMN), the Minneapolis Veterans Affairs (VA) Medical Center, the Hennepin County Medical Center, HealthPartners Research Foundation, and the Mayo Clinic in Rochester, MN. The Minnesota NORC is established under the authority of the UMN Dean's Policy Committee, with direct reporting to University Provosts Frank Cerra and Thomas Sullivan. A consortium arrangement exists with the Mayo Clinic for the purpose of creating the NORC and its Metabolic Studies Core. Specific authority for oversight for the NORC is with the Provost of the Academic Health Center.

Establishment of the Minnesota NORC was based on several successful groups working on the study and treatment of obesity. Among these were a very strong group of epidemiologists and public health professionals, a highly respected group working in the area of *in vivo* human metabolism, a very well known group of cellular and molecular scientists studying energy and fat metabolism, an internationally recognized group studying the role of eating disorders in obesity, and a group working on basic neuroscience of energy metabolism regulation. There has been expansion in all of these areas, in great part due to the presence of the NORC, which helps integrate functions and encourages interaction. Individual and collective research efforts greatly benefit from the focus and concentration provided by the presence of the Center. In accord with the obesity center's theme, prevention of weight gain, we have projects ranging from the level of nutrient regulation of gene expression through physiology to population interventions.

Minnesota traditions of intercollegiate cooperation in nutrition have been strengthened by the growth and development of the Minnesota NORC. The organization of the research base around the cores has promoted interactions among investigators engaged in the same type of research, but more importantly, it has fostered new collaborations between investigators. We have found that the Center has been able to promote profitable interactions across departments, across types of research, across campuses in Minnesota in ways that benefited the obesity research community in Minnesota, and across the nation.

The funded projects in our Center relate to a large number of population studies on (1) the etiology of obesity (cross-sectional and longitudinal studies), (2) health consequences of obesity, including the influence of different types of obesity on health over time (prospective cohort studies), (3) public health interventions through community education and health policy aimed at population control of obesity, (4) strategies to prevent weight gain, (5) understanding why individuals accrue excess body fat, (6) mechanisms underlying disorders of weight maintenance, and (7) pathological eating behaviors that result in extraordinary weight loss or gain. Our Core Laboratories have provided sharing, rather than duplication, of efforts. Also, many investigators cannot independently develop techniques that would be valuable to them due to limited time, fiscal resources, and risk/benefit issues. The Minnesota NORC has served as a nidus for further research development and better use of current funds.

Core Laboratories

Administrative Core: Allen S. Levine, Ph.D., Director, and Charles J. Billington, M.D., Associate Director

External Advisory Group Members:

Timothy Bartness, Ph.D., Department of Biology, University of Georgia

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Internal Advisory Group Members:

Chair: F. Abel Ponce de Leon, Ph.D., Associate Dean of Research, College of Food, Agriculture and Natural Resource Sciences (CFANS), UMN

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David O. Warner, M.D., Department of Anesthesiology, Mayo Clinic, Rochester, MN

Disordered Eating Assessment Core: Scott J. Crow, M.D., Director

Epidemiology and Intervention Core: Robert W. Jeffery, Ph.D., Director; Jennifer A. Linde, Ph.D., Associate Director

Metabolic Studies Core: Michael D. Jensen, M.D., Director; James A. Levine, M.D., Ph.D., Co-Director

Obesity and Energy Metabolism Core: David A. Bernlohr, Ph.D., Director; Howard C. Towle, Ph.D., Co-Director

Pilot and Feasibility Studies

GLP-1 Therapy of Weight Loss and Improved Glucose Tolerance in Obese Children: A Randomized, Controlled Pilot Study. Aaron S. Kelly, Ph.D., Department of Pediatrics, UMN. Behavioral therapy should be the foundational approach to treating obesity and impaired glucose tolerance (IGT) in children. However, many children are unable to alter their lifestyle sufficiently and may benefit from medical therapy to facilitate weight loss and improve glucose metabolism. Few drug therapies for weight loss exist for children, and novel options should be explored. Exenatide is a new glucagon-like peptide-1 (GLP-1) agonist that reduces postprandial glucose excursions and reduces body weight through its ability to slow gastric emptying and by suppressing appetite. Importantly, the weight loss effects with exenatide are progressive and sustained over a period of at least 2 years. Our primary aim is to examine the effects of 6 months of exenatide treatment on body weight, body mass index (BMI), waist circumference, body composition, and glucose tolerance in obese children with IGT. Our secondary aim is to examine the effects of exenatide treatment on arterial endothelial function and stiffness, blood biomarkers of endothelial activation, and adipokines in obese children with IGT. To accomplish these aims, we will enroll 20 obese children and adolescents in a randomized, single-blind, controlled clinical trial. Patients will be randomly assigned to exenatide (n = 10) or usual care (n = 10) for 6 months in addition to background behavioral therapy through the UMN Pediatric Weight Management Program. This multidisciplinary pilot study will result in the acquisition of valuable preliminary data that will be used to seek funding for and conduct a larger-scale clinical trial evaluating the safety and efficacy of GLP-1 therapy for weight loss and improved glucose tolerance in obese children with IGT.

Regional Free Fatty Acid Uptake Assessed by Positron Emission Tomography in Humans: A Pilot and Feasibility Study. Christina Koutsari, Ph.D., Endocrine Research Unit, Mayo Clinic.

Elevated circulating free fatty acids (FFA) are implicated in the metabolic complications of insulin resistance, obesity, and type 2 diabetes. Because of the health implications of elevated circulating FFA, body fat distribution, and ectopic fat, defining the contributions of tissues and organs to FFA clearance from the circulation can be instrumental in our understanding of FFA regulation and metabolism. There is currently limited information in humans regarding which tissues take up FFA and what proportion of FFA disposal is allocated to different tissues (muscle, adipose, liver, heart, kidney) or different sites within heterogeneous tissues (different muscle types and adipose tissue beds). It is possible to perform tissue biopsies after the intravenous injection of an FFA tracer or measure arteriovenous balance across a tissue bed, but these approaches are not easily applicable to all tissues. Positron emission tomography (PET) imaging is a promising, non-invasive method to quantitate regional FFA uptake that is especially suited to organs that are currently inaccessible. In the present study, we will test the use of [1-11C]palmitate and PET to study FFA uptake into adipose tissue beds, skeletal muscle, and liver. We anticipate that variability will exist between different adipose tissue depots (subcutaneous versus visceral) and sites (subcutaneous abdominal versus femoral), as well as between organs. In addition, we will compare the adipose subcutaneous FFA uptake data obtained with PET to those obtained with the use of our well-established technique of [1-14C]palmitate and tissue biopsies. Successful completion of the proposed studies will allow us to examine tissue FFA uptake in conditions of differing FFA concentrations and different disease states on tissue FFA uptake. This will allow a better, more integrated understanding of the potential role of FFA in insulin resistance.

Role of Skeletal Hormones in Adipocyte Differentiation and Function. Laura J. Mauro, Ph.D., Department of Animal Science, UMN.

A paradigm shift in our understanding of metabolic regulation has occurred with the discovery that the skeleton can serve as an endocrine organ capable of modulating glucose metabolism and energy balance. Osteoblasts, the bone-forming cells of the skeleton, are the primary source of a novel skeletal hormone recently identified as osteocalcin. When osteoblasts are engineered to express the bioactive form of osteocalcin called uncarboxylated osteocalcin (uOcn), transgenic mice expressing these cells exhibit lean body mass, hyperinsulinemia, and enhanced insulin sensitivity. At present, the actions of uOcn on adipose tissue have not been characterized. The goal of this proposal is to determine the direct effects of this skeletal hormone on adipocytes by pursuing two specific aims. In our first specific aim, we will test the hypothesis that uOcn can modulate adipocyte differentiation, utilizing the 3T3-L1 preadipocytes. We will treat these cells with uOcn during differentiation and monitor the expression of critical adipocyte-specific genes. These studies will define the actions of this hormone in inhibiting the progression from preadipocyte to mature adipocyte. In our second specific aim, we will test the hypothesis that uOcn can also regulate the metabolism of mature adipocytes. The ability of differentiated 3T3-L1 adipocytes to undergo cAMP-stimulated lipolysis and insulin-stimulated glucose transport will be examined following exposure to uOcn. In addition, the activation of insulin signaling pathways in these pretreated cells will be determined, and these studies will show that uOcn can inhibit lipolysis and enhance responsiveness to insulin stimulation. This proposed research project will clarify the role of this novel skeletal hormone in modulating adipogenesis and adipocyte function. In addition, it will provide the foundation for future studies to establish the

signaling mechanisms activated by uOcn in adipose and other tissues that will ultimately control energy balance. Our result will aid in the development of new therapeutics for treatment of serious metabolic disorders such as diabetes mellitus and obesity.

Bone and Cardiovascular Health in Obese Adolescents Following Bariatric Surgery. Moira Petit, Ph.D., Division of Kinesiology, UMN.

Bariatric surgery has become a popular treatment for weight loss in morbidly obese adolescents, with a five-fold increase in the number of bariatric surgeries conducted in the United States between 1997 and 2003 in adolescents. Despite the substantial increase in these surgeries, little is known about the effects of bariatric surgery on skeletal and cardiovascular health parameters in youth. Given that adolescence is a critical time for development of a strong skeleton and a healthy vasculature, determining the physiological benefits and risks of this procedure during this critical period of growth is of paramount importance. With the expertise in adolescent bariatric surgery, obesity, pediatric bone health, and cardiovascular health at UMN, we have a unique opportunity to design and conduct longitudinal studies in this growing population. The purpose of this pilot study is to examine the effects of bariatric surgery on indices of bone health and cardiovascular function in morbidly obese adolescents. We hypothesize that bariatric surgery in morbidly obese adolescents will result in (1) loss of bone mass and strength at 3 and 6 months post surgery and (2) improvements in indices of cardiovascular function, including endothelial function and arterial stiffness, at these time points. Ten morbidly obese adolescents (ages 12 to 17) undergoing bariatric surgery and 10 age, sex, and BMI-matched controls will be recruited for the study. Measures of bone and cardiovascular health will be taken at baseline (prior to surgery) and at 3 and 6 months post surgery. Data from this study will be used to frame objectives for an National Institutes of Health (NIH) R01 grant that will prospectively follow a larger cohort. This multidisciplinary pilot study will also establish our research team with collaborators from kinesiology, pediatrics, bariatric surgery, epidemiology, and family practice.

Work Environment and Eating Behavior among Health Service Workers. Kamisha H. Escoto, Ph.D., Department of Psychiatry, UMN.

Obesity rates are high among employed adults, making the workplace a feasible target for intervention programming. Interventions addressing obesity in the workplace commonly target the physical worksite, using strategies such as increasing the availability of healthy foods, nutrition labeling, and worksite enhancement to promote physical activity. Worksite interventions rarely include components that address organizational variables, such as work structure (e.g., work hours) or occupational stressors (e.g., workload), although such variables are associated with unhealthy eating behavior and excess weight. The aim of this pilot study is to examine associations between varied measures of the work environment and food choice/eating behavior among hospital-based health service workers, an occupational group that has among the highest rates of obesity in the United States and suffers from stressful working conditions. This research will provide pilot data to develop content and inform research design for a larger grant proposal using Ecological Momentary Assessment (EMA) methods. The study will employ a mix of quantitative and qualitative methods, using surveys, food logs, and in-depth interviews. Data will be collected to assess both the physical and social work environment, as well as psychosocial work factors (e.g., job demands, social support) and work structure (e.g., work hours). Eating and food choice behaviors that contribute most to excess weight will also be assessed. Identifying stressful characteristics of work and unhealthy food choice/eating behaviors

will be critical to the design of future research studies aiming to clarify relationships between employment and obesity.

Reduction in Adiposity and Change in Fuel Utilization by Viscous Dietary Fiber in Diet-induced Obesity in Rats. Daniel D. Gallaher, Ph.D., Department of Food Science and Nutrition, UMN.

The prevalence of obesity has reached alarming levels. The connection between excess adiposity and chronic diseases is becoming clearer, as it is now understood that adipose tissue is a major endocrine organ, which modulates insulin resistance and energy metabolism. Obesity is associated with chronic low-grade inflammation, the predominant source being adipose tissue, which plays a fundamental role in insulin resistance. It is desirable to identify food components that may reduce adiposity. Viscous dietary fibers are highly bioactive categories of dietary fiber. We have conducted animal studies showing that viscous dietary fibers reduce adiposity, independent of body weight changes. We hypothesize that viscous dietary fiber will also decrease the inflammation of obesity and increase fatty acid oxidation. We will investigate chronic consumption of viscous dietary fiber in rats fed an obesity-inducing diet, which leads to both obesity and insulin resistance, on measures of adiposity, insulin resistance, inflammation, gene expression related to glucose and fatty acid metabolism, and fuel utilization. The viscous dietary fiber to be used is a purified material, hydroxypropyl methylcellulose, as this avoids the confounding effects of other bioactive compounds present in food sources of viscous fibers. The studies described in this proposal will confirm this effect on adiposity and greatly extend it by examining the effect of viscous polysaccharides on adipose metabolism, fatty acid oxidation, inflammation, and adipose gene expression. If successful, this project may provide a dietary alternative to pharmacological approaches to reduction in body fat. This project represents a collaboration among investigators of several different areas. Dr. Gallaher's area of research has focused on dietary influences on cholesterol metabolism and colon cancer. Thus, research in obesity represents a new area of research for him. Dr. Chen has focused on adipose metabolism, particularly inflammation and insulin resistance, but not obesity reduction per se. Dr. Kotz's area of expertise is in neural regulation of food intake. The outcomes of this study will further establish the effectiveness of viscous polysaccharides on adiposity, as well as greatly expand our knowledge of the relationship between adiposity, inflammation, and adipokine secretion. This information will be useful in furthering our understanding of how changes in viscous components of the diet affect adiposity and will set the stage for human studies of the effects of these types of dietary fiber on adiposity.

Assessing the Home Food Environment of Somali and Hispanic Immigrant Families with Preschool-Aged Children. Mary O. Hearst, Ph.D., Division of Epidemiology and Community Health, UMN.

The purpose of this project is to refine and validate an existing home food inventory tool for low-income Somali and Hispanic families with preschool-aged children as a means of both understanding contextual influences on obesity and determining the appropriate intervention strategies that may fit the needs of low-income immigrant households and communities. The study has three primary aims, including formative assessment and refinement of the home food inventory, recruitment of the validation sample, and testing concurrent criterion validity of the revised and translated home food inventory with low-income Somali and Hispanic families in their homes. Building off a current collaboration, we will recruit families currently enrolled in an early childhood, school readiness project called "Five Hundred under Five." We will use an

existing, validated home food inventory and modify the content to be more culturally relevant based on focus group discussions. Thirty families (15 Somali, 15 Spanish speaking) will be recruited to independently complete the revised and translated home food inventory concurrently with a trained staff member to test criterion validity. The goal of this proposal is to produce a culturally relevant and valid tool for assessing the home food environment that can be used in subsequent obesity prevention grant applications.

A Pilot Study to Explore Energy Expenditure and Energy Intake among Youth Sport Participants. Toben F. Nelson, Sc.D., Division of Epidemiology and Community Health, UMN.

Participation in youth sport is recommended for increasing physical activity, but little research exists on whether sport can promote energy balance or prevent obesity. We reviewed existing research comparing youth sport participants with non-participants on weight status, physical activity, and dietary habits and found few well-designed studies. The available research suggests that youth sport may not effectively prevent obesity. Many youth sport participants are overweight; the proportion of sport participants who are overweight has risen over time; and the evidence on whether sport participants are less likely to be overweight is mixed. The research demonstrates that sport participants are more likely to be physically active than those who do not participate. However, available evidence suggests that sport participants consume more sugar-sweetened beverages, fast food, and overall calories than non-participants, leaving them at risk for excess body weight. We conducted a simulation of energy balance in youth sport using expenditure estimates based on the Compendium of Energy Expenditures for Youth (Ridley et al., 2008) and intake estimated from snacks and beverages commonly consumed by youth sport participants. We found that youth may actually consume more calories than they expend while participating in youth sport (Nelson et al., in review). In addition, many children may spend considerable time during youth sport on the sidelines while other children play so that actual energy expenditure in sport may be lower than expected, but this has not been objectively assessed. In this context of little empirical evidence, we propose to conduct a pilot study to objectively assess physical activity and track dietary intake among youth participating in organized sport programs in the Greater Twin Cities Metropolitan Area. The primary aim of the study is to assess within-subject differences in energy expenditure and energy intake on days when youth participate in organized sport activities and days they do not. The evidence collected from this pilot research will be combined with other preliminary studies conducted by the investigators to directly inform a grant proposal to conduct an in-depth longitudinal study of the factors that may inhibit or promote excessive weight gain in youth sport settings. Ultimately, the information gathered from this program of research will be used to direct interventions that reshape youth sport programs to be consistent with obesity prevention goals.

The Role of Small Molecule CD38 Inhibitors on the Development of Obesity and Obesity-related Metabolic Disturbances. Thomas A. White, Ph.D., Department of Anesthesiology, Mayo Clinic.

Obesity is one of the most serious health problems facing society today. Elucidating the signaling mechanisms by which high caloric diet induces obesity is critical for the understanding of this condition and for the development of therapeutic strategies for its treatment. Investigators have previously described a novel and unique role for the enzyme CD38 as a necessary component of the biochemical pathway that leads to the development of obesity and some of its deleterious metabolic effects. CD38 is a ubiquitous enzyme that catalyzes the synthesis of second messengers and has been implicated in the regulation of a wide variety of signaling pathways in

numerous cell types. CD38 is also a NADase, (NAD⁺glycohydrolase, where NAD is Nicotinamide adenine dinucleotide). We have previously demonstrated that CD38 plays a key role in the regulation of intracellular NAD levels and subsequently regulates NAD-dependent deacetylases such as sirtuins (also known as SIRT enzymes). SIRT enzymes have been implicated as regulators of energy metabolism and longevity. Recent studies have shown that activation of SIRT can protect laboratory animals from high fat (caloric) diet (HFD)-induced obesity and its deleterious effects. We propose that by decreasing intracellular levels of NAD, CD38 promotes inactivation of the SIRT enzymes. Decreased SIRT activity leads to inhibition of the peroxisome proliferator-activated receptor γ co-activator 1 α (PGC1 α) that is involved in the development of obesity. CD38 appears to be a nearly obligatory component of the cellular cascade that leads to HFD-induced obesity in mice. In fact, CD38-deficient mice are protected against HFD-induced obesity. We have recently identified small molecule CD38 inhibitors by a high throughput screening (HTS) assay. We hypothesize that small molecule CD38 inhibitors, such as apigenin, will prevent the development of obesity and its deleterious metabolic effects. Successful completion of these proposed studies will lead to a better understanding of obesity and may lead to new therapeutic approaches for this condition.

Pilot and Feasibility (P & F) Project Supplements

P & F Project Administrative Supplement: Intrinsic Aerobic Capacity, NEAT, and Obesity.

Colleen Novak, Ph.D., Endocrine Research Unit, Mayo Clinic.

Health problems associated with obesity continue to increase. Decreased physical activity levels in the population match this growth in obesity. Most investigations into the physiological causes of obesity, however, have focused on energy intake rather than energy expenditure. We consider how energy expenditure, specifically the energy expenditure of physical activity called non-exercise activity thermogenesis (NEAT), is altered with obesity and obesity propensity. Physical activity and NEAT vary in the population and, like any complex trait, have genetic components. Indeed, low levels of NEAT in several rat and mouse models of obesity suggest individual differences in NEAT that are of genetic origin. We have found a robust difference in daily activity levels between rats bred for high and low intrinsic aerobic capacity. This suggests that there may be similar biological determinants of high physical activity levels and high intrinsic aerobic capacity. In this study, we propose to take this investigation to a critically higher level and examine aerobic capacity and physical activity levels in a human population. We have completed measures of physical activity and NEAT in 30 non-exercising volunteers for 10 days using our Physical Activity Measurement System (PAMS). We plan to tap this rich source of information to test the hypothesis that human aerobic capacity is predictive of physical activity by measuring VO₂max in these same participants. We predict that high intrinsic aerobic capacity will correlate with high daily activity levels in these individuals. This would support the assertion that intrinsic aerobic capacity and spontaneous activity levels may be linked physiologically and genetically. This study would take our basic findings from animals to a critically higher level, plus provide unique insight into the factors underlying both intrinsic aerobic capacity and physical activity in humans.

P&F Project American Recovery and Reinvestment Act (ARRA) Supplement No. 1: GSTA4 Down-Regulation: A Potential Link Between Mitochondrial Dysfunction and Obesity.

Edgar A. Arriaga, Ph.D., Department of Chemistry, UMN.

Protein carbonylation is increased in adipose tissue in a variety of animal models of obesity and

insulin resistance (Grimsrud et al., *Mol. Cell Proteomics*, 2007). In these models, deficiencies in antioxidant defense systems could contribute to increased protein carbonylation. Evidence indicates that two of the down-regulated systems are glutathione S-transferase (GST) A4 and GSTA3, the enzymes primarily responsible for metabolism of trans-4-hydroxy-2-nonenal (4-HNE). 4-HNE covalently modifies the side chains of histidine, cysteine, and lysine residues of target proteins resulting in their carbonylation that typically leads to loss of protein function and targeted degradation by the 26S proteasome. In adipose tissue from obese insulin-resistant subjects, the expression of human GST4 (but not GSTA3) is decreased in a manner that parallels the down regulation of murine GST4. Decreased murine GSTA4 expression is specific to white adipose tissue of C57Bl/6J mice and is targeted to the adipocyte and not stromal-vascular fraction. When endogenous GSTA4 mRNA is silenced in 3T3-L1 cells, knockdown adipocytes exhibited increased protein carbonylation, increased lactate production, dysfunctional mitochondrial state 3 respiration, and increased levels of matrix superoxide. Extending these findings to animal models, mitochondrial respiration was significantly down-regulated in obese (but not lean) C57Bl/6J mice, as well as in both lean and obese GSTA4 knockout animals. These results suggest the following hypothesis: down-regulation of GSTA4 in murine and human obesity leads to increased protein carbonylation, decreased mitochondrial function, and increased oxidative stress, and contributes to the development of obesity-linked type 2 diabetes. To test this hypothesis we propose the following two aims: Aim 1, Identify carbonylated proteins using biochemical and proteomic methods from mitochondria of lean and obese C57Bl/6J mice, and compare these to proteins carbonylated in GSTA4 null mice. Aim 2, Assess mitochondrial function and the production of reactive oxygen species in organelles isolated from lean and obese mice.

P&F Project ARRA Supplement No. 2: Role of Adipose Autophagy in Insulin Resistance. Do-Hyung Kim, Ph.D., Department of Biochemistry, Molecular Biology and Biophysics, UMN. Our research goal is to increase knowledge on autophagy-mediated mechanisms pertaining to metabolic diseases such as diabetes, obesity, and insulin resistance. Autophagy is an evolutionarily-conserved nutrient-regulated cellular process through which eukaryotic cells digest macromolecules, organelles, or faulty cellular components under starvation or stress, and it has a significant growing number of links to a variety of human disease and physiology, including cancer, aging, neurodegeneration, and microbial infection. Despite such widespread appreciation for autophagy and its link to metabolic diseases, the molecular linkage between autophagy, obesity, and type 2 diabetes has not been widely examined and the role(s) of autophagy in adipose metabolism has not been explored at all. Our proposed study is intended to define the crucial molecular step of autophagy induction and the autophagy roles in the regulation of adipose energy metabolism and insulin resistance. *The central hypothesis* is that mTOR-regulated protein complex, which consists of ULK1 (Unc51-like protein 1) and mAtg13 (mammalian homolog of yeast AuToPhagy gene 13), plays a crucial role in the regulation of the induction of autophagy, insulin resistance, and energy metabolism in adipose tissue. Our recent studies led us to discover that mTOR regulates autophagy induction through phosphorylation of ULK1 and mAtg13. Given this knowledge on the fundamental mechanism underlying the regulation of autophagy induction, our proposed research will be more focused on understanding the physiological roles of adipose autophagy in insulin signaling and metabolism. We plan to test our central hypothesis by pursuing *the specific aim* to determine the roles of ULK1 and mAtg13, the components essential for autophagy induction, in the regulation of adipocyte differentiation,

fat metabolism, and insulin sensitivity. This project will be made possible through close, synergistic collaboration among three investigators: Dr. Kim having expertise in the mTOR field, Dr. Arriaga having expertise in mitochondrial research, and Dr. Bernlohr having expertise in adipose biology. The three laboratories have joined forces to study adipose autophagy by determining the crucial molecular steps in the regulation of fat cell energy metabolism and the relationship of autophagy to obesity and insulin resistance.

Other P & F Projects awarded through the Obesity Consortium of Minnesota, but not receiving funding directly from the Minnesota NORC, are listed below.

Modeling Trajectories of Optimal Pregnancy Weight Gain for Overweight and Obese Women. Patricia Fontaine, M.D., M.S., Department of Family Medicine and Community Health, UMN.

As the U.S. population experiences an epidemic of obesity, more women than ever before are entering pregnancy overweight or obese. The Agency for Healthcare Research and Quality recently conducted a comprehensive meta-analysis of existing studies of weight gain in pregnancy and found strong evidence that pregravid weight status and gestational weight gain (GWG) are related to maternal and newborn outcomes. Yet recommendations for optimal GWG, particularly for overweight and obese women, are limited by major shortcomings in the body of research. The reviewers identified specific research needs, stating, “To understand fully the impact of gestational weight gain on short- and long-term outcomes for women and their offspring will require that researchers use consistent definitions of weight gain during pregnancy, better address confounders in their analyses, improve study designs and statistical models, and conduct studies with longer follow-up.” The work proposed in this pilot application represents the critical next step in our work to examine relationships between GWG trajectories and maternal and child health outcomes, using a rigorously constructed database, with the eventual goal of obtaining extramural funding to develop an effective intervention to promote healthy weight gain during pregnancy. In July 2007, our project team received pilot funding from UCare Minnesota and the HealthPartners Research Foundation to create a large and comprehensive data set using prenatal health information derived from the HealthPartners Electronic Medical Record (EMR) data and chart abstraction data from UMN Physician-affiliated community clinics. The product of this collaborative effort is the database including serial weight measurements, maternal pre-pregnancy and prenatal health status diagnosis information, demographic data, laboratory data, and delivery and birth outcomes for an ethnically diverse sample of 2,540 women. We have begun deriving analysis variables from the database; however, we are only at the beginning of the most productive analytic phase of our initiative. This pilot proposal would allow us to pursue additional analyses and manuscripts, capitalizing on the strengths of this unique data set and providing key supporting data for future extramural funding, including an R01 grant to develop and evaluate a primary care-based intervention as well as a maternal-child registry in the Twin Cities Metropolitan Area.

Observational Ratings of Child Feeding Practices among Preschoolers. Jayne A. Fulkerson, Ph.D., School of Nursing, UMN.

The proposed study aims to comprehensively assess child feeding practices currently used by parents of at-risk preschoolers and develop a methodology that can be used to eventually test which child feeding practices are most effective in preventing excess weight gain among children. The proposed work directly addresses the early stages necessary to meet the goal put

forth by the NIH Obesity Research Task Force, namely, using prospective observational studies to identify potentially modifiable behavioral determinants of excessive weight gain and obesity in children. The present study aims are to (1) test the feasibility of recruiting preschool youth at risk for overweight; (2) test the feasibility of videotaping preschoolers' home meals four times in a 1-week period; (3) revise an existing mealtime behavioral coding scheme used for children with chronic disease for important components of mealtime feeding practices among preschoolers at risk for overweight; (4) quantify the prevalence of specific child feeding practices in a community sample; and (5) identify previously uncoded feeding and eating behaviors in the videotapes and incorporate them into the coding scheme. Forty children ages 2 to 4 years who are at risk of becoming or already are overweight and one parent/guardian per child will be recruited from local Minneapolis Park and Recreation Centers and Early Child and Family Education programs in Minneapolis, MN. Parents/guardians will inform project staff of their interest in the study and will be screened for eligibility. We will follow an existing successful videotape protocol of mealtime behavioral assessments used with children with cystic fibrosis. Research staff will schedule four home visits. At the first home visit, parents will complete a consent form and a brief questionnaire, and the child and parent will have anthropometry assessed by staff. At all four home visits, research staff will collect videotape data of the child's meals by setting up the video equipment and leaving the room/house until the meal ends. To assess reactivity to the video methodology, parents will be asked to rate the similarity of the videotaped dinner to routine meals in the home in terms of the child's eating behavior and general interactions with family members, and typical meal data will be used for analysis. Trained staff will code parent and child mealtime behaviors viewed in the videotapes using the Dyadic Interaction Nomenclature for Eating (DINE) as the base. The observational methodology directly assesses parent-child interactions rather than relying solely on parent report, and can assess the bidirectional nature of parent-child interactions, an important concept in weight-related behaviors.

A Randomized Controlled Trial of Standard Behavioral Weight-Loss Intervention on Reproductive Parameters in Obese Men. Ruby H.N. Nguyen, Ph.D., Division of Epidemiology and Community Health, UMN.

Strong evidence indicates that women with excess body weight are more likely to be sub-fertile and that the probability of pregnancy may increase with weight loss. While scarce data exist for making a similar claim for obese men, small studies have reported poor parameters of reproductive hormones important to spermatogenesis such as testosterone and testosterone-to-estradiol ratio. These findings are plausible since men's excess weight may disturb the hypothalamic-pituitary-gonadal axis, resulting in adverse changes to reproductive hormones, not unlike what occurs in women; these alterations may then affect spermatogenesis. Some studies have indicated that extreme weight loss in obese men may normalize some hormone values, but no data exist on changes to semen. We therefore propose to determine whether a standard behavioral weight loss intervention in obese men is associated with improvement of reproductive hormones and semen parameters to a level conducive to normal spermatogenesis. The goal of this standard behavioral treatment intervention is caloric reduction and increased exercise for men with BMI ≥ 30 , resulting in a loss of 8% to 10% of the man's baseline weight. Eligible participants will be recruited from the Reproductive Medicine Center at Fairview Riverside. Twenty men will be randomized into an intervention arm and 20 into a control arm, providing > 90% power to detect a difference. Baseline semen and hormone levels will be abstracted from the medical record, then blinded semen and reproductive hormone analysis will be determined at

mid-trial (6 months) and the end of the trial (12 months). For hormone values, fresh peripheral venous blood will be collected to determine total testosterone, estradiol, and sex hormone binding globulin. Criteria for semen analysis will be taken from World Health Organization guidelines, including semen volume, sperm concentration, motility, and morphology. Our primary analyses will determine whether hormone and semen values in the weight-loss intervention arm differ at 6 and 12 months from their baseline values (paired test), or whether their mean scores differ from that of the control group at similar times. We also aim to determine whether sexual/erectile function scores modify observed associations. Determination of feasibility and results from the statistical analyses will be used to inform an obesity-related R-series NIH grant application.

TEXTHealth–Teens Eating and Exercising 4 Health. Emily D. Parker, Ph.D., HealthPartners Research Foundation.

Despite the recognition that pediatric cancer survivors are at high risk for the development of obesity due to late effects of treatment and disease and the known long term risk of cardiometabolic diseases associated with excess weight, there is a dearth of interventions designed to meet the needs of this unique group. The overarching objective of this pilot study is to test the feasibility of a novel, technology-delivered obesity prevention intervention in adolescent cancer survivors. This study will recruit and randomize 40 adolescent cancer survivors to receive the obesity-prevention intervention or brief educational materials. Intervention participants will be invited to attend a workshop that focuses on obesity prevention actions, such as increasing fruit and vegetable consumption, increasing physical activity, and decreasing sedentary activity. Intervention participants will then receive 12 weeks of frequent (2 to 4 times weekly) cell phone text messages with concise, motivational messages that build on the baseline educational workshop. The comparison group will receive brief print materials. Body mass index, diet (Youth/Adolescent Questionnaire), and physical activity (Youth/Adolescent Activity Questionnaire) will be measured at baseline and 3-month follow-up. Because this is a pilot study, we will not have the power to detect differences in these measures. However, we expect to see biological (BMI) and behavioral (nutrition and physical activity) changes in the direction of hypothesized effects. The information yielded from the follow-up survey will provide valuable information with regard to the feasibility of delivering such an intervention, as well as provide formative data that will enhance the development of engaging intervention messages in the larger study. This study addresses an important research area relevant to public health, as it relates to adolescent obesity and cancer survivor research. Innovative methods of intervention are needed to address the increased risk of obesity in young cancer survivors. If successful, it will lead to a larger collaborative study to determine if the intervention can reduce excess weight gain among adolescent cancer survivors.

Funding Derived From Previous Pilot and Feasibility Studies

Relapse Prevention in Anorexia Nervosa. Scott J. Crow, M.D. Funding: McKnight Foundation, 6/98–5/03, annual direct costs \$100,000, total direct costs \$400,000.

Longitudinal Follow-up Study of Patients with Eating Disorders. Scott Crow, M.D. Funding: McKnight Foundation, 7/95–6/00, annual direct costs \$88,000, total direct costs \$357,000.

Generic Studies in Bulimia Nervosa. Scott J. Crow, M.D. Funding: Price Foundation, 1/99–12/99, annual direct costs \$52,000, total direct costs \$52,000.

Generic Studies in Anorexia Nervosa. Scott J. Crow, M.D. Funding: Price Foundation, 1/00–1/01, annual direct costs \$55,000, total direct costs \$55,000.

The Treatment of Binge Eating Disorder. Scott J. Crow, M.D. Funding: NIH/NIDDK R01 DK61912, 2/02–1/05, annual direct costs \$200,000, total direct costs \$675,000.

Increasing Lowfat School/Worksite Vending Choices. Simone A. French, Ph.D. Funding: NIH/National Heart, Lung and Blood Institute (NHLBI) R01 HL56577-03, 4/01/97–3/31/00, annual direct costs \$98,033, total direct costs \$438,603.

Increasing Availability of Lowfat Foods in High Schools (TACOS). Simone A. French, Ph.D. Funding: NIH/NHLBI R18 HL61305-01, 07/01/99–06/30/03, annual direct costs \$272,027, total direct costs \$1,346,393.

Nonexercise Activity Thermogenesis (NEAT) and Obesity in Mice. James A. Levine, M.D., Ph.D. Funding: Mayo CR75 Scholar Award, 1/99–12/01, annual direct costs \$132,000, total direct costs \$396,000.

Nonexercise Activity Thermogenesis (NEAT) in Humans. James A. Levine, M.D., Ph.D. Funding: NIDDK/NIH R01 DK56650-01, 7/01–6/06, annual direct costs \$314,187, total direct costs \$1,112,472.

Feeding Inhibition: Mapping of Neural Pathways. Catherine M. Kotz, Ph.D. Funding: Department of Veterans Affairs/Merit Review Type II, 4/98–3/01, annual direct costs \$116,300, total direct costs \$348,900.

Lateral Hypothalamic Hypocretin Pathways Modulating Feeding. Catherine M. Kotz, Ph.D. Funding: NIH/NIDDK R01 DK57573, 5/00–4/05, annual direct costs \$150,000, total direct costs \$650,000.

Effect of Leptin and Neuropeptide Y Induced Alterations in Uncoupling Proteins 1, -2 and -3 on Calorimetric Measures of Energy Expenditure. Catherine M. Kotz, Ph.D. Funding: Weight Research Investigators Study Council/Knoll Pharmaceuticals, 1/98–12/98, total award \$82,683.

The Effect of Insulin on Vascular Regulation in Viscerally Obese Humans. John R. Halliwill, Ph.D. Funding: NIH/NIDDK F32 DK09826-01, 07/22/98–07/21/01, annual direct costs \$31,492, total direct costs \$94,476.

Feeding Effects of the Melanocortin-4 Receptor Ligands: CNS Sites of Action. Silvia Q. Giraud, Ph.D. Funding: Department of Veterans Affairs/Merit Review Board, 4/99–3/03, annual direct costs \$119,100, total direct costs \$357,300.

Melanocortins, Opioids and Feeding. Silvia Q. Giraud, Ph.D. Funding: NIH/NIDDK R01 DK/NS59836-01, 7/01–6/04, annual direct costs \$189,000, total award \$567,000.

High Fat Feeding and Intramyocellular Lipid Abnormality. ZengKui Guo, Ph.D. Funding: NIH/NIDDK R01 DK60013, 8/1/01–7/31/06, annual direct costs \$125,000, total direct costs \$525,000.

Muscular Fat and Insulin Resistance in Dietary Obesity. ZengKui Guo, Ph.D. Funding: NIH/NIDDK R01 DK067419, 12/1/04–11/31/09, annual direct costs \$455,051, total direct costs \$1,856,961.

Mechanisms of Drug Induced Pulmonary Hypertension. E. Kenneth Weir, M.D. Funding: Department of Veterans Affairs/Merit Review Board, 4/99–3/03, annual direct costs \$119,100, total direct costs \$357,300.

Food-Borne Antibiotic-Resistant and Extraintestinal Pathogenic *Escherichia coli*. James R. Johnson, M.D. Funding: USDA-CSREES/00-35212-9408, 11/00–10/03, annual direct costs \$147,182, total award \$542,357.

Lipid Turnover in a Mouse Model of Familial-Combined Hyperlipidemia. Elizabeth Parks, Ph.D. Funding: American Heart Association, 1/02–12/05, annual direct costs \$65,000, total direct costs \$260,000.

Strength Training for Obesity Prevention. Kathryn H. Schmitz, Ph.D. Funding: NIDDK/NIH DK60743-01, 3/02–7/05, annual direct costs \$353,480, total direct costs \$1,829,793.

Weight Training in Breast Cancer Survivors. Kathryn H. Schmitz, Ph.D. Funding: The Susan G. Komen Breast Cancer Foundation, 10/1/01–9/3/03, annual direct costs \$125,000, total direct costs \$249,899.

Does Strength Training Alter IGF1BP-2? Kathryn H. Schmitz, Ph.D. Funding: UMN Cancer Center, 1/02–12/02, annual direct costs \$9,500, total direct costs \$9,500.

Effect of BDNF in the Central Nervous System on Energy Metabolism. ChuanFeng Wang, M.D., Ph.D. Funding: Department of Veterans Affairs/Merit Review Entry Proposal, 10/04–9/07, annual direct costs \$50,000, total direct costs \$150,000.

A Pair-Feeding Study for Regulation of Energy Balance by Enhancing Hepatic Glucose Metabolism in Obese Mice. Chaodong Wu, Ph.D. Funding: Minnesota Medical Foundation No. 3487-9227-05, 8/1/04–7/31/05, annual direct costs \$15,000, total direct costs \$15,000.

Novel Approaches to Weight Loss Maintenance. Nancy E. Sherwood, Ph.D. Funding: NIH/National Cancer Institute R01 CA128211, 10/1/06–9/30/10, annual direct costs \$435,268, total direct costs \$1,842,749.

Physical Activity Monitoring in Prepubescent Children. Lorraine Lanningham-Foster, Ph.D. Funding: NIH 1 R21 HD052001, 3/1/07–2/28/09, annual direct costs \$150,000, total direct costs \$275,000.

Lipocalin 2 in Inflammation and Metabolic Control. Xiaoli Chen, Ph.D. Funding: NIH/NIDDK R01 DK080743, 4/1/08–3/31/13, annual direct costs \$200,000, total direct costs \$1,499,000.

Brain Mechanisms of Non-exercise Activity Thermogenesis. Colleen M. Novak, Ph.D. Funding: NIH/NINDS R01 NS55859, 6/1/07–5/31/11, annual direct costs \$200,000, total direct costs \$800,000.

Parents as the Agent of Change for Childhood Obesity. Kerri N. Boutelle, Ph.D. Funding: NIH/NIDDK 1R01DK075861-01A2, 4/2010–3/2015, annual direct costs \$495,000, total direct costs \$2,329,700.

ICAT for Bulimia Nervosa. Carol B. Peterson, Ph.D. Funding: NIH/NIMH R34 MH 077571, 12/1/07–11/30/11, annual direct costs \$44,537.

Microvascular Dysfunction in Aging Humans. William G. Schrage, Ph.D. Funding: NIH/NHLBI R21 HL091397, 1/15/09–12/31/10, annual direct costs \$137,500, total direct costs \$275,000.

The Role of the ZEB1 Transcription Factor in Opposing Obesity. Michel M. Sanders, Ph.D. Funding: Minnesota Medical Foundation 3925-9227-09, 3/1/09–2/28/11, total direct costs \$14,000.

ATGL: Major Regulator of Hepatic Steatosis and Energy Metabolism. Douglas Mashek, Ph.D. Funding: NIH/NIDDK 1R56DK085008, 4/1/10–3/31/11, total direct costs \$150,000.

Mentored Career Development for Multidisciplinary Clinical Research Scholar (Topic: Obesity Research). Steven D. Stovitz, M.D. Funding: NIH 5K12-RR023247-03, 5/2008–5/2011, annual direct costs \$132,600.

Healthy Homes/Healthy Kids: Pediatric Primary Care-based Obesity Prevention. Nancy E. Sherwood, Ph.D. Funding: NIH/NIDDK 1R01DK084475-01, 9/10/09–9/9/14, annual direct costs \$592,611, total direct costs \$3,050,242.

Linking Home Environments and Primary Care: Obesity Prevention for 2–5 Year Olds. Nancy E. Sherwood, Ph.D. Funding: NIH/NIDDK R21 DK078239, 12/1/08–11/30/10, annual direct costs \$133,304.

Scientific Advances/Accomplishments

Adipose Biology

Notable Achievements

- Among the notable accomplishments is the availability of adipose cell lines from James Kirkland's subcore. The availability of these cell lines has driven considerable additional collaborations, which have substantially added to the previous network of collaborations and

interests in adipose cell function present prior to Dr. Kirkland's arrival. The NORC has been instrumental in making available the collaboration tools and cell lines for the benefit of this research group.

- The development of adipose-specific lentivirus expression vectors has provided a unique tool for workers in this area.

Notable Collaborations

- Michael Jensen, M.D. and James Kirkland, M.D., Ph.D., are collaborating on several projects relating to regional variations in preadipocyte biology, especially as it related to regional fat gain. In particular, they are collaborating to assess how adipose from various human depots varies with regard to its function and gene expression patterns.
- David Bernlohr, Ph.D., is a co-investigator on an NIH-funded grant led by Michael Jensen. The studies are to evaluate the potential role of fatty acid transport proteins in regional adipose tissue fatty acid storage in human obesity. This collaboration utilizes the Obesity and Energy Metabolism Core technologies and facilitates rapid acquisition of research results using Core resources. A major finding in this collaboration is that CD36 and FATP1 are expressed not only in the plasma membrane but also in the mitochondrion.
- Xiaoli Chen, M.D., Ph.D., is studying the function and expression of Lipocalin 2 (LCN2), an adipose-derived cytokine that binds and transports retinoic acid (RA). Dr. Bernlohr is a co-investigator on Dr. Chen's NIH-funded grant with particular emphasis on the RA binding characteristics of LCN2.
- The Bernlohr-Griffin-Arriaga groups recently had a new NIH grant awarded to examine the role of oxidative stress and mitochondrial function in obesity. Timothy Griffin, Ph.D., brings strong proteomics work to this project while Edgar Arriaga, Ph.D., lends expertise in mitochondrial bioenergetics and methodology.
- Dr. Bernlohr and Ann Hertzler, Ph.D., have a long-standing collaborative NIH-funded project on the role(s) of fatty acid binding proteins in obesity and type 2 diabetes.
- Do-Hyung Kim, Ph.D., has examined a number of proteins linked to autophagy, including those that are functionally linked with the mTOR pathway (TOR=target-of-rapamycin protein). Drs. Kim and Bernlohr are working together to assess how autophagy regulates mitochondrial function in obesity, and an NIH grant on this topic has been submitted.
- Using Obesity and Energy Metabolism Core support, lentiviruses were developed harboring shRNA corresponding to each of the putative transporters and produced 3T3-L1 cell lines with targeted silencing of each. The Cav-1 silenced 3T3-L1 cells are being evaluated for both fatty acid and glucose uptake (collaboration between Dr. Bernlohr [UMN] and Richard Pagano, Ph.D. [Mayo Clinic]).

Obesity and Energy Metabolism

- A collaborative project between Jeffrey Albrecht, M.D., and Howard Towle, Ph.D., is investigating the role of cyclin D1 in liver lipid metabolism mechanism and on the transcriptional activation of lipogenic enzyme genes. This work makes major use of the viral production facility of the Obesity and Energy Metabolism Core.
- The cluster of Douglas Mashek, Ph.D., Dr. Bernlohr, Chi Chen, Ph.D., and Dr. Towle has a funded project on the identification of bioactive food compounds that affect adipogenesis and

triglyceride accumulation. Using a fluorescent reporter developed in the Bernlohr laboratory, the Mashek laboratory is evaluating a natural products library for anti-obesity effect.

- Dr. Chi Chen (Principal Investigator [PI] of a NIDA R21 grant) has been working with the laboratory of Allen Levine, Ph.D., to study the metabolomic biosignatures induced by chronic cocaine exposure as a parallel to food addiction. Dr. Levine's laboratory is responsible for conducting behavior testing to establish and validate the addiction in rats.
- The laboratories of Drs. Kim and Griffin have been collaborating and have published together on a proteomic analysis of mTOR signaling and its role in nutrient regulation. This work assesses the roles of mTOR binding proteins and how insulin regulates mTOR signaling and mTOR controls insulin action.
- The collaboration between Drs. Mashek's (UMN) and Jensen's laboratories involves the use of stable isotopes to quantify changes in hepatic intracellular fatty acid trafficking mediated by adipose triglyceride lipase (ATGL). These studies may identify a novel role for ATGL in fatty acid partitioning and energy metabolism. Dr. Mashek has submitted an R01 grant application that proposes to take advantage of these new assays developed by the Metabolic Studies Core. Dr. Jensen is a co-investigator on that application.
- The Towle and Mashek laboratories collaborate to evaluate liver steatosis and triglyceride production regulation. Based on Towle's long-standing work on carbohydrate response element binding protein (ChREBP) and lipogenesis, the Mashek laboratory examines triglyceride turnover and the roles of hepatic lipases, particularly ATGL.

Neuroscience of Obesity

Notable Achievements

- Jennifer Teske, Ph.D., with mentorship from Catherine Kotz, Ph.D., and Charles Billington, M.D., has received a research career development award from the VA, as well as a Young Investigator Award from the Obesity Society. In addition, Joshua Nixon, Ph.D., has now also received a research career development award from the VA. These accomplishments extend the growth and development of the neuroscience group in Minneapolis.
- Two NORC Participating Investigators, Dr. Kotz and James Levine, M.D., Ph.D., were awarded a grant through Minnesota Governor Pawlenty's Bioscience initiative (UMN-Mayo Clinic Partnership for Biotechnology and Medical Genomics) titled "Non-Volitional Activity in Obesity Resistance: Role of the Brain." The Basic Mechanisms (now Obesity and Energy Metabolism) Core assisted by consulting on best molecular methods for obtaining the desired data points and providing a letter of technical support.

Notable Collaborations

- Drs. Allen Levine, Billington, and Kotz continue their long-time collaborations, resulting in additional publications and research support.
- ChuanFeng Wang, M.D., collaborates with Drs. Kotz and Billington on his successful studies of Brain-Derived Neurotrophic Factor (BDNF) in regulation of energy balance.
- Dr. Billington, Dr. Allen Levine, and Kelvin Lim, M.D., have begun a collaboration with new investigator, Tiffany Beckman, M.D., Ph.D., on the use of functional magnetic resonance imaging of human appetite.

- Dr. Kotz worked with Kevin Wickman, Ph.D., to define the phenotypic characteristics of obesity in GIRK4 knockout mice (GIRK = G protein-coupled inwardly-rectifying potassium channel). The work was published in *Proceedings of the National Academy of Sciences*. (Perry CA, Pravetoni M, Teske JA, Aguado C, Erickson DJ, Medrano JF, Luján R, Kotz CM, Wickman K. (2008). Predisposition to late-onset obesity in GIRK4 knockout mice. *Proc. Natl. Acad. Sci. U.S.A.*, 105: 8148–8153. PMID: PMC2430374.)

Metabolism

Notable Achievements

- By supporting studies of sleep apnea (Virend Somers, M.D.), incretins (Adrian Vella, M.D.), and gastrointestinal function with respect to ingestive behavior (Michael Camilleri, M.D.), we have enlarged the group of obesity investigators.
- Due to the Minnesota NORC and Dr. Jensen's leadership of the Metabolic Studies Core, Dr. Jensen was selected to lead the Mayo Department of Internal Medicine initiative on Obesity, Weight Management, and Nutrition. The department is providing more than \$150,000 per year for the next 3–5 years to help build a self-sustaining program.

Notable Collaborations

- Dr. Billington is collaborating with Dr. Vella on an NIH-funded study of how bariatric surgery and vagal nerve stimulation affect the incretin response to weight loss.
- Dr. Jensen is collaborating with Dr. Billington on a VA study of how deep brain stimulation therapy for Parkinson's disease results in weight gain.
- Johannes Veldhuis, M.D., continues to examine age effects and hormonal milieu on insulin action and, in so doing, collaborates with John Miles, M.D., from the Division of Endocrinology.
- Robert Rizza, M.D., collaborates with Dr. Vella and Rita Basu, M.D., examining models of glucose disposal. He also has worked with Sundeep Khosla, M.D., Dr. Jensen, and K. Sreekumaran Nair, M.D., Ph.D., to examine the effects of testosterone replacement in the elderly.
- Drs. Jensen and Khosla examined the role of sex steroids in the acute regulation of energy metabolism.
- Dr. Vella, a new NIH investigator, collaborates with Dr. Basu (another new NIH investigator) examining the effect of incretin in glucose turnover as well as obesity.
- Eduardo Chini, M.D., Ph.D., has become interested in obesity and has collaborated with Dr. James Levine.
- Dr. Nair has continued to collaborate with Drs. Jensen, Khosla, and Rizza on understanding the effects of aging, testosterone, and dehydroepiandrosterone (DHEA) on fatty acid metabolism.
- Dr. Jensen and Michael Joyner, M.D., have just completed a joint project examining the effect of Beta 2-adrenergic receptor polymorphisms on the cardiovascular and adipose tissue responses to exercise and catecholamines.

Eating Disorders

Notable Achievements

An NIH T32 postdoctoral training grant in Eating Disorders was funded in 2009 involving members of this group.

Notable Collaborations

- An NIH R01 grant was awarded to Nancy Raymond, M.D., to study energy expenditure vs. eating behavior in binge eating disorder. Dr. Jensen assisted Dr. Raymond in the grant process and with the doubly labeled water measures in the Metabolism Core at Mayo Clinic.
- The Disordered Eating Assessment Core is collaborating with Dr. James Levine through the Metabolic Studies Core in the development of a project looking at animal models of antipsychotic-related weight gain.
- The Disordered Eating Assessment Core is collaborating with Dr. Allen Levine on a study of dietary restraint in the general population.
- Scott Crow, M.D., is helping Michael Jensen establish psychological phenotyping methods for the newly established Mayo Internal Medicine Department research initiative “Obesity, Weight Management and Nutrition Program.”
- A study of food intake, satiety, and pain in obese binge eaters was done in collaboration with NORC investigators in the Department of Psychiatry. The Epidemiology and Intervention Core provided dietary assessment services through the Dietary Assessment Unit, and the Disordered Eating Assessment Core provided recruitment and behavioral assessment services.
- The Disordered Eating Assessment Core has been assisting the group in the Metabolic Studies Core at the Mayo Clinic in the design and conduct of a study examining the combination of pharmacotherapy plus a brief behavioral intervention for the treatment of obesity in individuals with diabetes. More recently, the Core has provided consultation on the development of a multimodal behavioral assessment routine.

Adult Obesity Treatment and Prevention

Notable Achievements

- The Epidemiology and Intervention Core led a collaboration of NORC investigators on a successful center grant application titled “Examining the Obesity Epidemic through Youth, Family, & Young Adults: Transdisciplinary Research on Energetics and Cancer.” The overall goals are to advance understanding of obesity and cancer, support career development, and disseminate scientific knowledge. The initiative has supported 24 additional research projects involving NORC investigators, and three have led to NIH funding.
- Robert Jeffery, Ph.D., Dr. Billington, and Dr. Kotz collaborated on a successful NIDDK T32 Minnesota Obesity Prevention Training grant. The training grant will involve key NORC investigators and have three training tracks: basic science, behavioral epidemiology, and clinical. The program would provide training for predoctoral, postdoctoral, and medical fellows.

- Dr. Jeffery, Mary Story, Ph.D., and Leslie Lytle, Ph.D., provided senior mentorship to Melissa Laska, Ph.D., on her research related to obesity in emerging adults. As a result, Dr. Laska has received an NCI K07 Career Development Award, an American Heart Association grant, and a TREC developmental project to support her work.
- Mark Pereira, Ph.D., was awarded his first NIDDK R01 grant, “Genetic and Environmental Determinants of Type 2 Diabetes in Chinese Singaporeans.” This study aims at identifying the genetic susceptibility factors for type 2 diabetes in Chinese living in Singapore.

Notable Collaborations

- Drs. Allen Levine and Jeffery conducted a study examining the effect of portion size provided in boxed lunches on caloric intake and weight gain. This study resulted in a publication. (Jeffery RW, Rydell S, Dunn CL, Harnack LJ, Levine AS, Pentel P, Baxter J, Walsh EM. (2007). Effects of portion size on body weight. *Int J Behav Nutr Phys Activ*, 4:27. doi:10.1186/1479-5868-4-27. PMID: PMC1929118.)
- Drs. Jeffery and Billington have collaborated with Sayeed Ikramuddin, M.D., on a study funded by Covidien titled “Global Randomized Study of Best Medical Management versus the Roux- en-Y Gastric Bypass for the Management of Type 2 Diabetes in Patients with Central Obesity.”
- Dr. Camilleri is studying the role of the stomach, satiety hormones, and genetic variation in appetite regulation of overweight and obese patients. He collaborates now with Matthew Clark, Ph.D., and Drs. Vella, Billington, and Rizza (NORC member of the Division of Endocrinology). This is a relatively new area of research for Dr. Camilleri, and the collaborations with members of the Minnesota NORC are largely the result of the Center grant.
- Dr. Clark collaborates with Virend Somers, M.D., D.Phil., in studies of the relation between sleep and obesity.
- Dr. Jeffery and Jennifer Linde, Ph.D., have begun work with an international group of obesity researchers, including, Knut-Inge Klepp, Ph.D., Norway; Johannes Brug, Ph.D., Netherlands; and David Crawford, Ph.D., Australia, to design a study on international comparisons of obesity etiology.

Childhood Obesity

Notable Achievements

- A successful NHLBI U01 grant, titled “Etiology of Childhood Obesity: A Longitudinal Study,” was developed under the direction of Dr. Lytle with collaborators including Drs. Jeffery, Linde, Laska, and Crow; Donald Dengel, Ph.D.; and Carol Peterson, Ph.D. The study is to examine etiology of childhood obesity considering possible risk and protective factors at individual, family, school, and neighborhood levels.
- Dr. Lytle was also awarded a NHLBI grant titled “Away from Home and Out of School: Adolescent PA and BMI Changes that Occur with Driving and Eating Out - TAAG 2.” This is a prospective observational study of the many individual and environmental factors implicated in the etiology of adolescent obesity.

Notable Collaborations

- Mary Story and Nancy Sherwood, Ph.D., worked together with the Obesity and Energy Metabolism Core studying gene markers to determine a potential relationship between these markers and the development of obesity. The resulting grant, "Decreasing weight gain in African-American preadolescent girls," received NIH funding.
- The Epidemiology and Intervention Core provided Ellen Demerath, Ph.D., support for a pilot project titled "Perinatal Influences on Infant Adiposity, the MINNOwS Study: Maternal Body Composition and Offspring Global DNA Methylation Status."

Activity Measurement and Intervention

Notable Achievements

- James Levine and Robert Jeffery have received funding from the Minnesota Partnership for Biotechnology and Medical Genomics for a mobile body composition and energy metabolism laboratory. The Mobile Obesity Laboratory will enable the Mayo Clinic and the UMN to complete outreach and outcomes-based research with respect to obesity prevention and treatment research.

Notable Collaborations

- Robert Jeffery is a collaborator on a pending NIH grant application submitted by James Levine titled "Real-World Office-Place Interventions for Obesity." The objective of this study is to test scalable obesity interventions that are delivered to representative offices where people work.

Health Plans and Policy

Notable Achievements

- Nancy Sherwood has received four obesity-related grants through support from the NORC Healthcare Delivery SubCore, including an NIDDK R01, an NIDDK R21, a HMORN Cancer Research Network Pilot, and a HealthPartners Discovery grant.
- Brian Martinson, Ph.D., was awarded an NIH grant titled "Passport: A Multi-Domain Lifestyle Intervention to Maintain Brain Wellness," which was a supplement to 5R01AG023410-05.
- Patrick O'Connor, M.D., received NIH funding for a study titled "Childhood Hypertension and Obesity: Diagnosis, Care and Costs." The project will examine electronic medical records at large medical groups in Colorado, Minnesota, and California to assess the stability of recently developed categories of hypertension in children and adolescents, patterns of care, and impact of elevated blood pressure on use of health care resources.

Notable Collaborations

- Nancy Sherwood, Dr. Jeffery, and Rona Levy, Ph.D. (from the University of Washington), collaborated on a pilot project to test the efficacy of brief pediatrician counseling with phone follow-up on rate of weight gain in children. The project provided data in a successful NIH grant application.
- Simone French, Ph.D., and Nancy Sherwood (Co-PIs) recently received NIH funding for “Linking Primary Care, Communities and Families to Prevent Obesity Among Preschool Children.” This study focuses on the development and evaluation of a multi-level, multi-component intervention to prevent obesity among at-risk, low-income, preschool-aged children. Other collaborators on the application included Ellen Demerath and Dianne Neumark-Sztainer, Ph.D., from Epidemiology, and Steven Stovitz, M.D., from Family Medicine.
- Nancy Sherwood collaborated with Patricia Fontaine, M.D., in Pediatrics on a developmental project titled “Modeling Trajectories of Optimal Pregnancy Weight Gain for Overweight and Obese Women.” The pilot examined relationships between weight gain in pregnancy and maternal and child health outcomes, with the eventual goal of obtaining extramural funding to develop an effective intervention to prevent excessive gain.
- The Epidemiology and Intervention Core has begun to foster collaborations with several other healthcare delivery organizations through collaborative grant submissions and provision of technical expertise. The partnerships have included HealthPartners, Blue Cross/Blue Shield of Minnesota, Kaiser Permanente, Group Health, Puget Sound Group International, Minneapolis VA Medical Center, and the HMO Research Network.

Obesity Consortium of Minnesota

The Minnesota NORC has been a key in promoting the transformation of the approach to obesity science and education in Minnesota. The success and visibility of obesity science at UMN, led by members of the Minnesota NORC, stimulated further obesity program development. The Obesity Consortium of Minnesota is the new umbrella organization that encompasses combined programs from the Minnesota NORC, the UMN Obesity Prevention Center, and the UMN Center for Transdisciplinary Research on Energetics and Cancer (TREC). In past reports, we have described the Consortium founding, which began as an effort to facilitate multidisciplinary collaboration and foster cooperation in obesity research, education, and outreach efforts at UMN.

A few years ago, the Consortium successfully carried out its first major collaborative project, the joint 2006 P & F Program. This program involved bringing together the pilot funding sources and procedures from the three major funding entities in the consortium, agreeing on the combined procedures, and then soliciting and evaluating the P & F applications. The program sparked great interest in the Minnesota research community and resulted in 36 applications, 12 awards, and a total of \$613,213 (Direct Costs) in P & F funds awarded over the subsequent 2 years. The combined effort produced broader publicity and generated a greater number of higher quality applications than had previously been achieved. Two years later, the Consortium conducted its second collaborative project, the joint 2008 P & F Program. This time, the combined program resulted in 26 applications, 8 awards, and a total of \$400,000 (Direct Costs) in P & F funds awarded over the subsequent 2 years. The future of the Consortium depends upon the renewal of funding for both the Minnesota NORC and TREC, but if funding is achieved, the

Consortium will continue to sponsor joint programs that will promote obesity education and research in Minnesota.

The Obesity and Energy Metabolism Core

Obesity and Energy Metabolism Core capabilities form an essential and critical component of several research projects carried out by Minnesota NORC investigators. Few investigators use all technologies but most utilize more than one. As such, projects carried out by Obesity and Energy Metabolism Core users frequently link to multiple Core activities.

The Obesity and Energy Metabolism Core supported Dr. David Bernlohr's laboratory in projects focused on several aspects of adipose lipid metabolism. One major theme of the laboratory addresses the role(s) of putative fatty acid transporters. Several proteins have been hypothesized to facilitate fatty acid influx into adipocytes. These include the fatty acid translocase CD36, fatty acid transport proteins FATP1 and FATP4, caveolin 1 (Cav-1), and acyl CoA synthetase long (ACSL1). Using Obesity and Energy Metabolism Core support, we have developed lentiviruses harboring short hairpin RNA (shRNA) corresponding to each of the putative transporters and produced 3T3-L1 cell lines with targeted silencing of each. The Cav-1 silenced 3T3-L1 cells are being evaluated for both fatty acid and glucose uptake, in a collaboration between Dr. Bernlohr (UMN) and Dr. Richard Pagano (Mayo Clinic). Using Obesity and Energy Metabolism Core support, each stable adipocyte cell line has been evaluated for fatty acid influx, efflux, and metabolism and the likely function for each protein identified. In the case of Cav-1, the protein facilitates many components of basal Free Fatty Acid (FFA) influx. CD36 facilitates basal and insulin stimulated FFA uptake. FATP1 facilitates just insulin-stimulated FFA influx, and FATP4 and ACSL1 do not play a role in FFA influx. In contrast, FATP4 and ACSL1 facilitate FFA re-esterification of internal FFA produced by lipolysis. A manuscript describing some of these findings is in press (*Biochem J.*, 2010, in press. PMID: 20085539).

It is important to note that the extension of this project into human lipid transport has formed the basis of an NIH-funded (NIH R01 DK045343) collaboration with Dr. Michael Jensen (Mayo Clinic). The Bernlohr and Jensen laboratories have used support of the Obesity and Energy Metabolism Core to assess the expression of lipid transporters in human adipose and muscle. Major findings in this collaboration are that CD36 and FATP1 are expressed not only in the plasma membrane but also in the mitochondrion and that the expression of fatty acid transporters is both gender-specific and depot-specific, and changes in transporter expression occur coincident with obesity.

In a second major project, the Bernlohr laboratory evaluates the role of the intracellular fatty acid binding proteins (AFABP, also known as aP2) in lipid metabolism and signaling. AFABP/aP2 knockout and transgenic mice, plus macrophages isolated from AFABP null mice, are being evaluated for their role(s) in mediating inflammation and cytokine production in a collaboration with former P & F fund recipient Dr. Ann Hertzell. The Obesity and Energy Metabolism Core has provided lentiviral delivery of shRNA, as well as real-time PCR technologies for evaluation of gene expression in the wild type and knockout mice/cell lines.

Lastly, the Bernlohr laboratory has identified the tumor necrosis factor alpha (TNF α)-dependent down-regulation of glutathione S-transferase A4 (GSTA4) as a key component linking inflammation to mitochondrial dysfunction and activation of the thioredoxin 2-apoptosis

signaling kinase-c-jun N-terminal kinase (Trx2-ASK1-JNK) pathway. Using resources from the Obesity and Energy Metabolism Core, the laboratory has pursued loss of function and gain of function models using the 3T3-L1 adipocyte cell culture system. Importantly, glutathione S transferase (GSTA4) silencing results in mitochondrial dysfunction, reactive oxygen species production, increased basal glucose uptake, and increased basal lipolysis while over-expression of GSTA4 (driven by the strong aP2/FABP4 promoter) leads to the opposite phenotype. An application based on this work was recently funded by NIH (R01 DK084669-01). Clearly, the success of the new application would not have been possible without the support of the Obesity and Energy Metabolism Core.

The principal focus in Dr. Howard Towle's laboratory is to understand how increased uptake and metabolism of glucose leads to the enhanced transcription of genes involved in de novo lipogenesis in the liver. In the past year, the laboratory has used the services of the viral production core for several projects. Carbohydrate Response Element Binding Protein (ChREBP) is a critical transcription factor that regulates de novo lipogenesis by stimulating expression of lipogenic enzyme genes. The activity of ChREBP is controlled by glucose in the liver. To better understand the molecular pathway for glucose regulation, the Towle laboratory is searching for protein interaction partners of ChREBP. To accomplish this, they have prepared epitope-tagged versions of ChREBP. The viral core has introduced these into adenoviral vectors to allow efficient delivery into hepatocytes. The laboratory is using these vectors to immunoprecipitate interacting partners and mass spectrometry to identify these partners. The work will hopefully help to elucidate the currently unknown molecular pathway by which glucose functions to control de novo lipogenesis.

In addition, the Towle laboratory has been exploring the roles of two gene products—S14 and S14R—that have been suggested to be involved in de novo lipogenesis. Using siRNA strategies, they were able to show that knocking down these two proteins dramatically reduced rates of lipogenesis in hepatocytes cultured in high glucose. Again, using adenoviral vectors from the Obesity and Energy Metabolism Core facility, it was shown that expression of either of these proteins in hepatocytes rescued the knockdown phenotype. These studies have been useful in demonstrating an important role for these two gene products and will be pursued in future attempts to learn more about the mechanistic basis for their actions.

The Towle laboratory has also extensively used the core facility for real-time PCR (RT-PCR) assays that are used routinely for monitoring mRNA levels of various target genes of ChREBP. Both primer libraries that are maintained in the facility and instrumentation for performing RT-PCR have been used on a regular basis. The availability of these resources has been of tremendous value in allowing the laboratory to explore new areas of research that would not have been otherwise possible.

The Obesity and Energy Metabolism Core of the Minnesota NORC has been an indispensable asset for the laboratory of Dr. Douglas Mashek, a new Assistant Professor at UMN. The Obesity and Energy Metabolism Core has supplied Dr. Mashek's laboratory with an extensive list of primer sets for qRT-PCR that is critical, given that a primary focus of the laboratory is on the regulation of gene expression. To date, approximately 40 primer sets have been supplied to the laboratory by the Obesity and Energy Metabolism Core. The Core has also subsidized costs of shRNA or expression plasmids used for gain and loss of function models. The Core's adenoviral

production facilities have been utilized to generate and amplify several over-expression or knockdown constructs. These research tools, along with the knowledge that the Core was there for continued support, were important components in the Mashek laboratory obtaining a Junior Faculty Grant from the American Diabetes Association (ADA 07-07-JF-43). Additionally, the Minnesota NORC has funded the laboratory in the form of a P & F Grant that allowed for the support of a postdoctoral fellow. The pilot project was part of the successful NIH application to characterize the role of hepatic adipose triglyceride lipase (ATGL) in fatty acid metabolism and signaling (NIH 1R56DK085008). Additionally, the Mashek laboratory has begun collaboration with other members of the NORC.

The resources available in the Obesity and Energy Metabolism Core significantly enhanced Dr. Catherine Kotz's research by allowing her to form important collaborations with several NORC investigators (Drs. C.J. Billington, A.S. Levine, CF Wang, J.A. Teske and K.A. Wickman), performing studies of feeding behavior, physical activity, and energy metabolism regulated by specific brain systems, including orexin, GIRK, and BDNF. The data collected in these collaborative projects were significantly enhanced by the high-quality systems available to measure energy intake, energy expenditure, body composition, physical activity, and sleep/wake states. These collaborations have resulted in several publications in top-quality journals (*American Journal of Physiology* and *Proceedings of the National Academy of Science*) and subsequently resulted in new funding for Drs. Billington (VA Rehabilitation Research and Development [RRD]), Kotz (NIH, VA Merit, and VA RRD), Wang (NIH and VA Merit), and Teske (VA Career Development Award). These research collaborations have also allowed training of several students in the disciplines of Nutrition, Neuroscience, and Pharmacology.

Research in Dr. Xiaoli Chen's laboratory is focused on the regulation of adipose-derived adipokines and inflammatory cytokines in insulin action, inflammation, and metabolic homeostasis. The main project in Dr. Chen's laboratory is to characterize the role of lipocalin 2, a new adipokine, in inflammation and metabolic regulation *in vitro* in 3T3-L1 adipocytes and *in vivo* in lipocalin 2 knockout mouse model. The use of gain or loss of function approaches has been the main goal to achieve Dr. Chen's research aims. The Obesity and Energy Metabolism Core has provided key support for the construction of lentiviral vectors, production of lentivirus, and real-time RT-PCR primers for gene expression studies in published work as well as ongoing research projects. The NORC P & F Grant funded the Chen laboratory to initiate and continue the lipocalin 2 project. Chen's laboratory has discovered that lipocalin 2 has a novel role as a potential negative feedback regulator of inflammation and insulin resistance. Such a unique negative feedback regulatory mechanism in the adipocyte function has not been previously established. A paper titled "The Role of Lipocalin 2 in the Regulation of Inflammation in Adipocytes and Macrophages" was published in *Molecular Endocrinology* in 2008. As a research mentor and collaborator, Dr. David Bernlohr and his group provide critical support and solid foundation for the research in Dr. Chen's laboratory. Most importantly, as a result of the collaboration between Drs. Chen and Bernlohr, an NIH R01 grant has been funded to support the lipocalin 2 project (NIH 1R01-DK080743). A manuscript based on the work in lipocalin 2 knockout mice has been accepted (*Diabetes*, 2010 in press. PMID: 20332347). The Core's support on the knowledge and research resources has also been critical to the Chen laboratory's other projects investigating the functions of new adipokines Selenoprotein P and NPC2 (a protein associated with Niemann-Pick disease, type C) in adipocyte biology and insulin resistance. The work on these two projects resulted in one manuscript to be submitted and

another manuscript in preparation. The Core has supplied the construction and production of six lentiviral vectors and more than 50 real-time RT-PCR primers for the Chen laboratory. Additionally, the use of microarrays and proteomic techniques will be vital for Dr. Chen's laboratory research.

Resources from the Minnesota NORC have been critical in enabling an ongoing collaborative research project between the laboratories of Drs. Tim Griffin and Do-Hyung Kim in characterizing the target-of-rapamycin (TOR) protein, the master regulator of nutrient signaling and cell growth and a key player in obesity and metabolic disease. Their collaborative project has identified a new connection of mTOR to regulating nuclear functions maintaining chromosomal integrity and DNA damage response, providing new insights into how mTOR enables cellular protection in growth processes that is described in the publication "Quantitative nuclear proteomics identifies mTOR regulation of DNA damage response" (*Molecular & Cellular Proteomics*, 9, 403–414, 2010, PMID: 19955088).

Additionally, the Obesity and Energy Metabolism Core has provided resources for lentiviral pLKO.1 shRNA clones that are heavily used in Dr. Kim's laboratory, which is mainly driven by discovery of novel genes involved in metabolism and growth. Understanding the function of these genes is often evaluated by utilizing loss-of-function assays using shRNA knockdown approaches. The Obesity and Energy Metabolism Core has helped the Kim group to design and produce lentiviruses encoding shRNAs for a number of signaling molecules (more than 50 genes) with multiple shRNAs for each gene. The shRNA lentiviruses allowed them to knock down a specific gene and analyze how silencing affects cell signaling and metabolism in adipose cells. The Obesity and Energy Metabolism Core has provided a list of primers for RT-PCR analysis of gene expression for a significant number of genes involved in metabolism and cell signaling, and this resource helped the Kim laboratory to save effort in finding appropriate primers to study gene expression. Given the support of the NORC, they completed two projects on characterization of novel components in the nutrient-regulated mTOR signaling pathway, PRAS40 and PRR5. The Kim laboratory has found that these novel components play crucial roles in the regulation of mTOR activity and cell growth in response to nutrient levels and insulin. The two novel components were discovered through a proteomics approach that was newly developed in collaboration with the mass spectrometry/proteomics laboratory of Dr. Timothy Griffin.

Given the shared resources provided by the NORC, the Kim research group established a collaboration with the Bernlohr laboratory to study the role of several components in the nutrient-regulated mTOR signaling and autophagy in adipose cell metabolism. The collaboration has led the group to identify that adipose autophagy is highly vulnerable to obese states and significantly enhanced in adipose tissue from diet-induced or genetically altered obese mice. Diminished adipose autophagy resulted in a significant loss of subcutaneous adipose mass, smaller-sized adipocytes in mouse tissue, and improvement of several metabolic parameters including higher capacity of mitochondria and resistance to oxidative stress. These preliminary studies motivated the laboratories to build collaborative efforts to evaluate the emerging concept of "autophagy regulation" in adipose tissue as obesity therapeutics. In the future, support from the Obesity and Energy Metabolism Core will be invaluable in further development of this collaboration.

Work in the laboratory of Michel Sanders, Ph.D., focuses on the Zeb1 transcription factor and a mouse knockout model with the basic observation that heterozygosity at the Zeb1 locus leads to obesity in female mice. Given this observation, Dr. Sanders and colleagues have developed the hypothesis that Zeb1 is a negative factor regulating either adipogenesis or lipid accumulation in differentiated adipocytes. One paper has been submitted on the Zeb1 null mouse and compelling data on broad aspects of mouse physiology is being done in collaboration with the Kotz laboratory sufficient for a second paper. Work in establishing the metabolic profile of the knockout animals is underway, as is a study on the effect of estrogen on Zeb1 mRNA expression in 3T3-L1 cells. The Obesity and Energy Metabolism Core provided real-time PCR support. In addition, a lentivirus harboring a shRNA targeting Zeb1 was produced in the virus production facility.

Although Dr. Michel Sanders has a long-standing interest in the regulation of gene expression by estrogen, she has only recently become interested in the role that estrogen plays in modulating metabolism and obesity. The Minnesota NORC and the Obesity and Energy Metabolism Core have proven invaluable in fostering this new research direction, and two publications have resulted thus far (Saykally, J.N., Dogan, S., Cleary, M.P. & Sanders M.M. (2009). The ZEB1 transcription factor is a novel repressor of adiposity. *PLoS One* 4(12):e8460. doi:10.1371/journal.pone.0008460. PMID: 20041147; Saykally, J.N., Sandri, B.M. & Sanders, M.M. (2009). The ZEB1 transcription factor mediates effects of estrogen on attenuating adiposity in mice. *Endocrinology* [in revision]). The Sanders laboratory has benefited tremendously from all of the Obesity and Energy Metabolism Core services. It has used the Virus Production Facility to produce lentivirus to manipulate the endogenous levels of the estrogen-regulated ZEB1 transcription factor in 3T3-L1 cells. The first data from this project are currently in press. The laboratory has also used the Real Time PCR and oligonucleotide libraries extensively to measure levels of about 20 different mRNAs both in 3T3-L1 cells and in a ZEB1 knockdown mouse model. The availability of tested primers and oligonucleotides has saved a great amount of time and money, as the laboratory did not have to test all of the primer sets before use. The Sanders laboratory also used the Microarray Facility to compare the expression profile of mouse embryo fibroblasts from wild type and ZEB1 null mice during adipogenesis. The data are currently being analyzed, but even at this point, it is clear that ZEB1 affects a number of metabolic pathways including glycolysis and lipolysis. It should be noted that the Sanders laboratory did not have the financial resources to do this on its own, so this project could not have been done without the Core Facility. These studies have set the future direction of the entire research program. The Small Animal Calorimetry Facility in collaboration with the Kotz laboratory was key to publishing the group's first paper on obesity. In that study, the group used the Facility to measure body composition using EcoMRI and demonstrated that ZEB1 heterozygous mice gained significantly more fat mass over time compared to wild type animals.

Obesity and Energy Metabolism Core member Dr. Gary Nelsestuen is the Director of the Center for Mass Spectrometry and Proteomics (CMSP). This Center underwent an external review, and based on that exceptional review, the UMN has expanded its support for the CMSP by 150%. Paralleling the increased support by UMN, the State of Minnesota legislature provided funding for mass spectrometry as a partnership grant between UMN and the Mayo Clinic. Such "partnership funding" increased access to low-cost mass spectrometry and proteomics technology for all faculty of the Minnesota NORC. Increased funding brought the responsibility to provide UMN and Mayo Clinic users with expanded access and consultation to mass

spectrometry services, thereby eliminating the need of the Obesity and Energy Metabolism Core to facilitate such interactions.

A new addition to the Obesity and Energy Metabolism Core is a small animal indirect calorimeter. The equipment (Columbus Instruments) measures oxygen consumption and carbon dioxide production in awake, freely moving rats and mice, and the data can be used to determine energy expenditure. Physical activity levels can be measured concurrently using a beam break apparatus (Med Associates) fitted around the cage. Body composition measurement for rodents is also available. The equipment, EchoMRI (Echo Medical Systems), provides a non-invasive means and non-anesthesia means of providing fat and lean mass in rodents. Measurement time is 1 to 5 minutes per animal. Recently, equipment funds from an administrative supplement were used to purchase a multi-chamber mouse calorimeter as part of the energy balance phenotyping service. The supplementary calorimetry equipment is needed for two reasons: first, the interest in energy balance phenotyping is growing at our institution as it has at many others, and this has resulted in demand that is greater than our current single multi-chamber calorimeter can meet. Second, the current calorimetry setup is primarily a rat system, which we have been able to adapt at times for mouse work. We will be better able to serve the necessary demand for both rat and mouse measurements with a separate and appropriately sized system for each type of rodent.

The Obesity and Energy Metabolism Core received ARRA support for an automated PrepStation for Metabolomics Studies, which is a device designed for high throughput analysis of metabolites by a GC-GC/TOF mass spectrometer. The station allows sample preparation to be developed by simple drag-and-drop functions that require no macro programming and are therefore user friendly for the types of biological scientists in the NORC. Low-cost operation of the instrument (typically \$12.00 of instrument time per sample) will make new experiment approaches available to NORC investigators.

Description of training/mentorship opportunities sponsored by the Core. The Obesity and Energy Metabolism Core has been a major driving force in the development of obesity research at the Mayo Clinic and UMN. In the cases of Drs. Gary Nelsestuen, Michel Sanders, Catherine Kotz, Jennifer Westendorf, and Kevin Wickman, each is a tenured senior faculty member at the UMN or Mayo Clinic who added new research themes in obesity and energy metabolism to their existing programs due to the availability of Core services and senior investigators in the area. In addition, senior faculty at UMN and the Mayo Clinic mentor beginning scientists, both junior faculty and trainees, towards research activities in the area of obesity research. At the faculty level, Drs. Xiaoli Chen, Tim Griffin, Do-Hyung Kim, Edgar Arriaga (a new P & F awardee), and Mashek are all Assistant Professors being mentored by senior faculty (Bernlohr and Towle) participating in the Obesity and Energy Metabolism Core. Arriaga, Griffin, and Kim were recruited to Minnesota with research programs that did not involve obesity or energy metabolism, and they have moved into that field due in part to the availability of Core services and the critical mass of investigators conducting obesity research.

As would be expected, each of the Obesity and Energy Metabolism Core faculty members trains graduate students, technicians, and postdoctoral scholars in her or his laboratory. As Co-Director of the Core, Dr. Towle, in the last year, has provided guidance and advice to several laboratories (Sanders, Lange) on the use of DNA microarrays for gene expression analysis. This advice has

included talking with graduate students on strategies for design of microarray experiments, as well as for analysis of data.

A significant training component of the Obesity and Energy Metabolism Core is conducted through the bi-monthly seminar series sponsored by the Minnesota NORC. In these seminars, participating faculty, students, and postdoctoral students give updates on their studies and find connections with other NORC investigators through the sharing of ideas, technologies, and reagents. For example, in one of the seminars Do-Hyung Kim introduced the use of shRNA-directed virus in over-expression models. This technique was modified in the Bernlohr laboratory by introducing a strong aP2/FABP promoter, which has streamlined the loss- and gain-of-function analysis for most studies. Moreover, the technology has been transferred widely to others at both the Mayo Clinic and UMN conducting projects distinct from obesity. Such users do not benefit financially from being a Core user but do benefit by virtue of access to clones, vectors, and methods. As such, the Obesity and Energy Metabolism Core has had the unanticipated benefit of expanding the technology base of both institutions into areas far broader than simply obesity and energy metabolism.

Lastly, through interactions linked to the Obesity and Energy Metabolism Core, several small group meetings between laboratories have developed around collaborative projects. These include the Bernlohr-Chen-Hertzel group, the Towle-Mashek group, the Levine-Billington-Wang-Kotz group, the Bernlohr-Griffin-Arriaga group, and the Griffin-Kim group.

Significant research advances made possible via the NORC. Utilizing resources of the Obesity and Energy Metabolism Core, several high impact findings/publications have come forth that affect our views of obesity and obesity-related disease. These include:

- Covalent modification of adipose proteins underlies mitochondrial dysfunction in obesity (Bernlohr, Griffin, and Arriaga).
- Obesity is linked to autophagy and the activation of an autophagy-controlled kinase cascade (Kim, Bernlohr).
- The Zeb1 transcription factor is a novel regulator of adiposity (Sanders).
- Triglyceride hydrolysis provides FFA that regulate nuclear transcription factors (Mashek, Towle, Bernlohr).
- Glycolytic flux regulates the mTOR signaling cascade (Kim).

In each of these major findings, the function of the Core, specifically the virus production capacity, made the work possible. The availability to test gain and loss of function models of specific targets through the use of lenti- and/or adenoviruses has been a major stimulus to scientific progress in the Minnesota NORC. The use of such viruses has expanded the research base of Minnesota NORC participating faculty and enabled their laboratories to carry out work where they previously would not have been able.

An additional and very significant impact of the Minnesota NORC has been on the recruitment of faculty to the Mayo Clinic and UMN. The recruitment of Dr. James Kirkland from Boston University to the Mayo Clinic was made in part through connections made between Minnesota NORC users and the Kirkland laboratory. With the recruitment of James Kirkland to the Mayo Clinic, we are expanding our use of human preadipocyte cell lines to parallel the classical 3T3-

L1 murine model commonly available. If use of the differentiating human cell lines develops, we may consider adding cell biology of these models to the Core function in the future. Dr. Kirkland's human preadipocyte cell lines are likely to be an invaluable resource to NORC users in the upcoming years. Indeed, collaborative work between the Bernlohr and Kirkland laboratory to evaluate anti-diabetes drugs will be realized because of the availability of such small molecules (Bernlohr laboratory) and cell lines (Kirkland laboratory).

The Minnesota NORC participated in bringing George Thomas, Ph.D., from Cincinnati to the campus to present his findings on the regulation of mTOR signaling in adipocytes. The result of that activity was a Bernlohr Ph.D. student (Brian Wiczler) doing a postdoc in the Thomas laboratory studying mitochondrial function, obesity, and mTOR signaling. Resources from the NORC were used to partially offset costs and matched by UMN funds for the seminar series.

The Disordered Eating Assessment Core

The Disordered Eating Assessment Core provides training in, consultation about, and direct provision of assessment and treatment for disordered eating, obesity, and general psychopathology. The Core is involved in the development and testing of structured assessment measures and provides high-level training and quality assurance for investigators who wish to conduct these assessments. When cost effective, the Core itself provides such assessments. As the Core has access to individuals with various forms of disordered eating and other kinds of psychopathology, it also serves as a resource for subject recruitment for some studies. The Core has developed increasing sophistication in the use of technologies such as personal digital assistants (PDAs) to collect ecological momentary assessment data and provides consultation on the use of such methods; this resource has been increasingly popular. Finally, the Core has also developed increasing interest in cost effectiveness analysis and provides consultation and analytical capacity in this regard.

Benefits and interactions resulting from the existence of the Core. The Disordered Eating Assessment Core continues to make important contributions to our understanding of the treatment, course, and outcome of obesity and eating disorders and supports efforts from a variety of investigators working at the interface between disordered eating and obesity. One major aspect of this work continues to be significant contributions to the multimodal assessment of disordered eating and eating attitudes. These include studies developing new treatments for obesity in children (Dr. Kerri Boutelle, P.I.), studies of novel treatments for binge eating (R01 DK61982, Dr. Scott Crow, P.I.), and bulimia nervosa (R01 MH59234, Dr. Crow, P.I.; vagal nerve stimulator treatment for bulimia nervosa, R01 DK0965167, Patricia Faris, Ph.D., P.I.). The Core helped with recruitment for a study of bone mineral density in several groups including subjects with anorexia nervosa (Moiria Petit, Ph.D., PI). The Core assisted with a study design for a recently funded CAPS K-12 Scholar, Jerica Berge, Ph.D., from Pediatrics, for a study examining family factors in obesity. The Core has provided consultation training and direct assessment for studies of postpartum depression and its relationship to weight gain conducted by an investigator in Family Medicine (Dwenda Gjerdingen, M.D.). Most recently, the Core has been instrumental in obtaining funding for a school-based intervention project titled "CHOICES" (NIH/NHLBI U01HL096767, Dr. Leslie A. Lytle, PI).

The Disordered Eating Assessment Core has brought about a number of interactions that otherwise would not have occurred. Most notable among the recent interactions are collaborative efforts examining depression and weight change in the postpartum period; without the Core interactions, this work would not have focused on weight gain or obesity at all and therefore would not have identified an important relationship that has now been described. Similarly, because of the Core, a collaborative study of weight loss in children with chronic disease is being conducted in the Department of Neurology, and this would not have occurred without the Core.

The Disordered Eating Assessment Core's assessment services are highly cost-effective and beneficial. It is impractical for most individual investigators to develop expertise in structured assessment or to train, standardize, and maintain staff with expertise in assessment; the Core mechanism is higher quality and more cost-effective. The importance of such assessment is growing, due to at least two factors. First, growing interest in defining eating behavior phenotypes (as emphasized by recent work looking at genotypic correlates of phenotypes such as binge eating) requires accurate definition of those phenotypes. The same is true of work looking at behavioral and psychophysiologic endophenotypes, which is garnering increased interest. Second, increasing recognition of the role of affective and anxiety disorders in medical (especially cardiovascular) illness outcomes make identification of these syndromes important in studies assessing these medical outcomes.

The Core focus on development and piloting of therapies is a highly cost effective function. Additionally, the Core has developed proficiency in technology-assisted data collection using PDAs and Digital Scanning, both of which are novel, high fidelity, and highly cost effective methods, and offers both to NORC participating investigators. The use of these technology-assessed data collection methods continues to grow.

Training/mentorship activities. The Disordered Eating Assessment Core remains quite active in the areas of training and mentorship. Core personnel, particularly Drs. Peterson and Crow, provide mentorship to junior investigators and, in some cases, more senior investigators as well as a substantial number of graduate studies and undergraduates interested in disordered eating or obesity and its treatment. For example, Dr. Crow is one mentor for Jerica M. Berge, Ph.D., a recently funded Advancement Program for Clinical Research Scholars (or CAPS) scholar through the internal K-12 grant mechanism at UMN. In addition, Dr. Peterson plays a particularly prominent role in training investigators and students at this institution in the provision of structured psychological and psychiatric assessments. Training cycles for instruments such as the structured clinical interview for DSM-IV and the Eating Disorders Examination are held intermittently through the year. In addition, Dr. Peterson directs a structured assessment seminar, which meets weekly throughout the entire year. This longstanding and successful assessment training seminar has been expanded to bring these services to a wider variety of investigators in the departments of psychology and psychiatry who are looking at weight gain in psychiatric illness, obesity, and eating disorders. Dr. Peterson organizes the Eating Disorder Journal Club, which meets monthly and includes active participants from five schools and roughly eight departments throughout the University. Dr. Crow along with Dr. Simone French from the Epidemiology Core have co-organized a yearlong seminar on the Ancel Keys Semistarvation study conducted at UMN more than 60 years ago.

Members of the Disordered Eating Assessment Core recently submitted a postdoctoral T32 training grant application that focuses on eating disorders; the application was funded (T32 MH082701) and the first class of fellows has begun training. The T32 postdoctoral training program, resulting largely from Core interactions, will be a powerful tool for expanding the number of investigators working at the interface of obesity disordered eating.

Epidemiology and Intervention Core

The Epidemiology and Intervention Core facilities have served as a basis for ongoing and developing research within the Minnesota NORC. The data collection, nutrition, intervention, and health care delivery services have played instrumental roles in supporting numerous pilot projects that have led to innovative obesity research. The impact of Core facilities is best evidenced by contributions to numerous scientific papers and to the development of new, externally funded research. The Epidemiology and Intervention Core has provided support for 299 different projects spanning a wide diversity of units at the University and outside the University. The Core has contributed to 79 successful proposals for external research funding over the last 14 years. The most notable accomplishments of the Epidemiology and Intervention Core in the past year have been contributions to the development of 56 grant proposals or projects, including five grants resulting in extramural funding to date. These grant applications illustrate the value of the Core in facilitating successful interdisciplinary research teams. The Core has provided an organizational network for drawing together faculty and resources for creative and innovative new research and continues to support the collaborations and organizational efforts needed to respond to the tremendous diversity of funding opportunities currently available. The Core has fostered greater interconnections between faculty members in diverse areas of the University community and has laid the foundation for further interdisciplinary research collaborations. Following are descriptions of the newly funded research grants.

- **Addressing Young Adult Obesity: Identifying Effective Opportunities for Prevention in 2-Year Community Colleges.** Dr. Melissa Nelson Laska, Division of Epidemiology and Community Health, UMN. Funding: American Heart Association, 7/2009–6/2011.
- **Linking Home Environments and Primary Care: Obesity Prevention.** Dr. Nancy E. Sherwood, HealthPartners Research Foundation. Funding: NIH/NIDDK, 7/2009–7/2010.
- **Innovative Weight Reduction Strategies for College Students.** Dr. Leslie Lytle, Division of Epidemiology and Community Health. Funding: NIH/NHLBI, 8/2009 -7/2014.
- **Healthy Homes/Healthy Kids: Pediatric Primary Care-based Obesity Prevention.** Dr. Nancy E. Sherwood, HealthPartners Research Foundation. Funding: NIH/NIDDK, 9/2009 - 09/2014
- **Childhood Hypertension and Obesity: Diagnosis, Care and Costs.** PI: Dr. Patrick O'Connor, HealthPartners Research Foundation, Co-I: Nancy E. Sherwood, HealthPartners Research Foundation. Funding: NIH, 8/2009–8/2013
- **Portion Size Effects on Body Weight: Free Living Setting.** Dr. Simone French, Division of Epidemiology and Community Health, UMN. Funding: NIH/NIDDK, 12/2009–11/2013

The Epidemiology and Intervention Core continues to provide support for the health systems section of the Epidemiology and Intervention Core at HealthPartners Research Foundation, a large managed-care organization in Minnesota. This section is intended to stimulate research on

obesity-related issues in a real world health care delivery system. This collaboration provides access to large populations and support and consultation around technical areas such as health care economics, health system database design and management, and survey implementation. The Core has also begun to foster collaborations with several other health care delivery organizations through collaborative grant submissions and provision of technical expertise. The partnerships include HealthPartners, Blue Cross/Blue Shield of Minnesota, Kaiser Permanente, Group Health, Puget Sound Group International, Minneapolis VA Medical Center, and the HMO Research Network, which focuses on studies using health plans for defined populations.

Training/mentorship opportunities. The Epidemiology and Intervention Core has been instrumental in the training and professional development of the next generation of obesity prevention researchers and practitioners. Through enhanced coursework, combined with interdisciplinary seminars and research, the Core strives for students and new investigators to gain the skills and knowledge necessary to successfully address the obesity epidemic. In collaboration with the Center for Transdisciplinary Research on Energetics and Cancer (TREC), the Core has helped to implement a successful career development program for junior faculty, postdoctoral fellows, and current doctoral students. The program provides trainees with exposure to advanced methods and experimental approaches in obesity research and with the skills needed to pursue independent research careers in this area. Trainees are able to establish a mentoring relationship with scientists of stature engaging in obesity research. A total of 16 trainees from five University departments are currently participating in the program. Two trainees have received NIH K awards due in large part to Core support.

A Minnesota Obesity Prevention T32 Training grant is funded by NIH/NIDDK. The training grant involves key NORC investigators and has three training tracks: basic science, behavioral epidemiology, and clinical. The program provides training for predoctoral, postdoctoral, and medical fellows. Robert Jeffery, professor in Epidemiology and Community Health, is the Program Director. Catherine Kotz, professor in the Department of Food Science and Nutrition, and Charles Billington, professor in Medicine, are the Co-directors. Core faculty members are also designated mentors on several other existing training grants.

Leveraging other resources. The Epidemiology and Intervention Core received ARRA funds to expand its successful, cost-effective equipment loan program through the purchase of the following items: Actigraph GT1M Accelerometers; Nutrition Data System for Research (NDSR) and compatible laptops for running the software; Tanita BWB-800S Digital Scales; and Ecological Momentary Assessment (EMA) devices. The equipment has been available on a first come, first served basis and provided free of charge to all investigators for use in obesity related P & F projects. The accelerometers have been used on three pilot projects involving nine data collection periods, scales and stadiometers have been used on four additional pilot projects, and the nutrition assessment software used on three other developmental projects. The EMA devices will be purchased after a specific pilot protocol is developed and a comparison of available equipment options is completed.

Equipment Funds from Administrative Supplement: The Epidemiology and Intervention Core was awarded supplemental equipment funds to purchase a BOD POD Body Composition Tracking System. The BOD POD is an air displacement plethysmograph, which uses whole-body densitometry to determine body composition. The equipment is currently being used on a P

& F study examining epigenetic influences on body composition and obesity in infancy and early childhood. The equipment is available for use in other current and planned obesity prevention and weight loss studies through the Core as requested by Center investigators.

Metabolic Studies Core

Human Studies

The Metabolic Studies Core has actively supported the establishment of an intensive development program for measuring physical activity and the energy expenditure associated with physical activity in free-living individuals. In this regard, we developed technological solutions to assess a wide range of physical activities in free-living individuals. We have collaborated broadly across the campuses in this regard, for example, 1) with Dr. Kaufman to examine the energy expenditure of amputees with a novel prosthesis, and 2) with Dr. Nair to examine familial physical activity patterns in human subjects spanning three generations. This technology we envision can be widely applied across Center activities to, for the first time, enable physical activity to be readily measured accurately in large numbers of individuals.

The Core facilities dramatically affect the projects on human physical activity that represent the research base of the NORC. For the first time, we will be able to provide investigators with cost-effective, broad-based measurements using validated tools for measuring physical activity. This will not only enhance knowledge with respect to the energy cost of physical activity but also enable, for example, the Cancer Center at UMN and obesity prevention program at UMN to enhance their studies with respect to objective monitoring of physical activity, which is widely viewed as a major limitation in this area. Beyond this, we plan to leverage the core program to seek additional Federal funds to mandate this mission even further.

We have developed a strong translational element with the founding of a new business model (Muve, Incorporated) by the Mayo Clinic to deliver scalable monitoring and weight loss solutions based upon the above-cited work. Muve, Inc. has delivered weight loss solutions to 12 U.S. corporations, including Best Buy and Medtronic, and we propose to expand these activities. Muve, Inc. is also delivering technology and solutions to the town Albert Lea, MN, in collaboration with the American Association of Retired Persons (AARP) and Blue Zones, an organization devoted to helping people live longer, healthier lives. The term “Blue Zones” refers to areas around the world that have been identified by a team of longevity researchers where people are living measurably better, reaching the age of 100 at rates 10 times that in the United States by living extremely healthy lives through diet, exercise, and healthy habits.

We have established new approaches to studying fatty acid metabolism utilizing the Metabolomics Facility that is part of the Mayo Center for Translational Science Activities (CTSA). We developed a novel LC/MS/MS method to measure the concentration and enrichment in plasma and tissue non-esterified fatty acids. The advantages of this new approach are that: 1) no derivatization is required, saving prep time for the samples; 2) the concentration and enrichment data are linear over a much wider range than with our previous GC/C/IRMS approach; 3) the run time for a sample using LC/MS/MS method is 6 minutes as opposed to more than 30 minutes for GC/C/IRMS; and 4) the need for frequent cleaning of the source, etc., is less with the new method. We have also established a method to measure the concentration

and enrichment of long-chain acyl-carnitines in muscle and are establishing assays for long-chain acyl-CoA's, diacylglycerols, and sphingolipids (ceramides) to better understand the role of extracellular fatty acids in intracellular signaling cascades.

Animal Studies

The Metabolic Studies Core has completed several years of collaboration with Columbus Instruments in order to build and disseminate small animal calorimeters that are readily usable not only at the Core center (in Rochester, MN) but also across the VA and UMN Campuses. These instruments enable us to perform the laboratory validations of the physical activity detectors described above and to readily validate these sensors as modifications occur during the next few years. We have succeeded in developing our animal calorimeter system to support studies on animal energy expenditure beyond our original anticipated goals. Colleen Novak, Ph.D., has been overseeing the small animal calorimetry facility and has a career development award from the American Heart Association to further these studies. Through collaboration with Dr. Kotz from UMN and VA Medical Center, Dr. Novak has acquired the skills to perform neurotactic placement of cannulae within subsegments of the animal brain, which she now performs at the Mayo Clinic in Rochester. This technique has allowed the study of putative mediators of physical activity to be assessed centrally. These endeavors have recently facilitated the funding of Cheryl Conover, Ph.D.'s R01 award and have enabled additional collaborations not only with Dr. Kotz at UMN but also, for example, with Dr. Nair in Rochester.

We have been trying to anticipate growth in this area and also recognize the difficulty of collaborators at UMN and the VA Hospital to bring animals to the Rochester facility for studies. In light of these concerns and others, we have facilitated the development of a site for animal activity and energy expenditure measurements at UMN. In addition, EchoMRI machines are now installed at both sites. This has greatly enhanced the capability of the Core to offer service across the campuses.

Dr. David Bernlohr, a basic scientist at UMN, a co-investigator on one of Dr. Jensen's NIH grants, has continued to collaborate with Dr. Jensen on the issue of adipocyte fatty acid transport proteins and fatty acid trafficking. The ongoing collaborative nature of the Minnesota NORC promoted and has supported this relationship. Dr. Kotz of the VA Medical Center Minneapolis (NIH) and Dr. James Levine are working together to investigate basic neuroscience mediators of physical activity in obesity.

In addition to conducting studies for his received NIH grant, R01 DK 76486, "The effect of TCF7L2 on glucose metabolism," Dr. Vella has submitted a revision of his grant application titled "Effect of bariatric surgery on glucose metabolism." His first submission was scored well, but missed receiving funding.

Dr. Novak was awarded an NIH R01 grant to investigate basic neuroscience mediators of physical activity in obesity. The success of this application is due in part to the collaboration between Dr. Novak and Dr. Catherine Kotz at the UMN. Together with Dr. Kotz, Drs. Novak and James Levine were awarded a State of Minnesota biotechnology grant.

Impact of the core facilities on the projects that form the research base for the Center. The Physical Activity Measurement System (PAMS) was developed within this Core facility. This system uses multiple interlaced sensors to provide second-by-second assessments of non-exercise activity thermogenesis (NEAT), the energy that humans expend during every day activities. PAMS is used by the following NIH-funded PIs: Dr. Nair, Dr. Jensen, Dr. Basu, Dr. Kudva, Dr. Wolf, Dr. Somers, Dr. Thompson, and Dr. Caples. PAMS is also used in China and in the International Activity Center in the West Indies. PAMS provides a unique capability to address hypotheses related to a host of human activities. This core also has a longstanding relationship with Mayo's Special Purpose Processor Development Group (SPPDG) (PI, Dr. Barry Gilbert, who is supported by the Department of Defense with approximately \$10M in annual grant/contract funding). Dr. Gilbert's laboratory specializes in the design and fabrication of sensors and microprocessors. Through this collaboration, a series of unique microtechnologies has been developed, including: 1) a microtechnology to recapitulate the functioning of PAMS in a 28g package (the Gruve) that allows physical activity to be measured every 1/2 second continuously for a year; 2) a microtechnology to assess physical activity within a standard earpiece; and 3) a unique thermal imaging technology to allow passive assessment of heat loss in real time. The Metabolic Studies Core will continue to develop these technologies, and make them available to investigators and nationally. We have already pursued several different approaches to carefully disseminate the concept of NEAT and the technologies capable of measuring NEAT available to investigators and to the public domain. One approach was to develop a Mayo Clinic owned equity company called MUVE Incorporated. The goal of this company was to develop a technology based upon our physical activity sensing system that enabled free-living individuals to monitor their NEAT and adjust their physical activity to expend more energy and decrease their energy intake so that they could lose weight. We have successfully done this in 48 companies in Minnesota and across the United States. The MUVE Company won the Minnesota Cup for entrepreneurship in 2007. An additional effort to translate non-exercise activity to the public domain was to develop a treadmill desk. This was associated with enabling free-living people to walk on a treadmill while using a computer system and conducting their normal daily activities. The invention subsequently won the NASA Invention of the Year Award and the Innovation Award at the World Trade Fair. It is currently a product made by Steelcase.

Description of training/mentorship opportunities sponsored by the Core. Examples of the results of our training activities are as follows. Dr. Lorraine Lanningham-Foster investigates activity and childhood obesity. She was a recipient of an NORC P&F Award; she gained an R21 and currently is a tenure track investigator at Iowa State University. Dr. Novak investigates neuroscience mediators of obesity. She was a recipient of an NORC P&F Award; she gained an R01 and AHA development award and currently is a tenure track investigator at Kent State University. Dr. Koutsari received a P&F award for her study "Regional Free Fatty Acid Uptake Assessed by Positron Emission Tomography in Humans: Pilot and Feasibility Studies." She has completed the first 10 studies designed to develop the proper blood sampling and scanning protocols. She has just started the second set of studies that will compare her established measure of adipose tissue FFA storage (¹⁴C-palmitate and adipose biopsies) with the ¹¹C-palmitate/scanning approach. She hopes to use this as preliminary data for an RO1 to be submitted late in 2010.

The Metabolic Studies Core, in collaboration with the Mayo CTSA's Metabolomics Core Laboratory, has provided opportunities for numerous postdoctoral fellows to learn mass spectrometry. Fellows who have worked in that facility (and the laboratories in which they worked) include Agnieszka U. Blachnio-Zabielska, Ph.D. (Jensen), Piotr Zabielski, Ph.D. (Nair), Christina Koutsari, Ph.D. (Jensen), and Robert Nelson, M.D. (Miles). The Body Composition Laboratory has provided training in software for DXA and CT scan analysis of fat for postdoctoral research fellows (Drs. Santosa, Mundi, Gupta [Jensen], Dr. Basu [Rizza], Drs. Bahgra and Irving [Nair], and Dr. Romero-Corra [Somers]).

Significant research advances made possible via the NORC. The Metabolic Studies Core of the Minnesota NORC has been successful in promoting cooperation and collaboration for obesity and obesity-related studies. For example, Dr. Michael Camilleri (gastroenterology) is studying the role of the stomach, satiety hormones and genetic variation in appetite regulation of overweight and obese patients. He collaborates now with Drs. Matthew Clark (an NORC member of our Department of Psychiatry and Psychology), Dr. Adrian Vella (an NORC member of the Division of Endocrinology), Dr. Billington (NORC–Minneapolis VA Medical Center), and Dr. Robert Rizza (NORC member of the Division of Endocrinology). This is a relatively new area of research for Dr. Camilleri and the collaborations with members of the Minnesota NORC are largely the result of the Center grant. Likewise, Dr. Eduardo Chini (NORC member, Anesthesiology at Mayo) has become interested in obesity and has collaborated with Drs. James Levine and Novak from the Division of Endocrinology. Dr. Jensen continues to collaborate with Drs. Basu, Rizza, and Khosla within the Minnesota NORC, as well as Dr. Buchwald (a surgeon at the UMN). Dr. Jensen also collaborates with Drs. Lopez-Jimenez and Romero-Corral (Division of Cardiology). Drs. Jensen and Joyner have just completed a joint project examining the effect of α 2-adrenergic receptor polymorphisms on the cardiovascular and adipose tissue responses to exercise and catecholamines. The NORC has continued to support collaborative efforts between Dr. James Kirkland and Dr. Jensen. Dr. Clark (Psychiatry and Psychology), in addition to collaborating with Dr. Camilleri, also collaborates with Drs. Lopez-Jimenez examining the quality of life of patients after bariatric surgery and Virend Somers in studies of obesity. Dr. Sundeep Khosla has collaborated with Dr. Melton from our Epidemiology Division as well as Dr. Spelsberg to better understand the interaction between skeletal development and diabetes and obesity. Dr. James Levine has collaborated with Drs. Novak and Lanningham-Foster both of whom have received new NIH funding. Dr. K.S. Nair has continued to collaborate with Dr. M. Jensen, Dr. S. Khosla, and Dr. R. Rizza in understanding the role of fatty acid metabolism in the elderly. Dr. J. D. Veldhuis continues to examine age effects and hormonal milieu on insulin action and in so doing collaborates with Dr. P Takahashi, from the Division of Gerontology, as well as Dr. Smith and Dr. Miles from the Division of Endocrinology. Dr. Pagano, from the Division of Thoracic Disease, collaborates with Dr. Bernlohr from the UMN; they are examining glut-4 storage vesicle formation and sphingolipids. Dr. Rizza collaborates with Dr. Vella and Dr. R. Basu examining models of glucose disposal. Dr. Rizza also works with Drs. Khosla, Jensen, and Nair to examine the effects of testosterone replacement in the elderly. Dr. V. Somers from the Division of Cardiology investigates the effect of sleep in the elderly and therein collaborates with Dr. S. Caples as well as with Dr. Lopez-Jimenez. Dr. Vella, a new NIH investigator, collaborates with Dr. Basu (another new NIH investigator) examining the effect of incretin in glucose turnover as well as obesity. Dr. Vella also collaborates with Dr. R. Lloyd from the Division of Pathology examining the effect of insulinomas on clinical outcomes after bariatric surgery.

The Metabolic Studies Core received ARRA support to obtain an Ultra Performance Liquid Chromatography system, as testing and experience has indicated that UPLC systems are far superior to standard HPLC systems for separation and identification of metabolites. This instrument will accelerate the analysis of samples. In addition, the new analysis capabilities of this instrument will permit more types of compounds to be measured in existing samples, thus increasing the value of experiments that are currently being conducted.

Specific Accomplishments

Women's Health

The UMN and the Mayo Clinic support the public policy aimed at enhancing participation of women and minorities in clinical research. The obesity and eating disorders research involving humans currently ongoing at the UMN is consistent with this policy. Although the Twin Cities and Minnesota generally have fewer African Americans than many other sites, it is quite possible to recruit sufficient numbers for clinical studies. In addition, Minnesota has a large population of Native Americans, both in urban residences and on reservations. Dr. Robert Jeffery has recruited a large population of African American women for his weight gain prevention project. Many of the other projects involving epidemiological research use a mixed population involving both genders, African Americans, Hispanics, and Native Americans. Dr. Mary Story and colleagues have several projects involving obesity and eating disorders in urban and reservation Native Americans. The clinical populations, particularly at the Hennepin County Medical Center, involve at least half minority populations. Projects involving eating disorders naturally have a high percentage of women in the study population.

Obesity and Energy Metabolism Core. The findings of the Sanders laboratory on the role of estrogen to regulate adipogenesis via the Zeb1 transcription factor is important, for it provides new insights into the relationship between obesity and women's health. The Sanders laboratory is traditionally considered a nuclear receptor laboratory, but the availability and proximity of her laboratory to the major users of the Core has brought her work into the obesity arena and connecting Zeb1 to adipose biology will be the major thrust of her laboratory for years to come. She is joined in this theme by Xiaoli Chen's laboratory that has recently discovered that lipocalin 2 is essential for estrogen production in adipocytes. As such, the NORC has developed a node of excellence in linking estrogen to adipose biology.

Disordered Eating Assessment Core. By its very nature, given the population prevalence of disordered eating, the majority of the work conducted by the Core addresses women's health issues. The Core has supported important work especially in the area of women's health in areas of mortality related to disordered eating and weight. In addition, the core has supported foundational work on the diagnosis, course, and treatment of binge eating disorder. Interactions spurred by the Core have expanded the consideration of weight issues in postpartum mood disorder.

- The Disordered Eating Assessment Core has collaborated with Dwenda Gjerdingen on studies of weight status and postpartum depression.

- Scott Crow and Allen Levine collaborated on a survey of a large cohort of primary care providers in Minnesota examining methods of treating obesity and attitudes about treating obesity with particular focus on differences in gender as they impact treatment decision making.

Epidemiology and Intervention Core. The Epidemiology and Intervention Core supported three pilot projects specific to women’s health. Results of the first two pilots awarded to Drs. Arikawa and Kurzer provided preliminary data for a Center grant application.

- “Changes in Inflammatory Markers of Young Women Following Exercise” (PI-Andrea Arikawa, Food Science and Nutrition) is a pilot study designed to identify changes in pro-inflammatory and anti-inflammatory factors in women following participation in a physical activity program.
- “Weight Loss and Biological Parameters in Obese Breast Cancer Survivors” (PI-Mindy Kurzer, Food Science and Nutrition) is a pilot study designed to assess the feasibility of a weight loss program combining calorie restriction and physical activity in obese breast cancer survivors, to determine the effect of weight loss and maintenance on biomarkers (insulin, glucose, inflammatory markers, IGF-1, IGFBP-3, and F2t-isoprostanes) associated with breast cancer risk and recurrence, and to assess the impact of weight loss on quality of life in obese breast cancer survivors.
- “Modeling Trajectories of Optimal Pregnancy Weight Gain for Overweight and Obese Women” (PI-Patricia Fontaine, Pediatrics) is a pilot project to examine relationships between weight gain in pregnancy and maternal and child health outcomes, using a rigorously constructed database, with the eventual goal of obtaining extramural funding to develop an effective intervention to prevent excessive gain.
- The Healthcare Delivery SubCore provided support for a successful developmental project application proposing to use prenatal medical records data to create clinically useful “Healthy Weight in Pregnancy” graphs. The project represents a critical first step in an overall plan to improve prenatal weight counseling, prevent excessive weight gain during pregnancy, minimize unwanted postpartum weight retention, and optimize birth outcomes.

Metabolic Studies Core. The Core has contributed to important research regarding women’s health.

- The Core has been involved with assessing how fat cell size varies as a function of body fat and body fat distribution in men and women (Tchoukalova YD, Koutsari C, Votruba SB, Tchkonja T, Giorgadze N, Thomou T, Kirkland JL, Jensen MD. Sex- and depot-dependent differences in adipogenesis in normal weight humans. *Obesity [Silver Spring]*. 2010).
- Studies supported by the body composition portion of the Metabolic Studies Core supported studies of the effects of sex steroids on body composition in obese women with polycystic ovary syndrome.
- Studies supported by the body composition portion of the Metabolic Studies Core supported studies to examine the effects of oral contraceptives on fat metabolism in women (Koutsari C, Ali AH, Nair KS, Rizza RA, O'Brien P, Khosla S, Jensen MD. Fatty acid metabolism in the elderly: effects of DHEA and testosterone replacement in hormonally deficient men and women. *J Clin Endocrinol Metab.* 94:3414-3423, 2009).

- Through support from the Metabolic Studies Core, Dr. Jensen has continued studies of the biology of body fat and fatty acid metabolism with emphasis on sex differences. Because of the collaborative network among obesity centers, he has collaborated with Jeanine Albu (The New York Obesity Center) and Samuel Klein (the Washington University CNRU) to study differences in free fatty acid metabolism between men and women.
- Through support from the Metabolic Studies Core, James Levine has started to explore the role of gender in physical activity and the biology of body fat distribution with a major emphasis on gender differences.

Minority Health

Epidemiology and Intervention Core. The Core provided support for several pilot projects, NIH grant applications, and the submission of a community grant application involving minority populations.

- “Jovenes de Salud: Cooks in the Kitchen” (Association for Non-Smokers of Minnesota) is a grant proposal for a community-based after-school program to promote healthy nutrition among Latina youth.
- The Epidemiology and Intervention Core provided consultation to young investigators on three developmental projects involving minority populations: 1) “Behavioral Characteristics of Diet: Developing Survey Instruments for Ethnically Diverse Populations” (PI-Melissa Laska); 2) “Obesity, Elevated Blood Pressure, and Insulin Resistance among American Indian School Children: Identifying Family- and Environment-level Determinants” (PI-Melissa Laska); and 3) “Metabolic and Behavioral Effects of Breakfast Frequency and Quality in a Bi-Ethnic Sample of Children” (PI-Mark Pereira).
- The Epidemiology and Intervention Core provided support for the submission of two NIH grant applications involving minority populations: 1) “Genetic and Environmental Determinants of Type 2 Diabetes in Chinese Singaporeans” (PI-Mark Pereira), a study aimed at identifying the genetic susceptibility factors for type 2 diabetes in Chinese living in Singapore, and 2) “Obesity Prevention Parent-Preschool Intervention Among Low Income Families” (PI-Simone French), a pending grant proposal to develop an intervention that targets parenting style and specific parent behaviors to examine the effects on child body weight and weight-related behaviors among 3-to-5-year-old overweight children from lower-income households. It is anticipated that these study participants would be largely racial and ethnic minority populations. One grant application has been funded.
- A pending NHLBI U01 grant, “Linking Primary Care, Communities, and Family to Prevent Obesity among Preschool Children,” was developed under the direction of Simone French and Nancy Sherwood. The application proposes the creation of The Minnesota Center for Pediatric Obesity Prevention, comprised of an interdisciplinary investigative team with extensive experience in community, school, primary care, home, and community-based intervention strategies. The goal of the Center is to translate a multi-level, multi-component intervention across settings to prevent obesity among at-risk low-income preschool-aged children.

Health Promotion or Disease Prevention

Epidemiology and Intervention Core. Core investigators provided consultation and support for the development of three grant applications focused on community-based obesity prevention interventions: 1) “Real-World Office-Place Interventions for Obesity“ (PI—James Levine, Mayo Clinic); 2) “Reducing Obesity at the Workplace: A Randomized Trial (PACE)” (PI—S. Beresford, University of WA); and 3) “Evaluating Innovative Weight Gain Prevention Strategies for At-Risk College Students” (PI—Leslie Lytle, Epidemiology). In addition, Dr. Jeffery, Core Director, provided advice on community education, medical interventions and environmental changes for the “Heart of New Ulm” project, an effort designed to reduce the number of heart attacks that will occur in the New Ulm, Minnesota, area during the next 10 years. Dr. Linde, Associate Core Director, also presented on “Worksite Interventions to Promote Healthy Weight Management” to community partners in Hennepin County.

- James Levine and Robert Jeffery have received funding from the Minnesota Partnership for Biotechnology and Medical Genomics for a mobile body composition and energy metabolism laboratory. The Mobile Obesity Laboratory will enable the Mayo Clinic and UMN to complete outreach and outcomes-based research with respect to obesity prevention and treatment research.
- Nancy Sherwood and Robert Jeffery worked together on a developmental project testing the feasibility of brief pediatrician counseling with phone follow-up on weight gain prevention in preschool children. The project resulted in an ongoing NIH grant titled “Healthy Homes/Healthy Kids: Pediatric Primary Care Based Obesity Prevention.”
- Robert Jeffery collaborated with Nancy Sherwood on a successful NCI grant, “Novel Approaches to Weight Loss Maintenance,” designed to evaluate the efficacy of an innovative approach to promoting weight maintenance among recent weight losers.
- Investigators from the Healthcare Delivery SubCore collaborated with Patricia Fontaine in Pediatrics on a pilot project titled “Modeling Trajectories of Optimal Pregnancy Weight Gain for Overweight and Obese Women.” The study examined relationships between weight gain in pregnancy and maternal and child health outcomes, using a rigorously constructed database, with the eventual goal of obtaining extramural funding to develop an effective intervention to prevent excessive gain.
- Nancy Sherwood was awarded a subcontract on the “Food, Attitudes, and Body Study” through the University of California-San Diego to participate in a multi-center trial evaluating the efficacy of two Jenny Craig weight loss programs (in person and phone-based) in comparison to a self-directed weight loss program. The four research centers include UMN, University of California-San Diego, the Kaiser Permanente Northwest Center for Health Research, and the University of Arizona.
- The Epidemiology and Intervention Core provided consultation to the Community Health Foundation of Wright County, Minnesota (northwest of the Twin Cities), regarding community intervention methods for weight gain prevention.
- Lorraine Lanningham-Foster with James Levine has developed a collaboration with the Foundation for Health Promotion to develop a countywide intervention to improve nutrition and exercise in children in rural Minnesota.
- L. Olson with James Levine has developed a program in human subject motivation for clinical research involving NORC investigators (i.e., Drs Jensen, Joyner, Nair, Rizza, and

Levine) to better understand what motivates volunteers and ultimately to increase the public trust in clinical research.

Reduction in Health Care Costs

Disordered Eating Assessment Core. The Core provides support for and consultation about studies examining cost effectiveness analysis and cost of illness estimates as ways of identifying health care costs and developing treatment strategies designed to minimize them. The core director, Dr. Crow, consulted to the Longitudinal Assessment of Bariatric Surgery (LABS) cost effectiveness working group, has conducted two cost effectiveness trials (one in binge eating disorder, one in bulimic nervosa), and has conducted or is in the midst of designing and supporting cost effectiveness analyses in the areas of childhood obesity, bulimia nervosa, treatment, and postpartum depression.

- Activity within the Disordered Eating Assessment Core led to an NIH grant submission proposing to examine the role of a stepped care approach to eating disorders treatment utilizing self-help followed by pharmacotherapy. This was generated in recognition of the fact that while effective treatments for eating disorders do exist they tend to be quite expensive and a stepped care approach might significantly reduce health care costs.
- With support from the Disordered Eating Assessment Core, the first significant trial examining the cost efficacy of various treatment strategies for bulimia nervosa is underway. The Disordered Eating Assessment Core has conducted the recruitment for this R01 funded by the National Institute for Mental Health (NIMH).
- Scott Crow was a member of the Longitudinal Assessment of Bariatric Surgery (LABS) cost effectiveness working group. He also received a K02 award from NIMH, which focuses on health care economics studies.

Epidemiology and Intervention Core. The Core provided support and consultation for two successful NIH grant applications addressing obesity prevention and treatment through the Healthcare Delivery SubCore at HealthPartners Research Foundation. A secondary aim of these projects is assessing program implementation costs and their impact on health care resource use. The projects include: 1) “Healthy Homes/Healthy Kids: Pediatric Primary Care Based Obesity Prevention” (Co-PIs: Nancy Sherwood, HealthPartners and Rona Levy, University of WA), a study to test the efficacy of brief pediatrician counseling with phone follow-up on rate of weight gain in children; and 2) “Childhood Hypertension and Obesity: Diagnosis, Care, and Costs” (PI: Patrick O’Connor, HealthPartners), a study examining detailed electronic medical records data at large medical groups in Colorado, Minnesota, and California to assess the stability over time of recently developed categories of hypertension in children and adolescents, patterns of care provided to children with elevated blood pressure, and the impact of elevated blood pressure on use of health care resources.

Professional/Public Nutrition Education Efforts

The Epidemiology and Intervention Core. The Core has been instrumental in the training and professional development of the next generation of obesity prevention researchers and practitioners. Through enhanced coursework, combined with interdisciplinary seminars and research, the Core strives for students and new investigators to gain the skills and knowledge necessary to successfully address the obesity epidemic.

Core faculty have continued to be centrally involved in the revised two-semester series of Obesity and Eating Disorders courses for a third successful year. The courses emphasize a multidisciplinary approach to understanding the etiology, treatment, and prevention of obesity. The course expansion to two semesters has resulted in increased enrollment of students, particularly from departments across the UMN other than psychiatry and epidemiology.

The Core also has continued to sponsor distinguished faculty visits and offer public seminars. Support was provided for visits and public seminars by Johannes Brug, Ph.D., director of the EMGO Institute for Trans and Extramural Health and Medical Research in Amsterdam, Netherlands, and Dr. John Blundell, Ph.D., a physiological psychologist from University of Leeds, Institute of Psychological Sciences in Leeds, United Kingdom. Both visiting scholars met individually with several Core investigators and students to discuss potential research collaborations.

The Energy Balance Research Group continued regular meetings through support from the Core. The meeting format was modified to specifically assist junior investigators with new grant submissions and data analysis for publications. Attendees and presenters have included faculty and students from several academic units. In addition, support was provided for junior investigator travel to various scientific meetings for presentation of developmental project results.

Educational Activities and Accomplishments

Enrichment Program. The Minnesota NORC Enrichment Program has two goals: (1) to inform the institutional community of the progress and accomplishments of obesity research and (2) to incorporate research findings into recommendations and services for educating the public. It does this by providing opportunities for interactions between investigators from different disciplines with a common interest—the causes and treatments of obesity. These capacities are achieved through several mechanisms.

Seminar Series. The Graduate Nutrition Program currently sponsors a weekly seminar series through nine months of the year. This program covers all aspects of nutrition, including basic, clinical, epidemiology, and education. In addition, there are regular research and clinical seminars in Endocrinology, Pharmacology, Veterinary Biology, Medicine, General Internal Medicine, Psychiatry, and Neuroscience. The Minnesota NORC has provided speakers throughout the University and has co-sponsored a variety of programs. The Center placed particular attention on making these obesity talks attractive and relevant to the public and has advertised the programs throughout the Twin Cities and Rochester campus systems. Each of the members of the executive faculty of the Minnesota NORC has presented at these seminars. The External Scientific Advisory group has participated in the obesity seminar series.

The Minnesota NORC serves the academic community by keeping it informed of obesity-related events. This is achieved by dispersing announcements throughout the Center's growing number of participating institutions. For this purpose, the Center maintains an extensive mailing list of academic and lay individuals, and pertinent departments. Additionally, activities are posted

electronically across departmental faculty listservs, as well as the Center's own listserv and website (see below).

One of the challenges for the Nutrition Graduate Program has been that individuals potentially interested in the seminar series are highly dispersed geographically. However, technology has progressed to the point where live (i.e., real time) webcasts of the seminars are now available. The webcasts appear on a computer screen with sound. They include the PowerPoint presentation and provide space to key in questions and comments. By sponsoring these types of conferences, the Minnesota NORC provides forums for discussions of obesity research findings among local investigators and nationally recognized obesity experts.

Center-wide Retreat. The Minnesota NORC holds an annual Center-wide retreat. In the past, the program has featured presentations by P & F Award recipients on the findings of their Minnesota NORC-supported research. In recent years, we have adopted a program featuring roundtable discussions and have featured guests from outside institutions who focus on obesity research. This forum allows Center participants extended time to interact and to communicate with other participants about shared research interests and potential collaborations. The retreat is a popular event and is well attended.

Focus Groups. The Minnesota NORC has established focus groups based on research interests to provide forums for junior scientists, trainees, and senior scientists to identify overlapping interests and pursue potential collaborative efforts. Focus group meetings have resulted in new research ideas, as well as the generation of ideas that have contributed to ongoing research efforts.

Obesity Research Groups. Obesity Research Groups have formed across the Minnesota NORC, involving weekly research group meetings at which faculty, fellows, and students interested in obesity and related topics present and discuss their work. The Epidemiology and Intervention Core sponsors one such group, while another has been organized among Neuroscience of Obesity researchers at the Minneapolis VA Medical Center.

- The Adult Obesity Treatment and Prevention Group meets regularly with the purpose of discussing new and innovative obesity studies. The research group has been expanded to include investigators from the Department of Kinesiology and has expanded its focus to include physical activity, food and nutrition, and body weight. Attendees and presenters have included faculty and students from several academic units including the Medical School, Pediatrics, Nursing, Psychiatry, Psychology, Applied Economics, Food Science and Nutrition, Epidemiology and Community Health, Kinesiology, Humphrey Institute, Center for Urban Design, and HealthPartners Research Foundation.
- The Cellular and Molecular Biology of Obesity Research Club meets quarterly and uses real-time broadcasting to connect via telecomm to the UMN, the VA Medical Center, and the Mayo Clinic. This research-based seminar series profiles two or three Minnesota Obesity Center members each session who describe their research project to others in the group. Since attendees are geographically dispersed, the Research Club utilizes video conferencing as a mechanism to stay connected and to carry out Obesity and Energy Metabolism Core business activities. At each Club meeting Dr. Bernlohr reviews Core functions and performance, and addresses questions or concerns of Core members about sub-core services,

charges, quality control, productivity, timelines, and new ideas for Core functions. As such, the quarterly meetings serve as both a business meeting dealing with Core functions and services as well as a research club connecting Minnesota Obesity Center users to the latest unpublished findings from their laboratories. Dr. Bernlohr establishes the speaker schedule and runs the meetings.

Journal Clubs. Many of the research groups within the Center operate regular (usually weekly) journal clubs, including the Neuroscience, Eating Disorders, Adipose Biology, Obesity and Energy Metabolism, Metabolism, and Adult and Childhood Obesity groups.

Newsletter. The Minnesota NORC has published newsletters in the past, describing the activities, research advances, and accomplishments of the Minnesota NORC investigators. Recently this information has been disseminated electronically through the listserv and website. A more formal newsletter to be distributed electronically is being planned. Distribution of the newsletter has served to heighten public awareness of the NORC's existence and provide information about the services offered through the Minnesota NORC.

Service Brochure. The Minnesota NORC brochure summarizes the research services provided by the scientific Cores. The brochure is distributed to Minnesota NORC participants and other investigators requesting information about the organization and resources of the Minnesota NORC. The Minnesota NORC has plans to expand the brochure to include information about some of the programs sponsored by Minnesota NORC, including the P & F Program and the Education Enrichment Program.

Web-related Activities. The Minnesota NORC website, <http://www.umn.edu/mnoc>, underwent another major reconstruction a few years ago, incorporating the look of the newly redesigned Minnesota NORC logo and letterhead. The website provides information about the Minnesota NORC and summarizes the advances and accomplishments of Minnesota NORC participants. An obesity listserv with more than 195 members is maintained for investigators to generate discussions and to provide a rapid response system for urgent questions and calls for information. Additionally, information about Minnesota NORC-sponsored events is distributed over the listserv and is posted on the website.

Obesity-related Courses. Several courses dealing with obesity-related issues are now offered at the UMN by Minnesota NORC participants. A team of NORC participants teaches a course currently offered through the School of Public Health on "Obesity and Eating Disorders," covering all aspects of obesity represented by the expertise of the Center investigators. The course was revised to emphasize a multidisciplinary approach to understanding etiology, treatment, and prevention. Expansion from a one-semester format to a two-semester offering has resulted in increased enrollment of students, particularly from other departments. A course titled "Management of Eating Disorders" is currently offered and is taught by a team of NORC investigators covering the aspects of obesity-related eating disorders represented by the expertise of the NORC investigators. These courses include FScN 5601 Management of Eating Disorders; PubH 6360 Obesity & Eating Disorders: Etiology & Epidemiology; and PubH 6079 Obesity & Eating Disorders: Treatment, Prevention & Policy.

The Disordered Eating Assessment Core continues to sponsor the longstanding and successful assessment training seminar and was expanded to bring these services to a wider variety of investigators in the departments of psychology, psychiatry, and pediatrics who are looking at weight gain in psychiatric illness, obesity, and eating disorders.

Through Drs. Billington, Jensen, and J. Levine, medical students, residents, and fellows at both the UMN and the Mayo Clinic receive regular lectures and updates on the clinical aspects of obesity.

Obesity Research Day. The Minnesota NORC sponsors a 1-day program of current findings in obesity. The speakers are members of the External Scientific Advisory Committee and other nationally recognized obesity experts from both outside and within Minnesota. The event stimulates significant interest and is quite popular. It has helped to increase awareness of the Minnesota NORC among the public.

Mayo Clinic Nutrition and Wellness in Health and Disease. In the fall, the Mayo School of Continuing Medical Education sponsors a course titled Mayo Clinic Nutrition and Wellness in Health and Disease. This course has taken place annually since 2001. The course focuses on how nutrition, physical activity, and other healthy lifestyle behaviors are vital components in the promotion of health and in the treatment of disease; it is designed for physicians, nurse practitioners, physician assistants, dietitians, nurses, and health and wellness specialists. The 2-day course provides a full spectrum, in-depth overview of challenging nutrition issues that clinicians encounter in the ambulatory setting. Current clinical nutrition topics are highlighted through lectures, interactive case studies, and panel discussions. Participants will be given many opportunities for interaction with course faculty, who have been selected for their expertise, knowledge, and clinical acumen. The faculty quite often includes several investigators from the UMN/Minnesota NORC. The collaboration between Mayo and UMN investigators facilitated by the NORC has clearly improved the course.

Mayo/ASPEN Annual Advances and Controversies in Clinical Nutrition. The Mayo/ASPEN Advances and Controversies in Clinical Nutrition has been offered annually for 19 years. This is a multidisciplinary educational course focusing on enteral and parenteral nutrition, diabetes, osteoporosis, lipids, obesity, pediatrics, and home and hospital nutrition. Each year, several members of the Minnesota NORC are included in the faculty for this course.

Public Service. Nutrition education must also extend to the public. The Minnesota NORC has formed an obesity rapid response team and makes the services of that team available to regional news outlets. The purpose of the rapid response team is to provide learned and appropriate perspectives on the constant barrage of new information (with respect to obesity and nutrition) that the public encounters. By providing a ready repository of expertise that can be contacted by the media, we trust that we have improved the general level of discourse and suppressed the misinformation so commonly appearing in the media, particularly in the area of obesity.

Additional Outreach Activities. The Minnesota NORC Administration Office maintains a phone bank that fields phone calls from the public seeking information on topics ranging from weight loss programs/camps to potential treatments. When obesity-related topics, such as a new obesity drug, are covered by the news media, the phone bank will receive phone calls requesting

additional information on the topic. Frequently, the office receives requests for specific information for which materials must be collected and distributed. Minnesota NORC investigators frequently provide interviews for local news programs and for public radio, and write articles for health newsletters. The existence of the NORC has certainly enhanced the perspective with which the public views obesity.

Benefits and Interactions Resulting From the Existence of the NORC

Basic Science/Clinical Investigation Interactions

The Minnesota NORC promotes translational research and the exchange of information about clinical and basic obesity research in various ways. The Clinical translational component is a great strength of our Center, with extensive and diverse work.

- Robert Jeffery, Director of the Epidemiology and Intervention Core, is a Principal Investigator on the Look AHEAD (Action For Health in Diabetes) Trial. The Minnesota NORC was the organizing force behind the establishment of the SHOW trial (now Look AHEAD U01DK057182) proposal from Minnesota. Investigators from the Medical School and School of Public Health were united to work together by the administration of the Center, resulting in a truly multi-talented group of investigators. Dr. Jeffery has since provided assistance to six different investigators on projects related to translating the Look AHEAD intervention to other clinical or community settings.
- Robert Jeffery and Charles Billington have collaborated with Sayeed Ikramuddin on a study funded by Covidien titled “Global Randomized Study of Best Medical Management versus the Roux-en-Y Gastric Bypass for the Management of Type 2 Diabetes in Patients with Central Obesity.”
- Scott Crow is helping Michael Jensen establish psychological phenotyping methods for the newly established Mayo Department of Internal Medicine research initiative—“Obesity, Weight Management, and Nutrition Program.”
- Robert Jeffery collaborated with Ronald Ackerman from the Indiana University Diabetes Translational Research Center on a successful NIDDK grant application for the community translation of the LookAHEAD intensive lifestyle intervention designed to reduce heart disease and diabetes. The Epidemiology and Intervention Core contributed directly to the development of the original clinical center grant for the LookAHEAD trial that was put together collaboratively by investigators in Epidemiology, Medicine, Psychiatry, and the Hennepin County Medical Center.
- A successful NHLBI U01 grant, titled “Evaluating Innovative Weight Gain Prevention Strategies for At-Risk College Students,” was developed under the direction of Leslie Lytle with substantial support from the Epidemiology and Intervention Core. The project will evaluate the efficacy of three intervention approaches based on a social ecological model to help students attending 2-year colleges or technical schools adopt healthier behaviors related to maintaining weight.
- Mark Pereira was awarded an NIH grant that is utilizing data from the CARDIA study to evaluate the propensity that television exposure may increase the risk for intentional and unintentional injuries, as well as obesity and chronic diseases through a variety of plausible and interrelated mechanisms.

- Simone French and Alex Rothman (Co-PIs) submitted a U01 grant application with a specific aim of translating basic principles from social psychological and learning-based models of behavior into innovative weight loss intervention strategies. Other collaborators on the application included Robert Jeffery, Nancy Sherwood, and Brian Martinson.
- Obesity treatment clinics have benefited from a new commitment by the University and University Hospital. Obesity clinics are active now at the UMN Medical Center under the management of Dr. Billington, Sarah Jane Schwarzenberg, M.D., in Pediatrics, and Dr. Crow; at the VA Medical Center under the direction of Dr. Billington; at the Mayo Clinic with Dr. Jensen; and at Hennepin County Medical Center with Dr. Hartley. In addition, the public health group associated with Dr. Jeffery has initiated a number of treatment clinics as well as obesity prevention clinics in a community-based program in the Twin Cities area.

Bringing New Investigators to Obesity/Nutrition Research

The Minnesota NORC is a source for P & F funds as well as the development of new collaborations. Our Center has allowed use of Core laboratories to junior faculty as well as senior faculty wishing to engage in obesity research for the first time. We also have access to a variety of training grant funds. We have encouraged the use of R21 and K awards to help the development of new obesity projects and to support salary of junior faculty as well as more senior faculty.

- The UMN has recently successfully competed for two training grants, in obesity and eating disorders, as indicated above. The obesity training grant provides multidisciplinary training for a new generation of obesity prevention scientists. The training program provides three tracks: basic science, behavioral epidemiology, and clinical. The program provides training for predoctoral, postdoctoral, and medical fellows. Trainees will be exposed to research and training in each of these fields and will complete research projects, publish manuscripts, complete a core curriculum, attend journal clubs and seminars, and receive training in grant writing, research ethics, and career development. The eating disorders training grant provides similar opportunities for trainees interested in eating disorders.
- Other training grants that are directly related to the topic of obesity include: endocrinology, adolescent health, maternal and child health, cardiovascular epidemiology, cancer epidemiology, and behavioral aspects of cardiovascular disease. Training grants are also operating for students of neuroscience, pharmacology, and psychology. The training environment at Mayo is noteworthy. There are also Mayo funded endocrinology fellows, all of whom participate in a 1-year research project. Drs. Jensen, Nair, Rizza, J. Levine, and Miles have trained or will take clinical fellows into their program for a 1-year research training. In addition, there is a foundation-funded nutrition fellowship available to any subspecialty trainee at Mayo. These nutrition fellows are urged to participate in the obesity/nutrition research program offered through the Endocrine Research Unit and the Mayo GCRC. In addition, Mayo has an NIH-funded Endocrine Training Grant. The opportunities for training research do not end with the completion of the fellowship. Opportunities are available through the Mayo Foundation for additional research training for Mayo staff clinicians with an interest in research; Drs. Jensen and J. Levine were recipients of such Mayo Foundation support. Mayo has recently received a K12 grant from the NIH for junior faculty transition support. This grant will supplement the existing opportunities for junior faculty to prepare for careers in obesity and nutrition research.

- The Epidemiology and Intervention Core has been instrumental in developing new researchers in the obesity field, in particular Dr. Nancy Sherwood, who accepted an obesity research position with HealthPartners; Jennifer Linde, Ph.D., who was the project director for a grant on obesity and depression; and Kerri Boutelle, Ph.D.
- Dianne Neumark-Sztainer's focus group work with adolescents on obesity prevention (supported by the Epidemiology and Intervention Core) served to expand her area of research interest (nutrition and eating disorders) to include a significant focus on obesity.
- The Epidemiology and Intervention Core has been instrumental in developing new researchers in the obesity field, in particular Dr. Mark Pereira who was hired by the Division of Epidemiology to conduct research on nutrition and physical activity in the prevention of obesity, type 2 diabetes, and cardiovascular disease, including interactions between dietary and exercise patterns; and Dan Graham, Ph.D., was hired as a Research Associate with expertise in physical activity assessment and has NORC funds to do an eye tracking food preferences pilot study for which data collection was recently completed. Dr. Graham is collaborating on other projects with Dr. Jeffery, Dr. Linde, Dr. Melissa Nelson Laska, and Dr. Dianne Neumark-Sztainer.
- The Disordered Eating Assessment Core provides consultation and support for Dwenda Gjerdingen, M.D., from Family Medicine, for a proposal regarding postpartum depression and weight change that will expand on her previous work. The Core has also played an integral role in the establishment of a UMN Eating Disorders Journal Club, a multidisciplinary group of researchers and clinicians throughout the Twin Cities who focus on eating disorders and disordered eating as it relates to obesity. This group meets on a monthly basis for empirical presentations, journal article reviews, and clinical discussions. Interactions resulting from these regular meetings have produced several collaborative studies. Additionally, a number of people who have been interested only in eating disorders are now conducting research in obesity, and vice versa.
- The Disordered Eating Assessment Core provides extensive standardized training in the conduct and interpretation of detailed standardized assessments of subjects with regard to eating and general psychopathology. Didactic assessment training seminars have also been conducted for collections of researchers from other groups needing training in one or more structured assessments; for example, 20 individuals who have been trained in the Structured Clinical Interview for DSM-IV (SCID-I and SCID-II). Continued quality assessment and ongoing consultation is provided to individuals who have been trained previously. The ability to provide such training is quite rare and has led to numerous requests for training of individuals from other institutions including the University of Wisconsin and Indiana University.
- In collaboration with the Center for Transdisciplinary Research on Energetics and Cancer (TREC), the Epidemiology and Intervention Core has helped to implement a successful career development program for junior faculty, postdoctoral fellows, and current doctoral students. The program provides trainees with exposure to advanced methods and experimental approaches in obesity research and with the skills needed to pursue independent research careers in this area. Trainees are able to establish a mentoring relationship with scientists of stature engaging in obesity research. A total of 14 trainees from 5 University departments are currently participating in the program. Two trainees have received NIH K12 grants due in large part to Core support. Core faculty members also have been designated mentors on several existing training grants as well as pending training grant submissions. Dr.

Ruby Nugyen, a new faculty member with a primary research interest in the area of the etiology of infertility, has formed collaborations with several Core investigators resulting in multiple grant submissions related to obesity.

- The Epidemiology and Intervention Core continues to be instrumental in developing new researchers in the obesity field. In particular, Dr. Ellen Demerath has recently joined the Core faculty. One of her areas of research interest includes genetic epidemiology of obesity. She has been involved in the development of a major grant application supported by the Core. Dr. Daniel Graham was hired as a Research Associate in the past year to assist with data analysis and manuscript preparation on several obesity-related projects. Dr. Jeffery has been working with Dr. Kamisha Escoto, a trainee in Psychology, on the submission of an obesity related research supplement to the LookAHEAD grant designed to promote diversity in health-related research.
- Beyond coursework and tutorials, mentorship has been provided by the director of the Obesity and Energy Metabolism Core, Dr. Bernlohr, who has expanded his journal club/group meeting every Monday at noon to include NORC users Drs. Chen, Towle, Griffin, and Kim into the network of investigators who study obesity and energy metabolism. Such large group meeting formats have led to collaborative grants between users (Chen and Bernlohr, Mashek and Bernlohr) and projects (Mashek and Towle, Sanders and Bernlohr).
- As part of their responsibilities as Core directors, Drs. Jensen and Levine have worked with a number of investigators interested in developing research projects in the area of obesity. Examples of investigators new to the study of obesity that Dr. Jensen has supported include Prachi Singh, Ph.D., (Cardiovascular Diseases) who received an R21 grant on the topic of “Molecular mechanisms mediating resistance to leptin signaling during fat gain” and has submitted related proposals to the Ellison Medical Foundation/American Federation for Aging Research for a postdoctoral grant application and to the American Heart Association for a scientist development grant; Helen Karalelides, M.D., (Endocrinology) who submitted a proposal to Amylin Pharmaceuticals, Inc. titled “Effect of Exenatide on weight, weight related co-morbidities and satiety in obese subjects who have undergone Roux-en-Y Gastric Bypass.” Drs. Levine and Jensen continue to work with Dr. Chini (Anesthesiology) to help with his research into how CD38 is necessary for the development of diet-induced obesity and how it is involved in steatohepatitis. Dr. Chini received an Endocrinology Career Development Award from Mayo to support his research in this area. The long-term goal is to submit an R01. Dr. Levine has worked with Dr. J. Clowes at Mayo and Dr. J. Slack, Director of the Stem Cell Institute, to examine stem cell differentiation with weight loss; two NIH grants have been submitted. Dr. R. Kumar (Nephrology) submitted an NIH grant to examine nephrolithiasis and precipitants thereof after bariatric surgery.

Leveraging Other Resources

The UMN has continued to expand the commitment to obesity research and education. The University President’s Interdisciplinary Academic Initiatives identified obesity and food health among eight priority areas. *Healthy Foods, Healthy Lives Institute* was chosen based on the following criteria: 1) areas of comparative advantage for the University and the State, 2) high quality foundational programs; 3) relevance to the University’s land grant mission and research enterprise, 4) relevance to the needs and resources of Minnesota; 5) likelihood that further investment will yield significant return in intellectual quality and capital; and 6) areas where considerable outside resources can be leveraged. Many University-based members of the NORC

are involved in the *Healthy Foods, Healthy Lives* initiative, as it strongly relates to the Center's vision of action from molecules to populations. The initiative brings together activities within four priority areas to address critical health issues during the next 10 years, bridging quality science to sound public policy and transforming what we know into what we do. The four aspirations of this initiative are: 1) to utilize and advance knowledge about the integration of agriculture, food science, nutrition, and medicine to promote healthy lives; 2) to emphasize prevention of diet-related chronic diseases and obesity through diet, exercise, and human behavior; 3) to enhance food safety at all stages, from farm to table; and 4) to inform public policy. The initiative has funded new faculty positions in the areas of obesity/nutrition research and in food safety.

Recognizing the magnitude of the obesity public health challenge and the internationally recognized expertise available, the UMN committed \$1 million to the establishment of "The UMN Obesity Prevention Center." Robert Jeffery (Core Director) is the Director of this Center. Allen Levine and other Center members serve on the Executive Committee of this Center. The Obesity Prevention Center complements the Minnesota NORC in mission and goals, and by leveraging institutional resources, amplifies the effectiveness of the NORC. The Obesity Prevention Center has an indirect cost-sharing agreement with the University that allows 20% recovery of indirect costs that are then used for pilot study funding shared with the NORC. This system has generated close to \$100,000 a year. The Minnesota NORC and the Obesity Prevention Center have also taken the lead in a successful application for a National Cancer Institute Center in the Transdisciplinary Research on Energetics and Cancer (TREC) program, which has further increased the support for obesity and nutrition research at Minnesota.

The UMN Hospitals and the Academic Health Center have resolved to confront the clinical challenge of obesity. The University established an Obesity Program within the Medical School. The clinical obesity efforts also represent commitments by the Medicine, Pediatrics, and Surgery departments. Dr. Billington directs these programs, which include leadership from Sarah Jane Schwarzenberg in Pediatrics and Sayeed Ikramuddin in Surgery. Collaborative relationships for this program continue with the Eating Disorders clinics at the direction of Dr. Crow. Additional clinical faculty members have been hired to support this effort.

The UMN is one of two universities in the United States that has a Medical School, a School of Public Health, and a College of Food, Agricultural, and Natural Resource Sciences all within 20 minutes of one another. A large number of Centers related to the biomedical sciences are present in Minnesota and include the Center for Magnetic Resonance Research, the Cancer Center, the Biomedical Genomics Center, the Institute of Human Genetics, the Center for Developmental Biology, the Biomedical Ethics Center, and the Center for Chronic Disease Outcomes Research. The NORC has enhanced this environment and utilizes the strengths of this unique University setting together with the internationally recognized capacity of the Mayo Clinic.

The Mayo Clinic Center for Translational Science Activities (CTSA) contributes to the success of the Minnesota NORC and vice versa. The CTSA includes the Body Composition Laboratory as part of the Clinical Research Unit. Dr. Jensen (director of our Metabolic Core) is the director of the Body Composition Laboratory. This laboratory exists due to the support of the NORC that allowed Dr. Jensen to develop the equipment, expertise, and personnel during the past 15 years.

The Mayo CTSA is the source of funds for new ideas, which allows Dr. Jensen to provide scans at no cost to investigators.

The Department of Medicine-Mayo Rochester has initiated the Obesity, Weight Management, and Nutrition Program with funding of at least \$150,000 per year for the next 3 to 5 years. Due in large part to Dr. Jensen's experience and role as director of the Metabolic Studies Core and to input from Dr. Crow that helped him respond to the RFA, Dr. Jensen was selected to direct this effort. The funding from the Department of Medicine supports a program to: 1) establish a support infrastructure for practices/physicians with a primary care practice that is needed for longitudinal treatment studies; 2) develop an obesity phenotyping "core" that will identify which patient factors relate to successful treatment—this database will be invaluable for investigators who wish to propose new studies; 3) support a study coordination unit that will allow interested investigators to more easily utilize existing treatment protocols. Dr. Scott Crow (director of the Disordered Eating Assessment Core of the Minnesota NORC) provided invaluable support for the psychological phenotyping of patients/volunteers. The program will be centered in the primary care practice at Mayo in Rochester, MN, in order to take advantage of the electronic medical record system that allows virtually 100% follow-up of any patient/volunteer who enters the program and continues to receive health care in the area. The phenotyping and basic treatment program is designed by the Nutrition Core group at Mayo in collaboration with subspecialists with an interest in obesity and primary care physicians with an interest in obesity treatment.

A further infusion of money has occurred at our State level. Minnesota Governor Tim Pawlenty has allocated funds specifically for the purpose of encouraging collaborative research between the UMN and the Mayo Clinic. The Minnesota NORC, which has already successfully established University-Mayo collaborations, has benefited in a major way from these funds. Catherine Kotz and James Levine (along with Allen Levine, Charles Billington, and Michael Jensen) received \$300,000 collectively to conduct research related to non-exercise activity thermogenesis (NEAT) and the brain (the Minnesota Partnership for Biotechnology and Genomics). Very recently, the Minnesota Partnership for Biotechnology and Genomics awarded \$900,000 support for Drs. James Levine and Robert Jeffery for a mobile laboratory to measure physical activity (NEAT) in humans participating in clinical trials of obesity management.

The impact that the Minnesota NORC has had also extends to the local business community, where the Cargill Corporation has provided an endowed Chair in Systems Biology of Human Metabolism to identify a leading researcher who studies the molecular basis of metabolic disorders linking obesity to cardiovascular disease, type 2 diabetes, and dyslipidemia. General Mills has endowed a nutrigenomics position in the Department of Food Science and Nutrition. These endowments would not have been possible without the strong faculty base and infrastructure in obesity and nutrition research.

Recognizing the growing programs and commitments to obesity nutrition sciences, the Obesity Consortium of Minnesota has been established by Allen Levine and Robert Jeffery to coordinate the basic, applied, and clinical obesity centers/collaboratives that have been developed at the UMN. Here again, the Minnesota NORC forms the foundation for expanding influence and effectiveness in obesity research and translational efforts. The Obesity Consortium of Minnesota has drawn together the Minnesota NORC, the Obesity Prevention Center, and the

Transdisciplinary Research on Energetics and Cancer Center for joint projects. The most important of these shared projects is the combined P & F Program for support of new and promising investigators in obesity and nutrition, which has allowed important leveraging of P & F funding for the Minnesota NORC.

Obesity Center Collaborations and Leveraging of Funds that Have Strengthened the Research Base

- A Healthcare Delivery SubCore has been created as part of the Epidemiology and Intervention Core with the HealthPartners Research Foundation to provide linkages between NORC investigators and obesity research in a managed care setting. This collaboration provides access to large populations and support and consultation around technical areas such as health care economics, health system database design and management, and survey implementation. To date, the collaboration has resulted in two major NIH obesity grants with a third application pending: 1) Healthy Homes Healthy Kids: Pediatric Primary Care-Based Obesity Prevention (R01 DK084475); 2) Novel Approaches to Weight Loss Maintenance (R01 CA128211); and 3) Linking Primary Care, Communities, and Families to Prevent Obesity Among Preschool Children (RFA-HL-10-004 pending).
- Dr. Jeffery, Director of the Epidemiology and Intervention Core, is a Principal Investigator on the Look AHEAD (Action For Health in Diabetes) Trial. Our Center was the organizing force behind the establishment of the SHOW trial (now Look AHEAD U01DK057182) proposal from Minnesota. Investigators from the Medical School and School of Public Health were united to work together by the administration of the Center, resulting in a truly multi-talented group of investigators. Dr. Jeffery has since provided assistance to six different investigators on projects related to translating the Look AHEAD intervention to other clinical or community settings.
- The Epidemiology and Intervention Core led a collaboration of NORC investigators on a successful Center grant application titled “Examining the Obesity Epidemic through Youth, Family, & Young Adults: Transdisciplinary Research on Energetics and Cancer” (TREC U54 CA116849). The overall goals of the Center grant are to advance transdisciplinary science in the advancement of understanding of obesity, youth, family, and cancer; to support the career development of new investigators in the field; and to disseminate scientific knowledge about the topic to broader audiences. The initiative has supported a total of 24 additional developmental research projects involving many NORC investigators from Kinesiology, Sociology, Nutrition, Epidemiology, Psychology, Biochemistry, Food Science, Genetics, Pharmacology, Family Practice, Communication, and Pediatrics. Three of these projects have already led to external funding from NIH.
- Drs. James Levine and Robert Jeffery (Epidemiology and Intervention Core) have received funding from the Minnesota Partnership for Biotechnology and Medical Genomics for a mobile body composition and energy metabolism laboratory. The Mobile Obesity Laboratory will enable the Mayo Clinic and UMN to complete outreach and outcomes-based research with respect to obesity prevention and treatment research.
- Robert Jeffery is a collaborator on a pending NIH grant application submitted by James Levine titled “Real-World Office-Place Interventions for Obesity.” The objective of this study is to test scalable obesity interventions that are delivered to representative offices where people work. The project goals are to 1) demonstrate efficacy for achieving obesity

decline with respect to weight loss, body fat decline, decreased blood pressure, and improved metabolic health variables such as glucose and lipids; and 2) perform process, psychological, economic, and productivity measures and/or analyses.

- In April 2010, the UMN was awarded an NIH obesity-prevention training grant (T32 DK083250) under the joint leadership of Drs. Robert Jeffery, Catherine Kotz, and Charles Billington. This training grant was organized by senior leaders of the Minnesota NORC.
- Drs. Robert Jeffery (Epidemiology and Intervention Core) and Charles Billington (Minnesota NORC Associate Director) have collaborated with Dr. Ikramuddin on a study funded by Covidien titled “Global Randomized Study of Best Medical Management versus the Roux-en-Y Gastric Bypass for the Management of Type 2 Diabetes in Patients with Central Obesity.”
- Minnesota NORC investigators are collaborating with researchers from the Neuropsychiatric Research Institute in Fargo and from the University of North Dakota. A research interest group has resulted from this collaboration, as well as grant submissions and ongoing research projects.
- Catherine Kotz and James Levine have established a successful collaboration related to Non-Exercise Activity Thermogenesis (NEAT) and the neuropeptide orexin. This collaboration has led to manuscripts, grant submissions, and support from the State of Minnesota Biomedical Partnership.
- During the past funding period, the UMN approved funding for several new positions dedicated to obesity/nutrition research as well as metabolomics research, with large start-up packages for new equipment.
- Of particular note was the establishment of the Healthcare Delivery SubCore at the Health Partners Research Foundation that is intended to stimulate and support research on obesity-related issues in a real world health care delivery system. This collaboration provides access to large populations and support and consultation around technical areas such as health care economics, health system database design and management, and survey implementation. Research grants on obesity have been submitted to the NIH through the Foundation due to this collaboration.
- The Disordered Eating Assessment Core played a role in the funding of a National Center of Excellence in Women’s Health at the UMN. Dr. Nancy Raymond, a Participating Investigator with the NORC, directs the Center.
- The Disordered Eating Assessment Core was critical in the successful submission of a postdoctoral T32 training grant in Eating Disorders Research (T32 MH 082761). Dr. Crow, the Core Director, is also Program Director for the awarded T32.

Listing of Core Services

Disordered Eating Assessment Core

1. Clinical Assessment: The Core provides consultation regarding assessment of disordered eating and other behaviors; training and ongoing quality improvement/quality assurance for trained assessors; and the conduct of structured assessments.
2. Treatment Development: The Core provides consultation to investigators regarding the development of manual-based treatments for obesity and disordered eating, and is actively

engaged in such development efforts. In addition, the Core provides certain structured therapeutic interventions (such as Cognitive Behavioral Therapy) for ongoing projects.

3. Access to Clinical Populations: The Core provides access to populations of potential subjects with eating disorders diagnoses; subjects with other psychopathology; non-affected comparison groups; obese samples; and archival data sets.
4. Technology-Based Methods of Data Accumulation: The Core provides access to several emerging technologies for the highly accurate on cost-effective accumulation of research data, such as ecological momentary assessment, and data scanning/online data entry.
5. Cost Effectiveness Analysis: The Core provides consultation regarding the collection of cost effectiveness data in clinical trials. Services provided by this Core are highly labor-intensive, requiring individuals with advanced training plus expensive, specialized experience in behavioral assessments, treatments or both. It would be impractical, expensive and often impossible for investigators to re-create this capacity in their own group.

Epidemiology and Intervention Core

1. Data Services: A data services section provides expertise in population selection, survey, study participant recruitment, and follow-up, data entry, data base management and statistical support.
2. Nutrition Assessment: The nutrition assessment section provides expertise in dietary assessment methods, including instrument design, data collection, and nutrient analyses.
3. Intervention Services: The intervention section provides guidance in the development of diet and exercise interventions for outpatient populations in clinic and community settings.
4. Health Care Delivery Section: The health care delivery section provides access to members, clinics, and health databases of a managed care organization that delivers a wide spectrum of medical services to a member population of approximately 800,000.

Metabolic Studies Core

1. Human Studies
 - a. Dual energy x-ray absorptiometry. A model DPX-IQ whole body scanner (Lunar Radiation Corp., Madison, WI) is present in the Body Composition Laboratory at the Mayo GCRC Integrative Physiology Core.
 - b. Total body water. We offer measurements of total body water using $^3\text{H}_2\text{O}$, H_2^{18}O , and $^2\text{H}_2\text{O}$.
 - c. Extracellular fluid space. We offer measurement of extracellular fluid space by radiotracer and biochemical methods.
 - i. Radiosulfate
 - ii. Bromide space

- d. Visceral fat by CT scanning. Investigators have access to measurements of visceral and subcutaneous abdominal adipose tissue content via the Mayo Department of Radiology.
- e. Circumference measurements. Waist and hip circumference measurements are provided to assist investigators in the simple anthropometric characterization of obesity.

2. Energy Expenditure Measurements

- a. Resting energy expenditure
 - i. Basal metabolic rate
 - ii. Resting metabolic rate
- b. Thermic effect of food
- c. Thermic effect of activity
- d. Doubly labeled water

3. Substrate Oxidation/Nutrient Partitioning

- a. Indirect calorimetry. Net carbohydrate, lipid, and protein oxidation are assessed by measuring O₂, CO₂, and nitrogen excretion.
- b. Endogenous substrate metabolism. The turnover of lipids (fatty acids and glycerol), glucose, and amino acids in the overnight postabsorptive state is a measure of the release of these endogenous nutrients into the systemic circulation. These events can be studied using stable isotope techniques or radiotracer techniques.
 - i. Lipid metabolism
 - a) FFA turnover
 - b) Glycerol
 - ii. Glucose
 - iii. Amino acid turnover. Stable isotopic tracers of leucine and phenylalanine are used for assessing endogenous amino acid turnover and oxidation ([1-¹³C] leucine).
- c. Meal nutrient partitioning

4. Plasma Hormone/Adipokine Concentration Measurements

A wide variety of substrate and hormone assays are available through this Core facility, including adiponectin, resistin, TNF- α , IL-6, CRP, and ghrelin.

5. Metabolomics:

Isotope Ratio/Mass Spectrometry (MS):

Thermo DeltaS dual inlet – ²H, ¹³C, ¹⁵N.

Thermo DeltaPlus GC/Combustion - [U-¹³C]palmitate enrichment in VLDL-TG

Thermo DeltaV-TC/EA – Total body water (²H₂O)

Thermo DeltaV-GC/Combustion - just installed - testing system

GC/MS:

Agilent Technologies MSD 5973N - plasma [¹³C₆]glucose, plasma [6,6-²H₂]glucose pilot

Agilent Technologies MSD 5975C - d₅-glycerol

Tandem (MS/MS):

Applied Biosystems Qstar XL LC/QTOF - peptide identification

Thermo TSQ 7000 GC/MS/MS - [ring-¹³C₆]phenylalanine plasma + total protein mpe

Waters Quattro Micro GC/MS/MS - [U-¹³C]lysine development

Thermo Quantum Ultra LC/MS/MS - Amino Acid profiles, Waters kit + Acquity UPLC

Thermo Quantum GC/MS/MS - [ring-¹³C₆]phenylalanine plasma + total protein mpe and citric acid cycle development

Applied Biosystems API 5000 LC/MS/MS - [U-¹³C]palmitoyl and oleyl-carnitine, novel method for plasma U-¹³C]palmitate

Thermo LTQ/Orbitrap LC/MS/MS – sphingolipid/ceramide concentration and enrichment (muscle and other tissues – development). Will move to Thermo Quantum Ultra LC/MS/MS eventually.

Being installed - Agilent Technologies 6220 TOF (LC/MS/MS) for Qualitative metabolomic profiling

6. Animal Studies

- a. Food intake
- b. Energy expenditure with activity determinations
 - i. Butane burn validation of calorimeter
 - ii. Determination of REE in the 12” (5.3 l) cylindrical cage and the 340 ml fast response chamber
- c. Body composition: *In vivo* body composition by DXA
- d. Carcass analysis: Support for full carcass analysis will be available to include
 - i. Homogenization
 - ii. Ash weight
 - iii. Bone mineral content by PixiMus (r=0.99 to ash weight)
 - iv. Body fat by quantitative fat analysis
 - v. Body energy by bomb calorimetry

Obesity and Energy Metabolism Core

1. Virus Production Facility
2. GeneChip Microarray Analysis Facility
 - a. Bioinformatics support for microarray GeneChip analysis
 - b. (Refiner, CoBi, Analyst)
3. Real-Time PCR and the Oligonucleotide Library Facility
4. Small Animal Indirect Calorimetry and Body Composition Measurement for Rodents